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.	)	

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IN THE UNITED STATES COURT OF FEDERAL CLAIMS

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Respondent.	)	

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

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C O N T E N T S

E X H I B I T S

RESPONDENT'S EXHIBITS:	ADMITTED	RECEIVED	DESCRIPTION
8	1238	--	Slide
9	1459	1459	Slide
10	1489	1489	Slide

P R O C E E D I N G S

(9:02 a.m.)

SPECIAL MASTER HASTINGS: Good morning to all here in the courtroom and listening in on the phone conference.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: All right. I'll welcome again those who are listening in to this hearing via conference call. Welcome to all those in the courtroom here for the second week of our trial in the Cedillo test case and the Omnibus Autism Proceeding.

We're going to start with the Respondent's case-in-chief this morning. I will give you folks who are planning your listening and attendance here a bit of updated information that I got just a few moments ago from the counsel for both the Petitioners and the Respondents.

They've conferred, and by mutual agreement, we've cut down the witness schedule. Three of the experts for the government who filed expert reports are not going to testify. That would be Dr. Fujinami, Dr. Zimmerman and Dr. Gershon. That will slightly alter our schedule.

For those who are planning ahead, we have

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

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 The Petitioners have withdrawn their request to cross-examine Dr.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

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

MR. MATANOSKI: Yes, sir, I do.

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

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

the Petitioners' favor.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

They went to him. They offered him money to

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

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

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

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

In 2000, he published another article

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

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

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

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

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

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

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

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

You heard from Dr. Krigsman. It was

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

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

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

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

You heard from Dr. Hepner, and frankly, I

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

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

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

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

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

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

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

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

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

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

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

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

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

SPECIAL MASTER HASTINGS: You meant Dr. Cook.

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

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

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

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

You already know something about the lab.

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

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

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

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

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

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

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

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

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

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

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

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

SPECIAL MASTER HASTINGS: Thank you, Mr.

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

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

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

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

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

Whereupon,

ERIC FOMBONNE

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

SPECIAL MASTER HASTINGS: Okay.

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

is going to be discussing?

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

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

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

MS. RICCIARDELLA: Correct.

SPECIAL MASTER HASTINGS: Let's mark this. I believe we would be at Respondent's Trial Exhibit 8.

(The document referred to was marked for identification as Respondent's Trial Exhibit No. 8.)

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

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

THE WITNESS: Yes. Can you hear me?

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

MS. RICCIARDELLA: That's why I was just

looking. I think he has it.

SPECIAL MASTER HASTINGS: Okay. Very good.

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

SPECIAL MASTER HASTINGS: I think you're okay.

MS. RICCIARDELLA: Okay.

DIRECT EXAMINATION

BY MS. RICCIARDELLA:

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

A My name is Eric Fombonne.

Q And would you please state your current academic appointment?

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

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

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

of his hypothesis at the time.

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

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

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

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

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

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

A Yes. In 1971, yes.

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

THE WITNESS: Yes. I know. I know.

MS. RICCIARDELLA: He has a soft voice.

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

THE WITNESS: No, no.

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

THE WITNESS: I know it's a problem.

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

THE WITNESS: Okay. Okay.

BY MS. RICCIARDELLA:

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

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

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

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

MS. RICCIARDELLA: We're high tech here.

THE WITNESS: I'm wired.

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

BY MS. RICCIARDELLA:

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

A Yes, that's correct.

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

A Yes.

Q Following medical school, where did you do your residency?

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

Q And in what field did you do your residency?
A I did training in general psychiatry and went on to do a specialization in child and adolescent psychiatry.
Q When did you start specializing in child psychiatry?
A I think I made that choice in 1978 or 1979. No. 1979.
Q And why did you decide to specialize in child psychiatry?
A Because I had an interest in the childhood antecedence of psychiatric disorders in adult life and then also a strong interest in neurodevelopmental disorders.
Q Doctor, what certifications do you hold in your field?
A I have a medical degree, and I have full training in child and adolescent psychiatry. I'm the equivalent of board-certified in child and adolescent psychiatry in the French system.
Q Is that the highest certification in your field?
A Yes.
Q Your CV, Doctor, mentions that you had some military duty. What did that entail?

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

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

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

Q And what training have you had in epidemiology?

A I did Master certificates when I was a medical student. I also worked in various research projects between 1974 and 1981 I think. For instance, I ran a multicentric randomized clinical trial from the conception of the study to the analysis of the data, so I learned hands on a lot of research skills.

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

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

Q And when did you begin your epidemiological research?

A My own?

Q Correct.

A In 1985, that was when I decided actually to embrace a research career after my training was finished. I was still doing clinical work but decided to develop empirical studies of child psychiatric disorders in my country. My approach was to develop the first epidemiological study of child psychiatric disorders. Not autism, just the range of psychiatric disorders, emotional disorders, disruptive disorders, in a large, population-based survey which I did in France and started that in 1985 through 1989.

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

A Yes.

Q What is INSERM?

A INSERM is the Institute National de la Sant, et de la Recherche M,dicale, which is the French institute which carries most of the biomedical

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

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

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

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

A Right. Correct.

Q What is Maudsley Hospital and Institute of Psychiatry?

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

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

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

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

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

A Yes.

Q Who is Michael Rutter?

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

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

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

appointment.

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

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

A readership is made in recognition of the particular academic accomplishments in a particular field by someone. So it's like being a chairman without the chair, and it's recognition of your academic excellence in that field.

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

A Yes.

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

A Yes.

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

A Yes. Correct.

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

A Since 1993.

Q 1983?

A 1993.

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

A Since 2001, so about six years.

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

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

Q Doctor, are you associated with any hospital?

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

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

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

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

A Yes.

Q Who do you teach?

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

Q Do you teach epidemiology methods in child psychiatry research?

A Yes.

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

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

Q How long have you been teaching?

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

Q And do you also teach child psychiatry?

A Yes.

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

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

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

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

A Yes, I do. Yes, I do.

Q Do you lecture worldwide?

A Yes, I do that.

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

A How many times?

Q Per month.

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

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

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

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

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

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

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

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

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

A Yes, I do that.

Q How many times?

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

Q Do you currently have a clinical practice?

A I do. I do see patients quite regularly.
Q And as part of that clinical practice, do you diagnose and treat children with autism?
A Yes.
Q How many per year approximately?
A I think currently in our clinic, we probably see about 350 new diagnosed cases per year, and I probably out of these see half of them about. It's hard to say.
Q And currently how many autistic patients are you following?
A That I follow? Probably I would say 200. I do see patients for initial assessments. I do follow up on them. I also am running a psychopharmacology clinic, which is to help for the handling of difficult behavior in children who are diagnosed but are older and where behavior interventions have failed. We sometimes use medication. I'm one of the medical leaders of that clinic, which is part of my autism program.
Q Do you meet with parents as part of your clinical practice?
A Well, all the time because they are present at all assessments. We work with families and parents very closely of course.

Q And you've been directly involved in epidemiologic studies of autism, is that correct?
A Yes.
Q Approximately how many?
A I've been involved in a number of studies, probably eight or 10 now in several countries.
Q Okay. And, Doctor, you've published over 160 articles related to childhood pervasive developmental and behavioral disorders, is that correct?
A Yes.
Q And are all those articles peer-reviewed?
A Yes.
Q In addition, you've published 34 book chapters pertaining to childhood psychiatric and developmental disorders, including on the epidemiologic study of autism, is that correct?
A Yes.
SPECIAL MASTER HASTINGS: Rather than nod, you need to say yes.
MS. RICCIARDELLA: It has to be audible, your response.
THE WITNESS: Oh, yes. Sorry. Sorry. I said yes. I didn't count them, but you did.
MS. RICCIARDELLA: I did.

BY MS. RICCIARDELLA:

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

A Yes.

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

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

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

A Yes.

Q What is JADD?

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

Journal of Autism and

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

Q And are you also a reviewer for other journals?

A Yes. I do review all the time.

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

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

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

to neurological meetings.

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

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

A Yes.

Q How did you participate?

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

Q Are you currently a member of IMFAR?

A Yes.

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

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

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

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

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

A Yes. Yes, I was.

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

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

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

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

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

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

A Very rarely.

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

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

Q And have you consulted for the pharmaceutical manufacturers?

A Yes.

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

A Yes.

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

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

Q And other than your testimony in the Easter

case at the Daubert hearing and your testimony today

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

A No, I have not testified otherwise.

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

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

Q The General Surgeon?

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

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

epidemiology

of autism, so that's what it was.

Q Were you paid?

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

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

A Yes.

Q Doctor, did Michelle's receipt of thimerosal-containing vaccines and the MMR vaccine cause or contribute to her autism?

A No.

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

A Yes. Yes.

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

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

MS. RICCIARDELLA: Certainly.

THE WITNESS: Okay.

BY MS. RICCIARDELLA:

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

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

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

SPECIAL MASTER HASTINGS: Right.

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

Secondly, they have abnormalities in the way

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

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

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

So eye contact, as opposed to be constantly lacking, could be present, but the quality of the eye contact would be different, so the child would stare at people or would not regulate sufficient interaction with very subtle change in the eye gaze.

BY MS. RICCIARDELLA:

Q Doctor?

A Yes?

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

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

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

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

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

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

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

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

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

If we can just take the time to discuss a few of these, particularly as they present young

infants, for instance, often there is language delay. There is no babbling. There can be no babbling in a young infant or the babbling can be very limited.

For instance, you could recognize that the amount of babbling is reduced or the quality of the babble is also altered. There would be very little babbling not directed to communicate. It would be self-directed, not used with a communicative intent.

Young babies when they babble are usually communicating in sort of a to and froing fashion, and often in autism, the babble would be already quite different. So we look at different qualities of the babbling.

What is important as well is when the child has no language or is delayed in his language development. What the child usually will do who has just language delay is they would use gestures to communicate to compensate for their lack of language.

In autism, we see precisely that it's not only the language which is lacking, but it's also the capacity to communicate with other beings. So the lack of gestures would be something which is critical to evaluate the communication deficits in autism and to differentiate them from language disorder, for instance.

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

The type of pointing that they use is what we call protoimperative, which they can point at objects that they want for needs, so that kind of pointing they would do. What they do not do is pointing at a distance to show something, to share an interest when someone is in the room. Now this is a different type of pointing.

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

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

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

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

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

Q And you're referring to Slide 4.

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

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

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

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

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

Q You mentioned a third domain as repetitive behavior?

A Yes. Yes.

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

A There are different types of --

Q Slide 5. Excuse me. Slide 5.

A Yes. Again, there will be different types of symptoms, and there would be some different levels of development.

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

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

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

One thing which is often seen at different developmental levels is unusual interests, so they have fixations for particular activities. They might seem to be normal activities, but what makes this affixation unusual is that they are always the same. They exclude social activities. They do not progress over time.

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

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

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

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

A Yes.

Q And you're on Slide 6?

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

For that, there are different ways to do it. You can do just a clinical assessment. The clinical assessments are often limited because they are volable, so we tend to use now our field different

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

The most recent instruments are the ADI and the ADOS. These are standardized measures which are used now worldwide both in clinical settings and in research settings, and I put them there because a lot of the published research refers to these diagnostic tools.

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

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

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

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

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

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

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

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

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

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

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

concern the parents during these first years of life.

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

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

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

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

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

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

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

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

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

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

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

Q Does the United States use the DSM-IV?

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

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

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

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

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

Q And you're referring to Slide 9?

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

Q Slide 10.

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

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

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

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

A I'm sorry?

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

A Yes.

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

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

ICD-10 is actually a nosographical system which provides categories for all the whole of medicine. So it's a system which is in use in many parts of the world, especially for administration of hospital statistics to report morbidity and other statistics because it provides a way to code any kind of medical condition. And within all these medical conditions, there is a whole section on psychiatry, which is the section which is like the DSM-IV with

1 some

variations.

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

A Yes. Correct. There was a task force which was asserted in 1990 to 1991, and I was a representative of WHO with Michael Rutter, and we met with the equivalent from the American Psychiatric Association with the child psychiatry group. We tried to make diagnostic criteria more compatible across the two schemes, the DSM-IV, which was in preparation, and the ICD-10, which was in preparation. We met and tried to make the criteria as similar as possible.

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

A Well, we use predominantly now DSM-IV.

Q DSM-IV?

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

Q Doctor, is autism a relatively new disorder?

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

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

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

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

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

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

A Okay.

Q I'm referring to Slide 12 now.

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

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

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

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

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

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

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

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

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

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

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

language and speech delays and then like the social difficulties were noted in just 40 percent of the cases. The main concern was in the majority of the cases the language difficulties.

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

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

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

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

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

could date that by the day.

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

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

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

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

BY MS. RICCIARDELLA:

Q Is this how you evaluate a child?

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

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

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

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

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

BY MS. RICCIARDELLA:

Q Doctor, what is regressive autism?

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

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

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

signs, or sometimes we have hand and finger mannerisms in the crib at age eight months. It can happen. So this is an early onset where the onset of autistic symptoms is seen before the first birthday.

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

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

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

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

So Professor Rutter's work quoted that at least half of the children who have the regressive subtype actually are abnormal before the regression occurs. There is a recent study by a network of the CPAs in the U.S. and a large study looking at regression versus nonregression where 70 percent of children with a regressive subtype were actually abnormal before their regression occurred.

Q Did you say 70, seven zero?

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

Contemporously to the loss of language or

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

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

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

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

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

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

different profile than the regressive subtype.

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

A Yes.

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

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

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

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

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

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

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

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

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

then nothing.

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

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

A I'm sorry, can you repeat?

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

A Yes.

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

A You mean before the loss?

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

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

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

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

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

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

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

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

A Yes.

Q This is now slide 17.

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

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

This risk is estimated at 5, 10 percent depending on the author. That allows us to follow up from birth onward young children we know are at risk of developing autism, so that provides for efficient study designs. And there is ongoing work what we call sibling study or infancy studies (ph), and there is a baby network which is currently looking at that.

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

So investigators started to ask families of children who were diagnosed with autism,

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

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

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

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

So you can see there the other signs. And the last point is that in several of the studies, people have looked at the interactive style developed by the parents, and it's also obsereved in our clinical settings, that in these children, although the abnormalities are subtle and the parents do not maybe realize them, and what they do is they try to develop interactive styles which compensate for the lack of response of the child.

So that, for instance, the child is not

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

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

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

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

MS. RICCIARDELLA: 18, sir.

THE WITNESS: The current view is that autism occurs in all social strata. There is no association with social classes.

BY MS. RICCIARDELLA:

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

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

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

A The next two slides, this one and the next one, are the two most robust findings which have been described in autism research for decades, which are still requiring an explanation. The first one is that there is an excess of male in this group of conditions. The four males for one female ratio that you see here is an average. So it's an average of many samples that would be typical of an autistic sample.

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

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

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

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

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

retardation range, which means IQ under 70.

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

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

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

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

Q Are seizures more common in the regressive

sub-type of autism?

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

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

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

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

important on this list are tuberous sclerosis and Fragile X.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Whereas, if you look at dizygotic pairs,

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

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

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

affected in autism but much lesser in terms of severity.

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

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

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

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

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

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

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

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

BY MS. RICCIARDELLA:

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

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

A Yes. Yes.

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

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

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

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

the cerebellum, which seem to be lost or decreased.

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

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

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

SPECIAL MASTER HASTINGS: Thank you.

THE WITNESS: So the next slide?

BY MS. RICCIARDELLA:

Q The next slide is slide 24?

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

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

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

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

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

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

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

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

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

(Whereupon, a short recess was taken.)

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

MS. RICCIARDELLA: Thank you, Special Master.

BY MS. RICCIARDELLA:

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

A Yes.

Q What are those signs?

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

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

Q Slide 25.

A -- that this, combined with some later analysis, that the rate of macrocephaly in autistic sample is about 20 percent. Macrocephaly is a clinical sign because it's -- if you are measuring the head circumference with a tape measure, and we have knowns of head circumference from birth to

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

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

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

So can I have the next --

Q Next slide, slide 26.

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

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

So it means that this large head is associated with a brain which is actually heavier. And this finding has also been confirmed with MRI studies. If we could have the next slide, which is slide 27, and on that slide you can see that the head circumference and the head volumes of children in the same study have been measured, and what is important here is that, at birth, it seems that the head circumference is normal.

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

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

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

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

So there is this pattern of accelerated head growth in the first year of life, and then it seems to plateau in terms of the speed of the acceleration of head growth decrease in the second year of life. So that's one of the most robust findings in the recent years. It is not very clear what is happening in the brain.

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

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

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

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

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

There was an epidemic of congenital rubella

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

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

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

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

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

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

They have different ways to do that, and

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

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

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

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

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

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

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

Q Slide 29?

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

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

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

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

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

So the point I want to make here is that there has been in the field of autism, including theories and treatments which were once proposed by psychiatrists like the refrigerator mother theory and the theories. There have been a flurry of other modles of autism or treatments of autism which have been like fashionable at the time but not founded on strong evidence.

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

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

A Yes, I did.

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

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

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

MS. RICCIARDELLA: Thirty. Correct. Okay.

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

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

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

BY MS. RICCIARDELLA:

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

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

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

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

documents several narratives of the mother, the recognition by parents that something was somewhat wrong, you know?

It occurred sometime between January and March 1996 based on narratives that the mother gave on several occasions, and also on professional reports like a speech therapist report in 1997, Dr. Roth's report in 1997, or the private accounts of a gradual onset during that time period.

Q Now, Doctor, you talked earlier about the signs of autism that may not be apparent to parental eyes at the time they're occurring. In your review of Michelle's medical records. Did you see anything that might suggest Michelle was not developing entirely normally prior to her MMR vaccination?

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

SPECIAL MASTER HASTINGS: Now you're looking

at Slide 32, Doctor. Is that correct?

THE WITNESS: Yes. Slide 32.

SPECIAL MASTER HASTINGS: Go ahead.

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

BY MS. RICCIARDELLA:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

illustrate that through a video?

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

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

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

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

(Video played.)

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

independent walking at that age.

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

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

THE WITNESS: Yes, I think so. Yes.

SPECIAL MASTER HASTINGS: Slide 34 gives that date.

THE WITNESS: Yes.

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

THE WITNESS: Yes.

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

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

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

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

motor development at a later stage.

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

BY MS. RICCIARDELLA:

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

SPECIAL MASTER HASTINGS: Now this is Slide 35?

MS. RICCIARDELLA: Yes, Slide 35.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

BY MS. RICCIARDELLA:

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

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

were available to me.

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

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

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

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

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

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

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

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

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

So there would be a range of communicative

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

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

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

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

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

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

(Video played.)

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

(Video played.)

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

(Video played.)

BY MS. RICCIARDELLA:

Q Doctor, what do we see from that video?

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

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

There is no gesture, there is on pointing and no showing. We didn't hear any babble, any words, certainly not even any babble. Her facial expressions are restricted and reduced. She doesn't join in when there is excitement. So all that has been described. We can see in terms of her posture that she's unstable and in line with the motor delay which I mentioned before.

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

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

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

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

Go ahead.

BY MS. RICCIARDELLA:

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

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

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

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

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

BY MS. RICCIARDELLA:

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

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

(Video played.)

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

(Video played.)

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

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

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

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

BY MS. RICCIARDELLA:

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

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

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

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

(Video played.)

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

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

BY MS. RICCIARDELLA:

Q The next slide, Slide 42, we're going to review a video taken of Michelle at nine months. That was June 20, 1995.

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

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

(Video played.)

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

intent.

BY MS. RICCIARDELLA:

Q So finally, Slide 43.

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

(Video played.)

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

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

Then soon you're going to see something

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

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

(Video played.)

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

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

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

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

(Video played.)

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

BY MS. RICCIARDELLA:

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

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

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

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

A I'm sorry?

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

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

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

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

throughout that clip.

Go ahead, Ms. Ricciardella.

BY MS. RICCIARDELLA:

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

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

MS. RICCIARDELLA: Excuse me, 44.

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

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

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

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

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

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

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

her age.

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

THE WITNESS: Yes.

SPECIAL MASTER HASTINGS: Go ahead.

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

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

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

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

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

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

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

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

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

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

BY MS. RICCIARDELLA:

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

A No, I do not agree with that explanation.

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

you agree?

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

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

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

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

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

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

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

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

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

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

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

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

A Yes, it's correct.

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

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

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

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

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

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

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

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

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

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

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

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

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

I want to ask one question right now, just

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

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

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

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

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

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

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

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

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

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

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

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

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

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A F T E R N O O N S E S S I O N

(1:52 p.m.)

SPECIAL MASTER HASTINGS: All right. We're ready to start the activities for the afternoon today. We'll be starting with the cross-examination of Dr. Fombonne.

Whereupon,

ERIC FOMBONNE

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

SPECIAL MASTER HASTINGS: Let me confirm before you go, Ms. Chin-Caplan, to make sure that we're back in conference. Operator, are we back in conference? Is the Inter-Call operator there?

THE OPERATOR: Yes, you are back in conference.

SPECIAL MASTER HASTINGS: Okay. Thank you very much. Go ahead, Ms. Chin-Caplan.

MS. CHIN-CAPLAN: Thank you, Special Master.

CROSS-EXAMINATION

BY MS. CHIN-CAPLAN:

Q Dr. Fombonne, you submitted a 62 page report on Michelle. Is that true?

A Yes.

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

A Yes.

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

THE WITNESS: Yes.

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

MS. CHIN-CAPLAN: Certainly.

THE WITNESS: Yes.

BY MS. CHIN-CAPLAN:

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

A Yes.

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

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

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

A Yes.

Q And you based it primarily on the handout,

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

A Yes.

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

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

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

A Yes.

Q A pediatric psychiatrist.

A Yes.

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

A Yes.

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

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

Q And what you would expect to see if a child

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

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

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

SPECIAL MASTER HASTINGS: Thank you.

BY MS. CHIN-CAPLAN:

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

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

Q On the right hand side?

A Yes.

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

A Yes, that's correct, yes.

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

A Yes.

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

A Yes.

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

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

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

A Yes.

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

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

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

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

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

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

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

A Do I know him?

Q Yes, do you know him?

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

Q Okay. He was scheduled to testify.

A Yes.

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

A Do I have it?

Q Can you show me?

SPECIAL MASTER HASTINGS: Can you give him a copy?

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

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

BY MS. CHIN-CAPLAN:

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

A Yes.

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

A Yes.

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

A Yes.

Q I've read that correctly?

A Yes.

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

A I'm sorry, could you repeat?

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

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

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

A So where are you looking on that page?

Q Paragraph 151.

A Paragraph 151, yes, okay.

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

A Yes.

Q By Dr. Roth?

A Yes.

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

A Yes.

Q And it was roughly 105, almost 106?

A Yes.

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

A Yes, from what I recall, yes.

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

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

Q But you have some general knowledge.

A Yes, sure, of course, yes.

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

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

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

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

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

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

Q Do you know that during that period of

immunosuppression that children are prone to opportunistic infections?

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

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

A Yes, that's more like five days.

Q Did you finish your answer?

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

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

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

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

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

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

fourteen day period, would that sound right to you?

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

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

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

Q I have one last question on this.

A Yes.

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

A Again, I have no opinion regarding the fever and the course of MMR immunization, or co-occurring infections, immunosuppressions, this is not my field of expertise. What I can just say is that there is no known association between fever and immunosuppression and autism. That's what I think we can say.

Q Now, Doctor, you don't dispute the timeframe in which Michelle received her actual diagnosis of autism, correct?

A What do you mean by the timeframe that she received her diagnosis?

Q When she was first diagnosed with autism.

A No, there is no dispute. She was diagnosed, as I recall, in the Summer of 1997, shortly before she was age 3, by Dr. Roth.

SPECIAL MASTER HASTINGS: Could you keep your voice up a little?

THE WITNESS: I'm sorry. I'm sorry.

BY MS. CHIN-CAPLAN:

Q Doctor, you don't dispute either the timeframe in which the gradual change in Michelle's communication skills were noted, do you?

A Could you explain your question? Because if there is a dispute, there should be different arguments.

Q Sure.

A And I don't understand what you mean.

Q Sure, the record documents that sometime between January 1996 and March 1996, Michelle lost words. You don't really dispute that, do you?

A No, I think the records show that Mrs. Cedillo went to her doctor on I think the 15th of March or early March 1996. This is when there is documentation in the medical records that mother was

concerned about the loss of words in Michelle in previous weeks.

There are other professional reports which mention the onset or recognition of first symptoms by the parents sometime between January and March it is said in several places initially, including, I think, in Mrs. Cedillo's narrative, which is dated 1997 or 1998, or something like that.

Q So we can agree that sometime between January or March of 1996, Michelle lost words.

A I would be more cautious about this last part of your statement. As I said earlier, the review of the videos gives sort of new light about the extent to which she had actual language before the MMR vaccinations, or before December 20th.

As I reviewed the tape this morning, the tape dated the 17th of December shows no single words whatsoever, and there was no use of words at all in all the video evidence that we reviewed. So whether she lost words in the weeks which followed, I think is very hard to estimate.

Q But you would agree that her March 1996 pediatric record says, "Lost words since illness in December"?

A Yes. In the medical record, mother reports

to the doctor that she stopped talking or lost words.

Q So you would agree with that?

A Yes, sure.

Q Now, Doctor, you've written numerous articles. Is that true?

A Yes.

Q Some were on epidemiology, some on other topics.

A Yes.

Q Doctor, did you write an article that looked at the reliability of a primary care physician when they made a diagnosis of autism?

A Off the top of my head, I would say no. Primary care physicians --

Q Give me a minute.

SPECIAL MASTER HASTINGS: Do you know the tab number, Ms. Chin-Caplan, or does anyone?

MS. CHIN-CAPLAN: I have the article printed. Let me see if I can find it.

SPECIAL MASTER HASTINGS: Okay. Does anyone happen to know so I can find it while you're looking?

MS. CHIN-CAPLAN: It's entitled, "Pervasive Developmental Disorders in Preschool Children: Confirmation of High Prevalence."

THE WITNESS: Oh, yes.

SPECIAL MASTER HASTINGS: Does anyone know where it is in the record? That's what I'm asking. I'm asking anyone in the courtroom.

(Laughter).

MS. CHIN-CAPLAN: It's Petitioner's Exhibit P, Tab 26.

SPECIAL MASTER HASTINGS: Thank you.

MS. CHIN-CAPLAN: You're welcome.

SPECIAL MASTER HASTINGS: Go ahead. I've got it. Go right ahead.

BY MS. CHIN-CAPLAN:

Q Doctor, do you have that?

A No, I know what you're referring to now, but I don't have the articles. It's the American Journal of Psychiatry. No. No, that should be the American Journal of Psychiatry. I think so.

SPECIAL MASTER HASTINGS: This is an article by D. Stefano.

MS. CHIN-CAPLAN: No, Special Master.

SPECIAL MASTER HASTINGS: Then it's not Tab 26, I don't think.

MS. CHIN-CAPLAN: It's Attachment 26.

SPECIAL MASTER HASTINGS: I'm sorry?

MS. CHIN-CAPLAN: I have it as Attachment 26.

SPECIAL MASTER HASTINGS: Tab?

MS. CHIN-CAPLAN: Twenty-six.

MALE VOICE: Petitioner's Exhibit P, Attachment 26.

MS. CHIN-CAPLAN: No, Respondent's --

SPECIAL MASTER HASTINGS: Respondent's Exhibit P -- I'm looking at Respondent's Exhibit P, Tab 26.

THE WITNESS: This is AJP, American Journal of Psychiatry, line 5, Chakrabarti.

SPECIAL MASTER HASTINGS: And I'm seeing an article by D. Stefano, et al, called "Aid to First Measles, Mumps, Rubella." Okay. Thank you. Okay. I've got it.

BY MS. CHIN-CAPLAN:

Q Doctor, I'm going to ask you to take a look at page 1136 of this article, and the section on Reliability Study.

A Which section?

Q Reliability Study?

A Reliability, yes, yes.

Q Yes, and the very last sentence --

A Yes.

Q -- have you read it?

A I read it, yes.

Q So, Doctor, just so we get this into the record here, it states, "Blinded raters were also asked to provide an independent global judgment about the presence or absence of pervasive developmental disorder, based on the parental interview, and they confirmed the presence of pervasive developmental disorders in all 38 children, yielding a 100 percent agreement with the original pediatrician's diagnosis." Have I read that correctly?

A Yes.

Q Doctor, could you just explain to the Court what that sentence means?

A Yes, my co-author on this paper is not a primary care physician. That's why I did not understand what you mean. He is a developmental pediatrician who has special expertise in developmental disorders. So he has set up a developmental center in his region where we did these studies.

So initially, the children that were identified in these two surveys, were referred by general practitioners from the local area, speech therapists, house visitors with the specific professions in the U.K.

They were referred after having been trained

to identify the first signs of autism by him, and we send them a brief on how to refer on this and which kind of symptoms are shown by which children at which age, and then to refer to this center where they are assessed by a multi-disciplinary team.

It was, I think, a one week complete, comprehensive assessment, in a hospital where they came all day with their parents or their mother. There were occupational therapy assessments, speech and language assessment, blood work being done, and were observed.

Then following that, some more standardized assessments were performed, using ADI in particular, which is the autism diagnostic interview, the standardized domestic measure referred to this morning. So Dr. Chakrabarti turned to the ADI, and did the diagnostic interviews on these children. He had first generated a clinical diagnosis on these children.

So after the one week assessment, they concluded as to whether or not the child has one form of ASD or PDD, and if yes, what was the precise diagnosis. Then he collected in developmental interviews, diagnostic interviews. Some of them were videotaped. As part of our concern when we conduct

research about reliability, I especially wanted to check the diagnosis on the subset of children which were included in that study.

So we selected some tapes that he had available, based on his autism diagnostic interviews, video-taped. He sent them to me, and they were rated in my department, on my team, by a research assistant, which were blind to the actual outcome in the child.

It's a long interview, so we score particular symptoms. Then at the end, you have different sub-scores that you can look at, for instance, a pair of interviewers would look at the same tape, you can then compare. If the blindly rate incentive, you can then compare at the end whether or not they agree on the score in communication polling in the sociointeractions.

So that's what we did in the study. We measured the inter-rater reliability by two blind raters of the subset of video tapes, using the ADI on a sub-sample of this study.

One of the questions which was asked at the end to the research assistant was, in your opinion, does that child meet criteria for any developmental disorder, yes or no? So they

//

are forced to make a choice.

All these tapes agree that the children had PDD, and that was conversion with the initial diagnostic impression of the pediatrician. It could have been, for instance, 80 persons in other cases or 90 persons on other cases. Now in all cases there were in agreement on the presence of a PDD in that subsample.

Q But the pediatrician who initially made the diagnosis --

A Yes, but that diagnosis was unknown to those who rated the tapes.

Q Now, Doctor, you're aware that Michelle had a pediatrician. Isn't that true?

A Yes.

Q And when you reviewed her medical records, her pediatric records, was there any indication that her pediatrician thought that Michelle was developmentally delayed?

A Not that I recall, but in later professional reports, there was clearly a mention of delay in several milestones, like social smiling, which is related to four to six months of age, or sitting at 11 months of age, which she is clearly motor delayed in the development. So while it is not documented in the

notes, it's documented later by other professionals when they reviewed the developmental history.

Q I'm speaking specifically about her pediatric record.

A Yes.

Q When you went through that record, was there any indication on any of those well child visits that Michelle was developmentally delayed?

A No, not by the pediatrician who saw her, up to the immunization.

Q Doctor, one of the reasons that you believe that Michelle was demonstrating early signs of autism was the evidence of motor delay.

A Yes.

Q Do you remember that?

A Yes.

Q As evidence of her motor delay, you cited the date 2/6/96, when she was age 17 and-a-half months. Is that true?

A Yes.

Q That's on page 34 of your handout.

A Yes, slide 32.

SPECIAL MASTER HASTINGS: Slide 34.

THE WITNESS: Yes, sorry, the videotape, yes.

BY MS. CHIN-CAPLAN:

Q That was 2/6/96, correct?

A Yes, correct.

Q That's evidence of the fact that she was delayed in her walking, that video clip that you showed us.

A This is one piece of evidence on the fact that she didn't meet motor development in milestones in due time. Again, she was not crawling before nine months of age, not sitting independently before eleven months of age, which is very late.

Although there is mention in some of the medical records or reports that she was walking by age 15 or 16 months, that's what is mentioned here and there. It's very clear from the video that by almost 18 months of age, she was not walking independently. This is the continuation of previous mental delays, which are well documented in the file.

Q You're aware that 2/6/96 is after she had suffered those two fevers, aren't you?

A Yes.

Q So the fact that she was motor delayed in what you're citing to as evidence of early autism, occurred after the MMR?

A Yes, I do note this as evidence of early

signs of autism. I said early abnormal development, which is very different.

Some children with autism do exhibit delays in their motor muscles, but not all of them by and large. The kind of delays that she has in her development are more consistent with the fact that in addition to her autism, she's globally developmentally delayed. That speaks more to the mental retardation which is documented later in our file. Mentally retarded children often have this pattern of late milestones in motor development, which she has.

Q You're saying she was globally delayed, correct?

A Yes.

Q Do you see any notation in her pediatric record that she was globally delayed?

A Yes. Yes. As I said, there are several milestones that she didn't meet in time. Social smiling is not there, motor delays of different types, much before the MMR was administered.

Then I would need to consult my report, but she has then been assessed with particular psychometric assessments, which documented the fact that she was delayed in her global development, using various tests like the Vineland, which showed

scores which were under the percentile. There is a consistency of evaluation to make sure that she is mentally retarded and developmentally delayed.

Q The question to you, Doctor, was did you see in her pediatric records that she was globally delayed?

SPECIAL MASTER HASTINGS: I think the reason you're having a problem here is, you mean one thing by the pediatric record, and he means another thing. I think she's asking you, do the pediatricians ever write out, "motor delay." You know, that's what I think she's asking you. Do they actually conclude that there's motor delay?

THE WITNESS: No, no, that's clear in the record. I couldn't see it, at any visits which preceded the last visit, which was March, 1996. But pediatricians in his note or her notes did not mention delays in motor development.

I don't recall the name. But this is mentioned later, when the careful developmental study was made. It is mentioned clearly that this is not inconsistent with what we see all the time.

BY MS. CHIN-CAPLAN:

Q But the records that were taken contemporaneously at her pediatrician's office do not

mention global delay, does it?

A No.

Q Now, Doctor, you indicated that there was evidence of early social communicative abnormalities. Do you recall that?

A Yes.

Q I was a little confused when you were going through that. But I did not understand specifically what you were referring to. So could you direct me to your handout, where the social communicative abnormality are listed?

A Yes, I've seen that, yes.

Q Where did you list them?

A Where do I list them?

Q In your slide show.

A Oh, what is the number of the slide that you want? It's slide 32.

Q Slide 42?

A It's slide 32.

Q Slide 32 -- but you gave specifics about what constituted early social communicative abnormalities, didn't you? And could you direct me to where that was in your slide presentation?

A I just spoke about them first, indicating that she was described in the medical record as an

infant, as being very silent, undemanding, very quiet, tending to be very content. These are descriptions that we often see in the autism literature, when the infant development is reviewed with respect to activity. So this is some evidence.

Secondly, I said that, as I recall, I think I mentioned that she was delayed in her social development. She didn't smile socially before four to six months of age, which is indicated in one professional report of 1997, I think. That, again, is a delay in social development.

Then the last argument, which I put forward this morning, was the fact that by 15 and-a-half, if we accept that she had 10 words which would be used consistently and with meaning every day, which is very debatable, if you plot her word production, compared to knowns which exists typically for developing infants in the U.S., using the scale I mentioned to you, which is the MacArthur Communicative Development Inventory. We have knowns.

So we know when she's going on average, start to produce words, as how many she has on average, at eight, nine, ten months, up to sixteen months, and onwards. Based on that, she would score in the last five percentiles very easily, which

indicates that she was delayed in her language development, based on the assumption that she had 10 words, which is not a very conservative assumption.

Q In the video that you saw, she smiled several times, didn't she?

A Yes.

Q That was roughly at nine months, correct?

A We'd have to see. But yes, she smiles on a few occasions, yes.

Q Okay. And do you recall the one with the jungle gym at all?

A The what?

Q The jungle gym. She was sitting up in the little jungle gym and she's batting a mirror?

A No, I don't, so I would need to see it again.

Q You don't remember that one at all?

A No, no, I don't know.

Q Okay.

A I must have seen it, because I've seen them all. I'm sure if there is something to see, we could watch it.

Q Now, Doctor, continuing on that topic, on page 59 of your report, paragraph 155, you state the very same thing that you stated right now, that she

was a good baby, cried little, awaken to be fed. She seemed to be very content. She didn't smile until four to six months of age, and she had about 10 words, that she said mostly in imitation. That's what you said.

A Yes.

Q About 10 words.

A That's what Dr. Roth says in his report in 1997, which I copied exactly, yes.

Q And you accept that, is that true?

A Yes, that's what is in the record.

Q Okay. And then you go on further in that paragraph. You say babies later diagnosed with autism are described as less socially responsive or active, and language when it develops progresses very slowly, lacks spontaneity and consistency and relies on various parental prompts to occur. You cite Bryson, et al, 2007, correct?

A Yes.

Q And Bryson is included at Respondent's Exhibit P, Tab 15, correct?

A I think so.

Q Doctor, what's the title of this article? This is the article you cited to, isn't it, in your report?

A Yes, yes.

Q What is the title of this article?

A A Prospective Case series of High Risk Infants Who Developed Autism.

Q Okay. And, Doctor, in the abstract, does it indicate what the article is about?

A I suppose. Do you want me to read that?

Q Certainly.

A Yes, okay.

Q Now, Doctor, in this abstract, does it indicate that they came to two groups essentially?

A Yes.

Q And the first group showed a decrease in IQ, between 12 and 24 or 36 months of age.

A Yes, correct.

Q And the second group continued to obtain average or near average IQs.

A Correct.

Q That next sentence, Doctor, does it say, "Signs of autism emerged and/or were more striking earlier in the first subgroup."

A Yes.

Q "In all nine children, early impairment and social communicative development co-existed with atypical sensory and/or motor behaviors, as did a

temperamental profile, marked by irritability, distress and dysregulated state." Have I read that correctly?

A Correct.

Q Doctor, it then goes on to look at some of these patients that they were studying, doesn't it?

A Yes.

Q Okay. And there were several children, correct?

A Nine.

Q Let's go through some of them to see what types of symptoms these physicians saw in these autistic children. So in Case No. 1, Doctor, who is on page 15, there's a diagnosis of autism made at 36 months, correct?

A Yes, yes, correct.

Q Okay. Now, Doctor, they seem to have divided into 6, 12, 15, and 18 months. So at 6 months, was there anything noted in this male child?

A Well, they mention sort of delayed motor development.

Q Okay. Was there anything beyond that?

A They mention, "Did not orient to name called, but oriented to mom talking, some babbling."

Q Then when they get older at twelve months,

what did they notice?

A That there is a change -- at twelve months, there is limited interest in pleasure in responsiveness to others; brief eye contact; some social smiling, more so triggered by physical stimulations such as tickling; no social anticipation; no anticipatory arm movement; inconsistent orienting to name; and other kinds of symptoms.

Q Okay. And when you go on to the next paragraph -- actually, it's a continuation onto the next column.

A Okay.

Q Does it say in that second sentence, "Little reaching for objects, flailed arms and legs in reaction to toys, acted on objects without looking at them, atypical sensory behaviors"?

As an example, it says, "Visual interest in copper pad and feeling with index finger"; "Atypical motor behaviors, hand flapping, and finger flicking; marked delay in motor development, generally hypertonic, but rigid when standing with assistance; seemed uncomfortable when being held, and easily irritated; reportedly poor sleeper; and refused food not smooth in consistency." That was at twelve months, correct?

A Correct.

Q And that child was eventually diagnosed with autism, correct?

A Yes.

Q Now if you go to case two, which is on page sixteen, is there anything at six months that we should know about?

A I'll have to read.

SPECIAL MASTER HASTINGS: I don't understand the question.

MS. CHIN-CAPLAN: I'm asking him to go through some of these case --

SPECIAL MASTER HASTINGS: Right.

MS. CHIN-CAPLAN: -- and the behaviors that these children demonstrated in comparison to what we saw as shown on the video.

SPECIAL MASTER HASTINGS: You're asking him to compare these people to Michelle?

MS. CHIN-CAPLAN: Yes.

SPECIAL MASTER HASTINGS: All right.

BY MS. CHIN-CAPLAN:

Q On page 16 of tab --

A Do you want me to comment? I don't understand.

MR. MATANOSKI: Can I clarify? Do you want

him to comment after he reads the case report, or do you want him to go through each of these case reports and then go back through and start again and comment on how it fits in? Because he's finished one, but you haven't asked him to comment on how this seems to have interplay with Michelle Cedillo.

BY MS. CHIN-CAPLAN:

Q Okay. Why don't we go through each case and then you may comment?

A Okay.

SPECIAL MASTER HASTINGS: How many cases do we have here?

MS. CHIN-CAPLAN: We don't have to go through them all, Special Master.

SPECIAL MASTER HASTINGS: Okay.

THE WITNESS: So as we discussed before, case one is a male that is three years of age. On the six month assessment, there were some concerns, but very mild, particularly, the orientation to name was inconsistent, depending on the caregivers. There was delay in motor development.

But at twelve months, which is six months later, there is more evidence of abnormal development, restricted interest in pleasure in responsiveness to others; brief eye contact; some social smiling, which

is reduced and often obtained through physical stimulations such as tickling; no social anticipation to peek-a-boo; no anticipatory arm movements; inconsistent orienting to name; and then we carried on -- little reaching for objects; atypical sensory behaviors; atypical motor behaviors; and flapping and finger flicking; marked delay this time in motor development, with general hypertonicity and a few other things.

Q Okay.

A So if I compare the description of that boy at twelve months of age, there are some overlapping symptoms from what we observed on the first birthday that we deal with this morning. She's clearly hypotonic on that video. She also has postural instability. Eye contact is inconsistent. There is no affection. There are a lot of similarities.

Q We'll just go through two more, okay, Doctor? Case number three, also on page 16, please --

A Also, so case two, have we done case two?

Q Case number three.

A Case three, okay.

Q Yes, on page 16.

A You want me to read six months, twelve months?

Q Yes, tell us what the child was like at six

months.

SPECIAL MASTER HASTINGS: Well, Ms. Chin-Caplan, I'm not one for wanting him to read long passages into the record. I'm still not understanding, and pardon me. It's probably me. Are you asking him to look through these and pick out item that he thinks that each of these children are comparable to Michelle, at the same age? Is that what you want?

MS. CHIN-CAPLAN: No, Special Master, I'm asking him to tell the Court the symptoms that these children were exhibiting at this particular period of their lives.

SPECIAL MASTER HASTINGS: It's clear in the article. I can read the article.

MS. CHIN-CAPLAN: Okay. Then let's proceed on.

BY MS. CHIN-CAPLAN:

Q So, Doctor, when you look at Michelle's pediatric records, from her pediatrician, as in case number one, was there any indication that she had limited interest or pleasure in responsiveness to others?

A Was it mentioned in the pediatric report?

Q Right.

A No.

Q Was there anything mentioned about eye contact and sometimes looking through, rather than seeing, people?

A No.

Q Was there any description of atypical sensory behaviors, such as interesting carpet patterns, and tracing them with the index fingers?

A No.

Q Was there any indication of motor behaviors like hand flapping or finger flicking?

A No, but are you asking me to comment on that.

SPECIAL MASTER HASTINGS: No.

THE WITNESS: No, okay.

BY MS. CHIN-CAPLAN:

Q I'm just asking if there was any indication in the pediatric records that Michelle was exhibiting these symptoms.

A And you want a yes or no answer.

Q Yes.

A Okay. No.

Q Was there any indication that she was easily irritated?

A No. Actually, yes, she was actually

described as fussy I think in the postnatal period, but it's irrelevant.

Q Did you say that she was a good baby?

A It's mentioned somewhere here.

Q She was a good baby. She was a content baby, that she had to be woken up to eat?

A Yes.

Q So she wasn't easily irritated.

A No, there was no mention of that.

Q Doctor, was Michelle fussy at all?

A I think there was mention of that at one point. But it's not a characteristic which, if it appears, it doesn't happen often. So there is no mention of extreme fussiness or irritability in the pediatric record.

Q Did she cling to her mother at all?

A How should I know that?

Q I'm asking you. Is there any indication in the medical record that she was?

A That she was clinging to her mother?

Q Yes, clingy.

A I don't recall.

Q So, Doctor, this article indicates the development of autistic behaviors in children, and they've listed the behaviors that they noted at 12

months. You've indicated that her pediatric records don't reflect these symptoms at all. Am I correct?

A Yes. I would be happy to offer more comments on that if you wish.

SPECIAL MASTER HASTINGS: No, let her ask the questions, Doctor.

THE WITNESS: Okay. Okay.

SPECIAL MASTER HASTINGS: You can answer what she ask you.

BY MS. CHIN-CAPLAN:

Q Now, Doctor, you spoke about the videos that you saw, and you commented on the videos that we saw.

A Yes.

Q You've also attached an article in support of your opinion, that comments on a retrospective video analysis of children, haven't you? It's contained at Respondent's Exhibit P, Attachment 8.

A I don't know where that is. Is this the Baranek study?

Q It is the Baranek study.

A It's one of the studies. There are many.

Q Okay. And, Doctor, did this paper indicate that there were certain early predictors of whether children might go on to develop autism?

A Yes.

Q What were some of those early predictors?

A Well, I have to read the paper again.

Q Certainly, take your time, and when you're ready, you can let me know.

A Okay.

Q I can refer you to page 114.

A Thank you -- 214, is it?

Q It's page, I'm sorry, 214.

A Page 214?

Q Page 214, yes.

A Yes, I remember it was like groups of behaviors. There were nine, I think, sets of behaviors.

Q Yes.

A They were quoted on the videotape, which included effective expressions, looking, gaze aversion, response to name, social touch responses, anticipatory posture, motor stereotypies, object stereotypies, tactile modulation, auditary modulation, visual modulations, and vestibule modulations, and this is also recognized in different ways each time.

Q Doctor, they compared three different groups of children, didn't they?

A Yes.

Q There was the autistic group, correct, the

developmentally delayed group, and the typical children.

A Yes.

Q And they saw that these different groups had different rates of activity in certain areas. Is that true?

A What do you mean by rates of activities?

Q Well, let me refer you to Table Three on page 218.

A Yes.

Q This table, was this criteria they were looking at to determine whether these children exhibited early signs of autism or not?

A Yes.

Q Doctor, when you look at this article, does it tell you the most critical criteria in children who would later come on to develop autism?

A I think that based on a discriminant, analysis that they could classify correctly subjects, and their goal was based on 91 percent of their cases, if I am correct. They had nine items in combination, discriminating the three groups with the correct classification rate of 94 percent.

Q Okay.

A So the combination of all of these

behavioral

indicators allowed them together to ascribe each to the group he belongs to, based just on these indicators.

Q So, Doctor, just to be clear, these nine criteria that are listed on Table Three were applied to three different groups of children, and based on the score that they receive, it would be indicative of what was more likely to happen within that developmental group?

A Yes.

Q It was sort of a prediction of whether a child would be autistic or normal, that type of thing, correct?

A Yes, it's a prediction early in the development, based on behaviors observed on the video, to a later diagnosis or lack of diagnosis.

Q Doctor, it compared all three groups, correct?

A Yes.

Q Then it compared the autistic group to the developmental delayed group. Is that true?

A Yes.

Q The results of that are contained at the bottom of page 219, isn't it?

A I have to check.

Q The last paragraph beginning with the word "since"?

A "Since", yes.

Q Does it say what the most predictive criteria of autism they learned from this test?

A Well, they give some class of behaviors, which -- I would have to look at the paper to look at their methodology because it's abstracting a paragraph, which doesn't tell me what the analysis is based on.

I suspect it's a discriminate analysis, and that they are looking here at a contrast which is only autism against developmentally delayed children.

They have looked at nine categories of behavior, and they provide a significant differentiation between autism and developmentally delayed, based on the nine items, of which six, in particular, were contributing to this discrimination. And the six are what is written here.

Q What were the six?

A Do you want me to read?

Q Yes.

A Mouthing, in orientation to visual stimuli --

SPECIAL MASTER HASTINGS: Can you tell me

exactly where you're reading from now?

MS. CHIN-CAPLAN: We're on Page 220, Special

Master.

SPECIAL MASTER HASTINGS: Page 220?

THE WITNESS: Yes.

SPECIAL MASTER HASTINGS: I'm on that page. Where on that page?

MS. CHIN-CAPLAN: Directly above the discussion.

SPECIAL MASTER HASTINGS: Okay. Go ahead.

THE WITNESS: So mouthing, or, in addition to visual stimuli, social-touch aversions, posturing, number of name prompts and affect rating.

BY MS. CHIN-CAPLAN:

Q Did Michelle demonstrate any mouthing?

A Mouthing?

Q Yes?

A Yes.

Q Could you tell the Court what mouthing is?

A Yes. There are multiple videos where she actually put toys in her mouth, and that's what she does with multiple toys. We showed a video this morning where she's given a red toy, I think, which she immediately put to her mouth. That's what mouthing is. And she'll also mouthed her fingers in other videos, and she mouthed other toys in several videos. So she's mouthing objects.

Q Is that's what's present in the videos that you showed today?

A One of them, yes.

Q Orientation to visual stimuli?

A It depends what they mean by that. It's a label that they gave to a category of behaviors. I have to see what they -- which kind of behavior and ratings they used in that category because it could be a different thing.

Q It explained on Table 3, which is --

A Okay. I'll have to go to it. What it says is occurrences of orientation, stroke attention to nonsocial, novel visual stimuli based on opportunities. It's quite hard to understand what they actually mean there. It's probably very specific, but it's not very obvious to me when I read that. And then it says visual responsiveness, stroke aversion rating. I'm not entirely sure what they mean by that.

Q Could that mean whether she's looking at it or whether she's turning away from it?

A Yes, but it's a bit unclear.

Q Okay. The next one is social touch aversion. What is that?

A Well, this probably would be referring to

children who have this what we call tactile defensiveness where they tend to arch back when they are taken so that's a certain behavior which you see some children exhibit but not all.

So if I look at the category on Table 3, it says social touch aversions. Yes. It's occurrences of social touch aversion based on opportunities for physical contact.

Q So essentially what you just said.

A Yes.

Q She's arching away from the person. You're turning away when somebody is trying to talk to you, that type of thing?

A Yes, but probably when you rate video tapes, you go into much more details to specify which kind of behavior you actually rate in that category. That is a global description which doesn't really give us a lot of details about what they observed.

So when they do video coding, it's much more specific. Because if you have a child who arches back, there is a point where if it's just a movement like that, you will not go there, so that particular operational definitions which are laid out in procedures and manuals. It's a more complex than it appears in Table 3, but that's the concept behind it.

Q Did you see, in the videos that you presented to us, any social-touch aversion by Michelle?

A No.

Q Then it says posturing. What is posturing?

A Posturing, the way you stand and you hold your body in various situations. If you stand on your feet, or if you sit, so it's the degree of balancing, righting the position, and balance that the child has.

Q Balance with your hands, is that what you just said?

A No, balance -- the overall balance that the child maintains.

Q Doesn't posturing mean abnormal placement of your arms, of your limbs?

A Usually -- no, it depends in which context. Sometimes with the expression is: use of hand posturing. When the hand is held in a particular way, it will be an abnormal hand posture. But it can be used in different ways as well, so I'd have to see what they included in that category.

Q I think you have already commented on the number of name prompts on the video, correct?

A Did I comment?

Q Yes?

A Yes, they have a category which is a number of name prompts, yes.

Q The last category they mentioned was: affect rating.

A Yes.

Q What is affect?

A Again, I have to check with the -- what did they include in this category, so I'm looking back on Table 3.

The number of name prompts is explained. basically, it's a response to name, and it's a proportion of the time the child responds to name, based on opportunities.

so number of prompts given by the adult. It's the proportion of interactions where the child is called and orients to his name.

Q Okay. How they react to people in general, is that it?

A No, it's more specific. It's when the name is called, does the child orient? And you have to -- when you rate a video, for instance, you try to insure that the orientation must be seen behaviorally.

Because if you have the child who is actually looking at you, and you call his name, or her name, it's very hard to see if there is actually a

behavioral response, or orientation, because the child is already looking in the same visual field.

Often we would not count that as a relevant behaviors. We would like to look at situations where, for instance -- our assessments, we have in the ADOS, we use that press to see if the child oriented to name. We are careful when we do that to not be in front of the child, or not be in his visual field.

If the child is playing in the room and doing these things, we stand behind him or sideways, so that when we call his name, then to see that if he reorients, there should be a clear orientation towards the examiner.

These are the precise ways to do it clinically. And there are, of course, I'm sure much more precise ways to stet that on tapes.

Q So the affect reading is not the same thing as affective expressions?

A I don't know.

Q That would be on the table, again on Page 218.

A They call that affect writing on 220. In Table 3, it seems to be affective expressions. I suppose it's the same category. I don't know.

They use different terms. The affective

expressions in Table 3 means frequencies of positive and negative expressions. Because all intervals, the qualitative writing of range and intensity of affective expressions, so it's displayed. They use a different terminology later, which they call: affect rating.

Q Thank you. So, Doctor, when we to go on to Page 221 of this article, right under the table, the very last sentence in the first paragraph, doesn't it say: it appears premature, however, to use these items as a screening tool until they can be cross-validated in future retrospective, as well as prospective studies.

That's what it says, correct?

A Uh-huh.

Q So they're cautioning you to use these types of tools, aren't they, because they don't know the validity of them yet, correct?

A No. I think you don't read the way they say yes. They are talking here about extrapolating the results of their work into a context where they would be screening in a different context: population screening of young children with autism.

That is not something that they advise to do at this stage. It doesn't mean that their results are

invalid. In fact, what you just made me review is

that the comparison, or the contrast, between children with autism and children with developmental disorders, they can achieve a nice separation on six of the categories of behaviors between these two groups. So they could do it in their study based on video analysis.

Now, in the discussion, the goal of that is to try to identify early manifestations of the autism phenotype, not for to talk about it, just to apply that to screening, or early detection efforts in context where you would have much more quick screening in instruments, or testing done by people who don't have necessarily professional expertise in autism.

So before you move towards applying these results to a screening approach at a population level, you need to be cautious and you need more data to insure that you're correct.

But it doesn't invalidate what they found, which is that they could discriminate between children with autism and children without autism but developmental delays. The behaviors which differentiate the two groups are, as we said, affective expression, response to name, and also the behaviors that we have seen this morning.

Q The take-away message is really: Use with

caution, isn't it?

A Yes, of course. The screening is not done by people like me understand. I am an expert and I see hundreds of kid who I can make a professional opinion, or a diagnosis in a situation that would not be applicable to the common general practitioners, pediatricians, or nurses. So the screening is in a very different context.

Q Okay. Doctor, you've written a number of articles, as we've discussed earlier today, correct?

A Uh-huh.

Q Quite a few of them are epidemiological studies, correct? And there a few that aren't, though, or they have a different type of topic, isn't that true?

A Yes.

Q Doctor, you did write an article: MMR in Autistic Enterocolitis. That's Respondent's Exhibit P, reference 64. Do you recall this article?

A Yes, it's a commentary that I was asked to write for Molecular Psychiatry following the publications of the Wakefield group and --

Q Okay. Doctor, I'm just going to ask you, what is your conclusion in this article?

A Well, I dealt mostly with the epidemiology

and concluded that, up to that point, in 2003, that there had been a consistent failure to support the hypothesis of Wakefield in terms of an increasing risk of autism following MMR immunizations, or in terms of identifying an autistic enterocolitis phenotype, which would have its own validity.

Q Doctor, when you compared in this article, did you come to the conclusion that there's no such thing as autistic enterocolitis?

A Yes, I said there was no evidence for a new phenotype of MMR-triggered autism with associated enterocolitis, yes.

Q Do you believe that autistic children do not have bowel problems?

A Actually, I have no beliefs in general. I'm a scientist. What I look at is the evidence, which I generate myself in studies, or when I review studies of others. So I have no particular set of beliefs which drive my opinion.

Q When you say you have no belief, does that mean that you have no opinion?

A No, I have opinions. I don't believe things just for the sake of believing them.

Q Okay. So you're opinions is that you don't believe they have bowel problems, is that it?

A No, I think this is a question which needs empirical data to address that. What is your question exactly, bowel problems?

Q Yes, that's what I asked you. So your opinion right now is you need more data?

A About what, exactly. Could you --

Q As to whether autistic children have bowel symptoms?

A Bowel symptoms, as opposed to bowel disorders?

Q Bowel symptoms, first?

A Okay. I think it is still unclear. Clearly, you have several reports which are based on clinical samples, which have often been referred to particular clinics, particular gastroenterology clinics.

And that is part of the problem in the initial case series of Dr. Wakefield's: That, of course, they have GI symptoms because in order to be seen by him, they had to be having GI symptoms. That doesn't really address the questions in our reports, which have been deriving from clinical centers where the gastroenterologists look at that are not informative on this question. For that, we need to have epidemiological data on representative samples of

children with autism.

It's not always easy to obtain, but that's what we would need to assess whether or not they have bowel symptoms of different kinds.

In addition to that, besides obtaining a representative series of cases of autism, the question is: Compared to what? So you need to think about which kind of control group is necessary in such studies. And, in addition to comparing the rates of bowel symptoms in autism to these symptoms in typically developing children, it will be also very useful to have the same data on children who have non-autistic other kinds of developmental abnormalities.

This kind of data I've been, up to now, I think largely missing and the MRC Review, which was published in 2002, I think, precisely pointed out to this problem that there are no good epidemiological data on this issue and there needs to be a few studies, these, but not so many.

Q So this article here is your article, correct?

A Yes.

Q Is this an epidemiological study?

A This is not a study. This is a commentary.

Q So the topic is: MMR an Autistic Enterocolitis, consistent epidemiological failure to

find an association. It's a review, is that what you're telling me, of the literature out there?

A You could say that it's a commentary which was invited by the editor of the journal just to quickly -- it's based on a review of existing data, at the time about this question, yes.

Q Okay. You say it's a commentary. Do you have any conclusions in your commentary?

A I don't recall what I said. Yes.

Q What is your conclusion?

A Where do you want me to start?

Q Wherever you would like.

A Well, let me see. In that paper, what might be interesting and relevant to our discussions. I reviewed some studies which addressed the question of: Is there an increased risk of autism following MMR introduction, in various countries.

We had, at that time, data from, in particular the UK, which showed that there was no such evidence. I referred in particular to the studies by Brent Taylor, which looked at case series at that time of children studied between 1979, as I recall, up to 1991, a large sample size of almost of 500 children.

They tested in various ways whether or

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not the introduction of MMR in the UK on a large scale in 1988 was associated with an increase in the rates of autism. And using a various approach, they said that they failed to find any such association, so that's one study.

There was another study by DeWilde et al., which was interesting in the sense that they followed up on the assumption by Dr. Wakefield that if the onset of autism was immediately after MMR, as he has posited in his original paper. He actually said: 6.3 days after the MMR vaccination on average, there would be a profound regression, loss of skill and GI symptoms occurring de novo in a child who was otherwise developing normally up to that point.

Obviously, that should worry parents, and we should see parents going to consult their GPs in the weeks following this change in their child. The UK has a multiple existing database, which can be used to test hypothesis of that kind and DeWilde used one of the existing general practitioner's electronic database.

They looked at, I think, controlled children and children who were later diagnosed at the age of three or four. On all of these children, they had information about MMR exposure, whether or not they

received the vaccination and the date.

So what they did is they created an interval for children who were either normal children throughout or later diagnosed with autism. They looked at the MMR date, and they looked at how often following the MMR immunizations parents of these children started to consult their GPs. And the prediction is that if indeed there is a massive change or regression, something new occurring, you should expect to see parents consulting their doctors in the weeks or a few months following this change.

So, in the sixth month after the MMR immunizations, they looked at rates of activity or consultations by parents with their GPs. They found no difference, suggesting that there was no particular increased frequency of consultation with doctors following the MMR immunizations.

They found that just before the diagnosis was made, at three or four years of age in children who ultimately were diagnosed in the six months which preceded the diagnosis, then there was increased consultation by the families, suggesting that the database was sensitive enough to capture health services contacts which were meaningful, by the parents of these children.

Q Those two studies that you mentioned, they

were looking at whether MMR could cause autism, wasn't that it?

A The first one, yes. The second one is more -- yes. It's testing the hypothesis. It's more testing the idea that there is a regression following MMR in otherwise previously normal children.

Q My question to you was, do you believe autistic children have bowel symptoms?

A Again, I have no beliefs on that. I'm looking at the evidence.

Q Well, Doctor, what is the conclusion of this commentary on MMR in Autistic Enterocolitis, Consistent Epidemiological Failure to Find an Association. What are you referring to here?

A Let me go a couple of sentences before.

SPECIAL MASTER HASTINGS: Ms. Chin-Caplan, I'm not sure what you're trying to ask, what you're asking. Your asking him to summarize the conclusion of the commentary?

MS. CHIN-CAPLAN: Correct.

SPECIAL MASTER HASTINGS: The point of the commentary?

MS. CHIN-CAPLAN: Yes.

SPECIAL MASTER HASTINGS: Dr. Fombonne, does that help?

THE WITNESS: I'm not sure exactly what's the question. Yes, but I can summarize the conclusions at the time of this commentary, which is to say: So far, in 2003, when we looked at studies of an epidemiological nature, and design, which have looked at the hypothesis of Wakefield, that implies different designs, different set of hypothesis.

There was no support for this association, so that's what is the main conclusion of the paper.

Also, the paper points at flaws in Dr. Wakefield's research. For instance, something that has never been addressed by him in subsequent studies whereby I identified that when one of these sample, I think the 2000 sample, he included not only children with autism but also children with ADHD, and children with dyslexia, and children with schizophrenia. Because that's what he did in one of these studies.

And I suspect in the Uhlmann paper there are also children who were not autistic in the same sample which is analyzed in various papers. This is something that is written in this commentary, and this is a serious flaw in his original results which have not been addressed by him since then.

But, otherwise, looking at the other epidemiological efforts at that time, there was no

support by research from others, including mine, to argue for the existence of a new phenotype of autism, which would be MMR induced associated with enterocolitis or GI symptoms, or GI disorder.

And there was no evidence that there was an increased risk of autism in populations where MMR was introduced, or an increased risk in children who where individually exposed to MMR.

BY MS. CHIN-CAPLAN:

Q My question to you, though, Doctor, is, what study are you relying upon when you say that there is no relationship between MMR and autistic enterocolitis?

A On the studies which are referenced in the commentary.

Q Do those two studies specifically look at a child with bowel disease?

A You ask me about bowel disease now?

Q Yes, bowel disease. Let's start with bowel symptoms. Does either one of these studies look at children with bowel symptoms who happen to be autistic?

A Yes.

Q Which one?

A It's reference No. 11, reference No.

14, referenced No. 15.

Q No. 15.

A Reference No. 16.

Q There is just a citation, Black Sea at British Medical Journal, is that it? Is that what you're referring to?

A Yes.

Q Is there a difference between bowel symptoms and bowel disease in your mind?

A Yes.

Q What's the difference?

A One is symptom, the other is disorder. It's very different.

Q Do you have an opinion on whether these children have a bowel disorder?

A Yes.

Q What is your opinion?

A My opinion is based on studies again. At lease in that reference, you can see the reference 16, which is my paper in The Lancet in 1998. You can see at reference 15, which is Black in 2002.

Let me explain these studies because you are asking about them. When Dr. Wakefield published his results, I was in the UK and there was an MRC review of his research, which includes rules.

And I was involved with many others to review, his findings. At that time, because I was interested in looking at empirical evidence in support of his ideas, or to refute his ideas, I had already actually conducted some research on this particular issue.

The research I did was to look at the incidents of inflammatory bowel disorders, including Crohn's disease, ulcerative colitis, and other kinds of IBDs in two large samples of British children who were referred at the Maudsley Hospital at which we had a huge database, which collected data on psychiatric diagnosis, but also medical conditions.

We had, as I recall, about 750 children with a PDD diagnosis and about 8,000 psychiatric controls with other diagnoses than autism. In these children, we had data about Crohn's disease and ulcerative enterocolitis.

And there was another sample. It was a French epidemiological sample, which comprised I think 174, maybe, children with PDD's, and a control group of over 5,000 children, epidemiologically defined who had different types of handicaps of psychiatric diagnosis than autism.

Again, we had on these children information

about their medical history, and whether or not they had inflammatory bowel disorders. In both samples, there was no case of autism in the British series, in the French series, with any of this inflammatory bowel disorders.

There were a few cases in the controls suggesting that were reported in the two samples, but there was no association clearly in that study between autism and inflammatory bowel disorders.

This was presented as a preview to Dr. Wakefield. I had done that study because it was to follow-up what I knew about his previous research, which was mentioned this morning. Before he moved onto the autism MMR question, he had done about ten years of research which was published here and there, where he was claiming that the measles virus was responsible for an epidemic of Crohn's disease in adult populations, and that created some concern.

There was a string of other research studies done by others who never replicated his findings. And then, he moved onto autism later, and it's a fight which has been forgotten by many that he had done so.

My hypothesis was because he posited that the measles virus was leading to Crohn's disease, and was leading now to autism, I said: If he's right, we

should see an increased incidence of inflammatory bowel disorders in children with autism, based on his theories. And that was not supported at a very early stage.

It has been since then replicated. You could see the Black study, which is in reference No. 15, in the British Medical Journal, is based on a large general practice research database, the GPRD. They published that in the BMJ. It's again testing this particular hypothesis and showing no increased incidence of IBD in children with autism compared to controls.

So, there are now two studies showing no increased incidence of IBD in children with autism. There is also a study published I think last year by Richler et al. based on a large sample of the CPA network in the U.S. based on investigators in autism research where they looked at regressive autism versus nonregressive autism.

They provided results about the incidence of IBD in regressive versus nonregressive autism and showed that there was no difference. So not only there is no increased risk in autism in general, but there is also no increased risk in children with a sub-type of regressive autism.

So my opinion based on the evidence which I reviewed then and has not changed is that there is no association and that autism does not increase the risk of inflammatory bowel disorders in children. So I think there is no association between the two.

Q Okay. You cited Black in support of what you just stated, and you mentioned a French epidemiological study, is that true?

A No, the reference 16 --

Q Sixteen?

A -- is my own study published in The Lancet shortly after the Wakefield paper, which received much less attention, I must say. But it's baaed on large sample with control groups. So it has some validity.

Q It's 15 and 16, is that what you're saying?

A Yes.

Q Now, Doctor, you were here in the courtroom last week, correct?

A On and off.

Q Did you say that you are a member of Autism Speaks?

A No, I didn't say I was a member of Autism Speaks.

Q Are you associated with Autism Speaks in any

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capacity?

A It depends by what you mean by associated with them. So do you want me to expand?

Q Do you have a role in the organization at all?

A No, they invited me to part of the review board to review the grants that they allocate.

Actually, I could not do it two years in a row, but I did that three years ago. I was part of the scientific review committee for the location of funds for research in mostlythe U.S., it's not just North America. It's world wide. That's an activity I did for them.

The other connection I have with them, and I don't know if it's an association, is: They fund some of my research. The training grant that was mentioned before, which is this six-year attempt to boost research capacity in autism in Canada, which involves several universities, summer school.

The funding is a mixed funding coming from CIHR, which is the equivalent of NIH in Canada. But Autism Speaks, or more exactly NAR, which was a previous organization which is now Autism Speaks, has contributed to that grant.

Then I am -- you know, they invited me to

various -- they have been influential with the CDC and other people at NIH to develop a network of investigators, which are interested in the epidemiology of autism, or conducting research on the epidemiology of autism either in the U.S. and they try to promote worldwide efforts to study autism with an epidemiological perspective.

There is this network which is informal that they have. So I was invited to brain storm on the creation of this network. Then there as a couple of meetings, so I had discussions with them about that. And a few other things, if you --

Q You heard in Court last week, though, that Autism Speaks hosted a gastroenterological workshop in Boston, correct?

A Yes, I know, yes.

Q Doctor, didn't Autism Speaks indicate that autistic children's GI problems deserved to be worked up?

A I do not know what they indicated. I didn't see the papers, but I can assume that it said that. That's okay.

Q I'm going to refer the Court to Petitioner's Trial Exhibit No. 5. Could you just kindly read that into the record, Doctor?

A Where do you want me to read? Here?

Q Yes.

SPECIAL MASTER HASTINGS: Not the whole thing.

MS. CHIN-CAPLAN: No.

SPECIAL MASTER HASTINGS: What are you asking him to read?

MS. CHIN-CAPLAN: Just the two paragraphs.

SPECIAL MASTER HASTINGS: Okay.

THE WITNESS: Responding to community interest, Autism Speaks hosted a workshop on autism and gastroenterology in Boston on October 13, 2006.

The objectives of the workshop were to review current scientific evidence for GI issues associated with autism, to develop up consensus scientific priorities for autism gastroenterology research, and to suggest an approach to establish best clinical practices for autism and gastroenterology.

You want the next paragraph?

MS. CHIN-CAPLAN: Please.

THE WITNESS: In an effort to capture all perspectives on this topic, the participants included members of Autism Speaks Scientific Affairs Committee, and leading experts on pediatric gastroenterology and autism.

The discussion was comprehensive and productive. Please watch this space for a synopsis of the consensus recommendation.

BY MS. CHIN-CAPLAN:

Q Thank you, Doctor. So from what you read, Doctor, would it be fair to state that Autism Speaks believes that autistic children have gastroenterology problems?

A No, I would not endorse what you just said. Autism Speaks is an organization, which has an agenda, which is very different than the agenda of scientific institutions or academies. So, they pursue scientific activities, but they, also, are sensitive to needs or pressures of a different nature. So, what they say doesn't mean that it's entirely driven by the needs of scientific agenda. I would say that first.

Secondly, I don't know exactly who in Autism Speaks involved in that, so I cannot say. Autism Speaks is a large organization with different tendencies, different people. So I wouldn't say Autism Speaks is an organization that endorses that necessarily.

But, if your question is to say, and if you want my opinion on that, is to say, is it important to investigate that. Yes, certainly. And there are

multiple aspects of the management of autistic children, which need to be improved. That includes GI symptoms, if they have more than usual, also, sleep disorders, behavioral problems. And various institutions are doing that. But, that has to do with the clinical care and the management of a complex problem. It has nothing to do with the fact that GI symptoms are causally related in some sort of pathways to the disease or the disorder. So, I think it's important to separate the issues. One has to do with management concerns that the families need to access in order to better medical care, which is obvious, and that's fine, and a question, which has to do with an association between autism and related medical conditions, both.

Q Doctor, you've written another article, which is contained under Respondent's Exhibit P, Tab 32. Doctor, the title of this article is 'No evidence of persistent measles virus and peripheral blood mononucleal cells in children with autism spectrum disorder,' is that correct?

A Yes.

Q And you are the second author on this article?

A I can tell you why?

Q Pardon me?

A I can tell you why I'm the second author, because that article is mostly the work of the McGill Laboratory of Dr. Brian Ward, who will speak later this week. And all questions, which have to do with PCR or the virology should be directed to him.

Q Okay. So what was your contribution to this paper?

A Well, we had the idea, Dr. Ward and myself. We met when I came to Canada. I met with him vis-…- vis the MMR issue, because I was coming from the U.K. and still involved in various things. And I was actually looking at the profound and durable effect of this controversy on rates of vaccination. And in 2002, the uptake of MMR vaccination in the U.K. had dropped from 95 or 96 percent, the level at which they were before Wakefield's publication,, to a low of about 82 percent on average, which meant that her immunity was not guaranteed anymore.

And as we said before, outbreaks of measles were appearing. There were modeling of epidemics to come. Children died in Ireland, and parents came to be very worried. Parents of autistic children were worried, asking questions. So some research needed to be continued even though the evidence was already

quite solid to refute this association.

So, as we met, I was developing a service for autistic children which developed substantially in the last five years. I was thinking of ways to use our clinical activities to ask research questions. And what I did is I actually submitted a grant in which we would look at various aspects of the biology of autistic children. We looked at their immune system. We looked at heavy metals, including mercury, but not only mercury. And we looked at the MMR issue in that grant.

So it was a grant basically saying we assess young children. We often take blood samples from them, so it's not a big deal to take a bit more blood and address these questions by doing further research. So that was how it developed. And in that -- well, that's it. I speak too much.

Q So, you gave him the idea, is that it?

A No, no, no, no, no. No, I didn't give him the idea. He's not a man where you really need to give ideas. He has his own ideas and I had my own ideas and we just met and decided it would be possible to do that and that's what we did.

Q So my question to you is what input did you have in this article?

A Oh. I did -- well, first, we conceived -- we designed the study together. And there was an aspect of the selection of patients, which is extremely important here. And all the patients in this study had been assessed by myself. They were characterized. They all had had ADIs, ADOSs, and that was my main contribution, in terms of the data collection on this one. My second contribution was the funding and the initial discussion and the design of the study was by all. All the lab work was his. And then I was, of course, involved in the writing up, especially in the part, where I can have ideas or comments.

Q Okay. So, Doctor, there is a statement underneath here, 'financial disclosure in the United States.' Do you have it in front of you?

A Yes. Where is it? It's on the first --

Q It's on the first page.

A The copy is not clear, so maybe you --

Q Actually, it's 'financial disclosure in the United Kingdom.' I think I said 'the United States.'

A Yes.

Q Are you there?

A Yes, I'm here.

Q Okay.

A It's the --

SPECIAL MASTER HASTINGS: Why don't you read it to him?

THE WITNESS: My copy is not good, so I can't read it.

BY MS. CHIN-CAPLAN:

Q So, Doctor, just follow along with me.

A Yes.

Q 'Dr. Fombonne has provided advice on the epidemiology and clinical aspects of autism to scientists and advising parents, to MMR vaccine manufacturers for fee and to several government communities between 1998 and 2001.' Have I read that correctly, Doctor?

A Yes.

SPECIAL MASTER HASTINGS: Actually, you said 'communities,' rather than 'committees.'

MS. CHIN-CAPLAN: Oh.

SPECIAL MASTER HASTINGS: But, go ahead.

MS. CHIN-CAPLAN: Okay.

BY MS. CHIN-CAPLAN:

Q Doctor, if you would skip down to the beginning of the third sentence. It says, 'since June 2004, Dr. Fombonne has been an expert witness for vaccine manufacturers in the U.S. thimerosal

litigation.' Have I read that correctly?

A Yes.

Q Doctor, with respect to your work in the U.K., can you just tell us when you started working in the U.K. on the MMR litigation?

A When did I started to work on --

Q When did you start?

A -- on the litigation?

Q In the MMR litigation in the U.K.

A I was not really involved in the litigation in the U.K. As is mentioned here, when we discussed this morning that this advisory committee with the chief medical officer, it had nothing to do with the litigation. It was just to give him some basic scientific facts and advise him on the science. It has nothing to do with the litigation. So, the only contact I had with the litigation in the U.K. was to consult twice with a vaccine manufacturer. They asked me, can we meet with you to discuss about autism, the epidemiology, what do you know. So, that was one meeting. And then there was a second meeting, where they asked me similar questions and they asked me to review the notes of a child, the medical notes of a child, to get my opinion. So, that's what I did. I made it clear to them initially that I didn't want to

be part of the U.K. litigation. So, that's -- and that's what I say, I sent them a letter and that was it. I was not involved further in the U.K. litigation.

Q And when was that?

A It was -- I would say probably my first contact with them was fall 2000, I would think, and the second one was spring 2001, because then I moved to Canada.

Q Okay. And, Doctor, it indicates here that since 2004, you've been consulting to drug manufacturers in the United States on thimerosal litigation.

A Yes.

Q Is that correct?

A Yes.

Q Now, Doctor, this is the first time I've seen this type of financial disclosure on your part. Have you disclosed this previously?

A I don't know.

Q Well, let's take a look at your publications that you cited here.

A Which one?

Q Let's start with Respondent's Exhibit P, page --

SPECIAL MASTER HASTINGS: Do you have a tab number?

MS. CHIN-CAPLAN: I am looking for it, Special Master.

SPECIAL MASTER HASTINGS: Okay.

BY MS. CHIN-CAPLAN:

Q Let's start with Tab 67. You indicate that you began working 2004 for vaccine manufacturers in the United States. This was accepted in March 2004. Did your involvement predate this?

A Sorry, which involvement?

Q Did your involvement with the drug manufacturers predate the article publication date here?

A You mean in the U.K. or in the U.S.?

Q I mean here. But, you said the U.S., didn't you, for thimerosal?

A Yes, in the U.S.

Q Right.

A This was done before.

Q Okay.

A I mean, I think so. It was published in March 2004.

Q Okay. And do you recall when you began working with the drug manufacturers here in the United

States?

A Oh, you just read it. It's June 2004.

Q June 2004. And this was published in March of 2004 --

A Yes.

Q -- correct? Okay. What about the next article? That would be Tab 68. This article was published in 2005.

SPECIAL MASTER HASTINGS: Before we leave this, I didn't understand -- maybe you can help me, Doctor. You said, you just read it, when she was asking about when you began with the drug manufacturer. Was that in the previous -- I'm confused about what you meant by that, 'you just read it.'

THE WITNESS: I'm sorry, she -- counsel just read the financial disclosure --

SPECIAL MASTER HASTINGS: From the previous article.

THE WITNESS: The article.

SPECIAL MASTER HASTINGS: Okay. That's what you were referring to?

THE WITNESS: Yes.

SPECIAL MASTER HASTINGS: Okay.

THE WITNESS: And there is a sentence, which

says, 'since June 2004.'

SPECIAL MASTER HASTINGS: Okay. Thank you. Thank you. Sorry. Go ahead, Ms. Chin-Caplan.

MS. CHIN-CAPLAN: Thank you, Special Master.

BY MS. CHIN-CAPLAN:

Q So, Doctor, on Respondent's Exhibit P, Tab 68, the title of this is 'the changing epidemiology of autism.' It was published in 2005. Is there a financial disclosure in this article?

A Yes.

SPECIAL MASTER HASTINGS: Your answer was yes?

THE WITNESS: Yes.

BY MS. CHIN-CAPLAN:

Q Where is it?

A It's in the article at the end.

Q Can you show me? I couldn't find it.

SPECIAL MASTER HASTINGS: At the end, did you say?

THE WITNESS: Yes, at the end, page 292.

SPECIAL MASTER HASTINGS: All right.

BY MS. CHIN-CAPLAN:

Q Okay. 'Dr. Fombonne is an expert witness for vaccine manufacturers in the thimerosal litigation.' And did you do the same for Tab 69?

A It doesn't seem to appear here. If it does not appear, it's by choice of the editor, not by me.

Q Okay. Because I didn't see one.

A Uh?

Q I did not see one.

A No, no, no, no. It was something about -- they sent a form and everything was determined that parties selected to put something. I think their concern -- because this was organized by -- yes, this was organized by -- it was an educational grant by the drug industry in fact. It was a whole issue about autism and there were also like lectures done on the web to educate doctors.

And I think their main concern was to what is appearing at the end of the article, which is disclosure of -- so I think they were concerned about links of funding that drug study. But my disclosure would have been forwarded to them.

Q I'm sorry, I missed that.

A My disclosure would have been forwarded to them, most of them.

Q And it's not included here?

A No, but it's not my choice, is what I said.

Q The next three articles, Doctor, they appear to be book chapters, am I correct?

A I don't know.

SPECIAL MASTER HASTINGS: Can you repeat?

BY MS. CHIN-CAPLAN:

Q Sure, Tab 70, 71, and 72, they appear be book chapters, is that correct?

A Yes, yes.

Q Okay. You don't normally disclose things like that in a book chapter, do you?

A No. It's neither requested or required. It's not something that you do, not that I know of.

Q And I see under Tab 74, it states, 'since 1June 2004, Dr. Fombonne has been an expert witness for vaccine manufacturers in U.S. thimerosal litigation. None of his research has ever been funded by the industry.' Is that what it says?

A That is correct.

Q That seems to be it, the articles that you cited, am I correct?

A Yes.

Q So, Doctor, have you testified for drug manufacturers in the United States?

A Yes, once.

Q One? Could you just generally describe to the Court where it was?

A It was what is called a Daubert hearing in a

court in Texas.

Q And how much did they pay you to testify?

A What do you mean

Q For the Daubert hearing?

A To testify?

Q Yes.

A I'm paid by the time I spend reviewing the records, writing affidavits, being deposed, or testifying in court. So, it's based on an hourly rate.

Q And what is your hourly rate?

A It's $500 an hour.

Q And, Doctor, you said it was a Daubert hearing. Did the case end, at that point?

A Yes.

Q And how much in total were you paid for that Daubert hearing?

A The case, you mean?

Q Yes.

A I don't keep track of that. You want a figure? I don't know. I started on this work in June 2004 and I think the hearing was in, I think, February or March 2005. So, there was about eight or ten months of work. And I would guess, I have no clear -- I would guess probably $70,000 or $80,000 in total for

that court.

Q And are you currently working on any other cases for the drug manufacturers?

A I am, very -- yes. Occasionally, I've been involved in reviewing some medical notes of, I think, a couple of cases, on which I have no -- I didn't have to produce affidavits, because the cases were dismissed by the court in the process or suspended. It seems to be very long and changing all the time. And there was another case, which is active, which I am involved in, but I have not submitted any report yet.

Q So, there is one active case currently pending?

A Yes.

MS. CHIN-CAPLAN: I have no further questions at this time, Special Master.

SPECIAL MASTER HASTINGS: All right. Mr. Matanoski, will you be having any redirect for this witness?

MR. MATANOSKI: I may well have a little redirect, yes, sir.

SPECIAL MASTER HASTINGS: All right. Why don't we take a 15-minute break, at this point, for the afternoon and convene shortly after 4:00.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: All right. We are going to start our afternoon, the second part of our afternoon activities now. I want to say one thing for those in the courtroom, as I noted at the beginning, our Court has very generously allowed the use of this courtroom by the U.S. Court of Appeals for the Federal Circuit. It is very important that no food or drink be brought into the courtroom at all. Those at the counsel tables and the bench can drink water out of the pitchers. That is it, nothing else in the courtroom, please. We want to be good guests to the Court of Appeals. Although I will say, those at home, you can either drink whatever you want.

(Laughter.)

SPECIAL MASTER HASTINGS: But with that, Ms. Ricciardella has some redirect examination of Dr. Fombonne. Go ahead, Ms. Ricciardella.

MS. RICCIARDELLA: Thank you, Special Master.

REDIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Dr. Fombonne, Ms. Chin-Caplan walked you through the laboriously certain articles that you have written since June of 2004 and asked you whether or not you included a financial disclosure statement

regarding your participation as a consultant to the pharmaceutical companies in the thimerosal litigation. If I am understanding, it is true that only one of those articles, there is no financial disclosure statement, is that correct?

A Printed on the article, yes.

Q But to be clear, you did not inform the journal editors where that article appeared of your participation in the thimerosal litigation, correct?

A Correct.

Q And it was their decision not to print the financial disclosure, is that right?

A Yes, absolutely.

SPECIAL MASTER HASTINGS: Doctor, you need to say a word rather than nodding so we can pick it up.

THE WITNESS: Okay. Yes.

BY MS. RICCIARDELLA:

Q Doctor, there was also some discussion about your participation as a consultant for the pharmaceutical companies in the Easter case in Texas. Do you recall that?

A Yes.

Q What was the time frame of your participation in Easter? When did you first become

involved in the Easter case?

A As I said, since June 2004. I had been actually approached before by various -- even when I was in the U.K. to be consulting with that. I denied doing that. And I was not particularly interested in this activity. As I said it when -- years after the MMR controversy given up after the initial Wakefield paper, when I saw -- again, it has to do with the impact at two different levels. I see a lot of families. So, in my clinics earlier last week, people still come and ask questions about safety of vaccines and they asks questions about MMR. They ask questions about mercury. I spend a lot of time trying to give the evidence to the parents and it's very hard to convey, to disseminate this evidence when there is a general rumor or fear of the public. It is hard to counteract. And I've seen that when I was in the U.K.

There is a very interesting historical example, which has to do with the whooping cough vaccination. In 1971, there was one study which incriminated the whooping cough vaccination with a neurological design. It was one piece of research released probably in the BMJ. Immediately, people started to be afraid of this vaccination. And what happened is within 18 months of this initial

publication, two studies looked at the initial results and basically dismissed, failed to replicate that and dismissed the result. Yet what happened, if you look at the trends over the next 10 years, from '71 to 1980, there was a massive drop in the uptake of whooping cough vaccinations in the U.K. And then you could see the notifications of whooping cough disease occurring and there were outbreaks and there were actually death of that. And it took 10 years to put back the vaccine on the agenda, in an effective way.

And it's exactly what happened in the U.K. with the MMR vaccine. This drop in uptake, which I mentioned, which has effected public health in the U.K., in Ireland, and it creates a big concern for public health. It's a preventable disease. I think it was said would say that half a million of the people die every year. I recall that there was an epidemic in the U.S. in 1990-1991, when 150 people died from measles. And, again, there was an outbreak 18 months ago in this country. So, unless we keep our eye on these vaccinations, it's very important to -- well, we need to be proactive at maintaining vaccination rates at a high level.

Although, at the same time, when the initial concerns were raised, I did research immediately to

look at this. So, it's not that I was actually biased against it. I looked at the evidence. There was not much plausibility to start with with the arguments put forward by Dr. Wakefield. But quickly, the research did not give any empirical support to these ideas.

So for me, the MRC did a big review document published in 2001 or 2002 in which I was involved, concluding that there was no evidence for this association. But yet, the effect was negative and it's still there. So, when I came here and I saw this concern about thimerosal, which I had been involved in the American Academy of Pediatrics in 1990 when they reviewed this whole issue about TCVs and autism, what happened, we have witnessed a development of, for instance, chelation therapy, which are absolutely based on false ideas, no evidence, are dangerous, and I think it's very important that as autism clinicians, we tackle this issue with the science. There is a lot of scientific evidence which gives no support to this association, and we need to disseminate this information.

That's why I am here. I am here as a clinician, who works with families with autism. Also, I am here, because my background gives me a sort of sensitivity to public health issues, broadly speaking.

Q Is that why you are also participating as a consultant to the pharmaceutical companies in the U.S. --

A Yes. It's exactly the same.

Q -- other thimerosal litigation?

A Yes, absolutely.

Q Now, Doctor, Ms. Chin-Caplan began her cross-examination of you asking you to acknowledge that the pediatric records in this case of Michelle Cedillo do not mention certain development abnormalities. In your practice, as a child psychiatrist, with a specialty in autism, is this an abnormal finding? Do you have pediatric records not reflect or note abnormal development delays?

A Well, it's absolutely true, every clinic -- autism clinic, when we see the children at age -- for me now, it's more like two, two-and-a-half, and three, much younger than 10 years ago or 20 years ago, which is good, but still the story is consistent across the families. They go and see GPs, often, as I said before, age 15 months, 18 months, 20 months, and then there is a sort of dismissal of the matter of concern. The child is not speaking. It's true that there is wide individual variability in language development. They say, don't worry. He's going to speak. Then the

family comes back three months later, they want to check the hearing. And then it takes like months before the child is referred from the GP pediatricians to -- and understandably. Their level of training to detect autism, it is very limited unless they have a specific interest for that. So they don't detect the signs.

And to detect the signs, I hope I conveyed this morning that you need specific expertise. Sometimes it's very obvious, so you might not miss it. But in many, many cases, you need to look at the child and do with him the right things to elicit the autistic symptoms, which means you need to ask targeted questions of the parents.

And a pediatric or GP consult with a child who is 12 months or 15 months usually lasts about five minutes, seven minutes. I think you can have seven minutes on average. And they do weight and height and they look at feeding and growth and then that's it. So you understand why it in this case that in the pediatric record, there will be no documentation of developmental issues unless the parents push that on the agenda as a concern of theirs. And actually research, which I should add.

So, in the U.K., for instance, this is

research, not clinical experience. There are several countries where health records are kept. So at birth, you have the Apgar scores and everything, and the parents have a record, a booklet, and every visit is documented. So we have used that as a tool. There was in the U.K. a study by, I would say -- Frith, I can find the exact reference for you, where they showed that at six months, at 20 months, in the medical records, there was no documentation of abnormal development in children that later turned out to be autistic. It started to occur about 18 months of age. So what we see in that case is not atypical. It's actually quite average what we see, in terms of the contacts with the health system of these children. It's often delayed. The recognition is delayed due to multiple factors.

Maybe I want to add something else, which is questions where directed to me, trying to compare the absence of particular behaviors in the pediatric record to what was the study of young children assessed at six months and 12 months of age, which were done by direct observations in the lab, by people with expertise to assess infants with autism. So, it doesn't compare like with like.

I mean, on one hand, you have behaviors

identified by Autism experts who have the eye for that who assess the children directly in interactive sessions. And we cannot infer anything of the absence of these behaviors beings recorded by the pediatricians in sessions which are not directed at developing that and which last for just a few minutes. So I think there is a methodological confound in the questions which we are asked to maybe form.

Q Ms. Chin-Caplan also questioned you about your Slide 35, which is the chart of Michelle's head circumference. And then she put on the screen, I believe it was Petitioner's Exhibit 70 at 9 and 10, which she seemed to suggested that perhaps you were not taking into account Michelle's growth, at the same time, her height and weight, at the same time that her head was growing. Doctor, in your report, did you address the concomitant weight and height of Michelle, in relation to her head circumference?

A I think I did.

Q May I direct you to --

A I think it was page 54 or 59.

Q I believe it was on page 60, paragraph 157.

A Thank you. Yes. On that particular -- just let me -- the sentence at the bottom of that page on 60, it says, from six to 18 months, the head

circumference chart shows clearly that Michelle's head circumference is consistently off the chart and far beyond the 97 percentile, that defines macrocephaly with a maximum rate of head growth in the second semester of life. This abnormal head growth cannot be certainly attributed to the general overgrowth syndrome displayed by Michelle, shown in her length and her weight curves, as the head circumference abnormal growth clearly exceeds that of body length. This pattern has been described in the chapter on autism. And I quote a study by Lainhart et al. I would like actually to -- if I could show you some figures, which are from this reference. If you could --

Q Do you have a slide for that?

A I have a slide for that, yes. This one. This is a large study done by, again, a group of autism experts. It is part of the CPA network of research in the U.S. And they gathered also the information on the head circumference and looked at it in various ways. And on the top left graph is a standardized head circumference in this sample. And you see on the horizontal axis, there is a zero. Zero should be the mean of the population. So, there should be a normal curve that we have. We should be

centered on the mean, which would be zero, because we are using standardized scores. But, in fact, the mean of the autistic samples, as you can read on the right of this graph, is I think 0.65. That means that on average, there is a shift towards the right of the distribution of head circumference in the autistic samples There are larger heads on average, and it's shifted to the right by two third of a standard deviations, which is substantial.

On the bottom left, you see just a graph which indicates the relationship which exists between head circumference and height, and you can see there is a strong correlation between the two. These are the standardized scores. So what they did therefore was to look at if we take into account the height of the subjects, the body length, which is correlated with head circumference, do we still have an macrophaly, which is seen. And this is what the graph on the bottom right shows. It's a graph which says ZHC-ZHG, basically it's a standardized score of head circumference minus the standardized scores of height. So it is therefore a quantity which takes into account the body length and looks at head circumference, adjusting for height. And still you find that there is actually -- the deviation on the right of this

variable is still the

same. There is a division of .7, some of the deviations. So that's what I said earlier. Even when you adjust for height, you still have this phenomenon. And on Michelle's Cedillo's chart, this is what you can support, because the deviation in body length is much lower than the deviation in head circumference. So, even when you adjust for that, there was still excessive head growth even when you adjust for body size, body length.

Q So, Doctor, is it fair to say that in assessing Michelle's having macrocephaly and saying that that is one clinical symptom of her autism, that in making that assessment, you did not discount her weight and height in your assessment of macrocephaly? Is that a correct statement?

A No, it was clearly stated in my report.

SPECIAL MASTER HASTINGS: Now that last slide that you just showed on the screen there and Dr. Fombonne was just referring to, that's not in the --

MS. RICCIARDELLA: That would be a new trial exhibit, Special Master.

SPECIAL MASTER HASTINGS: Okay. And I think we would be up to No. 9, I believe, by my count.

(The document referred to was marked for identification as

Respondent's Trial Exhibit No. 9 and was received in evidence.)

MR. MATANOSKI: Yes, Special Master. Dr. Fombonne had much more evidence than presented here.

SPECIAL MASTER HASTINGS: Okay.

MR. MATANOSKI: We pared it down to what we thought was necessary for your consideration.

THE WITNESS: I think for reference, these graphs are extracted from the study by Lainhart, L-A-I-N--H-A-R-T, 2006, American Journal of Human Genetics.

BY MS. RICCIARDELLA:

Q Now, Doctor, Ms. Chin-Caplan also asked you, she said, do you accept that Michelle had 10 words, and she was referring to paragraph 155 of your report. Do accept that Michelle had 10 words?

A No. No, I do not share that view. To you, she might appear that she had 10 words. They were saying that she would use consistently word meaning spontaneously 10 words by then, and this is based on two obvious line of evidence: the video, which she showed at 15 month-and-a-half, where she produced absolutely no words when she is playing with the balls, and she has even very little babble, which is

not used communicatively, clearly indicates that whatever words she might have pronounced in the few weeks before that would have been very haphazard or random. So, I think that's -- and secondly, I think Michelle's mother, in her testimony last week, listed a few words, not even 10, and there was no evidence of a language in the child before the MMR.

Q Finally, Doctor, one last question. Ms. Chin-Caplan asked you why you had selected the February 6, 1996 video as evidence to show Michelle's motor delay, and she made point of the fact that that video was following the MMR vaccination. Why did you select that video as evidence of her motor delay?

A Because it's the latest video in time which shows that she doesn't walk independently. I am not aware that the Plaintiffs are saying that MMR triggered motor deficits in Michelle. So wherever we see that, it's just the smooth continuation of a motor development and it shows delay at that age, as there is evidence of delay at much earlier stages in her development.

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

SPECIAL MASTER HASTINGS: Let me ask, while we are on that topic, did you see any of the earlier

videos? You looked at all the videos that were

supplied by the Petitioner. Was there any evidence of unassisted walking at any time prior to that?

THE WITNESS: Never, never.

SPECIAL MASTER HASTINGS: Okay. Go ahead.

MS. RICCIARDELLA: I have no further questions, Special Master.

SPECIAL MASTER HASTINGS: All right. Thank you, Ms. Ricciardella. Anything further for this witness, Ms. Chin-Caplan?

MS. CHIN-CAPLAN: No, Special Master.

SPECIAL MASTER HASTINGS: Anything from the other Special Masters? I think I may have had -- well, on that very topic of the walking, what is the normal -- when do children normally walk?

THE WITNESS: There is variability, but beyond 16 or 17 month of age, it would be concern that the child is not walking independently. That is clear. And I said in the 18 month of age, if the child is not walking, it is clearly a sign of a problem. She is seventeen-and-a-half month there and she doesn't have independent walking. Again, if you look at the milestones earlier than that, sitting independently at 11 months is extremely delayed. Children usually sit independently between six and seven months of age. At eight months of age, we would

consider that to be a significant delay.

SPECIAL MASTER HASTINGS: One further question, then. Most of the questions that I have written down here have been asked, it looks like. But, the clinical treatment of somebody with autism, who typically sees autistic children? What discipline? Now, you are a psychiatrist. I've seen neurologists listed. Who is the one -- what is the specialty that most often deals with autism children?

THE WITNESS: In terms of treatment? In terms of --

SPECIAL MASTER HASTINGS: In terms of treatment, evaluation and treatment.

THE WITNESS: Okay. These are two different facets.

SPECIAL MASTER HASTINGS: Okay.

THE WITNESS: In many centers, now, you have teams, which are an autism expertise for the evaluation, diagnosis, and assessment, initially of these children. And these teams are all multidisciplinary in nature. So, it's always involving different disciplines. You need speech and language therapy. You need occupational therapy. You need child neurology. You need medical genetics, at times. You need pediatrics. You need psychiatry.

You need psychology. So, you need all of that discipline. So the people who are leaders, clinical and academic leaders in the field, actually come from very different disciplines. Many of my best colleagues in the U.S. are actually developmental clinical psychologists, who are leading teams which are assessing, diagnosing children with autism. They are consultant in neurologist and they consult geneticists. Others are led by child neurologists. Others are led by developmental pediatricians. Others are led by child psychiatrist.

So it depends on the organization of services, the history of service in a given hospital or institution. But the problem is that whatever is the discipline, all these people in addition to their background training have specific training, interest, and expertise in autism, which is added to their core training. And there are different disciplines which are brought in in assessing the child.

If you then refer to treatment and management, that's variable. It depends on which kind of services are available. In many countries, it's really people who have an educational background or a psychology background who are doing behavioral interventions. So they would be psychologists who

have an interest in behavioral management or educational psychologists or people of that kind.

And they put programs which are individualized which take into account the strength and deficits of the child as targets to the treatments so that the child can be promoted in his development in different domains. Treatments are reviewed very periodically to adjust the goals. Treatment teams work closely with parents who know their child and there is a need to have a flow of information both ways.

And then at that time, when the child is moving in the educational and parental system, the contribution of medical disciplines become less significant often except that we provide specific expertise, for instance, in managing complex behavioral problems with particular medications or for medical care. On my team, we have pediatricians who have a specific interest for the medical issues of children with autism. So any medical issue, she is here and she can fast track them for tertiary care- if required.

SPECIAL MASTER HASTINGS: All right. Thank you, Doctor. We appreciate your testimony. You're done for the day. I understand we'll see you again

next week.

THE WITNESS: Yes, thank you.

SPECIAL MASTER HASTINGS: Thank you.

(Witness excused.)

SPECIAL MASTER HASTINGS: Mr. Matanoski, shall we start with Dr. Cook?

MR. MATANOSKI: Yes, we're ready to do that, sir.

SPECIAL MASTER HASTINGS: All right.

Whereupon,

EDWIN COOK

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

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

DIRECT EXAMINATION

BY MS. PATTON:

Q Dr. Cook, can you state your name and current place of employment for the Court, please?

A Edwin H. Cook, Jr., M.D. I am at the University of Illinois at Chicago.

Q Have you ever testified in court before?

A Yes, on several occasions. The notable ones are, I testified on behalf of patient with catatonia, who needed electroconvulsive therapy. Even though his parents and guardians agreed, in the State of

Illinois, it requires court agreement to that. So, a guardian ad litem advocated actually against the electroconvulsive therapy, but the judge found in favor of the treatment, and he had a successful treatment.

Another occasion was actually on court order that we requested. University counsel actually tried to avoid me basically being forced to testify about one of my patients and her mental state. I was required to testify, because it involved child custody of her grandchild.

Q Any criminal cases?

A Oh, yes. A criminal case in which I was an expert for the defense in defending a young woman, I guess she had just turned 18, when she was accused of attempted murder.

Q To your knowledge, have you testified in any lawsuits?

A Not to my knowledge or recollection.

Q Do you hold any patents, Dr. Cook?

A Yes. I hold a patent. It's a pharmacogenetic patent for actually a drug that is the first drug pharmacogenetic patent. In other words, it's the first time in the PDR that a gene is linked with a drug treatment. It relates to my work as a

molecular genetic core director for a cancer pharmacogenetics research grant. In the process of supporting that, there's a relationship between the gene UGT1A1 and treatment of colon cancer with ironotecan. I'm listed as a co-holder of the patent but do not receive royalties or any other benefits.

Q No financial benefits from that patent?

A No financial benefits.

Q To your knowledge, do you have any financial conflicts of interest that would influence your testimony about the role of genetics in autism here today?

A I do not have any specific conflicts relating to what I am going to testify about.

Q Okay. Let me turn to your educational background now for a moment. Can you, please, tell the Court what degrees you hold and from where you received those degrees?

A I received a Bachelor of Arts from Southern Methodist University in biology and a medical degree from the University of Texas Medical Branch of Galveston.

Q And when did you receive your medical degree?

A 1981.

Q And where did you complete your residency?

A I went to the University of Chicago, where I completed my residency in psychiatry.

Q Did you hold any honors or any special positions during your residency?

A I was the chief resident.

Q And after residency or towards the end of it, did you do any specialization or any fellowships?

A Right. So, I, also, completed fellowship training in child and adolescent psychiatry.

Q Are you board certified?

A Yes. I'm board certified in psychiatry and also board certified in child and adolescent psychiatry.

Q Do you have any other roles in the board certification process?

A I have several times served on the -- I have participated in the examination of candidates for board certification in child and adolescent psychiatry, in which we would conduct an oral examination, in which they would interview a live patient, and we would evaluate whether they performed adequately, in terms of the evaluation of the patient, and in the use of that information.

Q What is your current position at the

University of Illinois at Chicago?

A I am a professor of psychiatry. I am also the visiting director of autism and genetics.

Q And when did you start there?

A In 2005.

Q And within the University of Illinois at Chicago, there is a special center that you work at?

A Yes. Within the Department of Psychiatry, I work in the Institute for Juvenile Research, which will be having its 100-year anniversary, in two years as the first University-based clinic -- actually, the first child psychiatry clinic in the country.

Q And what is done at the Institute for Juvenile Research?

A We take care of patients with a range of child and adolescent psychiatric disorders. Autism is certainly one of the emphases, but we see a whole range of child and adolescent psychiatric disorders. We, also, train -- we train medical students there, residents and fellows after their medical training, and also train people, and we consider postdoctoral fellows and research as well.

Q You said you train a lot of people. Do you teach --

A I teach --

Q -- at the University?

A Yes, I'm sorry. I teach the introduction to human genetics part of the introductory genetics course for the graduate students in biology at the University. I, also, supervise residents and fellows and also mentor both at the University of Illinois at Chicago and across the country, several research faculty.

Q Have you ever diagnosed and treated a patient with autism?

A Yes, since approximately 1984.

Q Do you have any idea in the course of your career how many patients you have diagnosed and treated with autism?

A I would estimate in terms of evaluation and diagnosis about 1,000; in terms of treatment, probably several hundred, I would say around 300.

Q Do you currently see patients with autism?

A I currently have a clinic and follow patients, some of whom I've seen for over 15 years. I have two clinics a week, largely following up patients over a long term, but also conducting new evaluations.

Q And these patients that you see in clinic, are they involved with your research?

A Well, my clinic, they may have been research

subjects. But, we, also, conduct, during the rest of the week, I'm involved in research diagnostic evaluations, as part of our research studies, primarily genetic research studies.

Q So, two days a week, you have clinic, where you're actively involved in the treatment of autistic patients?

A That's correct.

Q And then the rest of your time is spent on research?

A That's correct.

Q Is that research primarily research on the genetics of autism?

A It's primarily on the genetics of autism and also includes work, as I mentioned before, where because of my genetic expertise, I'm helping colleagues study the pharmacogenetics of cancer, both colorectal cancer and childhood leukemia, in term s of the genetics expertise, and also involves continued work that we've been doing in terms of ADHD genetics.

Q When did you began research or working in the field of autism?

A In 1985, in the second year of my fellowship, I began studying serotonin and it's relationship to autism.

Q And in what areas has your research focused?

A It's gone through various phases, starting with studying neurochemistry. I chose to study serotonin in autism, because having looked at the literature, it was a finding that had withstood much test on what might possibly be an artifact, in terms of a portion of children with autism having high blood serotonin. We conducted and continue to conduct careful studies to understand the mechanism of that elevation. We know the elevation is there, but we haven't tied it sufficiently cleanly to exactly what's happening in the brain yet, which, of course, is the ultimate goal.

In the process of those findings, it became clear that the findings in the blood were likely giving us clues as to mechanisms in the brain and what was likely is that there were genes expressed in the blood, specifically in the platelet, that were also expressed in the brain. And so, genetics provided us a clue as to what might be leading to a symptom or a sign in the periphery that also was more directly relevant to brain development. So, around 1993, we shifted to not only studying serotonin as a chemical, but also studying serotonin genes in relationship to those chemical changes.

Q So, that was the neurochemistry. And then clinical pharmacology, you've been involved in that?

A Well, the best question about clinical pharmacology is why do I do -- or why do I lead a group studying chemistry and genetics, and that's because the ultimate goal are better treatments for autism. And it is almost certain in those treatments, in least in terms of what I can provide, there are many other people, who can provide much better behavioral and educational therapies and improvements in those areas, but in terms of my role as a medical researcher, personally, I want to develop the very specific mechanistic understanding that will lead us to much better treatments for autism targeted to the mechanism of the disorder.

Q On Dr. Fombonne's direct, he had a chart of different treatments that had been tried and failed with autism. One of those was secretin. Were you involved in those trails?

A Yes. We have been involved in trials of medications that are available for other treatments and trying to see if they would be helpful for autism. And because we had developed that expertise on clinical trials, when, as Dr. Fombonne mentioned, there was a possibility that in a sense someone had a

sort of lucky finding, that perhaps secretin might be helpful to autism, because of the three case reports. We understood the importance of that and as opposed to this sort of previous thing that had happened right before secretin was facilitated communication. We weren't able to help in studying facilitated communication, but somebody else had the expertise to under -- to test does it work or does it not work. Because, of course, I understand how important it is for these things to be studied and I personally feel the desperation for us to have better treatments today.

And so, I had to sort of stand by as facilitated communication went through the phase of being a fad, where everybody was doing it. People were being falsely accused of abuse. Parents were being falsely accused of abuse. But, then, to see somebody put it to the test and then became discredited. Secretin was -- we were in the -- we then had the opportunity to test it quickly.

Now, one could have the impression, the way that I'm saying this, that the goal of testing it was to show it didn't work. But, I actually have a very strong conviction that our research resources should not be directed to things where going in, we don't

think they're going to work. So, yes, there were these exciting case reports and we had the resources to test secretin versus saltwater. And I was very proud that within a few months, we were able to conduct this study, which I thought had high public health importance, given how many people were receiving it. And we put it to the test and, frankly, we were excited, because some children looked better after the study. Of course, we were carefully blinded. Secretin is actually something that's fairly easy to blind. And I was disappointed when saltwater was slightly better than secretin.

This is not what one looks for. And I am very aware that some of our best medication treatments have come from the kind of luck that led to secretin. But, it didn't hold up to the test of was secretin better than placebo. Interestingly, all the children got better and it wasn't because we were somehow wanting them to get better and not being careful scientists. I think we had a large group of families, who were desperate and feeling the hope that secretin was providing at the time, provided parents, who were much more -- everybody around the child was just more upbeat, because at least momentarily, it was helping people with the understandable process that people

have to work through, in terms of having a child with any kind of serious problem. It's really a grief process that eventually -- and it's a difficult time and the parents, who were coming to see us, were in great despair and at least momentarily were much more hopeful. What I hope is that eventually they work through that process, accept their children for who they are, and I know the parents do. It's a difficult time for parents in the very early years.

Q What initially made you decide to focus your study or research on autism?

A Well, that's pretty easy. When I was six, my younger brother was born. There was some difficulty around his birth. But, basically, we thought he was doing okay for about six months. Then, we knew there were problems for another, I would say 12 months. And I do remember acutely when my parents decided that something was definitely going on and it was when my mother took my brother over to visit one of her friends, who had an 18-month old child, and the contrast was stark. So, if you ask my mother and father now when something started, they would say six months or even wonder about the first six months. But, it's understandable, one has hope that what one is seeing would just sort of go away and children will

'go back to a normal pathway.'

So, anyway, my brother had -- wasn't responsive to people very much in the early years of his life and also had the characteristic preoccupations with people with autism, many of which I fondly remember. You wouldn't know this today. You would have to have a different preoccupation, I suppose, but he could find exactly what track on the -- which groove on a record had what point of a Sesame Street or Mr. Rogers passage he wanted to see.

One of the reasons I bring this up is that he -- no one ever thought that he had autism yet, like today's classification and criteria. He would be thought of as one of the most severe cases. So, it's somewhere around the time I was 10, just seeing how much pain it was causing my parents, I think, and the struggles -- and his struggles, frankly, was a sort of childhood wish to try to do something about this.

Q And when did you start focusing -- or why did you start focusing on the genetics of autism?

A The chemistry work that we had done leading up to 1993, actually, it was a failed grant review, where we were studying platelet serotonin and basically it was a grant review, a grant we eventually did not receive, where they said the only logic of the

platelet being involved in autism would be a gene that was expressed in the platelet brain. We shifted that. We, also, had findings in the neurochemistry that said the next step was to look for mutations in the genes that were leading to the chemistry changes. And, as a matter of fact, it was really more of a colleague that found that recently. Jim Sutcliffe found in a pretty classic American Journal on Human Genetics paper that certain people with autism have specific mutations in the serotonin transporter. And one of our earlier chemistry findings had been that some patients with autism had very increased serotonin transport function.

Q And that is what initially sparked your interest in the genetics of autism?

A There was some hope that genetics would somehow deal with the fact that autism is a very heterogenous syndrome, as mentioned by Dr. Fombonne. To tell you the truth, if one really thinks about it, genetics has as much trouble with heterogeneity as anything else. I must say that the same reason that we were attracted to the serotonin finding is why we were attracted to the genetics finding, because it became very clear that genetics, as a discipline, has an approach where, as opposed to other things that we

might learn about the brain in autism, that you might not know what was chicken and egg, what came first, in genetics, there's a much more direct idea about causation when you do genetics, as opposed to correlation alone.

Q Now jump back to your CV for a moment here. Are you on any editorial boards?

A I'm on several: the editorial board for Biological Psychiatry, the Journal of Child and Adolescent Psychopharmacology, Neuropsychopharmacology, and have recently accepted an appointment as a corresponding editor for the new Journal of Autism Research that will be published by the International Society of Autism Research.

Q Do you have any other positions that would be relevant to your testimony today?

A I am also the co-chair of the American Academy of Child and Adolescent Psychiatry, Autism, and Intellectual Disability Committee.

Q What is that committee?

A So, it's for the organization, the American Academy of Child and Adolescent Psychiatry, which is the professional organization of American Child and Adolescent Psychiatrists, and the committee is composed of people interested in caring for and

1 studying people

with autism and intellectual disability, formerly known as mental retardation.

Q Do you or have you served on any autism advisory boards?

A I was one of the first members of the Cure Autism Now Scientific Advisory Board and served for several years and, also, served for one year as the chair of the Scientific Advisory Board.

Q What was your role as chair of that advisory board?

A I would help organize and conduct the scientific review of research proposals to the organization.

Q But, you're no longer on the advisory board?

A That's correct.

Q Have you been directly involved in genetic studies related to autism?

A Yes, since 1993.

Q Okay. I note on your CV that there appears to be over 150 published peer review articles on autism. Does that sound correct?

A I think there's over 150 in general. There would be less specifically pertaining to autism. So, that would include ones on ADHD or even ones on cancer pharmacogenetics.

Q Of those articles, do you know about how many were peer reviewed publications on the genetics of autism?

A Certainly over 30.

Q I think we counted 60, but I think over 30 counts in there. What has been your involvement in those studies?

A It's ranged from studies that we propose that only included subjects from our particular university and laboratory, in which the subjects were recruited, evaluated at our site, and in which the laboratory studies were conducted in my laboratory. And it has ranged all the way up -- there are several levels of studies, in which we might collaborate with three or four other groups, studies at the level of the International Molecular Genetic Study of Autism Consortium, that includes dozens of investigators from several countries in Europe and North America, all the way to the participation of that consortium and what we consider the consortium of consortia, the Autism Genome Project, which includes over 100, well over 100, investigators and many more people who are involved in the study in some role.

Q Why do you believe so many geneticists are drawn to the study of autism?

A It actually came from a paper in the 1990s, in which Plomin published in Science a comparison of estimates of heritability of autism compared to other disorders that people were very interested in, disorders that might not even be as common, such as Type II diabetes, such as Type I diabetes, such as asthma, such as hypertension, such as coronary artery disease. And what they found was that the heritability was much, much higher for autism than those other disorders, in which a lot of geneticists were working on. So, I think they've basically been drawn into it, in terms of seeing it as a scientific opportunity.

Q Why do you continue to spend so much time on the genetics of autism?

A It's an outstanding question, because I feel very much drawn to do the things that maybe not everyone else is doing. I've commented on several venues about some of my own autism-related traits and I suppose going and doing something different might be one of those. So, the fact that there are so many people working on the genetics of autism and, frankly, so many giants outside of the field of autism genetics coming into autism genetics makes me think, well, that's really what we want happening for our children,

adolescents, and adults with autism, and their families. We want to bring people in to study autism, because it's so important.

Why do I continue to do it? I suppose because I still go back to the perspective of the brain is so complex in studying it. We have that as a problem. And even when we go into the brain studies and we find abnormalities, we don't know whether they might be three or four levels down the line, particularly if we're studying, as I hope, that we don't have brains to study until people are ideally the same ages when everybody else passes away. We don't want people to pass away early and have their brains to study. But even if we have brains at five, what was happening was thought to largely be prenatal. So, you have this problem of what you're studying, this whole chicken and egg problem.

And the other problem, frankly, is that we need to study brains. There aren't that many to study. There are many more. I'm working to try -- work with the autism tissue program and with Margaret Bauman's tissue program, to try to help with that situation, in terms of having people study the brains that are available. But the reality is that through genetics, we can study genes that are having effects,

in terms of brain development, from thousands or eventually tens of thousands of people while they're alive.

Q Do you think that research on the genetics of autism may eventually lead to some treatments for autism?

A Well, that is the goal. And I think that we -- so, right now, as a matter of fact, it was mentioned before the Fragile X Syndrome is one of the genetic causes of autism in a few percent of cases. Taking the other direction, 25 to 50 percent of people with Fragile X, depending on how you define it, have autism. That gene was cloned, Fragile X gene was cloned in the early 1990s and it's very easy in 2007 to go, oh, we cloned the gene. We can diagnose it, but what else can we do with it. And, believe me, I don't want us to pretend that we can do more than we can. We have to be honest about our limitations. I am excited, though, that through 16 years of basic science, with that information from that gene, that, for example, a model in fruit flies have been created. A model in mice has been created, and not by correcting the genetic defect per se, but by understanding how it effects signaling between nerve cells. There are now methods that will improve

behaviors in those animal models. And as a matter of fact, we are now working with a company called Seaside Therapeutics, to be thinking about the first trials of drugs basically moving up those models and with that very specific information, to be doing clinical trials in autism that come from that specific genetic information.

Now, I would not want anyone to mistake my excitement that that's coming along, to say that we know it's going to work, because we don't. In fact, we've tried a couple of -- we've been involved in a clinical trial with what's called an ampikine that uses a related approach to treatment that, frankly, wasn't effective. It was helpful, though, because now we had done the trial that sets the stage for those later trials, that if we do have something that's effective, we will know how to test for that effectiveness.

Q Let me turn now to a couple of terms and ask you how you would define or use those terms. How would you define the term 'possible?'

A Well, possible has some meanings, but I generally think of possible as could happen. I'm a pretty imaginative. So, possible doesn't tell us much. Possible could be things such as the earth

possibly is the center of the solar system.

Q So, just about anything is possible?

A Yes.

Q Do you believe that it's possible that individuals can be genetically predisposed to react to thimerosal and/or MMR vaccine, in such a way to cause or trigger autism?

A It's less possible than the earth being the center of the solar system.

Q Petitioners' experts and Petitioners have focused on the term 'plausible.' And Mr. Matanoski, this morning, in his opening, talked about plausible. How do you define that term or how do you use the word 'plausible?'

A Well, I think plausible, I would say, has to be a reasonable possibility. So, it may be how many people think of possible. But, plausible, to me, and the terms I use it are not the way it was defined earlier. Plausible does not mean probable to me.

Q Okay. Do you believe that it's plausible that vaccines or one of their components can trigger something in genetically predisposed individuals to cause them to develop autism?

A No.

Q Dr. Kinsbourne, on Friday, used the term

'reasonable medical probability.' Would you need to believe that something is more likely than not, in order to describe it as having reasonable medical probability?

A At least that. Because of an important tradition in medicine to do no harm, I think that reasonable medical probability has to be higher than just slightly more probable than not.

Q Based on your previous answers, I would imagine that you don't believe there is evidence that a vaccine or vaccines has actually been demonstrated to cause autism in genetically susceptible individuals. Would that be right?

A That's correct. I don't actually even know of a specific test of that possibility.

MS. PATTON: I am going to pause for just a minute. We have two slides we have and I have the handouts.

(Pause.)

SPECIAL MASTER HASTINGS: Did you have one for the court reporter? I don't know if there is any hard words in this one, but -- perhaps not. It doesn't look like it.

BY MS. PATTON:

Q Dr. Cook, in your report, you say that

autism is a strongly genetic disorder. Does that primarily come from twin studies?

A Yes. This is actually the sort of data that I alluded to in terms of Plomin publishing this data in Science and attracting many geneticists in the field.

Q Let me turn to your slide for a moment.

SPECIAL MASTER HASTINGS: Before you do, just for housekeeping purposes, let's mark this as Respondent's Trial Exhibit No. 10, and we can refer to it that way.

(The document referred to was marked for identification as Respondent's Trial Exhibit No. 10 and was received in evidence.)

SPECIAL MASTER HASTINGS: So you now are going to go to page 1 of that, I assume?

MS. PATTON: Yes.

SPECIAL MASTER HASTINGS: Go ahead.

BY MS. PATTON:

Q One in five children have autism. How is autism defined in that?

A One in 500.

Q One in 500. How is it defined there?

A This is according to a narrow definition, so it would be according to saying DSM-IV, autistic disorder. It would not be saying what's the number for autism spectrum disorder. But, this would be the narrow autistic disorder.

Q Would that rate go up significantly, if you included the broad autism spectrum disorder?

A If you include the whole spectrum, it would go up to somewhere around one in 160.

Q What is the evidence? If you could explain through your slide, what is the evidence that genetic -- excuse me, that autism is a strongly genetic disorder?

A Right. So, the first evidence is just one step and that is if one child has autism and the same couple has another child, there's about a five percent chance the next child will have autism. First of all, this is a 25-fold increase relative to the one in 500 in the population. Given many things run in families, the twin study becomes much more important, because identical twins and fraternal twins are exposed to largely the same environment as each other, but they share very different amounts of genetics similarity. So, if one identical twin -- so, in this case, an identical twin shares 100 percent of genetic variation

with the other identical twin, whereas a fraternal twin only shares half of the genetic variation across the genome. So, in a sense -- and the other thing to recognize is a fraternal twin, from a genetic perspective, is the same as a sibling or brother or sister, in terms of 50 percent sharing.

So, the idea is that if the increase, for example, one in 500, to five percent is related to environmental factors, then you would see the identical twins having a five percent chance of autism or if one has autism, the other one has it five percent of the time, and for the fraternal twin, if one had it, the one of it would have it five percent of the time would not go up, because of the sharing of 50 percent of genetic variation to 100 percent.

In the case of autism genetics, from the narrow definition of autism, if one identical twin has autism, there's a 60 percent chance the other identical twin will have autism. This is now a 300-fold increase over the general population. And it's also interesting to note, this is not just a doubling of the 25-fold increase to say 50-fold increase, but this is what's called the multiplying of risk. It's a strong signature, that not only is it strongly genetic, but that it's multiple genes interacting

together, when you go from such a low number like five percent. It's also probably included interacting genes, all the way up to 300 fold just from the doubling of sharing genetic variation.

Now, sometimes, people go well, where there's 40 percent that did not share autism. It's important to note that over 90 percent of the identical twins, where one has autism, that over 90 percent of the time the other identical twin will have significant social impairment. Let me put that in perspective.

A That means for example... in the study of Bailey and colleagues in '95, that out of 25 people they were following up, only two had employment, competitive employment which required substantial social skills, and only one had a confiding relationship by adulthood or was married. The others, it wasn't just that they weren't married. They didn't have evidence of a longstanding, intimate relationship.

This is in contrast to disorders where people are focusing quite a bit and for a good cause on genetics such as schizophrenia where there actually are unaffected identical co-twins. And autism, these reports are interesting because in a sense, you can

see there was one of the 25 that by a broader criteria

wasn't affected.

It's also very interesting that some of the environmental risks for some of these were one of the five where they didn't both have autism. Of the ones that did have autism, they had environmental influences around the time of birth or before, which included things like cardiac arrest in the neonatal intensive care unit, included extreme prematurity relative to the other twin.

Okay. So now of course if the fraternal or what was referred to earlier as dizygotic twin who are only sharing 50 percent, if they also had a dramatic increase, we would be thinking about environmental effects of being twins, but in this case, there's no increased risk in autism for fraternal twins relative to siblings. And this signature of a very relatively high risk for identical twins relative to fraternal twins is exactly why so many people who aren't really interested in autism but are interested in genetics have started to study it.

Q You touched upon it briefly, but back to the identical twins. They share 100 percent, close to 100 percent, of their genes. You had said cardiac arrest or other things around birth. Would that be referred to as environment, environmental factors?

A Right. So the estimates from the data that you see here put all together into models are genetic factors over 90 percent, 90 to 92 percent, and then there's 8 to 10 percent that's nongenetic. And then the question is, what is that 8 to 10 percent that's nongenetic? Some it is what we would call random.

In other words, the brain once there's risk, there's a lot of preprogramming in the brain, but a lot of the reason we can do what we can do is that we're not rigidly, our brains are not rigidly, constructed. So when there's a risk or a vulnerability from, for example, a genetic risk, there are still some random factors in terms of what happens there. It's not all left over as environmental.

But then, yes, my point about this paper had a lot of emphasis on whether there were obstetrical environmental risks and prenatal environmental risks. So when we think of environment and gene interaction, particularly in very early child onset, we're very typically focusing in on what happens before birth.

Q So gene environment interaction as that's often used in the papers, that doesn't necessarily mean what I as a layperson -- when I think of environment, I think of the outside world around us, far beyond postnatal, things like heavy metals, as

Petitioners are referring to. But in these papers, gene environment, is that environment often or most commonly referring to the prenatal environment?

A Most commonly. I think people are open to when we think about environment, just off the top of my head and it would take us a while for me to go through them, but I'm sure we're thinking of hundreds if not at least 1,000 different possible environmental factors, among which hundreds would be prenatal, hundreds would be perinatal, and relatively much less likely for let's say people in the United States would be postnatal environmental factors, but they're possible in the sense of anything is.

Q In his report, Dr. Kinsbourne opines that if the onset of autistic spectrum disorder is delayed until the second year of life that collective medical knowledge to date suggests a triggering event has played a crucial role. He also talked about this during his testimony and used this in terms of the gene environment interaction. How would it be possible for the onset of a disorder like autism to appear later in life if it's not triggered by an environmental factor?

A Well, most classic genetic syndromes causing normal development and regression, many of which later

lead to death, are storage diseases which are genetic disorders in which the onset of the disorder, basically the risk is present from birth, but the symptoms do not manifest themselves until a later date, sometimes a fairly sudden or precipitous date.

Q And that's not because of a specific triggering event or factor?

A No.

Q Would Rett syndrome be an example of this?

A Yes. Rett syndrome is an example of, and this was mentioned earlier, is an example of early normal development, followed by regression in skills. And as mentioned before by Professor Fombonne, it's a DSM-IV pervasive developmental disorder or ASD. Development is relatively normal at least in the first six months, typically 12.

There's regression typically at 12 to 18 months, including social impairment and language impairment which looks very much like the regression in social and language impairment in cases of autism without Rett syndrome where there is regression. And over 80 percent of classic cases are due to mutations in MECP2.

There's actually something that's very interesting about finding the gene for Rett disorder.

One of the things that's very interesting is that the patient that I saw was atypical in that her head size did not decelerate, as was mentioned previously. Professor Fombonne talked to us about the classic presentation of Rett, which is the only thing we could count on before we had the gene.

Now that we can identify girls with Rett disorder because of their mutation, we know, for example, the patient that I saw did not develop some of the neurological signs that Professor Fombonne talked about. The only difference between her and a case of regressive autism is she lost use of her hands. It wasn't really hand-wringing. She just couldn't use them that well.

And so I would sort of reassure myself and say, well, girls who have a regression in the typical time of 12 to 18 months with autism who don't lose hand use, they must not have Rett. But as it turns out, there are other girls that don't lose hand use with Rett syndrome. So, in this case, the knowledge of the specific gene in 1999 has contributed to understanding quite a bit more about these patients.

Q So, in Rett syndrome, children appear to develop normally. There is no environmental trigger. There's a certain point in time when that gene turns

on?

A Well, it is a very interesting question, and people like Huda Zoghbi who cloned this gene are doing outstanding work in understanding how this relates to the mechanism not only of Rett disorder but autism more broadly. And the mutation is present from conception, but the expression of the gene only becomes critical in the six- to 18-month timeframe. And not only that, but at the time at which the expression of the gene becomes critical, also it's thought that the symptoms, as mentioned by Professor Fombonne, often follow the change in function of the gene by several months after its key role.

For example, it appears to be very important in the maturation of nerve cells, and there are several phases of brain maturation, several of them actually tied to, for example, when there's social smiling, when there's sitting, when language comes in. So there's quite a bit of remodeling of the brain in the first 18 months and particularly most in that time period. And the issue is that the MECP2, which is the gene that's mutated in Rett disorder, only becomes critical in the timeframe of when the symptoms develop.

Q So perhaps it would be helpful for a little

explanation on how gene expression works. Sort of like a computer program, that everything's sort of preprogrammed and there are specific times that certain genes turn on and turn off?

A Right. Right. And I think of it as genes are constantly getting green lights and red lights and some are getting yellow lights to be only partially expressed. So of all the genes that we have, in any given cell in the body at any given time, there's a completely different sort of toggling of what's on and what's off across that pattern.

Q So for certain diseases or disorders, if the symptoms of those are not apparent until later on, whether it's autism, that it's within the first couple years of life, or whether another disease like Huntington's where it could be decades later, that doesn't mean that genetics aren't involved, does it?

A Huntington's is a classic example of a disorder in which we actually have the problem that we can diagnose with what I think that we would consider certainty in the Court that someone will develop the disease with absolutely no symptoms at say the age of 20 but yet know that they will go on to develop the disease by 70. It's a simple genetic disorder, a simple dominant genetic disorder.

Q And by simple, is that that one gene is involved?

A One gene is involved, and almost everyone who has the gene will develop the disease.

Q Okay.

A But only decades after conception.

Q So there are disorders where it's kind of preprogrammed from birth or from before birth that something will happen, but the expression of that isn't until later?

A The only genetic disorders that don't manifest themselves that way lead to death either as miscarriage or as death before birth.

Q You said Huntington's is a simple genetic disorder. Would Rett be a simple genetic disorder too because it involves one gene?

A Rett is starting to get a little bit more complex because it's not always the same mutation within the gene. So the patient that I described that we had seen actually is missing more of the gene, but because she's missing more of the gene on one chromosome, it looks like that doesn't interfere with the normal chromosome function as much.

So given that there are different mutations in the gene, it has some complexity to it so that

patients with Rett disorder will vary in terms of the severity of different symptoms. They will also vary in terms of their onset.

Q So all genetic disorders aren't similar in complexity?

A No, they're certainly not.

Q What would be the difference between a simple genetic disorder like Huntington's and a complex genetic disorder?

A So a complex disorder, as I said in Rett disorder, we're already getting a little bit more complex because it's one gene but different mutations in different parts of that gene. The next level up would be two genes interacting with each other. And then we get to what we consider complex genetic disorders, which includes Type I diabetes, Type II diabetes. It includes inflammatory bowel disease and definitely includes autism. So although autism is strongly genetic, it is not remotely simple.

Q If we can go back for just one moment to the gene environment interaction. In his report, Dr. Kinsbourne cites an article by Purcell in support of his theory that the differential between the concordance for autism of identical and fraternal twins would be observed if autism were entirely due to

gene environment interaction. Does the Purcell paper support his statement?

A No. The Purcell paper doesn't say anything about autism. It's a simulation or basically mathematical modeling paper referring to a situation much more analogous to what people think of in fact, the examples they use are major depression where there are known environmental influences and also demonstrated through the same way as autism has its genetic influence, demonstrated genetic influences, but known to be much more of a 50/50 scenario than a 90/10 scenario.

Q So that's simulation. It's not based on autism, just a mathematical construct?

A Yes.

Q Okay. Very briefly, on Monday, Dr. Aposhian, Petitioners' toxicologist, testified that there's a subset of the general population that has a genetic hypersusceptibility to mercury injury. Are you familiar with any evidence that would support that statement?

A He cited a paper that talked about different metabolism, an effect of mercury, and he cited a relationship with a gene to that. That's not exactly what you're asking, but he was mentioning that I know.

And I looked at that paper, and nowhere did it say that the changes that it was seeing were damage as you're using in your question. And also in the paper, it frankly was not a positive association in the paper.

Q Recently Petitioners had filed a paper by Beaudet I think is the pronunciation which stated that autism is heritable but not inherited. What is the difference between heritable and inherited?

A Well, my esteemed colleague, Professor Beaudet, is trying to make a distinction between genetic risk that gets passed on in terms of genetic variance present in parents to their offspring. He's trying to make a distinction between that and what we would consider de novo abnormalities. So perhaps the best example and one that he uses would be what he's calling heritable I want to call genetic, because heritable makes us think too much about inheritance.

So let's just make it simpler and say he's saying if you follow what he says in the paper, he's saying that it's highly genetic. He's not debating that, but he's saying it's not inherited in the sense of risk variance coming from both parents in the sense of most complex genetic disorders.

The example that he uses is actually an

outstanding one where Down syndrome is the most common genetic cause of intellectual disability. But you heard Professor Fombonne say that the most common inherited cause of intellectual disability is Fragile X syndrome.

So how could something be 100 percent genetic in the case of Down syndrome but not inherited? Well, that's because most cases come from a mother who has two chromosome 21s, one of which should go to the offspring, but both go to the offspring, so now the child de novo, meaning nothing was abnormal in the parents that we know of -- there may be risk factors for that passing on of the additional chromosome 21, but the only risk factor we know at this point is maternal age. Older mothers have a higher risk of that.

So that is genetic in the case of the typical Down syndrome with three chromosome 21s, but it's not inherited. There is a form of Down syndrome that accounts for 5 percent or so of Down syndrome that has to do with translocations that are inherited from the parent.

So in no way is he meaning to minimize the importance of genetics in autism. He's simply highlighting as I have highlighted in previous papers

for at least close to a decade in terms of complexity of genetics means that it's not necessarily all inherited like Huntington's, and it's not necessarily all de novo like Down syndrome.

Just as Down syndrome has both de novo cases and inherited cases, in autism, we expect a combination of de novo events, in other words, chromosome changes that a child has that a parent does not have, and we also expect a proportion of it to come from something quite a bit more complex than Huntington's but basically genetic variance coming in and contributing to risk.

Q So whether the term heritable or inherited is used, it still implies genetics?

A It's still genetics.

Q Petitioners' experts have talked about certain children being genetically predisposed to have adverse reactions to thimerosal in vaccines or to be genetically predisposed to be unable to clear thimerosal from the body. To your knowledge, is there any support for this genetic predisposition?

A It's speculation.

Q Okay. In your opinion, I guess based on that, you would believe that members of the scientific medical community who study genetics wouldn't believe

that this is an accepted principle at this point in time?

A It's certainly not been established.

Q Have you had the opportunity to review the records in this case?

A Yes.

Q Is there any evidence in the record from your review that Michelle Cedillo had a genetic predisposition to react to thimerosal and/or the MMR vaccine?

A I see no evidence.

Q Did you see the results of any genetic testing in Michelle's records?

A I was concerned that genetic tests had not been performed until recently and that in the records, we do not have the results of genetic tests. I would expect and particularly want because of the increased growth and the fact that the length and weight of the child has accelerated in addition to but not as strongly as the head circumference makes it even more important, I think that this is a case where the standard workup should have included a clinical genetic evaluation, at a minimum a chromosomal analysis in terms of autism, FISH or other studies of chromosome 15q11-q13 duplication, Fragile X testing,

and then in terms of the increased growth, one should also be looking for mutations in the gene for p10 and also the Sotos syndrome gene.

Q Even if Michelle had had genetic testing and if those results were in the record and came back normal, would that rule out a genetic basis for her autism?

A No, not at all. We see an over 90 percent genetic contribution of genetics to autism, and I don't know how many cases we will be able to identify once our technology has gone to the point, for example, of complete genome resequencing, which we expect as a medical test in 5, 10 years.

What is very clear, what I have witnessed is that even using microscopic tests for chromosomal disorders, we are much better able to detect things than we were 10 years ago, but we are currently literally as we speak in a phase of the resolution of the chromosomal testing going from basically -- the equivalent in telescopes would be from what we could see with a light telescope to there was eventually a shift to basically telescopes using electromagnetic radiation and not light. And we're going through that kind of shift.

I don't know what percent we'll have after

that. I suspect 20 percent in which we'll be able to identify a known cause at least by the time we've done complete genome resequencing. The issue is that many of the cases if there is an inherited component, which there's a lot of evidence for and not just a genetic de novo component, then one would expect that many of the risk variants may only by themselves confer a slight increase in risk.

So then you go, well, if it's only a slight increase in risk, say it's in each individual gene, not the whole together, all together we know that the genes are conferring a lot of increase in risk, if you go, well, who cares if this particular gene only increases risk 8 percent relative to somebody without that variant, my answer for you is that in Type I diabetes, the second strongest gene only increases risk 8 percent, but that gene is insulin.

And I must say that I don't think we would be here if we had something as effective in autism in insulin. So the point is weak genetic effects may be powerful indicators of rational development of treatment down the line.

Q This morning with Dr. Fombonne's testimony and on cross, there was a lot of discussion about whether this was early onset autism or true regressive

autism. Would the opinions you've given today on the genetic basis for autism be any different or would your ultimate opinion that there is no relationship between the vaccines and/or thimerosal and autism differ depending on whether it was early onset autism or true regressive autism?

A I'm not sure. Could you restate?

Q I don't think I phrased that well. This morning we saw a lot and heard a lot about whether this was early onset, whether her symptoms were seen early on, or whether she regressed after the MMR vaccine. Does that make any difference to your opinion on whether genetics are the most likely -- how important genetics are in the role of autism?

A It wouldn't affect the role of genetics as a whole. I guess that's all I would say.

Q Okay. It wouldn't really affect your opinion?

A No.

MS. PATTON: Okay. I don't have any further questions for Dr. Cook.

SPECIAL MASTER HASTINGS: Ms. Chin-Caplan, did you have any questions?

MS. CHIN-CAPLAN: Yes, I do.

SPECIAL MASTER HASTINGS: Please go ahead.

CROSS-EXAMINATION

BY MS. CHIN-CAPLAN:

Q Doctor, you're indicating that autism is a genetic disorder, is that it?

A Strongly genetic, yes.

Q Strongly genetic. And you talked about single gene defects such as what you would see in Rett's.

A Yes. I'm not sure I'd use the word defect, but single gene mutations.

Q Single gene mutations. Okay.

A I don't like to use the term defect around anyone having autism or intellectual disability.

Q Good of you. Single gene defect. And your research has concentrated on the genetic causes, right, of autism?

A That's been an emphasis, yes, ma'am.

Q And you started that a while ago, didn't you, Doctor, your research?

A That's correct.

Q For instance, Article 71 in your CV, the International Molecular Genetics Study of Autism Consortium, and it spoke of the further characterization of the autism susceptibility locus, AUTS1, on chromosome 7q, Respondent's Exhibit B.

A Yes, ma'am.
Q 71?
A Yes.
Q So you were looking on chromosome 7q, is that correct?
A That's correct. Do you have the paper with you?
Q No. I'm just asking if that's what your research focused on.
A That paper is a followup of the previous linkage study. Right.
Q Okay. And did you find the autism gene on 7q?
A That's something that we are all still looking for.
Q So you haven't found it yet?
A Haven't found it and confirmed it yet.
Q Okay.
A Actually some of it if I talked to you about I'd get in trouble for sharing what's about to be published.
Q Well, I wouldn't want you to do that.
A But I think it's fair to say that we have not gotten to where we're headed there.
Q Okay. And in 76, again, the International

Molecular Genetics Study of Autism Consortium, a genome-wide screen for autism, strong evidence for a linkage to chromosomes 2q, 7q, 16p. Have I read that correctly?

A Yes, ma'am.

Q Have you found the gene yet on 2q?

A We have not found the gene on 2q, but I would say that the evidence that there is a gene there is quite strong. The interesting thing about the evidence on 2q is that initially only our study was finding something there, but then the other studies truly replicated our study by looking at children with language delay, because as been discussed before, not everyone with autism has language delay.

Once other studies have emphasized children with language delay, there is strong support across different studies for linkage on 2q. The problem with linkage is you get a linkage signal and then you have a very large region of 10 to 20 million base pairs to map down from, and it's very difficult, and it's very difficult in a complex genetic disorder. So as a matter of fact, we find ourselves in the same position as some of those other disorders I mentioned before such as asthma, such as Type II diabetes.

Q So you didn't find it on 2q, and you didn't

find it --

A We haven't found it yet.

Q And you haven't found it yet on 7q.

A This is correct.

Q Did you find it on 16p?

A 16p is another place we are continuing to work. And so in response to you, my answer is we have not found it yet. It is a hard road, and we are continuing to work down it, and we will not tell you that we are sure we have found it until we are sure.

Q And then in 82, you're continuing your research in genetics?

A Uh-huh.

Q And in this one, you talk about an association between a GABRB3 polymorphism and autism?

A Yes, ma'am.

Q So you're looking at another area of the genome?

A This is right. This is a replication of our previous association. This is a completely nonoverlapping sample with the previous study, I don't know what the number is, but also GABRB3, the exact same polymorphism, GABA beta 3 155CA2 in autism, this is an independent replication of that finding. And at the time, we did not consider that polymorphism to be

the specific risk variant in autism.

We and other groups are continuing to look around that original finding for what specifically in that region confers risk. Again, this puts us in the same position as other disorders. I keep coming back to Type II diabetes.

Q And then, Doctor, in the immediate following publication, you're looking at the serotonin transporter gene, the SLC6A4 region in autism.

A This is correct.

Q So this is like the fifth area of the genome that you're looking for, is that it?

A We are looking at the fifth area of the genome because as I mentioned before, the complexity of autism includes multiplicative inheritance with multiple genes conspiring, interacting to cause autism. That is what the twin data suggests when you go up from a 25-fold increase to an over 300-fold increase going from siblings to monozygotic twins. So we expect multiple variants contributing across the genome, which is very similar to what's expected in Type I diabetes and Type II diabetes, asthma and other disorders.

Q And then in No. 84, you said FOXP2 is not a major susceptibility gene for autism or specific

language impairment. So you discovered one that wasn't one for susceptibility, correct?

A Well, it's very interesting about FOXP2 because FOXP2 mutations were studied there because it's in the 7q linkage region, so you have to hammer through a lot of genes in those regions. And FOXP2 is particularly interesting because the interest in FOXP2 comes from a family that has a complex language disorder with FOXP2 mutations. And since Dr. Monaco had helped find those FOXP2 mutations in those large families with language disorders, this was a logical place to look.

I would also add that that study acknowledges and all subsequent studies this outstanding gene to be studied in this linkage region have not been sufficiently tested for involvement. So, in some sense, the statement that it's not a major susceptibility gene for autism susceptibility disorder should say our evidence to date does not support it, but we have not sufficiently done what we need to do to very carefully fine map in that gene.

Q And of course the title to this is that it's not a major susceptibility gene for autism or specific language impairment?

A Yes, that's correct.

Q Okay. So, Doctor, then if you go to the following article, No. 85, you're looking at the receptor gene, HTR2A, in autism, correct?

A Correct.

Q Is that different from the previous serotonin receptor gene that you were looking at?

A Yes. The serotonin transporter gene is different than the serotonin 2A receptor. Those are the two specific genes that our lab headed into because our neurochemical findings of high serotonin in autism pointed to a subset that had high serotonin transport function and another subset that had low 5H22A receptor function.

And this one if you'd like to know did not provide evidence in support of the serotonin 2A receptor gene, although I would like to point out that a particular hapotide when inherited from one parent or the other was P less than .05, in other words, less than a 5 percent chance of being a false positive.

But we considered that that was not sufficiently strong enough evidence to support that as a contributor to autism susceptibility and also pointed out what will need to be done to fully test that and see if that finding that by some standards would -- I mean, less than 5 percent chance that it's

not related, we take a conservative approach and say it's not related.

Q And in No. 87, Doctor, you looked at the arginine vasopressin receptor 1A or the AVPRIA polymorphism in autism?

A That's correct.

Q And did you find the gene there?

A Well, we actually found evidence for association in one of the polymorphisms. There have been two subsequent studies, and each of the three studies has been positive, and we are actively following that up, partly because of findings of differences in expression of arginine vasopressin receptor 1A having effects on social behavior. So this is an area of continuing investigation.

Q And you're continuing the research, and you started looking at Reelin as a candidate gene for autism, and that would be No. 98, correct?

A Correct.

Q And is Reelin the candidate gene for autism?

A Well, a previous group had found evidence for Reelin being involved. And in this study, we did not find evidence to support Reelin.

Q Okay. So is Reelin out then? Reelin is not even a candidate any longer?

A It's complicated because there are two or more studies at P less than .05 positive, but in our conservative approach to saying whether something contributes to susceptibility, we consider that it might be. And when I say might be, we're talking about --

Q Possible?

A -- probable as a matter of fact. When you have two or more studies at P less than .05, the most likely thing is the negative studies are false negatives. But recognize we're talking about a stringent level of certainty in the first situation. These are studies where Reelin is mechanistically, biologically plausible because of its role in the development of the brain. The initial study was positive P less than .05, and a subsequent study has been positive.

And given the heterogeneity of autism and partly because I'm talking about someone else's finding, and I'm not going to be as hard on them as I would be on myself, we're probably dealing if you want to talk about probability a more than 50 percent chance that it contributes to susceptibility. That's probably where we find ourselves, but we don't consider that an adequate standard to say yes, that is

the gene for autism and we found it.

Q You said contributes to susceptibility.

A Uh-huh.

Q You said contributes to susceptibility.

A Right.

Q Is that an indication that you don't necessarily have to get it?

A You don't have to get it? That's part of the complexity. So I mentioned Fragile X syndrome. Twenty-five to 50 percent of patients with Fragile X syndrome have autism. That is an incredibly high rate having that disorder. But all the gene is doing is increasing susceptibility.

The one that I know of that I would say susceptibility is approaching 100 percent -- see, susceptibility ranges from something that would be so low you wouldn't consider it a susceptibility factor all the way to 100 percent or near 100 percent for Huntington's. People that have maternally inherited duplications of chromosome 15q11-q13 have 100 percent susceptibility to autism.

Q And when they have 100 percent susceptibility, that means that they will get autism?

A They develop autism spectrum disorder.

Q Okay. But at 50 percent, there's a 50

percent chance that you won't get autism, is that it?

A Correct.

Q And so there's something about this 50 percent? Fifty percent of the people will potentially get it, but then there's another 50 percent who may not get it, is that it?

A Right. And if you were talking about something that conferred risk in which the population risk was 50 percent, then you would say it's not contributing to susceptibility. But when you're talking about something like autism where the population risk is 1 in 500, then 50 percent is a very large increase in risk.

So you think of a term called relative risk. So the relative risk, if something conferred a 50 percent risk, the relative risk is 50 percent divided by 1 over 500, and I can't do that math without taking pause, but it's a large number.

Q And then, Doctor --

SPECIAL MASTER HASTINGS: Before we go on --

THE WITNESS: It's actually 250.

SPECIAL MASTER HASTINGS: I'm sorry. I interrupted you.

THE WITNESS: I interrupted. I'm sorry.

SPECIAL MASTER HASTINGS: How do you spell

Reelin?

THE WITNESS: R-E-E-L-I-N.

SPECIAL MASTER HASTINGS: Go ahead.

MS. CHIN-CAPLAN: Thank you.

BY MS. CHIN-CAPLAN:

Q Doctor, in '99, you went back to 2q, and that article indicates that you were looking for nine candidate genes for autism. Did you find it?

A I would not say we have found the genetic variation on Chromosome 2q accounting for the significant linkage signal on Chromosome 2q.

Q Okay. And then, in 103, you were looking at the functional row of RAB3A and its genomic localization. DNA variants in the human RAB3A gene are not associated with autism. So you found another one that wasn't associated with autism.

A That's correct. A lot of work to do; there's a lot of genes.

Q A lot of work to do. So then we go to 106, and, in 106, you were looking at the MECP2 structural and 3UTR variance in schizophrenia, autism, and other psychiatric diseases, a possible association with autism. Did you find it? Was there a possible association with autism?

A There is a possible association with autism.

There have been families published with intellectual disability or autism that convincingly, within those families, there is autism without Rett disorder due to the MECP2 gene, and, in this paper, we provide more support that some patients with autism without Rett disorder may have, at least, as a susceptibility gene, MECP2 playing a role. This is an area of active investigation of geneticists around the world, particularly Dr. Zoghbi, who cloned the Rett gene is very interested in its relationship with autism.

Q So this is the gene that is the single-gene defect that we had spoken of earlier for Rett's.

A In Rett disorder, it is a single-gene defect. We're looking here at whether it may not be a single gene having such a strong effect that one of the genes that, with other genetic variants, contributes to the disorder.

Q Then, Doctor, in 119, you looked at neuroligin 3 and 4.

A Yes.

Q Did you find the gene there that could be causing autism?

A This is an example where we found mutations in neuroligin in 3 and 4, and this had followed a very important paper that had been published in Nature

Genetics in terms of finding mutations in neuroligin 3 and 4 in autism. These are rare variants.

So we have de novo variants that are much more like chromosomal disorders. We have what we consider "common variance." This is the common variance, common disease, view of genetics, and it is the one that is dominant in the field of human genetics and is paying dividends in disorders I keep mentioning, like diabetes, asthma, and inflammatory bowel disease.

Studying these genes already through other de novo events in a family with autism and finding mutations that are changing function of the gene, and so this is evidence -- it wouldn't be that these genes are going to be the ones that, say, in 50 percent of people with autism, this gene is active, but it's much more like not so much Fragile X disorder, but less common things than Fragile X disorder that we know from our study of intellectual disability in general are going to add up to contribute to risk.

Q Am I right in my thinking, what you just said, that it's not one gene; it's multiple genes that might be adding onto the risk. Is that what you're saying?

A Correct.

Q So they are all susceptibility genes. Is that it?

A That's correct. Some have a stronger effect by themselves than others. Some, by themselves, are sufficient to cause autism.

Q But you haven't discovered which one yet. Right?

A Oh, no. Fragile X syndrome is one. MECP2 is one in terms of autism spectrum disorder. I can go off on a relatively long list: tuberous sclerosis. There are many, many that are not going to account for more than 1 percent of autism but added up account, as was mentioned before already, up to 5 to 10 percent of cases of autism.

Q What about the other 90?

A So for the other 90 percent, we are in the phase where there is a lot for us to know, nothing that we have had trouble finding to date. I think part of your point is, how many autism genes have you found, Dr. Cook?

The reality is that this is a tough thing, and we knew it would be tough going in because, even though the relative risk to siblings is 25-fold greater, this is compared to Type I diabetes, where the increased risk to siblings is 15-fold greater, and

the prevalence is one in 500.

Many people, I don't think, realize that autism is as prevalent, certainly more severe, even as the father of a child with Type I diabetes than diabetes. It's more prevalent. It's a hugely important health problem, and it's more strongly genetic than diabetes.

So the fact that we haven't found them is not surprising. If one gene -- this is the concept of a major gene. If we were dealing with one gene, or if every single case had the same two genes, if every case of autism was the same, and the genetics were simple, then we would have had no trouble finding that gene or those few genes.

But from the very beginning, this idea of multiplicative risk, and our estimate that at least five genes will be required, means it's not fivefold increase in risk for one gene and fivefold increase in risk for the next one, all adding up to 25. It's the fifth root of 25, which is only a little bit more than one.

Again, you can come back: Why are you looking for genes that, by themselves, only increase it a little bit? Well, because, in the aggregate, they contribute to over 90 percent of the risk for

autism and because we keep coming back to -- let's take Type I diabetes where a small effect risk, the kind we're looking at for autism, the kind that, if they were having to find the insulin gene related to diabetes instead of having it thought of as a candidate, they'd still be fine mapping where the insulin gene is. They'd be exactly where we are in autism. And, of course, in diabetes, we've had insulin for quite a while. We don't have it in autism.

So that's why we're continuing this effort to find what the specific variants are and to confirm them.

Q You continued your work in number 131 where you were looking for the SLC25A12 and CMYA3 gene variants, and you said that those weren't associated with autism.

A So the important thing, and this is very important, how the title of this article is worded, so I want to read to the Court the title of 131.

Q Okay.

A "SOC25A12 and CMYA3 Gene Variants Are Not Associated with Autism in the IMGSAC Multiplex Family Sample." Now, the reason we emphasize that is because not every sample is identical. We actually enrich for

language delay. There are various differences across populations that make genetics different, depending on what sample you have.

What's particularly notable about this one is there have been two extremely carefully done studies, at least two, that have replicated the SLC25A12 gene's role. This may very well be the gene, under the 2q linkage peak, and I would actually say the evidence for SLC25A12 is approaching the level at which we start calling this one of the confirmed autism-susceptibility genes.

But now think about this. We have multiple studies, P less than .05, supporting this, maybe three out of four, and we're still not sure. That's the level of evidence that we need before we're going to say, "Yes, we have that susceptibility gene."

So, in some respects, to say, "Haven't you found anything yet?" we are holding this to a very high standard.

Q Because you're a scientist. Right?

A Because we are scientists, and we do not want to mislead people. The other thing, frankly, is, so we have the gene SLC25A12. Until my colleague, Joseph Buxbaum, or others can translate that knowledge into something that may be helpful and be carefully

tested as to whether it's helpful or not, it's not that much to talk about outside of the scientific group.

Q Okay. It's fair to state that, as of right now, the title of this article is indicating that it is not associated with autism in the IMGSAC multiplex family sample.

A In that particular sample, yes.

Q Okay. Doctor, in 135, you looked at ITGB3. It's associated with serotonin level and autism susceptibility. This seems to be the first time you've used the word "susceptibility" when it comes to autism.

A Well, you mentioned susceptibility earlier, and, obviously, I guess that was because I had used the term. So I think if you go back to as early as 1995, I had used that term.

Q In your articles?

A Yes.

Q Okay. And then, in 137, you're talking about the genetic interaction between ITGB3 and SLC6A4 in autism susceptibility. What did you find about that genetic interaction?

A We find that Integrin Beta 3, which is ITGB3, and SLC684, which is the serotonin transporter,

are interacting genetically to contribute to autism susceptibility.

This follows previous work showing that they interact to contribute to blood serotonin levels, which I mentioned we've been interested in before, and, frankly, this interaction that's both genetic and apparently also physical, I'm very excited about because we came at this through genetics, but, as it turns out, Integrin Beta 3 and serotonin transporter physically interact with each other, and, frankly, this may give us clues as to how to improve treatments that we already have, such as using serotonin transporter inhibitors through a better understanding of the interaction of these two proteins.

Q Doctor, one last one. You were looking at Neurexin 1B --

SPECIAL MASTER HASTINGS: Which number was that?

MS. CHIN-CAPLAN: 143.

SPECIAL MASTER HASTINGS: All right. Thank you.

BY MS. CHIN-CAPLAN:

Q The title is "High Frequency of Neurexin 1 Beta, Signal Peptide Structural Variants in Patients with Autism."

A Yes. This is a very interesting paper. The reason Neurexin 1 Beta was chosen is because it physically interacts with neuroligin. So neurexin is a protein that comes from the first neuron and interacts with neuroligins coming from the post synaptic neuron.

This is a kind of protein-protein interaction that establishes and maintains important synapses, such as GABA and glutamate, which, for various other reasons, we have to think are involved in learning and memory and seizures that may be related to autism.

In this case, we found rare variants in terms of mutations affecting function in this gene. It's very interesting because this predated the finding of copy number variation or de novo changes in Neurexin 1 found through copy number variation studies in a recent Nature Genetics paper.

Q So, Doctor, would it be fair to state that, right now, there really is no one autism gene?

A I would say it would be fair to say there will never be only one autism gene because we already have multiple autism genes in the case of tuberous sclerosis, in the case of Fragile X, and I could go on for a while.

Q You've indicated that it's probably multiple autism genes. Is that it?

A It's even more complicated than that. So the inherited group with the common variants is multiple genes interacting with each other. Then there is a group of rare variants. Then there is a group of what you would consider chromosomal disorders that are sort of a flavor of the rare-variant forms. So we have at least three forms.

Q You spoke earlier of your brother. Had there been some sort of obstetrical environmental injury?

A Well, it's very interesting that you ask that because we always referred to him as "brain injured" because the idea was that because of a footling breach birth, that this had contributed to it. This is not a delivery that, after 1961, anyone would have done. It wouldn't be the standard today.

The interesting thing about that is that, as it turns out, he has exactly the same syndrome as those that have Chromosome 15q11-q13 duplication in terms of the type of seizure he had, even the type of, as eventually having a kind of friendly autism syndrome and having more preoccupations than perhaps social dysfunction.

I'm sorry to say that we are now learning, and the parents that are in the organization, the parent-led organization for this syndrome, 15q11-q13 duplication, have, unfortunately, become aware of something else that my brother shares with them, which is sudden death in adolescence and young adulthood.

So we always thought it was environmental, but I don't know. Looking at him, he has exactly the same syndrome as the patients I see with 15q11-q13 duplication.

Q Doctor, since you are a doctor, is it possible that your brother could have had a susceptibility gene, and the obstetrical injury triggered this gene to flare?

A Actually, I suspect that there was not an obstetrical injury and that that's basically a red herring for what was a genetic syndrome.

Q In the twin studies that you spoke of earlier, is that the Bailey study?

A That's the one that I emphasized the most because it was done with such complete ascertainment for the twins. Twin studies have to try to avoid certain kinds of ascertainment biases.

Q Doctor, in most twin studies, most "monozygotic twins" meaning they are identical --

correct? --

A Yes, ma'am.

Q -- they share the exact same genes.

A There is an exception of the mitochondrial genome. It would round off to 100 percent of genetic variation.

Q Okay. There is not 100 percent concordance here, though, is there?

A That's correct.

Q It's a 60 percent concordance.

A Well, the 60 percent concordance for narrow autism.

Q True.

A And it's important to note that when one includes cognitive disorders and severe social disorders, basically, when one starts to think of autism spectrum disorder, the concordance is 90 percent.

Q This is where I wonder about this, Doctor, because, say, you have an MS patient, and MS twin studies that have been done, and you have concordance, even there it's only 50 percent, but they don't bring in other people who have neurodemyelinating disorders to raise the rate.

Here, what you're saying is 60 percent

concordance with a narrow autism disorder, but then you bring in the broader spectrum of related cognitive or social abnormalities. Isn't that a little unusual?

A It represents-- This would be similar... would be similar to a multiple sclerosis. There would be actually two different ways of doing that study. So, without referring to a specific study, let me talk about how one would get a very similar example to multiple sclerosis.

So, very commonly, in multiple sclerosis, you might have a very strict definition where you have to have two demyelinating events.

Q But you do.

A Pardon me?

Q That is the definition of MS.

A Okay. Perfect. So, if it requires two demyelinating --

Q -- demyelinating events.

A Thank you.

Q -- welcome -- separated by time and place.

A Then the reality is, yes, you will find an increase in people that have a single demyelinating event. You are talking about a spectrum. You are talking about whether you're applying, to some extent, a very rigid diagnostic approach.

Autism and autism spectrum are two different

things. Autism is actually, from the perspective of being practical in terms of people have a serious-- they have impairement. People with autism spectrum have impairment. It's not, oh, a little bit of autism just because you don't meet research diagnostic criteria.

We have about 160 people in this country and other countries who are having to struggle with, many of whom are actually doing quite well with -- I don't want everybody to think that this is something that you can't work with in some cases, and I don't want people not to be upbeat about wherever they are.

But the point is that when you go from one in 500 to one in 170, or you go to the perspective of saying, "Well, this is a social disorder, but you don't have any intimate relationships," that's a reasonable spectrumed account, yes.

This is completely different than in schizophrenia, where basically 50 percent do not have schizophrenic spectrum disorder. This is 90 percent having autism spectrum disorder. So that one in 25 that's doing just fine, in a sense, that's the 4 percent unaffected.

Now, let me get back to the point: The 90 percent genetic influence of autism uses the 60

percent number. If we use the 92 percent or the 96

percent number, heritability would go well into the high nineties. There is no point in that. It's strongly genetic. It's not purely genetic.

Q Strongly genetic but not purely genetic. There's environmental influences then.

A Well, we don't know what the other 8 percent is.

Q Eight percent. If you bring it up to 92 percent after bringing in all of the associated disorders.

A Ninety percent genetic, the other 8 percent is other.

Q Doctor, this is Respondent Exhibit P, Tab 4. It's the Bailey study: "Autism as a Strongly Genetic Disorder." He cited it in his report.

A Okay.

Q Okay. Just a few questions here, Doctor. We had discussed earlier the potential of a contributing factor from obstetrical environmental causes. Doctor, can you take a look at page 64 of this article, at the very bottom, the sentence starting with "Consequently," right-hand side?

A Yes.

Q Okay. It says: "Consequently, despite the evidence for strong genetic influences, both groups

implicated obstetric hazards as environmentally determined etiological factors in some pairs, possibly leading to an excess of autistic twins in the Scandinavian series."

Doctor, I read that statement, and I think to myself, okay, they have a susceptibility gene, and the obstetrical hazard that occurred environmentally affected the outcome.

A That would be incorrect. What they are saying here is that obstetrical hazards are accounting for why the concordance is not 100 percent.

Q I'm sorry. I missed that.

A In other words, in twins in general there are more obstetrical hazards, and so it is not always equal between the two identical twins. So, in some cases, there is much less fetal growth in one twin as opposed to the other, and what they are saying is that that accounts actually for the discordant twins.

So, basically, what they are talking about is an environmental influence. We're talking about this 8 percent. Much of that is related to obstetrical and prenatal events.

Q Okay. Then further on, that sentence says: "Gilbert has suggested that only the minority of cases that the family history of autism of Asperger's

syndrome represent a genetic form of the disorder, the majority being a consequence of obstetric hazards or medical disorders."

SPECIAL MASTER HASTINGS: Can you tell me where you were reading from there?

MS. CHIN-CAPLAN: I'm on the bottom of 64 to the top of 65.

SPECIAL MASTER HASTINGS: Which attachment was that?

MS. CHIN-CAPLAN: This is Respondent P, Tab 4, and I'm on page 64.

SPECIAL MASTER HASTINGS: And what's the name?

MS. CHIN-CAPLAN: This article is called "Autism as a Strongly Genetic Disorder: Evidence from a British Twin Study."

SPECIAL MASTER HASTINGS: It's Tab 5, not Tab 4?

MS. CHIN-CAPLAN: I'm sorry. Tab 5. It's a long day.

SPECIAL MASTER HASTINGS: Okay. And you're on 64 where?

MS. CHIN-CAPLAN: Into 65.

SPECIAL MASTER HASTINGS: Okay. Go ahead.

BY MS. CHIN-CAPLAN:

Q So I read that correctly, Doctor. Right?

A Yes. You read a citation of Bailey of a previous study by Gilbert.

Q Right. Does Gilbert say that Asperger's represents the genetic form of autism, and the rest are a consequence of obstetric hazards from medical disorders?

A Well, all I can do is tell you that this paper cites Gilbert to that effect. I don't have the Gilbert paper in front of me.

Q Okay.

A I have to point out that what Gilbert would be referring to, in terms of medical disorders, would include things that we would consider genetic but not inherited. This gets back to this previous discussion about what Art Beaudet said. So, under "medical disorders," he would be including things like tuberous sclerosis that are known to be genetic.

Q Then, Doctor, if you go on to page 67, and it talks about the follow-up of the original pairs, nine lines down, beginning with "None." It states: "None of the five monozygotic co-twins have been diagnosed as autistic in childhood, and only one had an autistic-like disorder." Have I read that correctly?

A Yes.

Q So it sounds like, Doctor, that simply because you are a monozygotic twin doesn't mean that you will necessarily come down with autism. Correct?

A Do you mean if one twin has autism, it is not 100 percent likely that the other monozygotic twin will have autism.

Q Correct.

A Correct. That's what I meant by saying it's a 60 percent risk.

Q Doctor, is your opinion that these are all gene-to-gene interactions? Is that it, the cause of the autism?

A No. Sometimes single genes, a very strong effect; gene interaction with genes; and also environmental contributions.

Q When you say "environmental contributions," what do you mean?

A I mean everything ranging from things like maternal age at birth is an environmental contribution. So the environment has to do with the fact that, frankly, the egg is older, and it's harder to maintain homeostasis in the egg. It seems to be that the paternal age has been implicated as an environmental factor.

These are both preconception environmental factors. It could range all the way up to whatever time in which you think there is an onset, but the point is that the number of potential environmental factors and their timing precedes conception.

Q So is it your opinion that you can never get a postpartum type of autism?

A Post-delivery?

Q Yes.

A No. There is a series of cases in Tanzania where it appeared that malaria contributed.

Q So infectious causes.

A Uh-huh.

Q How about anoxia, Doctor?

A The studies on anoxia have implicated much more motor skills impairment rather than autism.

Q So, Doctor, what if I told you that a child had had an MMR, suffered a seizure, became encephalopathic, and then developed autistic symptoms. Would that be implausible?

A You just told me something that occurred, and you're saying that somebody had an MMR vaccination, they had a seizure, they became encephalopathic, and then they had autism.

Q Uh-huh.

A Okay. You just told me something that happened. Could that happen? Yes. In fact, any time between 12 and 18 months, which we know to be a time of regression in autism, you could have also told me -- the whole point is you're wanting me to say, yes, there is some relationship with MMR vaccination. The point is, kids between 12 and 18 months are having vaccinations.

Now, the reason that I'm not going to acknowledge what you're asking -- in other words, there is a relationship between the MMR vaccination and what happened later -- is because that is the same logic that was used to blame mothers for causing autism because there is a mother, they take care of their child, and they develop autism. It's exactly the same logic.

Q Would it surprise you if this Court has awarded compensation under that very scenario?

A On what scenario?

Q On the very scenario that I just related to you.

A The scenario that you related to me. Would it surprise me? That's a tough question. I don't know enough about the Court and its history to answer one way or the other.

Q Fair enough. Doctor, are you aware that IOM held a meeting in April of this year on autism and the environment?

A I'm aware of a meeting, yes.

Q Did you attend?

A No, I did not.

Q Doctor, at this meeting, they were looking at potential environmental causes of autism, weren't they? One of those presentations was "How May Environmental Factors Impact Potential Molecular and Epigenetic Mechanisms?" and it was by, I think, Dr. Beaudet.

A I could imagine him giving that presentation. I did not attend, so if you want me to comment on this --

MS. CHIN-CAPLAN: Petitioners' Exhibit 76.

SPECIAL MASTER HASTINGS: Okay. Thank you.

MS. CHIN-CAPLAN: You're welcome.

BY MS. CHIN-CAPLAN:

Q How about this one? "Environmental Epidemiologic --"

SPECIAL MASTER HASTINGS: What are you reading from? Are you reading from that Exhibit 76?

MS. CHIN-CAPLAN: Yes. It was all bound together.

THE WITNESS: If I'm going to be asked about Professor Beaudet's presentation, I would like to comment on the presentation and see it.

MR. MATANOSKI: Actually, there was no question.

SPECIAL MASTER HASTINGS: Right. I don't think there has been any question yet, so you'll have to wait until you get a question.

You're going to start to read from Exhibit 76.

MS. CHIN-CAPLAN: Correct.

SPECIAL MASTER HASTINGS: Could you tell me what page number it is?

MS. CHIN-CAPLAN: They were presentations.

SPECIAL MASTER HASTINGS: There's no tabs in Exhibit 76.

MS. CHIN-CAPLAN: They were all presentations by different individuals at the IOM conference.

SPECIAL MASTER HASTINGS: I see pages. I'm looking at Exhibit 76. Do you have it in front of you, Mr. Shoemaker? I can't believe I got to it faster than you did. But it's got page numbers on it, the electronic version that you folks filed, so it does have page numbers.

MR. SHOEMAKER: I have it broken out by the presentation of all of the different tabs.

MS. CHIN-CAPLAN: We did not number them, Special Master.

SPECIAL MASTER HASTINGS: So you don't have the copy that you filed.

MR. SHOEMAKER: Not of the whole thing put together. I just have the presentation and the various tabs.

SPECIAL MASTER HASTINGS: Okay. How long of a document is it? Okay. The presentation; who is it by?

MS. CHIN-CAPLAN: This one is by Irva Hertz Piccioto --

SPECIAL MASTER HASTINGS: Okay.

MS. CHIN-CAPLAN: -- and it's entitled "Environmental Epidemiology Studies: New Techniques and Technologies To Find Environmental Triggers."

MS. PATTON: We don't have a copy of that with us. We don't have every one of the exhibits you filed in the courtroom here.

MS. CHIN-CAPLAN: This is the only one I have. I'll be glad to show it to you.

MS. PATTON: If you're going to ask Doctor --

MS. CHIN-CAPLAN: I'm not going to ask him any questions, no. I'm just asking him if --

SPECIAL MASTER HASTINGS: Go ahead. Ask him a question.

MR. MATANOSKI: Wait. Just a minute, Your Honor. You're not going to ask him any questions?

MS. CHIN-CAPLAN: I'm asking him if this is what was presented at IOM.

MR. MATANOSKI: He said he wasn't there. How can he even be asked to answer the question?

MS. CHIN-CAPLAN: Well, let me ask this question.

MR. SHOEMAKER: I'm sorry. Which presentation was that? I found a list of the letters of the presentations.

SPECIAL MASTER HASTINGS: Yes. Hertz Piccioto.

MR. SHOEMAKER: That's Tab I.

SPECIAL MASTER HASTINGS: Yes.

MR. SHOEMAKER: I'll bring it up.

SPECIAL MASTER HASTINGS: What question are you going to ask him?

BY MS. CHIN-CAPLAN:

Q Doctor, let me ask you this question. You didn't attend the conference. Is that true?

A That's correct.

Q And the topic of that was environmental causes of autism. Isn't that true?

A My recollection is something -- I don't know that that's the exact title, but I know there was a meeting about that.

Q So would it be fair to state that there is a number of people who disagree with you that autism is a purely genetic disorder?

A I never said that autism was a purely genetic disorder. I said it was a strongly genetic disorder.

Q And is it influenced by environmental factors?

A It is likely to be influenced by environmental factors. The challenging thing, in terms of studying environmental factors in autism, is because the effect is relatively weak, so the epidemiological studies that have been done have had difficulty in confirming factors that have come up.

Q Thank you. Doctor, would you agree that the rate of autism has increased within the past 20 years or so?

A The measured prevalence of autism increased. The real rate of autism has not been confirmed to

increase, to my belief.

Q So, in your mind, it has not increased. Is that what you're saying?

A The measured prevalence has increased, but no one has demonstrated that there has been a real increase other than by changing and definition and particularly by changing in ascertainment of the rate.

Q So if you assume that there was an epidemic, would it be fair to state that you don't get an epidemic from genetic causes within one generation?

A Well, the first thing is we have to think about what we consider an epidemic, and if, by "epidemic," we mean something that is much more important and common than previously assumed to be, then autism is an epidemic.

If you are asking, is autism related to an increase in rate, I do not believe that that has been shown to be a real increase in rate, and I have much personal experience as to the spurious nature of that increase. Again, it's an epidemic from the sense of it's much more important than previously recognized.

The families that I have been treating, many of whom were not able to get a diagnosis before I saw them because we did not have the careful research diagnostic criteria, and, frankly, in Chicago, we had

a logical fallacy where the two major places that would have diagnosed autism, one of them said, Oh, you have an intellectual disability; you don't have autism; you have intellectual disability. Then if they would see somebody with autism who didn't have intellectual disability, they would say, Well, you can't have autism because you don't have intellectual disability.

That is not a systematic approach to diagnosis, so I'm not willing to grant the assumption that there is an epidemic in the sense of a real increase in prevalence.

In addition, Illinois is often cited as having an increase in cases in the educational system, and I was involved in a task force in 1986 that allowed children in Illinois to be classified as having autism. So, of course, it went up 14,000 percent because you couldn't have autism in Illinois in the school district until we changed that in 1986.

Q Doctor, you wrote an article, or you're one of the co-authors of an article, about maternal smoking during pregnancy and severe antisocial behavior in offspring.

A Yes.

Q It was a review.

A It's a review article.

Q Doctor, based on your review of the literature -- is that it? -- your conclusion was, "Existing evidence provides consistent support for, but not proof of, an etiologic role for prenatal smoking in the onset of antisocial behavior." That was your conclusion, wasn't it?

A Yes.

Q And that was just based on a review of the literature.

A The conclusion was based on research studies that had carefully demonstrated that. And I'm continuing to collaborate with my colleague, Dr. Lauren Wakschlag, on careful studies to further make sure -- in this case, it's very interesting -- to make sure that that is an environmental influence and not something that's subtlely influenced by genetics instead of environment.

Q Okay. Doctor, just one last --

SPECIAL MASTER HASTINGS: Before you move on, what were you just reading from?

MS. CHIN-CAPLAN: Some research that we had done.

SPECIAL MASTER HASTINGS: Okay. Nothing that's in the record?

MS. CHIN-CAPLAN: Nothing that's in the record.

SPECIAL MASTER HASTINGS: All right.

BY MS. CHIN-CAPLAN:

Q Doctor, just one last question. If somebody had an inherited immune deficiency and was asymptomatic and received a vaccine and the immune deficiency flared, in your opinion, would the vaccine be an environmental trigger of the flaring of that disorder?

A Well, the situation that you're asking me about is implausible in the sense that if somebody has an immune deficiency, they would have been exposed to many environmental agents before the time of vaccination, and one would have expected symptoms before that. So, no, the idea... of it triggering the onset of the disorder would not make sense.

Q And you weren't here for Dr. Kennedy's presentation, were you?

A No, I wasn't. Sorry.

MS. CHIN-CAPLAN: Thank you, Doctor.

SPECIAL MASTER HASTINGS: You're done, Ms. Chin-Caplan?

MS. CHIN-CAPLAN: I am, Special Master.

SPECIAL MASTER HASTINGS: Any questions for

this witness? Go for it.

SPECIAL MASTER VOWELL: Doctor Cook, in your report, you use the analogy of-- looking down the road. Well, to continue that analogy, certain things turn those lights green or red. It may be a car parked at an intersection, triggering a sensor. It might be speeding vehicles. It might be timers. Can environmental things trigger a gene expression?

THE WITNESS: Environmental events can trigger changes in gene expression, yes. Your analogies would all be true. All of the same ways in which those lights might be turned on and off --

SPECIAL MASTER VOWELL: So the timer would be Huntington's.

THE WITNESS: Huntington's would be the timer analogy. It also could be, as you say, cars passing sensors, would be more the example of something perhaps in the environment changing. I'm sorry.

To follow up, actually, I think a lot of that signaling has to do with another concept of environment in development of the brain, is that the environment of each cell is changing as that cell may be migrating through the brain as it may be shifting

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from the environment of the less-mature brain to a more mature brain, is also helping turn on and off.

SPECIAL MASTER VOWELL: One of the Petitioners' expert witnesses referred to an article by Herbert, which is at Exhibit 61, Tab FF, Martha Herbert in Clinical Neuropsychiatry: "Autism: A Brain Disorder or a Disorder That Affects the Brain?" is the title. Are you familiar with this article, Doctor?

THE WITNESS: Just in passing, more having heard it cited.

SPECIAL MASTER VOWELL: Do you have any comments on it? Her approach seems to be that there are environmental factors in this strongly genetic disease or syndrome.

THE WITNESS: I thought it was a comprehensive review, in looking at all potential possibilities. So I think she was putting, side by side, the chance of probably even a more pure genetic causation than we have, side by side with some alternative interaction concepts. So in this context review article, I think it's good to think about all possibilities.

If you look at the possibilities represented in a couple of tables from that -- let me see if I

can. If you look at Table 1 on page 356, two disease models, we can find quite a few manifestations, in a sense, of different models, and I think actually the model of strongly genetic, brain-based -- both of the models are extremely complex. I must say, when you come up with complex possibilities to explain autism, you're getting close to what's happening. If this was simple, we would be a lot further along to understanding it.

The one thing that's good here is, if you read this, it's hard to -- I've heard this article quoted quite a bit as just having one idea being posited from it, but it's incredibly complex, and, again, we are dealing with a complex developmental neurobiological syndrome.

SPECIAL MASTER HASTINGS: Anything further? Do you have any questions?

Any redirect for this witness?

MR. MATANOSKI: I just have one question.

SPECIAL MASTER HASTINGS: Go for it.

REDIRECT EXAMINATION

BY MS PATTON:

Q Dr. Cook, in the early part of the cross, Petitioners' counsel seems to imply with the questions that you're running a little behind schedule in

finding the genes that cause autism. How many areas are there on the human genome?

A I'm sorry. How many areas?

Q How many genes are involved?

A I guess it just got reset to 20,000 genes, and the one thing I didn't point out is that we're quite excited. What's happened in the study of genes is that some of the things that we were doing that might take us another five years are rapidly changing now that there are whole genome associations, and we're eagerly anticipating the results of those first whole genome association studies in autism. It will be similar to other disorders that have been hard to pin down the genetic variants and have led to a plethora of publications in Science and Nature recently on disorders like diabetes.

So we now have tools to not do linkage and then spend 10 years following up but to look at a million markers in the genome to be able to pinpoint almost all of the genetic variation in one experiment.

Ms. Patton: Thank you.

SPECIAL MASTER HASTINGS: Anything further?

MS. CHIN-CAPLAN: No, Special Master.

SPECIAL MASTER HASTINGS: All right. Thank you, Dr. Cook. We appreciate your testimony.

(Witness excused.)

SPECIAL MASTER HASTINGS: With that, we're done for the day, and we'll start at 9 a.m. tomorrow with Dr. Wiznitzer's testimony. Is that right, Mr. Matanoski? Dr. Wiznitzer tomorrow?

MR. MATANOSKI: Yes, sir.

SPECIAL MASTER HASTINGS: And that will be the only witness for tomorrow.

MR. MATANOSKI: That's correct, sir.

SPECIAL MASTER HASTINGS: All right. At 9 a.m. tomorrow, we'll start. We're adjourned today.

(Whereupon, at 6:37 p.m., the hearing in the above-entitled matter was adjourned, to be reconvened 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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