UNITED STATES
COURT OF FEDERAL CLAIMS

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

Pages: 3231 through 3429/3530

Place: Washington, D.C.

Date: May 27, 2008

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

Tuesday,
May 27, 2008

The parties met, pursuant to notice of the Court, at 9:05 a.m.

BEFORE: HONORABLE PATRICIA CAMPBELL-SMITH
HONORABLE GEORGE HASTINGS
HONORABLE DENISE VOWELL
Special Masters

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C O N T E N T S

WITNESSES:	DIRECT	CROSS	REDIRECT	RECROSS	VOIR DIRE
For the Respondent:					
Michael L. Rutter	3236	3322	3413	3422	--
	--	3376	--	--	--

E X H I B I T S

PETITIONERS' EXHIBITS:	IDENTIFIED	RECEIVED	DESCRIPTION
8	3328	--	Paper by Rutter, Autism and Known Medical Conditions: Myth and Substance
9	3340	--	NIH grant, Minocycline to Treat Childhood Regressive Autism
10	3411	--	Paper by Rutter on MMR

P R O C E E D I N G S

(9:05 a.m.)

SPECIAL MASTER CAMPBELL-SMITH: Good morning. Please be seated. We are back on the record for our third week as part of the second theory of the Omnibus Autism Proceeding to continue with Respondent's case.

Respondent to call your next witness. I will observe briefly based on some preliminary discussions, and perhaps, Respondent, you would care to share the schedule adjustments for today.

MR. MATANOSKI: Yes, ma'am. The adjustment would be that the United States is not calling Dr. Casanova because of some difficulties in getting here, for example, but we will proceed on.

The United States will now call Professor Sir Michael Rutter to the stand.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

Sir Rutter, would you raise your right hand, please.

Whereupon,

MICHAEL L. RUTTER

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

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

DIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Good morning, Dr. Rutter.

A Good morning.

Q Would you please state your name for the record?

A Michael Llewellyn Rutter.

Q And please describe your current appointment.

A I'm Professor of Developmental Psychopathology at the Institute of Psychiatry, Kings College, London.

Q Dr. Rutter, would you please briefly describe your educational background?

A Okay. I trained in general internal medicine at first, at the Wilson (phonetics) Neurology and Pediatrics before moving on to training in psychiatry and then in child psychiatry.

Q Do you have a medical degree?

A I have a medical degree in 1955.

Q Okay. Do you have the equivalent of a Ph.D.?

A Yes. In England, at the University of Birmingham M.D. is the equivalent, so I took an M.D. by thesis, which I got in 1962.

Q Your CV states that you have an FRC in psychology. What is that? In 1971. What is that acronym?

A An FRC in psychology?

Q It says FRC Psych.

A Oh, FRC Psych.

Q I'm sorry.

A It's the equivalent of boards in psychiatry.

Q Okay.

A England does it by these strange mixtures of letters.

Q So do you hold what we would consider to be board certification?

A Yes. I have board certification in internal medicine and psychiatry.

Q And do you have what we would consider to be licenses?

A Yes.

Q Okay. Is that the same thing?

A Which is the same thing.

Q Would you please briefly describe your medical and clinical training?

A Okay. My medical training was initially in terms of training at the University of Birmingham, and then I went after that to various places, including

the Heart Hospital where I was in cardiology before moving into psychiatry.

I trained then at the Maudsley Hospital, and then I had a year in the United States where I came in the Department of Pediatrics out at Einstein College of Medicine, and then I returned to a research position.

Q Do you also have training in neuroanatomy and neuropsychology?

A Yes. That would have been as part of the training in psychiatry at that time and also included a substantial amount of training in psychology so that I do actually have certification in psychology as well.

Q And when did you begin your work in child psychiatry?

A Basically I suppose about 1959, 1960.

Q And what made you go into child psychiatry?

A That's an interesting question. In those days the boss, i.e. the director, had a lot of power, and he decided that's what I should do.

I was initially actually a bit reluctant, but I said I'd give it a go. I became hooked, became very much committed to child psychiatry and have remained so at the same, but it wasn't my initial

choice.

Q Would you please briefly discuss your academic employment history and other professional appointments that you've held?

A Okay. Moving on from the sort of training type appointments, I was appointed initially at the Institute of Psychiatry in the Maudsley Hospital as a senior lecturer in 1966 and then went on to a redisposition, which is equivalent to associate professor, and then full professor in 1973.

I've had a consultant appointment in the National Health Service since 1966, and I still hold that.

Q And what is the National Health Service?

A That's the state medical system. Then in 1984 I set up the Medical Research Council Child Psychiatry Unit and was honorary director there until 1998 and then set up the Medical Research Council Social, Genetic and Development Psychiatry Center in 1994 again until 1998.

Since 1998 I've had what is in effect a research chair, although I continue to do both clinical work and teaching.

Q And what is the Medical Research Council?

A It's equivalent of NIH.

Q Now, your CV also lists external appointments. Would you please discuss a few of those?

A By the external appointments do you mean like being clinical vice president of the Academy of Medical Sciences, which covers the whole of biomedicine?

I've been a trustee of the Nuffield Foundation, which is looking at the interface between science and policy, and really quite a range of other organizations. I'm on advisory committees around the world dealing with various research enterprises.

Q Now would you please highlight some of your personal achievements inside child psychiatry generally over the course of the past 40 years of your practice?

A Well, I suppose the overriding thing is a concern to integrate science with clinical issues so that I've always been concerned to try not just to be involved in science and clinical work, but to integrate them in a meaningful sort of way.

The research that I've done has covered quite varied things, so we undertook the first systematic epidemiological study out of Wight and then in London looking at mental disorders in children and

young people.

We did the first study looking at what is now called co-morbidity, i.e. the co-occurrence of apparently different disorders, both in a range of longitudinal studies of both general population samples and high risk groups of one kind or another.

I've been involved in genetic studies, but initially quantitative genetic studies, i.e., twin and adoptee studies, and then more recently in the last decade or so with molecular genetics as well, plus other odds and ends, including I should say one of the first systematic study looking at the relationship between neurological disorders in children and psychiatric problems.

Q Now with regard to your work in autism specifically, could you please highlight some of your personal accomplishments in that field over the last 40 years?

A Okay. Again there are many. So that the longitudinal study that I did in the 1960s was the first study to show that children who had not had any detectible neurological abnormalities when young nevertheless showed a high rate of development of epileptic seizures during adolescence and early adult life. So that was the first evidence really of

thinking that we were dealing with some kind of organic disorder, neurodevelopmental disorder.

We're also involved in development of methods of measurement, the diagnosis based on parental, the ADIR with colleagues in this country and elsewhere and the methods of observation of children, the so-called ADOS, again with colleagues in this country and elsewhere.

We had a prolonged period of looking in some detail at cognitive functioning in autistic individuals because at that time there was a concern that these were motivational problems and so we set out experimentally to test some of those notions, the genetic studies, so we did the first systematic twin study of autism back in the '70s and the first systematic family study a little bit after that in parallel with a similar study by Susan Folstein and her colleagues at Johns Hopkins, so amongst other things.

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

A Yes, I was and also the ICD-10 at that time, so that was a time period in which steps were taken by both these organizations to try and bring the two classifications closer together, so I was involved in

both, but also in the bridging operation.

Q Now would you please briefly discuss your clinical experience with regard to the diagnosis and treatment of autism and other autism spectrum disorders over the past 40 years?

A Well, that goes back to the early '60s, and I've been involved with that ever since. The amount of clinical work I do in relation to autism has been less in recent years, but I continue to see more complicated cases mainly in adults, but raise issues that people want my advice on.

I used to be involved quite heavily in the treatments of autistic individuals, but during the last decade my work has been much more of an advisory capacity.

Q Approximately how many children would you say you've diagnosed with autism over the course of your career?

A Many hundreds.

Q And did you follow them into adolescence as part of your career?

A Yes, indeed. We have done that as part of clinical practice, but also we have done actually two major systematic follow-up studies going not only into adolescence, but also into adult life.

Q You mentioned that you still have somewhat of a clinical practice. Do you follow adults with autism?

A That's involved with autism, but also another study I've been involved with is looking at the psychological outcomes of children adopted from very deprived, depriving Romanian institutions into generally well-functioning adoptive homes in the U.K. We have been following those from age four most recently to age 15.

They have thrown up a number of clinical problems and so I've been available. Again, because they're scattered all over the U.K. and to some extent the rest of the world now because some of immigrated, my job is advisory rather than taking on the individual treatment.

Q Do you still have a research practice?

A Very much so.

Q And could you please describe what your research practice entails?

A I guess what is most distinctive about my research is that I tend to have an integrated approach across different strategies, so I'm involved in quantitative genetic studies, twin and adoptee studies. I'm involved in molecular genetic studies of

autism.

I'm involved particularly in looking at genetic environmental interplay with respect to gene/environment interactions, but also other forms of interplay. I'm involved in long-term longitudinal studies so that we have recently followed up into middle age the children that we saw in the Isle of Wight in the 1960s.

Q Now, according to your curriculum vitae you have published over 400 scientific articles pertaining to child psychiatry and development. Is that correct?

A Something of that order.

Q And are they all peer reviewed?

A Yes.

Q And according to your CV, you have written over 200 book chapters related to child psychiatry. Is that correct?

A That is correct.

Q And you've authored 40 books pertaining to child psychiatry and genetics as it impacts on the issues of child psychiatry? Is that correct?

A Yes. Actually a bit more than that now.

Q Do you have some manuscripts of books in press?

A Yes, I do.

Q And do a substantial number of your publications pertain to autism spectrum disorders?

A Yes. I've never counted them up, but quite a lot do because that's been a major research interest, as well as a major clinical interest.

Q Now, your CV also indicates that you've served on numerous editorial boards for psychiatry and development-related scientific journals. Is that accurate?

A Yes.

Q Could you please highlight a few of those?

A In the children's field, *The Journal of Child Psychology and Psychiatry and Allied Disciplines* would be one which is one of the higher impact journals in the field, the *British Journal of Psychiatry*, *Psychological Medicine*, a range of different journals as well as more specialized journals such as *Autism*, so quite a range.

Q Now, earlier in your testimony you referred to your previous academic appointments and employment history. Could you briefly discuss your former and your current teaching responsibilities?

A Okay. It's all now at the postgraduate level so that I run a course primarily geared on people from the Third World training in child

psychiatry. This is an interdisciplinary group of pediatricians, psychologists, psychiatrists. So it's a one-year course, and that covers a range of different issues.

I also do a course on social development, which amongst other things deals with gene/environment interaction and also the use of natural experiments to test causal inferences on environmental causes of disease which I did this last year. That's the Ph.D. students taking a special four-year program which spans basically clinical at the Institute of Psychiatry.

Q How long have you been teaching?

A Since I started in the field half a century ago.

Q Do you also give lectures to professional groups or organizations?

A Yes, both nationally and internationally.

Q On what topics?

A Reflecting my wide range of interests on all sorts of things, so most recently a series on ADHD in Oslo, a series in New Zealand last year on gene/environment interaction, a series recently on autism. A great mixture.

Q Now, as indicated on your CV you've received

numerous awards and extensive international recognition for your work in child psychiatry and autistic spectrum disorders. Would you just highlight a few of those honors and awards that are most meaningful to you?

A The most prestigious probably is the election to the British Royal Society, which is the equivalent to the National Academy of Sciences in the U.S., where I was elected in 1987. I was also elected to the Institute of Medicine in 1988 I think it was.

I've got the Helmut Horton prize, which is one of the big prizes in medicine, for my work on autism back 15 years ago. I don't remember which year. I've had the NARSAD award, the Luvain award. I've got quite a range of those.

Q Your CV states that you're a founding member of Academia Europaea. What is that?

A That is a bringing together across the whole of Europe of the academies both of science, but also the academies in humanities and social sciences.

Q It also states that in 1992 you were honored as a Knight Baronet for your work in the field of child psychiatry. Would you please describe what that honor is?

A That's a strange British thing that is given

for people who have contributed beyond their posts, i.e. it's not given for holding particular jobs, but in terms of making major contributions, in my case in both medicine and education actually.

Q Now, your curriculum vitae has been filed as Respondent's Exhibit HH in this litigation. Is Respondent's Exhibit HH an accurate summary and description of your education, qualifications and publications?

A Yes, it is.

Q Doctor, in your report you stated that four years ago you agreed to serve as an expert witness with respect to thimerosal litigation. Would you please describe what you're referring to?

A Yes. That was litigation actually in the United States, and I as part of that did a partial incomplete report, but the litigation was put on hold or abandoned -- I don't know which -- so that I never actually completed that report, and it never of course appeared in final form.

Q And you also reference that you were involved in the MMR litigation in the United Kingdom. Could you describe your involvement in that litigation?

A Very similar. That I had agreed to give

evidence as an expert witness, but the trial was abandoned and my report was never completed or filed.

Q Doctor, I'd like to turn now to a discussion of the nature of autistic spectrum disorder. What is meant by the term autism or autistic spectrum disorder?

A Okay. It's a term that goes back to 1943 when Leo Kanner at Johns Hopkins described a series of 11 children with patterns that seemed distinctly unusual and differentiated them from other disorders and where the characteristics would now be considered particularly in relation to three domains of functioning:

Firstly, in terms of problems with social reciprocity; secondly, problems in terms of social communication; and, thirdly, unusual circumscribed interests and repetitive patterns of behavior. It's the occurrence of those three plus the fact that the origin is in early life, which are the distinctive features.

Q Now, in your report you used the term qualitative to describe the three domains. What is meant by the term qualitative?

A It means that it wasn't just that the children are delayed in these functionings, but that

the quality was unusual in children of any age. It's abnormality in type, not just in degree or timing.

Q Could you please describe what you mean by qualitative abnormality in reciprocal social interaction?

A Okay. Even young babies, those are a kind of to and fro quality. It's one of the fun things about babies that you smile at them. They gurgle back again. There's a to and fro.

As children grow older of course that becomes more complex, but it is essentially reciprocity in the sense of responding to the other person. It's not doing a particular form of behavior. It is an interplay, and it's an interplay that develops over time.

So that's the particular feature which is so strikingly human and so strikingly impaired in individuals with autism.

Q And would you please explain what you mean by qualitative impairment in communication as one of the domains?

A The same sort of issue that it's not just that children with autism are delayed in speaking, although they usually are, but that they fail to use language in a communicative way so that they may talk,

but they don't converse.

Let me move ahead to an older age group. The thing about conversation in middle childhood or in adult life is not just that you produce a set of words, but you're talking with the other person. You're responding to them. What they say influences what you say. What you say influences what they say. There's a to and fro.

It's that kind of communicative interchange that is the thing that is most strikingly impaired in autism. In addition, they have a variety of atypical features of various kinds like reversing pronouns and so on, but it's the nonsocial that's the most characteristic.

Q And the third domain? Would you please explain what you mean by restricted, repetitive and stereotyped behavior, interests and activities?

A Yes. This is something that both Leo Kanner and his paper in '43 but also Asperger in his somewhat comparable paper in '44 emphasized.

They were not talking about sort of funny movements, although some individuals with autism have funny movements, but rather than they are of a tiny, particular kind so that one child I had would not turn right. If you wanted him to turn right at the

crossroads he had to go left and left and left until he got going in the right direction.

Another children was preoccupied with drains, knew a vast amount of drains and whenever visited somebody's home looked carefully at their drain system and how it worked.

So circumscribed, focused stereotype, but often quite complex so that these are not just simple, repetitive movements. These are things that are a much more complex kind.

Q And when do these symptoms typically become manifest in an autistic child?

A The social and communicative tend to be much earlier than the repetitive stereotype behavior. The repetitive stereotype behaviors can be evident in the preschool years, but it's during the later preschool years that they tend to become more obvious.

Q So by definition do they have to become manifest before the age of three?

A Some aspect of the autistic features have to be evident by three by the standard classification criteria, yes.

Q You touched on this earlier, but do clinicians have a method for diagnosing and assessing autism spectrum disorders?

A Yes. The instruments I described -- the ADIR and the ADOS -- have become pretty standard as research instruments, but the principles of those have been much more widely employed clinically as well.

In some specialized clinics they would actually use these instruments, but even where they don't do that they would follow the principles in a more modified way, depending on the time and resources available to them.

Q Doctor, what disorders comprise the autism spectrum?

A These are a range of disorders where the qualities are very similar to the kind that I've just described, but which in essence vary in their severity.

So-called Asperger's Syndrome is an example where the overall delay in language functioning is not found, although the social and communicative qualitative abnormalities are, so that would be one example.

Whether that is distinctively different from higher functioning autism or not remains uncertain, but that would be a key feature. It would include a range of other less specific syndromes which tend to get lumped together under atypical or pervasive

developmental disorders not otherwise specified.

In the existing classification systems, Rett Syndrome is also usually included there, but virtually all clinicians would actually see that as rather different. That is not really a variety of autism. It's just that in the early stages it can be modeled with it, so it's a range that mainly varies in severity.

Q Is Child Disintegrative Disorder among the spectrum disorders?

A Yes, that would be one. This is a condition first described a very long time ago in which children after apparently normal development show a profound loss of skills, profound disintegration of functioning and later on look very much like a severely handicapped individual with autism.

It's been subjected to much less research, and again it's unclear whether it's a variant of autism or simply something that may be confused with it, but you're right. That would also be included in the autism spectrum. It obviously is at the more severe end.

Q Will the disorder of autism in an individual persist as he or she ages?

A Yes. Quite a number of long-term follow-up

studies from Kanner himself to much more recent investigators such as ourselves have shown that on the whole although there are changes and the young people may sometimes become independent, able to hold down a job, but the kind of qualitative abnormalities do persist.

There are some individuals, a quite small proportion, who appear to recover completely, but they are a minority.

Q Does the condition improve in some individuals rather than --

A Yes. Oh, yes.

Q Is autism associated with mental retardation or intellectual disability?

A Yes, it is. That was observed again early on and has been confirmed many times since.

There was a time when people assumed that that was usual, and one of the things that has emerged out of both the genetic research and the epidemiological research is that autism can occur in individuals of normal intelligence, as well as those who are intellectually disabled, and that is what has led to a broadening of the diagnostic concept.

Q Now, you touched on Leo Kanner back in 1943. So autism is not a relatively new disorder, is it?

A No. There have been quite a few studies done looking back at case records or reports of one kind or another of individuals before 1943, and it's quite clear that once people knew what to look for it had occurred at an earlier point in time.

It didn't suddenly begin in 1943. It's just that Kanner was the first man to have the astute observations to recognize these were different than other problems.

Q Now, earlier you said that you did one of the first systematic comparative studies of autistic symptoms compared with other forms of mental disorders. Could you explain what you mean by that?

A Yes. At that time there were various comparisons between autism and normally developing children, but it seemed to me that that actually wasn't the real issue. The hall porter could probably do that without a diagnostic assessment. The real question was whether autism differed from other developmental and psychiatric disorders.

So we took a group of children from the Maudsley Hospital Clinic who had autism, although in those days it was called an infantile psychosis, but that amounts to the same thing nowadays, and a group who were matched for their intellectual level and

their sex who attended the same clinic, and we followed both of those over time.

And so it was that study which, amongst other things, showed this unusual picture of epileptic seizures developing late. Ordinarily in the general population all individuals with intellectual disability, what used to be called mental retardation, develop their seizures early, so early childhood is the typical time.

So it wasn't that the rate of seizures was strikingly raised, but that they began at a very unusual time, later adolescence. They do occur at other times as well, but that was the peak period.

Q Now, in your report you refer to the distinctiveness of autism as compared with other forms of mental disorders. Could you please describe what you mean by that?

A Yes. A whole lot of research has shown that it's not just in the symptom pattern that individuals with autism are different, but there are all sorts of other ways.

For example, the early studies that we did during the 1960s and the experimental studies by people like Byata Hamlin and Neil O'Connor showed that the particular pattern of cognitive skills was quite

different in autism as compared with other groups.

The fact that the head circumference of children with autism was raised has been shown initially by studies measuring head circumference using a tape measure and more recently with structural brain imaging, and what is characteristic is that the head circumference and the brain size is roughly normal at birth, but increases during the preschool years, whereas in individuals with intellectual disability, mental retardation, their heads tend to be smaller rather than larger. That's something that came out of a study, for example, that Eric Fombonne did.

Q Now, at what age do a child's parents typically begin recognizing developmental problems in their children that turn out to be autistic?

A Typically around about 18 to 24 months. It varies. Of course, it does vary, as one might expect, to whether they had had an earlier child with autism or whether there are other autistic children whom they knew, but the recognition is usually around and about that age period.

With Asperger's Syndrome, because of the lack of overall language delay it tends to be a bit later.

Q And what are the first symptoms that are typically recognized by parents?

A Quite varied. The communication problems and the lack of social reciprocity are often the first things to be picked up, but it can be quite a range of different things.

Often, as is typical with developmental disorders, parents are first aware this child isn't behaving in a way that seems right so that they find it difficult to put their finger on it, but they have recognized there's something unusual in the way the children are behaving. They are picking up the social and communicative abnormalities as a rule.

Q Now, in your report you state that subtle social abnormalities are evident in many cases at 12 months of age, but study findings do not indicate that an autism diagnosis can readily be made at that time on the basis of ordinarily clinical assessment. Could you please explain what you mean by that?

A Yes. There have been a number of studies which have tried to look at whether even though the parents may not have recognized it at the time there were subtle features that were evident at an earlier point.

The two main ways this has been done has

been from home videos, the films that many families take at birthday parties and family gatherings, looking at whether you can see abnormalities at that time.

More recently there have been so-called baby sibs studies which is taking families in which there is one child with autism and following the other children, the rationality being that the genetic studies suggest that a proportion -- five to 10 percent -- will develop an autism spectrum disorder, and therefore by assessing them at different ages throughout these early years you can see when the abnormalities appear.

What the results show is that if you're looking at it at a group level -- that's to say you're taking a group with autism and a group of normally developing children -- there's very little to show before the age of 12 months, but at 12 months you can find some differences, not in all children, which differentiate the groups.

But when this has been done by experienced clinicians who were looking at the videotapes but not as it were during all the complicated measures they actually don't do better than charts, so what the evidence suggests is that there are earlier

manifestations, but they're incredibly difficult to pick up and at an individual diagnostic level they are too varied to be of a great deal of use.

Now, they have been very useful in one sort of way. That's to say if on looking at these videos you see indications of behavior that is clearly abnormal that is reasonably good evidence that there were abnormalities present at that time.

It's less satisfactory the opposite way around because the videos are of course taken to illustrate forever a happy occasion so they're not designed to focus, so the fact that you don't see abnormalities is much less useful than if you definitely do.

Sorry. That's rather a long answer, but it is complicated.

Q That's fine. That brings me to my next point. In his report on page 5, Dr. Kinsbourne states that the majority of autistic children exhibit some level of autistic behavior in the first year of life. Do you agree with his statement?

A No.

Q For the reasons that you've just articulated?

A For the reasons that I've just given.

Q Okay. Is a review of pediatric records during the first year of life a reliable measure of entirely normal development?

A No. That's true both of the records that I've seen in the U.K. and in the U.S. The reason of course is that those making the records at the time aren't focusing on the possibility that somebody may later want to know whether there were signs of autism at that time.

So they're not bad in terms of clear-cut abnormalities, so that if the record states the child is not yet walking independently that's probably valid. If the record says child seems socially okay that's not much help because you have no idea what they looked at. You have no idea what is meant by that.

So again a bit like the videotapes. If there's a clear-cut description of something that is manifestly abnormal then that's quite reasonable evidence. The fact that it's not mentioned other than in a very general way, even not mentioned at all, doesn't help.

Q Now, in your report you say there are many variations in the manifestation of autistic spectrum disorders. Could you explain what you mean by that?

A Yes. One of the characteristics not just of autism, but of almost all medical conditions, is how varied they are.

So let me illustrate that by referring to one monozygotic identical twin pair that was part of the study that Susan Folstein and I did. They are both autistic and they have various things in common, but at an IQ level they're 50 points apart so one is functioning in the normal range; one is in the intellectual disabled/retarded range. If you look at the details of the symptomatology you would see similar variations of this kind.

Q Is this evidence that there are environmental risk factors at work to explain the variance?

A Not at all. So that, for example, if one takes a condition like tuberous sclerosis, which is a mendelian condition -- that's to say due entirely to genetic factors, not environmental conditions -- some individuals show minor skin abnormalities that require an expert to detect them. Others have large tubers in the brain which are associated with mental deficiencies, severe intellectual disability and epilepsy.

So here we have a condition that has no

evidence of environmental factors playing a role, but with a similar degree of variation, and that would be true generally. I mean, that's nothing very special to autism.

Q Are there any known medical causes of autism?

A Yes, there are. So that tuberous sclerosis is associated with a much increased rate of autism. The Fragile X anomaly is associated with a small proportion of cases. So there are a number that play a part in causation.

I deliberately put it play a part in causation because it is quite difficult to know whether this fully accounts for the disorder or not, so to come back to tuberous sclerosis, yes, there is quite a strong association.

There's every reason to support it's part of the cause of the process, but there's also evidence that the risk goes up according to where in the brain the tubers, meaning tumors, are found and whether there is associated intellectual retardation.

So that it's not clear whether it's the genes are interconnected or the parts of the brain that are involved bringing it together, but, yes, there are some. The estimates of the proportions of

cases due to diagnosable medical conditions vary, but it would be somewhere around the 10 to 15 percent level.

Q Now, in your report you mention that there have been case reports of individual cases of herpes encephalitis that give rise to autistic-like features. Are those case reports evidence of a postnatal cause of autism disorder?

A They have been claimed as such, and I included them in my report really out of fairness because of those claims.

If you read carefully the reports, they're not actually terribly convincing that this is autism as we understand it, and of course because there are some autistic features of a kind that are parallel they are utterly different in the cause, the age of onset, I mean all sorts of other features, and they are rare. There are isolated, rare reports, so I don't find those actually very convincing.

Q Now, in your report you state that rarely brain abnormalities acquired postnatally can give rise to ASD-like features. Can you please explain what you mean by that?

A Yes. Because we don't know the precise neuro basis, i.e. the precise brain basis, of autism

it is difficult to decide whether you're dealing with true postnatal causes or whether you're dealing with what are called phenocopies, things that look a bit like autism but are actually very different.

So that the evidence which is reasonably solid applies all to prenatal causes, but it is certainly possible that very early postnatal causes might do the same thing, but I put it in terms like that rather than that there are good examples that are really proven to a satisfactory degree.

Q Are there objective signs of abnormal brain development in some autistic individuals?

A Oh, yes. The findings of increased brain size during the preschool years is an example of that. What we don't have is an objective test so that if one's concern as a medic is to diagnose diabetes there are laboratory tests that can tell you whether the person does or doesn't have diabetes. You don't have to rely on just the symptoms.

But in almost all of psychiatry, including child psychiatry and autism, we don't have tests like that.

Q You had mentioned that some individuals with autism develop seizures in adolescence.

A Yes.

Q What percentage?

A About 25 percent.

Q You also touched on this earlier that brain imaging studies are consistent --

A Yes.

Q -- in showing a systems abnormality rather than a localized brain area abnormality. What do you mean by that?

A There was a day, if we go back several decades, where neurologists and psychiatrists were thinking that autism might be due to a particular part of the brain that was malfunctioning. It's quite clear from all research that's been done over the recent decades that it isn't like that. There is not a part of the brain that's gone wrong that causes autism.

Rather what the research suggests is that it's much more a systems abnormality in the brain in which the interconnections between different parts of the brain is not working the way that they should so that the functional imaging studies would be striking in showing that.

So these are studies in which you are examining brain function in relation to either specific cognitive tasks such as the mentalizing skill

for agent theory of nine or in relation to specific drugs, and what you find is that the parts of the brain that are working when these tasks are dealt with are different in individuals with autism than in normally developing individuals.

But they don't end up with a clear-cut answer why it's there rather than there. It's that the interconnections are not functioning in the way that they should.

Q Now, your report also states that there are congenital physical anomalies found in some children with autism.

A Yes.

Q Could you please explain what you mean by that?

A Yes. Let me start with a preliminary statement that the way biology works is probablistic. That's to say that the development of human beings or indeed any animal is designed to work in a particular sort of way, but there aren't instructions from each gene to say what each and every cell does.

It as it were specifies a path, and there is a need then later to have ways of correcting that path. That means that things go wrong quite often so that many people will know of children who have been

born with extra teeth or missing teeth or an extra nipple. They are minor things that mostly have no functional significance.

But these are things which relate to prenatal development and where the rates of these kinds of abnormalities is increased. Not just in autism. It's increased in schizophrenia, ADHD and a range of other disorders. So they are of interest in showing developmental perturbations; that the way in which development should proceed is not functioning quite right for reasons that must have gone wrong at a prenatal stage.

Q Now, in your report you state that autism is associated with a deficit in what you term theory of mind.

A Yes.

Q Could you please explain what you mean by that term?

A Yes. It's not actually a term that I particularly like because it sort of sounds as if the children have got some theory like Darwin or Einstein or whatever, but it isn't like that.

What it refers to is the fact that human beings are really very good at recognizing from the social context and a broader range of cues what

another person is likely to be thinking. That's a mentalizing skill, and it's as it were being able to read into the other person's mind.

The example that I can give is a case that I actually wrote up in 1983 of a young man, a higher functioning autistic individual, who complained that everybody else seemed to have an extra sense that he lacked.

He said that he would go into his boss' office and his boss was on the phone and so he would start asking him a question and the boss would get angry and tell him to get out because he was busy on the phone. He hadn't picked up that if the man was on the phone it was likely that he didn't want to be interrupted.

In the same sort of way, we do this all the time. So with young children you can see them sizing up social situations. If they're trying to join a group of other children are they going to be welcomed? Are they not being welcomed? What must they do to try and join the group?

These mentalizing skills of understanding from the social situation is what is meant by theory of mind. There are special tests which I could describe if you wish that are designed to test that

specifically, but it's a very universal skill that appears very early.

Q Is that considered to be a cognitive deficit?

A Yes.

Q And what do we know about the effect of genetic influences on one's liability to autism?

A The twin studies are consistent in showing that there is a strong genetic liability so that the concordance rate in monozygotic pairs or identical twin pairs is about 60 percent for the full picture of autism. It's about 90 percent for a broader phenotype, i.e. with milder estimates, milder manifestations.

Whereas in dizygotic pairs the full picture is found in a very small proportion, five percent or less, and up to about 10 percent with these broader manifestations, so the gap between the identical pairs that share all their genes and the dizygotic pairs that share half their genes indicates a strong genetic liability.

In order to quantify that you have to know something about the frequency in the general population, but the estimates are that about 90 percent of the liability to autism is genetically

influenced.

Q Now, you addressed earlier that you conducted the first twin study of autism, correct?

A Yes.

Q What did that study entail?

A Indeed just as I've described, but it was also important for the first time in indicating that the genetic liability applied outside the traditional handicapping disorder so it was actually one of the first indications that there needed to be a broadening of the diagnostic concept.

Q And what have twin studies shown to be the concordance rate of autism? You just said 90 percent with MZ twins.

A Yes.

Q What was the percentage for dizygotic twins again?

A About 10 percent --

Q About 10 percent.

A -- with the broader phenotype.

Q Okay.

A And less than five percent with a full picture.

Q The full picture being autism?

A Yes.

Q Autistic disorder? Okay. Now, there have also been studies done in families with autistic family members, correct?

A Yes.

Q When we talk about family studies, what does that mean?

A It means looking at autistic-like features in this instance, but also other features in family members.

The studies that were set up by Susan Folstein and her colleagues at Johns Hopkins and my group in London at about the same time after the initial twin study was comparing the families of individuals who had one or more -- some individual -- affected with autism with a Down Syndrome group where we were equating for a handicapping condition to try and equate the people's awareness of the sort of things that might be important, but where there was no reason to suppose that the same genetic factors applied.

What this showed was that the rate of autism and the rate of the broader phenotype, these milder conditions, was much more common in the individuals with an autistic individual than it was in the group with a Down Syndrome individual.

Other studies have used different comparison groups, but the results are all pretty much the same in showing that what is usually called the familial loading -- that's to say the proportion, members of the family who show these sorts of features -- is much up in relation to autism.

So the strategy is different, and you can't tell from that per se whether it's genetic, but the pattern is very similar to what was found on the twin studies.

Q Now, in your opinion do nongenetic risk factors have a contributory role in some instances of autistic spectrum disorder?

A Yes. The evidence from the twin studies, but also the family studies, is that autism is a multifactorial disorder. That's to say it's not a mendelian condition in which one gene fully accounts for autism.

What that means is that you must expect that the resulting condition, i.e. autism or an autism spectrum disorder, comes from the combination of multiple genes -- in the case of autism probably a modest number; the estimates have been something between three and 12 or something of that order -- and also nongenetic factors.

Now, the terminology of nongenetic factors rather than saying environmental factors brings in the important consideration that the nongenetic factors need not necessarily involve a defined measurable environmental hazard so that the congenital anomalies would be one example.

We know that the rate of chromosome abnormalities is raised in autism compared to the general population. It's not that a particular chromosomal abnormality, with one exception, is particularly associated with autism. It is the chromosomal anomalies more generally are increased.

More recently there's been a study of what are called copy number variations, which is meaning minuscule, submicroscopic deletions or substitutions of bits of the genetic code, are also more common in autism. Now, all of those are not due to a defined environment, but they're not genetic in the ordinary sense of the word.

In addition, there's a very interesting study published last year by Reichenberg which showed that the risk of the offspring having autism was raised if the fathers were unusually elderly.

It's not that that's causing a direct effect. It's that we know from the larger study of

mothers -- I don't mean by Reichenberg, but by loads of people -- that when children are born to older mothers they have higher rates of what I have termed these developmental perturbations, and it may be that it's that sort of nongenetic factor instead of the defined environmental course.

Both are possible, but one has to as it were bear in mind that what is not genetic is not necessarily an environmental hazard.

Q Now, in your report you say that it's wrong to assume that because the heritability of a liability to autism is as high as 90 percent this leaves little room for any major environmental influence. What do you mean by that statement?

A Heritability is a population-specific characteristic. That's to say it tells you the variation in a particular population at a particular point in time what is the importance of genetic factors.

Obviously if a new environmental factor comes on the scene that will change that. Equally, if new genetic factors come on the scene that will change that.

The most obvious example that people know about is with human height. Height also has a

heritability of about 90 percent, but the average height studies I know are in the U.K. and Netherlands, but as far as I know the same applies all over the world.

Well, let me refer to the British and Dutch study. Between 1900 and about 1950 the average height rose by approximately 12 centimeters. That's a big rise. We don't know for sure what it's due to, but it's almost certainly due to improved nutrition and partly also to a reduction of the impairments caused by infection.

So here is an example of something which is highly heritable, but nevertheless a major environmental factor could and did make a difference.

Q If there were an environmental influence, speaking to the heritability of a liability to autism, when in the course of development would that influence occur?

A It's likely to be in the prenatal period. It could be I suppose in the very early postnatal, but the evidence suggests prenatal is more likely.

Q Now, during his testimony Dr. Kinsbourne discussed concordance rates in monozygotic twins as being approximately 60 percent for autistic disorder and 90 percent for the broader autism phenotype as

you've described.

He then agreed to a statement made by Petitioners' counsel that the other 10 to 40 percent of autism in twins must therefore be unexplained by genetics. Do you agree?

A No. Because that is modeling up a population statistic that has no implications for any single individual with an implication that it does, so that the concordance rates say that in the populations studied that is the proportion of the variance.

It definitely is not saying that that means that 40 percent or any other percent don't have genetic factors. It is saying that in the population as a whole there is a mixture of the two and that overall genetic factors tend to be more important than environmental, nongenetic factors.

It tells you nothing about whether they operate in this way or that way in an individual. You can't do that from a twin study.

Q Now, on page 9 of his report, which will flash on the screen, Dr. Kinsbourne states that the causal role of gene/environmental interaction has become firmly established in the mainstream of autism research and theory. Is this correct?

A No, it's not correct. It is, I think from

the way he puts it, confusing two rather different issues. The first is the acceptance that both genetic and environmental or nongenetic factors are likely to play a role. That I agree with, but he is putting it in terms of gene/environment interaction.

Gene/environment interaction is a specific concept in which the genetic influences operate on the environmental susceptibility to disease or some other kind of outcome. There is no evidence that I'm aware of that that has been shown in autism with respect to identifying genes and identifying environments, so that's not only not firmly established; it's not established at all.

It is a possibility because we do know that in other conditions gene/environment interaction is important, but at the moment that is entirely speculative with respect to autism.

Q Now, Dr. Kinsbourne in his report at page 6 states that it is generally agreed that the incidence of the ASD diagnosis is rising spectacularly. Do you agree with that statement?

A No. What is generally agreed is that the diagnosis of autism has risen spectacularly so that by incidence, and he's implying that it's new cases and that it is, as it were, a true increase in a

condition. That remains uncertain.

We know that it has been diagnosed more frequently, and everybody would agree that at least a large part of that rise has come from a broadening of the diagnostic concept, which we've already discussed, and better ascertainment.

That's to say that pediatricians and family doctors and psychiatrists and psychologists have become more aware of the early manifestations of autism, so diagnosed autism has risen spectacularly. We do not know whether the incidence has or has not.

Q Now, in your report you state that earlier epidemiologic studies showed rates of ASDs that are much lower than the more recent studies. In your opinion, why is that?

MS. RICCIARDELLA: Maybe you can bring that down. Thank you.

THE WITNESS: Well, because of better ascertainment and better measurement and a broadening of the concept.

So actually in the earlier accounts by Victor Lotter, the first epidemiological study in the 1960s, he did have a category of autistic-like disorders. He didn't pay a lot of attention to those at the time, but it was saying that the broadening

actually was being envisaged at that time.

Now, if we look at the modern studies of the rate of autism I think one can have a lot of confidence that they're well conducted using good, sound, clean methods, good instruments of measurement, and they are highly consistent in what they show, so they're on solid ground.

The difficulty of, as it were, looking backwards is that you can't reconstruct samples and measures that weren't available at that time to say whether the earlier rates were equally satisfactory.

I thought virtually everybody would agree that they weren't as satisfactory, so modern rates I have confidence in as being probably reasonably accurate. I think the change is mainly methodological, but it's very difficult to rule out the possibility that in addition to that there has been a true rise due to some as yet to be identified factor.

BY MS. RICCIARDELLA:

Q Now, you state that there has been a broadening of the diagnostic concept. You've used that term a few times in your testimony. What do you mean by a broadening of the diagnostic concept?

A Well, I think the main thing is a

recognition that individuals of normal intelligence can and do show something that there's every reason to suppose is autism, i.e. it's not just it looked like autism. It probably is autism.

Although that was adumbrated by both Kanner and Asperger back in the '40s, it wasn't articulated quite like that and so people were reluctant to diagnose autism in individuals with normal intelligence.

There are other ways in which there has been a broadening, but alongside that is diagnosing autism in individuals who in their way are holding their own in society, albeit in a somewhat unusual fashion.

So the broadening I think has good research support. There are two difficulties though. The first is that whereas everybody would agree that it's broadened, it's not quite so clear where you draw the line. Does it stop here or here or here? There isn't research that tells us that. All it says is that it's a lot broader than we used to think.

The other is that the group with these milder manifestations differ in two key respects from ordinary autism; that is, that they're not mentally retarded and not intellectually disabled, and they don't have an increased rate of epilepsy, and we

really have very little idea as to why.

Q Doctor, I'd like to talk a little bit about regression in autism.

A Yes.

Q What is regressive autism?

A It's not a term that I like to use because it implies a different category, so let me turn back to the way it's usually been talked about.

For many decades there have been repeated clinical studies which have noted that a proportion of individuals with autism go through a period in which they appear to lose skills that they had previously. Indeed, the Kanner and Eisenberg follow-up noted that a long time ago.

The term regressive autism was introduced I think initially with MMR claims, but then more recently with thimerosal claims, as if this was a distinctive, new category. Well, it's not new. It's been observed since many, many years.

And moreover the evidence suggests that it's not a yes/no phenomenon. That's to say that there certainly are children who show a dramatic loss of skills. Equally there are those where the loss is much more minor, much more difficult to spot, and then there are all varieties in the middle.

So regression is for real. The studies both from home videos and from the baby sibs studies confirm the reality, but it's not as far as one can tell a distinct group that is quite different.

Q At what age does regression typically take place?

A Typically around and about the second half of the second year, 18 to 24 months. It does occur both earlier and later than that, but that's the typical period.

Q And what percentage of children who are autistic have suffered a regression?

A The figures vary from study to study, but a quarter to a third or something of that order. So it's reasonably common, but it's a minority.

Q Has the rate increased over time?

A As far as one can see, it's remained very stable.

Q I would like to flash on the screen a paragraph from Dr. Kinsbourne's report on page 7. It's lengthy, but I will read it out loud. He states that:

Furthermore, the proportion of ASD children of the regressive subtype remains at a level of between 20 and 30 percent. There have not been any

changing diagnostic criteria for regression and regression of development into nonautistic states, though it does occur due to certain brain degenerations is rare. I think I might be reading this incorrect.

Regression is so much more striking and even shocking as compared to slow development that it is hard to imagine that in the past it was simply not noted in many cases. Diagnostic substitution is a nonstarter since alternate descriptions such as mental retardation and learning disabilities are not characterized by regression.

These considerations indicate that the rise in the number of cases of regressive autism is no artifact, but is very real. Genetic causation cannot explain this, but gene/environment interaction can if exposure to proactive environmental factors is correspondingly increasing.

That's a long paragraph, but, Doctor, do you agree with Dr. Kinsbourne's statement?

A No, I don't really.

Q Why?

A Let's start with what I do agree with. The first statement that the proportion with regression has remained at roughly the same level is something

I've already mentioned, and as far as one knows that's correct.

It has to be said that the quality of the measurement in these studies is pretty variable so that it's a lack of evidence of change rather than a solid finding of no change, but by and large I agree with what he's said.

There have actually been changes postulated -- put forward -- for the diagnostic criteria of regression, but I would agree with him that it's not likely that those account for any differences. The problem comes in this sort of jump from saying the overall rate of autism has gone up. The rate of regression remains the same.

Therefore, let us assume that the rate of nonregressive autism, to use his terminology rather than mine, has gone up for other factual reasons, better ascertainment and so on. It can't have applied to regression. Therefore, the regression is real.

Well, that involves a whole series of assumptions, none of which have good support, that if there had been a new phenomenon that had come on the scene then you might expect that it would be evident in the proportion going up and that that would be shown in the overall figure so that you can't go from

one statistic to the other in the way that he has.

He says that there are no other cases characterized by regression other than rarely. Well, it depends what you mean by rarely. A genetic causation can't explain this, but that seems to imply that genes as it were cause something now and can't explain changes later, but there's a massive genetic research which shows the opposite. That's to say genes influence development just as much as they influence things at the beginning.

Let me give two very different examples to illustrate what I mean. Huntington's disease is a rare disease caused by a particular single gene. It's a mendelian condition. Nobody has ever suggested environmental factors play a role, and there's a lot of evidence that they don't and couldn't, but it only becomes apparent in middle age as a rule. Very rarely it can begin earlier than that.

So here it's genetic. It's fully genetic, but the effects only come on later and there is a loss of skills in the early forties or some time period like that. Nothing to do with the environment.

Let me take a different example, in this case not a disease. Women go into their menarche, the onset of menstrual periods, during early adolescence.

This is strongly genetically influenced. It's part of the biological programming brought about by genes. It's not that girls encounter some environmental hazard that brings on the period. This is what genes are doing.

So that there are lots of examples where genes are influencing things way down the line. There are hundreds more examples one could give, but it's just wrong to support that if it's genetic it has to be present early.

So let's just move closer back again to the evidence of increased brain size in autism in the preschool years. There's no evidence that environmental factors have brought that on. It is presumably part of what the genes are doing.

In the same way, schizophrenia is known to have a high heritability. The first manifestations of schizophrenia are in the preschool years. There are studies which show that difficulties with language comprehension and with motor coordination are more common in individuals who later go on to develop schizophrenia than in the general population or indeed in other disorders such as bipolar disorder.

There are then findings in childhood and early adolescence, again all connected with this

process, so that here we have a strongly genetically influenced disorder. It's not that some environmental hazard comes in in early childhood that translates these early developmental abnormalities into schizophrenia. It's part of the genetically influenced disorder.

So there is no reason to invoke an environmental factor unless there's positive research evidence that that is what has happened.

Q Thank you. Now, on page 6 of his report Dr. Kinsbourne describes regression as "unexplained encephalopathy". Is there evidence to support this statement?

A No. Well, encephalopathy implies that we know that there's something going wrong in the brain when this is happening.

Well, obviously something is happening in the brain for the regression, but whether it's an encephalopathy, which is ordinarily assumed to mean some kind of inflammatory process, there's no evidence of that.

Q Does regression mean that a child is developing normally before the regression occurs?

A Not necessarily. In some cases it's clear that there were abnormalities before the regression

occurred, and there are other cases in which as far as one can tell there weren't.

Q Now, in your report you state that substantial regression is a relatively common feature rather than a rare one.

A Yes.

Q Could you explain what you mean by that?

A Well, the studies come out 20 to 30 percent. Twenty to 30 percent is quite a substantial minority so that it's not dealing with rare phenomenon. To the contrary, it's dealing with a reasonably common phenomenon.

Q Again, Dr. Kinsbourne in his report on page 4, which we'll put on the screen, states that classical what he terms congenital and regressive autism differ sharply with respect to their known medical causation. Do you agree with his statement?

A I have no evidence supporting that. The fact of the matter is that there have not been systematic studies comparing so-called regressive with so-called nonregressive autism in relation to medical factors that might be causative, so it's pure speculation that they're different. They may be. They may not be.

Q Why isn't the fact that some children

regress evidence of some sort of external trigger or trauma?

A Well, the examples that I've already given with Huntington's disease and the menarche would be one example, but let me give two rather different ones.

There is a strong temptation for all of us to suppose that when a certain change occurs that there must be some environmental trigger that has brought it about, but let me give two other examples.

It is well established that children with profound congenital nerve deafness show normal vocalizations for about the first six months of life, but they then develop this kind of guttural vocalization, which is so characteristic of deaf children that anybody who has visited a school for the profoundly deaf is familiar with this.

Now, they've been deaf since the word go so the condition has been there throughout, but the loss of clear vocalizations came because the input of language becomes in part in vocalizations around and about the middle of the first year of life. There's no environmental change. It is part of the normal developmental process.

In the same sort of way, babies all over the

world have the same range of phonological skills. That's to say the different sounds they make are much the same, so Japanese babies, French babies, English babies, even American babies, all make much the same sounds again up to about the first six months of age.

Thereafter they lose the ability to make sounds that are not part of their language environment so that what is happening, the early sounds are not dependent on verbal input. The later sounds, the later vocalizations, are. This is a loss of a skill.

The example that people tend to know about is the difficulty that Japanese people have in differentiating between R and L. That has no part in the Japanese language. It is, of course, a crucial part of most other languages. So that because it's not part of their language environment that differentiation between R and L which they will have had up to the first six months they have lost.

So there are lots of examples where the brain systems that are necessary for particular functions change with development, and as they change with development skills may be lost or acquired as part of this biological programming.

Q Now, in this litigation it's alleged that the very existence of regression in autism is evidence

that the autism was caused by an environmental trigger, in this case thimerosal. Is this a valid conclusion to draw about the cause of regressive autism?

A No, for all the reasons I've given. What would be needed is positive evidence that thimerosal, A, was a causal factor in autism, and, B, it was particularly a causal factor with autism involving regression.

Q Now, you said earlier that there is no evidence that regressive autism is a distinct disorder from autism.

A Yes.

Q You say it may be, but it may not be based on the evidence.

A Yes.

Q What would you say the probability is that it is a distinct disorder, based on the evidence?

A I don't know. As I think Dr. Kinsbourne in his evidence talks about, most biological features work on a continuum, and I would agree with that statement.

For some reason he seems to think that regression is an exception to that usual biological rule. I don't think it is. I have no idea what the

proportions would be.

Q Now, with respect to causal inferences that can be drawn from the studies that have looked at the neurotoxic effects of mercury, what, if any, causal inferences can be drawn from those studies?

A Okay. Well, I think we need to turn first to the studies looking at high levels of mercury and what we know about the effects of mercury.

I'm not a toxicologist so I can't speak to the specifics of that, but the epidemiological and clinical studies make quite clear that high doses of mercury are toxic to the brain and cause damage. That's not in dispute.

There are then epidemiological studies like the one in Seychelles or the one in the Faroe Islands -- there's also a New Zealand study -- which are looking at levels below these very high levels where we know there are obvious clinical effects to see whether there are more subtle effects.

It's difficult to come up with a firm answer on that, but I think that my conclusions would be pretty much in line with most commentators. That's to say there is some suggestive evidence that there may be slight cognitive sequelae with these intermediate levels.

So that it's difficult to say where there is a bottom limit when exposure to mercury is entirely safe. It is notable, however, that none of those studies identify autism as one of the sequelae so that there is good evidence that very high doses of mercury is damaging.

There is slight suggestive evidence that levels below that may be in mild degree, but no evidence from these studies that autism is one of the outcomes.

Q Are there differences between the symptoms of mercury poisoning and the symptoms of autism?

A Yes, numerous differences. I know of a paper that drew parallels, but if you look at the list of features that you get with mercury poisoning and the list of features you get with autism, the thing that jumps out at you is that there are very few similarities and there are lots of differences, so I think that's really completely unpersuasive.

Q In your opinion, is there any reliable evidence that chronic low dose exposure to thimerosal in vaccines causes regressive autism?

A No.

Q I'd like to turn briefly to epidemiology that's been conducted in this area.

A Okay.

Q Is epidemiology an important field of science in assessing whether thimerosal-containing vaccines cause autism?

A Yes. Let me answer first in a general way that throughout the history of medicine it has been important to use epidemiological evidence to look at environmental causes of disease.

It's important because there are so many potential causes that you couldn't study directly in the laboratory for ethical reasons in humans, so the question is have there been successes epidemiology in this way.

So a working party to the American Academy of Medical Sciences which I chaired and which reported late last year looked very systematically at this and the whole issue as to when and how one can use epidemiologic type evidence to draw causal conclusions, and what we sought to do was to compare ones where there would be general acceptance, but it has worked, and other examples where it hasn't.

So the best known, but by far from the only example, of success would be smoking and lung cancer. So that the study by Richard Doll back in the '50s showed a strong association between smoking and lung

cancer, and then a variety of other studies were done, in particular a study looking at what happened to the rates of lung cancer in doctors, because he did a study of doctors, who stopped smoking and found that the rate of lung cancer went down when they stopped smoking.

Now, it took actually quite a long time for the evidence to be seen as pretty decisive, although back in the mid '60s the U.S. Surgeon General's report and the parallel independent report from the U.K. both pointed to this being a likely cause.

Over time other evidence came in so that experimental studies with animals showed the carcinogenic effects of tar and so a mechanism was then found and so the successful cases where epidemiology has worked has come about because of the care of the methodology and with recognition that all epidemiological findings are open to what epidemiologists talk about as confounders, meaning variables that aren't a cause, but are associated with the supposed causal factor and the outcome and therefore create a misleading impression.

And so one of the things that was done with the smoking example was to work out how big an effect a confounder would have to have to overturn the causal

effect between smoking and lung cancer. The estimate was it would have to increase the risk ninefold. Nobody but nobody could think of any confounder that might have an effect anywhere near as big as that.

So I've gone on at some length on that one example because it illustrates how powerful epidemiological evidence can be, but how careful one has to be in how the epidemiological studies are done and how important it is to combine it with other research strategies.

The other successful examples like fetal alcohol syndrome would be another that shows the same kind of good epidemiology, good experimental studies. So epidemiology at its best, properly done, proper attention to confounders, proper use of other research strategies is a crucial part of studying environmental causes of disease.

Q Now, in your report you discuss the epidemiologic studies that have been done that have looked at the relationship between certain dose amounts of thimerosal and autism.

I'm referring to the Heron study, which for the record is Petitioners' Master List 14; the Andrews study, which is Petitioners' Master List 4; the Verstraeten study, which is Petitioners' Master List

247; the Fombonne study, which is Petitioners' Master List 40; and the Hviid study, which is Petitioners' Master List 238.

Taken as a whole, Doctor, what do these studies demonstrate with regard to the purported association between thimerosal-containing vaccines and autism?

A They're all unsupportive of a causal association. In my report I go carefully into the strengths and limitations of each of those studies.

So that I followed the British tradition of giving expert reports. That's to say my duty as a scientist is not to speak for or against any particular hypothesis, but to look at the evidence as a whole and to note the limitations, to note the strengths and then put it all together as a whole. That's what I have attempted to do.

That of course is the usual scientific procedure. There is no science that is free of limitations, but the best studies all have limitations. That's just the way everything is.

And so one always has to be very careful about drawing any strong conclusion from one's study. All you have to do is to say are the limitations all of the same kind in the different studies and do they

amount to such a problem that you really have to say you have to put those on one side; they're not worth looking at.

Or rather do you say well, there are some limitations, but actually they've been looked at as carefully as they can be, and if you look across studies the strengths and limitations don't have quite the same pattern. When that's the case, one is on much stronger ground in saying it probably is valid.

So that let's take the Heron study first. It's a good epidemiological study. It's well conducted. They have a high response rate. There are all sorts of good things about it, but they don't actually have a recognized measure of autism so they're having to use special education or treatment, have to use questionnaires of one sort or another so that the outcome is indirect. So on its own that wouldn't take one very far, but for what it's worth the findings are very negative, but they could test for confounders in quite a thorough sort of way.

The Andrews study was not so strong in being able to test for confounders, but on the other hand they had a much larger sample, it too similarly a negative. And so I could go on. The Verstraeten study is in many ways the most satisfactory of the

studies, and because of that I looked particularly carefully as to whether there were problems that might invalidate the findings.

Its strengths are several. It includes a large sample which when looking for an infrequent outcome is really very important. They used a standard methodology, and the study was thoroughly and appropriately analyzed. The results do not show an association between thimerosal and autism.

I noted that the early findings didn't necessarily coincide with the later findings. I mention that because it received sort of attention in the press, but what I concluded is actually that's usual. When you're dealing with multivariant analyses of complex data sets you do reanalyze and reanalyze to try and test data so they did the right thing, and in their evidence the reanalysis by Austin and Lally said the same thing.

Austin and Lally in their commentary made a suggestion that the way they dealt with the -- they dealt with three sectors, not including the one center they would be mildly critical of and I would be mildly critical of, but like them it seems very unlikely that that would affect their results.

I think it would have been preferable to

have dealt with it in a slightly different way, and it's not clear why the findings weren't the same in the different centers, but when you're dealing with effects with broad confidence intervals you often find that.

The third point that I mentioned was that Verstraeten, at the time the paper was published, had an appointment with GSK, and I think he should have declared it. He did declare it shortly afterwards. I see no reason to suppose that affected anything, but it was an error of judgment is all I can say.

So having looked carefully at all the problems of this, and I did look very carefully at them, I would still rate this as a sound study with sound conclusions on what one can draw conclusions.

Q Now, you also discussed various time/trend studies or ecological studies in your report that have looked at whether thimerosal was responsible for the rise over time in diagnosed cases of autism.

I'm referring to the Madsen study, which for the record is Petitioners' Master List 239; the Stehr-Green study, which is Petitioners' Master List 230; and -- I'm going to butcher this name -- the Atladottir --

A Atladottir.

Q That one, which is Respondent's Master List 17, and the Schechter and Grether study, which is Respondent's Master List 439. Doctor, what do those studies tell us?

A They are primarily used in dealing with the hypothesis that had been put forward initially that MMR had led to an epidemic of autism and, more recently, that thimerosal had led to an epidemic of autism. And so the time/trend studies are useful in seeing whether the ups and downs as it were were associated with changes in the rate of autism.

They have manifest strengths. That's to say they can be based on very large numbers. They have some important limitations, the most particular of which that they are dealing with it at a population level. They're not dealing with it at an individual level.

Secondly, that they can't deal with confounders in the way that you can do if you're dealing with individuals, but the evidence -- let me focus particularly on Stehr-Green. Stehr-Green was interesting in explicitly comparing what was happening in Scandinavia where thimerosal had been phased out and in the United States where because of the way in which vaccination schedules have changed it has

actually been going up.

So the question is were the trends in the rate of diagnosed autism going in different directions in the two countries or two areas of North America and Scandinavia? Now, if there had been a true causal effect when thimerosal was withdrawn you should see a drop in cases, whereas with thimerosal continuing it should either remain the same or continue going up.

But what Stehr-Green showed was that the rates showed the same trajectory, the same direction over time in both countries, so that the rate of diagnosed autism showed the same trend irrespective of what was happening with thimerosal.

In epidemiology one pays particular attention to what happens when either a risk factor is introduced in one population and not another where you can see what's happening or, alternatively, a risk factor is removed in one population and not another.

And so it is this fact-finding that the trajectory over time is similar irrespective of the removal of thimerosal which makes it really rather unlikely that thimerosal played a role in the overall rate of autism.

Epidemiological studies by their nature of course can't deal with unusual idiosyncratic

reactionism. We may want to turn to that at some point. But in terms of an overall effect, I think the answer is pretty compelling.

Q And do you find those studies to be credible studies?

A Yes, I do.

Q Now, you do point out by the nature of their design ecological studies cannot be used to examine whether a small group of children have an unusual susceptibility to thimerosal.

If the subgroup were defined as those children who have regressive autism would the ecological studies likely speak to that population?

A That isn't the way you would tackle it. So that there are, of course, many examples in medicine of idiosyncratic reactions, so the notion that there might be in relation to thimerosal is certainly plausible, but the way you would tackle it is having a test for the susceptibility.

So let me personalize it. One of my grandchildren has an anaphylactoid reaction, a massive, life-threatening reaction, to cashews and pistachios. Now, cashews and pistachios for most of us are perfectly safe. They don't cause any problems, and indeed they are two of my favorite nuts, but in

his case they are life-threatening.

Why do we know its causation? Maybe he had a panic attack. But, no, because skin tests show that the skin reaction to those nuts is identifiably different in a huge way, and if you also apply it to the tongue you get a swelling of the tongue from exposure to these nuts, so you've got a really good test that can identify this susceptibility.

There are other medical examples where that is so. So what you do is not create a soup of everybody. You look in a focused way on what happens with individuals with a defined susceptibility as measured by an objective test.

The problem here is that although it's theoretically possible that there are individual differences in response to thimerosal, as far as I'm aware there is no test that can demonstrate that.

Q Now, according to Dr. Kinsbourne the epidemiologic studies that you discussed in your report and that we've discussed here today are not informative at all as to the purported association between thimerosal-containing vaccines and regressive autism because none have looked at the regressive autism specifically. Are these studies, Doctor, irrelevant to this litigation here today?

A No.

Q Why?

A Well, mainly because the rate of progressive autism is sufficiently high that it probably would have picked them out.

So that if you were dealing with something like a nut allergy, which occurs to a tiny proportion of the population, then general studies of nuts wouldn't be much use, but dealing with something that occurs in a quarter of the population, yes, they are informative.

If there is evidence of a susceptibility of a very specific kind that can be identified separately then that's another matter, but that isn't so, so at the moment that is the best evidence one has today.

Q Now, in your report, and I've heard you say this today, you use the term biologically plausible.

In your report you say that it's biologically plausible that there might be an unusual idiosyncratic response to thimerosal in a subgroup of individuals. By the term biologically plausible, what are you meaning by that?

A I'm meaning simply that what one knows about biology means that it's possible that that might occur. It certainly does not mean that it's likely to

be the case because there's no evidence in support of the notion.

So that the evidence on gene/environment interactions in relation to other outcomes and other genes and other environmental factors indicates it can occur. The question is what is the evidence here that it does occur? So it is a theoretical possibility, but at the moment it is speculative.

MS. RICCIARDELLA: At this point, Special Master, I have about 20 more minutes with Dr. Rutter. Would it be a good time to take a quick, midmorning break?

SPECIAL MASTER CAMPBELL-SMITH: That sounds great. I have about 11:07. How long were you thinking for your break?

MS. RICCIARDELLA: Ten minutes? Fifteen minutes?

SPECIAL MASTER CAMPBELL-SMITH: Fifteen minutes?

MS. RICCIARDELLA: Fifteen? Okay.

SPECIAL MASTER CAMPBELL-SMITH: That would put us back here at roughly 11:25.

MS. RICCIARDELLA: Thank you.

SPECIAL MASTER CAMPBELL-SMITH: Thank you. We'll take a brief recess.

(Whereupon, a short recess was taken.)

SPECIAL MASTER CAMPBELL-SMITH: Please be seated.

Respondent's counsel to continue the direct examination of Sir Rutter.

MS. RICCIARDELLA: Sir Michael Rutter.

SPECIAL MASTER CAMPBELL-SMITH: Sir Michael Rutter.

BY MS. RICCIARDELLA:

Q Isn't that right?

A Yes. Yes.

Q Doctor, before we go on to the next topic I'd like to just finish up with a discussion of the epidemiology.

Before we broke you were talking about how, given the proportion of regression in autism, it would likely have been detected by the epidemiological studies. What are you basing that statement on?

A On the evidence that in the studies overall the rate is about 25 to 30 percent or sometimes even up to 40 percent.

It's a big enough number to make a difference overall. If one was talking about something that only affected say one percent of the population that would be quite different.

Q Is that based on your understanding of what you know about autism in general?

A Yes. Yes, indeed.

Q Now, in your report you state that there is no good evidence to support the speculative suggestion that thimerosal results in a form of ASD characterized by regression.

Could you please explain what you mean by that statement in 10 words or less?

A Well, the suggestion as far as I can see is not based on any empirical evidence that that is the way it happens. If it were it would be quite different.

So it's difficult to know how to comment further other than that that is just speculation.

Q Are there any reliable biomarkers that represent a measure of susceptibility to thimerosal?

A No.

Q What evidence would be needed to demonstrate a susceptible population to thimerosal?

A You need some test which would show that in response to ethyl mercury you are having an unusual reaction so that in theory at least it would be possible to develop a test of that kind, but so far as I know there hasn't been such a test that's been

applied to determine whether that is the case.

The studies that have been done that we were referring to earlier of human populations with high doses, what is quite striking is that it does seem to affect everybody. It's not that you're finding unusual individuals who are showing a big response and most individuals no response at all, so it's not like the nuts example that I gave.

The animal evidence similarly seems to show something that applies more generally rather than only in a small subgroup, so although there have been suggestions that there may be particular susceptible populations the evidence is singularly unconvincing up to now.

Q Doctor, I'd like to talk now about the theory that has been espoused by Dr. Marcel Kinsbourne in this litigation. Did you review the report that he submitted?

A I did.

Q And on page 14 of his report he states, and we will put this on the screen for you: The late onset of the regressive subtype and subsequent remission or relapses become more understandable if autism is due to disease than if it is the aftermath of congenital maldevelopment. Do you agree with his

statement?

A No. I mean, it comes back to the point we were discussing earlier that both prenatal or genetic influences will affect cause, as well as the occurrence at the time of birth, so it's a non sequitur. It does not follow logically from what we know about the way biology works.

Q And earlier we put on the screen a quote from Dr. Kinsbourne's report in which he described regression as striking and dramatic. Is that characteristic of all regression in autism?

A No. To the contrary, it's often very subtle. There are examples where it is very striking and dramatic, I agree, but they actually are very unusual rather than the opposite way around.

That's to say the usual picture is reasonably subtle changes that amount to something that is very worrying, appropriately worrying the parents, but it doesn't occur dramatically in either the sense of it was not there on Tuesday, but it is there on Wednesday, nor is it a question of a loss as it were that is so severe that it is obviously a total change in the child's behavior.

That can occur. I have seen cases like that, but they are distinctly unusual. It is a more

gradual occurrence of a milder kind, which is the more typical.

Q Now, beginning on page 13 of his report Dr. Kinsbourne discusses what he believes is a neuroinflammatory response within the brain due to accumulated inorganic mercury in the brain. He states, and we'll put it on the screen:

ASD has traditionally been regarded as a static neuropathy or encephalopathy that originates from before birth. If that were so, it would be unclear how autistic regression can occur as late as the second year of life and even later in childhood disintegrative disorder.

Is this a correct assumption on the part of Dr. Kinsbourne?

A No.

Q Why not?

A Let me come back to the schizophrenia example that I gave where the evidence is strong -- a major genetic influence, high heritability -- but where there are early manifestations but then later changes and that the follow-up study, for example, by Judy Rapopart and her group at NIH has shown that schizophrenia has both an early manifestation and changes later.

So that what is being described here is very exceptional and unusual and causing a problem in terms of understanding is actually something that one sees in many conditions. I would agree that we don't understand what is going on in the brain at the time that happens.

An encephalopathy sort of implies inflammatory process. We don't know that that's what is happening, so when I say that clearly something must be happening in the brain, I mean, the workings of the mind have to be based on what is going on in the brain, but exactly what those changes are and whether they're structural or functional we don't know that.

Q Now, Dr. Kinsbourne describes what he terms his overarousal model as an explanation for autistic behaviors. Are you familiar with his discussion of his overarousal model in his report?

A Yes, I am. It is of course an old theory so that I was surprised to see this put forward as novel.

So the Tinbergens in a report back in 1972 put forward a closely comparable model in which they were arguing that autism was not a disorder of social reciprocity. It was a disorder of emotional overarousal in relation to social situations, which is

pretty similar to what he is suggesting.

So it's an old theory. It no longer even gets referenced in textbooks so that, for example, the two-volume *Handbook of Autism* edited by Fred Volkmar and colleagues, you won't find it even in the index, let alone anywhere else either under Tinberger, who is the most prominent proponent of that view, or in terms of emotional overarousal.

So it disappeared simply because of the contradictory findings which did not really support the notion.

Q Now, Dr. Kinsbourne cites a paper by Goodwin, which is Petitioners' Master List 496, and a review paper by Baron, which is Petitioners's Master List 550, in support of his model. Do these articles provide reliable support to Dr. Kinsbourne's overarousal model?

A No, I don't think they do actually. The fuller review is actually in the Goodwin, et al. paper rather than in the Baron chapter in the textbook. In that they review the numerous methodological problems that there have been over the years assessing arousal and of tying it to anything in particular so that there are different physiological measures that one needs to use.

Whether somebody looks aroused is not the same thing as whether from a physiological point of view they are aroused. Showing whether or not the arousal is in relation to social situations rather than more generally becomes another issue, so it's quite a good review of the multiple difficulties.

They then go on to a comparison of five individuals with autism and five comparison individuals where they present some quite interesting findings, but they are based on a tiny number, and they blend up really with the same kind of inconclusive findings of the earlier research done.

Q Dr. Kinsbourne also cites a paper he published with the first author by the name of Liss, L-I-S-S, which is Petitioners' Master List 373. Have you reviewed this study?

A Yes, I have.

Q And do you have any comments with regard to the validity of this study?

A Well, it's a questionnaire study so that it's looking at what parents have reported about various phenomenon, some of which are concerned with children's responses to sensations and matters of that kind.

It's something that's been looked at for a

very long time so that the work of Hornedge back in the 1960s and early '70s was trying to do exactly the same thing.

So the question there is new, but is very similar to earlier ones, but they're based on observed children's responses and not measuring actual responses to sensory stimuli so that you're having to rely on making inferences as to what the observed behavior might or might not mean.

He refers, for example, somewhere -- I can't remember where in the report -- to the study by Lovaas looking at overzeal activity which received a lot of publicity at the time, but Lovaas' own research, as well as those of other people, later went on to show that this was not specifically associated with autism. It was a function of the low developmental level, and once you took that into account the association with autism disappeared.

It's another example of in this field of needing to consider carefully what the possible confounding factors are and the need also to be concerned that the behavior which you think is dealing with overarousal is specific to the social situation.

So the fact that autistic individuals get overexcitable sometimes, certainly. That's been know,

from Kanner onwards. The fact that autistic individuals can sometimes also appear apathetic, again known from Kanner onwards.

So the need is to go beyond that to try and link it up with what is happening physiologically and how that relates to the specific social situation, and that's what is lacking. The Hornedge points of view of section Constancy (phonetic), which is sort of brought in in the Liss paper a bit, he abandoned later because the evidence really didn't support it.

Q For the overarousal hypothesis to account for social abnormalities in autism as Dr. Kinsbourne suggests, what would have to be shown about the nature of arousal responses in a social situation?

A Well, you'd want to have a physiological measure of arousal rather than just an account because we know from animal studies, as well as human studies, that what you observe and what you can measure in terms of heartbeat and EEG changes and all the range of things that measure of physiology of arousal don't necessarily coincide, so you'd want that.

And you'd want to show that the overarousal is something that applies to social situations because if it doesn't particularly apply to social situations it's difficult to see how it could account for the

problems in social reciprocity.

So one is not trying to explain autism as something which is generally due to being too excitable or not excitable enough. It's in relation to social. That's what has never been shown.

Q And in your opinion has Dr. Kinsbourne explained how overarousal leads to regressive autism only?

A No. In fact it's quite striking by its absence in his account.

That is to say in laying all the emphasis on regressive autism and applying it particularly to overarousal, I assumed that he would go on to explain how the overarousal might lead to this interesting phenomenon of regression, but as far as I could see that wasn't present in his report.

Q Now, Dr. Kinsbourne has stated that toxins and viruses and other metals can all operate to initiate this inflammatory response in the brain that he is talking about.

Do you think that this lack of specificity supports his hypothesis in this litigation?

A No, it doesn't. One of the famous set of guidelines for causal inferences put forward by the British statistician, Bradford Hill, included

specificity as one of the things that didn't prove causation, but was a pointer in its direction.

So the lack of specificity doesn't disprove causation, but it certainly is not in support.

Q In your opinion, how would you describe Dr. Kinsbourne's hypothesis as to what might underlie regressive autism?

A Interesting, but entirely speculative.

Q Doctor, in your opinion is it more likely than not that thimerosal causes regressive autism in a subgroup of genetically susceptible children?

A No. I think the evidence suggests it does not.

Q And do you hold that opinion to a reasonable degree of medical certainty?

A I do.

Q And finally just one last question, Doctor. Why did you agree to fly to the United States and testify here today for the United States Government?

A Well, because I think the scientific issues are important ones, and the public health considerations are very important.

The issue of identifying environmental causes of disease, including autism, has been a special interest of mine for a very long time and is

something I know a good deal about so it seemed to me I had a duty to do that.

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

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

Petitioners' counsel, are you ready to commence cross?

MR. WILLIAMS: I am.

CROSS-EXAMINATION

BY MR. WILLIAMS:

Q Good morning, Dr. Rutter.

A Good morning, sir.

Q I am Michael Williams representing the Petitioners Steering Committee here today. I want to start by asking you a kind of general question about what you think underlies autism in the brain.

In particular, do you think that for all the children who meet DSM-IV criteria they have the same underlying brain pathology?

A I think we have no idea, but let me answer it in a slightly different way that the history of medicine and of medical genetics indicates that heterogeneity rather than homogeneity is the rule.

So that one must expect both that there may be different ways of reaching the same endpoint and

that within a population there may be different patterns. So now I don't assume that there will be one, and we have no idea at the moment what the neuro basis for autism is. A host of interesting ideas, but that's what they are.

Q Because I think I heard you say at least once, maybe twice, that you believe it is medically plausible that a postnatal insult of one kind or another could trigger or contribute to the development of symptoms that meet DSM-IV.

A Yes. I used British rules in preparing my report, which is that I must be scrupulous in looking at the evidence against and the evidence for with equal thoroughness, and that is what I've tried to do.

I think the evidence on postnatal causes, and I gave the example of the herpes encephalitis. There are clinical case studies which I don't actually find very convincing. I included them though because they have been claimed to illustrate how a postnatal course, indeed very late -- one of them was adolescent -- can cause autism.

Now, the problem of course is that is one talking about a cause of autism as we ordinarily understand it or are we saying there are similarities in some of the features? I certainly accept there are

similarities in some of the features. I am less certain that this actually means the same sort of thing as autism as we all currently understand it.

I am cautious about saying it couldn't happen because early postnatal factors could have an impact. I think the particular example that people have put forward are not very convincing.

Q Isn't it medically reasonable to think that if you have two children, one who before the age of 12 months is showing lack of eye contact, failure to respond to social smiles, no words at all at age one, compared to a child who seems to develop normally until 18 or 20 months of age.

Isn't it medically reasonable to think that there may be a different etiology to those two different patterns of the development of autism?

A That is one possibility, but I don't think it's medically reasonable if by that you mean that that would be a strong assumption.

I put it the opposite way around that the issue as to why one child does and one child doesn't is an important question for scientists to examine, and the evidence to date doesn't actually show systematic differences.

I would instantly have to go on to say that

the studies that have been done are really quite few and quite limited in what they have looked at, so we are not in a position of being sure that they are due to the same factors in the same way, but by the same token there's no evidence that they're due to different ones.

MR. WILLIAMS: Now I want to show you page 11 of your report.

If we can pull that up? I want to focus, Scott, on paragraph 16 at the bottom of the page.

THE WITNESS: Yes.

MR. WILLIAMS: And if you would highlight the sentence that begins: First there is a tendency to assume.

THE WITNESS: Yes.

MR. WILLIAMS: I'm going to ask you a question. Just a second, Doctor. I just want to highlight the sentence I want to ask you about.

THE WITNESS: Okay.

BY MR. WILLIAMS:

Q This sentence says that there is a tendency to assume that if the heritability of a liability to autism is as high as 90 percent this leaves little room for any major environmental influence, and then you say: It is crucial to appreciate that this is a

wrong assumption.

Now, when you say major environmental influence what were you referring to?

A Well, the example in my evidence earlier was of height where height is strongly heritable, but yet improvements of a major kind in nutrition and in infectious disease were associated with a big increase in height. There are other examples, but --

Q Phenylketonuria, PKU disease, is another example, isn't it?

A Well, that hasn't changed over time, but that is an example -- you're quite right -- where the genes actually work through susceptibility to a particular food substance.

MR. WILLIAMS: I want to show you an announcement of a grant proposal by the Department of Health and Human Services, the Respondent here. This was published in the *Federal Register* while this trial was going on a couple weeks ago on May 23.

Let's just show the top first there, Scott. This was out of the *Federal Register* on May 23, 2008. Then go down to the title here, Scott, which is Disease Disability.

It says Disease Disability and Injury Prevention and Control Special Emphasis Panel

Associations of Vaccine Adverse Events and Human Genetic Variations Request for Proposal, and it gives the proposal number.

Then lower in the same announcement it says there's going to be a conference call on June 12, a couple weeks from now, and the matters to be discussed -- if you would highlight that, Scott? That's what I want to ask him about.

BY MR. WILLIAMS:

Q It says the matters to be discussed include the review, discussion and evaluation of proposals already received in response to Associations of Vaccine Adverse Events and Human Genetic Variations.

Now, are you involved in any way in these proposals, or will you be involved in this discussion?

A The reason I'm looking it up is to see whether I've got anything down on June 12.

I haven't, so not only do I have no memory of being involved; I obviously am not involved in that discussion.

Q The Respondent didn't think it needed your advice on this yet apparently. Just for the record, this is from the *Federal Register*, Volume 73, No. 101, page 30105.

Now, Dr. Rutter, you may not remember this,

but you actually attributed autism to an immunization in one of your papers. Do you recall doing that?

A No, I don't.

Q Let me show you.

A Please remind me.

Q Yes. Sure. This is a review paper that you wrote back in 1994. I guess we're going to make it trial exhibit next. I've got a copy to show you.

A Okay. The one on autism and known medical conditions, yes?

SPECIAL MASTER CAMPBELL-SMITH: That's going to be Petitioners' Trial Exhibit No. 8.

THE WITNESS: Okay.

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

BY MR. WILLIAMS:

Q First let me make sure that that is you that's the first author there.

A It is indeed.

MR. WILLIAMS: Okay. The general subject here is Autism and Known Medical Conditions: Myth and Substance.

If we turn to page 314 of this paper, which

is the fourth page of the exhibit, down at almost the end of the column, Scott, where it says: Only eight of the cases. If you would highlight that?

THE WITNESS: Yes.

MR. WILLIAMS: There. That's good.

BY MR. WILLIAMS:

Q Now, you're actually discussing in this paragraph a review paper that you had published, actually a study you had published back in 1993 on Systematic Investigation of 100 Individuals With Autism.

And you say here that only eight of these cases can be regarded as having probably a causal medical condition, one being a child with epilepsy and temporal lobe focus on the EEG who had an onset following immunization. Do you see that?

A (Nonverbal response.)

Q I assume that that was a case of regressive autism, wasn't it?

A I have no memory as to whether it was or it wasn't. I'm sorry. I can't help you on that.

Q Wouldn't you have checked to see if there were any signs or symptoms of autism prior to the immunization before you attributed it to the immunization?

A Well, I'm not attributing it to the immunization. I'm simply saying that of this group this is one of a small number with a probable cause of immunization.

Now, we know that there are adverse vaccine reactions. They are rare, but they are real, so I don't have any doubt about that. The paper here doesn't specify what the vaccine was. What is striking about it, it was associated, however, with the onset of epilepsy and a temporal lobe focus.

So that the fact that that occurred, i.e. it's not just that autism arose, but that there was a neurological feature there that plausibly was connected with the immunization, is the reason I put it in that probable causal group.

Q And in this case where it was probably caused by the immunization, you don't know whether there was thimerosal in that vaccine or in the vaccines that that child received?

A Well, it pretty certainly wasn't because of the time when these cases were seen. These are dealing with the twin and family studies in the 1970s, so that's before MMR and before thimerosal was widely used. Yes. I don't know is the answer.

Q Okay.

A But it's not likely to have applied to either MMR or thimerosal.

Q Now just a few questions about head circumference and head size. You discussed it briefly in your direct, but is your opinion that head circumference is a diagnostic tool that you can use to determine whether a child has autism or not? The pattern of the head circumference changes?

A Putting it as a diagnostic indicator is putting it more strongly than I would wish to do.

The metaanalysis undertaken by Eric Courchesne going right across studies showed that the increase in brain size -- because this was a metaanalysis I think I'm right in saying of structural brain imaging -- indicates that it is a robust finding which is distinctive of autism as distinct from other conditions.

Why do I hesitate before saying it's a diagnostic feature? Well, because of course it doesn't apply to all autistic individuals so that it is very different, for example, from the microcephaly that you see with Retts syndrome or the microcephaly that you see with many cases of intellectual disability.

The fact that a particular individual showed

this increase in head size -- let's suppose we got all the evidence, okay? Showed an increase in head size or brain size measured by imaging over the preschool years, which would certainly be a strong pointer for this being likely to be autism rather than something else. An absence of that wouldn't necessarily rule out autism.

Q In the studies that have measured head circumference in association with autism do you know whether they controlled for the time when the birth head circumference was taken?

A Do you mean which era in time?

Q No. Well, does it matter at what point after birth the first head circumference measurement is taken for these studies?

A Probably not because the changes are quite small at that time, but usually it is measured at birth. That certainly in the U.K. would be the standard way.

Q You called Dr. Courchesne, Eric Courchesne -- is that how you pronounce it?

A Yes.

Q Is that how he says it, or do you know? I thought maybe you're the authority on autism. You might actually have met him and know how.

A I have met him. I think that's how he pronounces it.

Q Because some of the defense experts have referred to him as Courchesne. I just wondered. We'd like to know how to pronounce it.

A I've never heard him called Courchesne, but I'm open to correction.

Q Okay.

A For me he's Eric Courchesne.

Q Coming into this trial we looked really, really hard to try to find some kind of an animation of brain growth from birth to two years of age.

Could you just summarize the brain growth that does occur after birth up to two years of age in the normal child?

A That's not something I've personally done so I hesitate before giving a summary on that. Of course, the studies are based on not multiple measures taken over short periods of time. They're putting together when taken over a longer period.

I doubt that the evidence is sufficient to say precisely when this occurs other than there is not an increase at birth. As far as I know, none of the studies have found an increase at birth. It develops sometime over that preschool period.

Whether the timing is consistent from child to child I don't know, but I'd be surprised if it was because so few things in biological development are consistent from child to child.

Q I was trying more to get at the notion of just the amount of brain growth that would occur in a normal, healthy child from birth to two in terms of increase in volume, increase in number of cells, increase in number of connections.

A Oh. Well, there's more evidence on that. So that there is a time -- let me put it in simple terms -- where there's an overgrowth of neurons and an overgrowth of neuronal connections. This is in line with what I was saying earlier about biological development being a probablistic model.

So what normally takes place during that period, but also takes place again in adolescence, is that there is a pruning so that the connections that aren't working properly, aren't necessary, are pruned out.

So whether the increase that you see in autism is due to a failure of normal pruning or whether it is due to an overgrowth we don't know at the moment. Either is a possibility.

Q Pruning is required though for a healthy,

normal brain?

A Yes.

Q And isn't it likely that environmental insults during that period of time between birth and two years of ago could affect the pruning, as well as the overgrowth of neurons?

A It's possible. I think we don't have evidence whether it is likely, but it's possible.

Q Now, I checked your report again over the weekend to make sure I was right about this. You discuss for a couple pages of your report a number of brain autopsy studies --

A Yes.

Q -- on autistic children.

A Yes.

Q But you do not mention any of the studies that have found neuroinflammation. For example, you did not cite the Vargas 2005 paper. Why did you leave that out?

A No particular reason. I think that I only became aware of the Vargas paper after I had done the report. I have read the Vargas paper now.

You will understand that I'm not a neuropathologist so that the detailed findings of that go beyond my expertise, but, yes, I am aware of the

paper.

Q And in your direct testimony today there wasn't anything about neuroinflammation as an explanation of the symptoms of autism. Do you think that neuroinflammation is irrelevant to the discussion of autism?

A I think we have no idea whether it's relevant or not.

I mean, if one turns to the Pardo paper, which references Kinsbourne's report, I think, and one looks carefully at what is said there they report interesting changes, but they're very careful to point out the meaning of these remain quite uncertain at the moment.

Insofar as I understand the evidence, I would be in agreement with that, so as is often the way when one has got new findings, particularly ones that are not the same as what have been found earlier, one needs to be very cautious as to what conclusions to draw.

Whether the findings are causal or are caused by or are due to some incidental thing, we really don't know that. So of course I pay careful attention to this evidence. I go along with Dr. Pardo's portion as to what it means.

Q Dr. Courchesne has written a paper that we showed several times during this trial called Autism at the Beginning where he discusses neuroinflammation as an explanation not just of the symptoms of autism, but of the brain pathology underlying autism.

You didn't mention that in your report. That was also published in 2005.

A Right.

Q You don't mention that in your report or in your direct testimony. Why not?

A It's not an area of my expertise, so I have noted some of the key findings.

On my reading of the evidence the neuroinflammation does not show clearly what changes are happening nor when they're happening so that the early Kemper and Bauman findings, for example, did not show evidence of that kind. Were they wrong and the more recent ones right? I have no idea.

Techniques have improved over time, so I'm open to be persuaded that the new evidence as it were needs to be taken seriously as a real contender, but I am aware of the uncertainties as to what causal implications you can draw from it.

Q Do you know whether Dr. Kemper and Dr. Bauman looked for neuroinflammation in those earlier

brain studies?

A I don't know. They certainly looked for glial changes, but that's not quite the same thing.

Q You do agree, don't you, that the studies that have looked at brain function in live autistic children, as well as the studies that have looked at brain pathology, seem to imply that there is a system abnormality in autism as opposed to some focal brain lesion?

A I do agree with that.

Q Isn't neuroinflammation throughout the brain a plausible biological explanation of that systems abnormality?

A The trouble with biology is almost anything is plausible, so the question that I would want to ask is is it likely.

The kinds of brain wave changes that one sees, could they cause autism? Well, I suppose so, but if one looks at what we know about, for example, I was involved in studies of head injuries where there were global effects from closed head injuries, as well as focal effects.

Autism did not appear in any of the cases that we saw, although because that was a major interest of mine we certainly looked for them. And so

a brain-wide general thing like inflammation, could it occur? Yes. Do I think it's likely? No.

Q You mentioned a two-volume textbook on autism by a friend of yours earlier today.

A Fred Volkmar.

Q Right. If you look in the index to that two-volume book neuroinflammation is not there yet. Is that just because the U.K. is behind?

A It's an American book.

Q Published about 2005, right?

A Yes, 2005.

Q So it hasn't had time to put this stuff in there yet.

A Okay.

Q The word microglia does not appear in the index of that book.

A Okay.

Q Does that surprise you?

A It's not my book, and I would hesitate to comments. There are a lot of things that aren't there.

At the time the book was written the notion that autism might arise in this way had not received much attention. It's now received attention through being put forward in this case. It hasn't got much

scientific attention of yet.

Q You don't think it has? Let me show you an NIH grant.

A Okay.

MR. WILLIAMS: Let's pull that NIH grant up, Scott.

Do we have just one exhibit, or do we have two? Okay. This will be Trial Exhibit 9.

(The document referred to was marked for identification as Petitioners' Trial Exhibit No. 9.)

MR. WILLIAMS: I'll give you a copy of this too.

THE WITNESS: Okay.

MR. WILLIAMS: Let's highlight the title of the grant first, Scott.

BY MR. WILLIAMS:

Q This is a study that the NIH has funded, and it's actually recruiting participants as we speak, on Minocycline to Treat Childhood Regressive Autism. Were you aware that the NIH was funding studies to look at regressive autism treated by antibiotics?

A No, but it doesn't surprise me. NIH expected to fund long shots, as well as surefire

applications, so, yes, that's one of the things they're looking at. It's an open label study. It's not a very tight study.

Q Do you know what Minocycline is?

A Not in detail, no.

MR. WILLIAMS: Okay. Let's look at what it says the purpose of this study is. Highlight the first paragraph there, Scott.

BY MR. WILLIAMS:

Q It says there is a subgroup of children with autism that appears to develop typically for a period of time and then loses social or language skills or regresses.

A recent study by Vargas and co-workers at Johns Hopkins has demonstrated that this regressive type of autism is associated with chronic brain inflammation as shown by an abnormal production of inflammatory cytokines and other abnormalities.

Now, I can represent to you that this grant, it is the Pardo group that obtained this grant.

A Yes.

MR. WILLIAMS: We thought we were going to hear from Dr. Pardo today, but we're not going to now so all we can go by is what the grant says, but I want to show you what they're trying to treat here and ask

you if it makes sense.

In that second paragraph, Scott, highlight that last sentence where it says: Medicine with anti-inflammatory properties may be beneficial for children with regressive autism.

BY MR. WILLIAMS:

Q Do you agree that's a reasonable study to undertake, Doctor?

A Yes. I think the NIH has funded over the years a number of studies which were very long shots, and that's a proper thing for them to be doing. So that they've funded I've forgotten how many, but a large number of studies.

A claim based on three cases in UCLA that Fenfluoramine made a massive difference to autism. Fenfluoramine, as you probably know, was later withdrawn because of its toxic properties, but a lot of money was spent testing this study.

Secretin. A lot of claims were made. A variety of studies were done to test whether that was so or not. The studies were consistently negative.

So over the years NIH, in an entirely proper fashion, has taken some suggestions of varying degrees of plausibility and implausibility and considered that okay, it doesn't sound very likely, but on the other

hand we need to know whether in fact it works.

I would see this as one of those. I don't criticize that. It's obviously not based on very strong evidence, but it's worth a try.

Q And let me just show you what they believe the target of the drug is. On the second page let's pull up this paragraph. It says that the antibiotic Minocycline is a powerful inhibitor of microglial activation.

A Yes.

Q Now, what is your understanding of what happens in the brain when microglia are chronically activated, Dr. Rutter?

A It's not something I'm expert on so I'd rather not comment on it.

Q And then I'd like to show you a diagram that we've used in Court before from the Pardo group. This is out of the 2005 review paper by this group from Johns Hopkins.

I need to show you a copy of the paper. This is Petitioners' Master Reference List Exhibit 424.

A Okay. Thank you.

Q Let me get back to the microphone. This is a review paper written by Dr. Pardo's group at Johns

Hopkins published in 2005. Have you read this before?

A Yes, I have.

Q You didn't cite it in your report.

A No.

Q You didn't discuss it on direct.

A No.

Q Let me show you the diagram that they have in here that kind of summarizes their theory, and then I want to ask you a few questions about it. It's on page 8 of the exhibit up in the left-hand corner.

Did I give you the wrong one? Let me give you the right one.

MS. RICCIARDELLA: I think you have the wrong paper, Dr. Rutter.

MR. WILLIAMS: Yes.

THE WITNESS: Okay.

MR. WILLIAMS: It's not 424. It's 72. Give us just a minute.

I'll give you one that we've highlighted as long as you give it back to me when we're done.

THE WITNESS: Sure thing. Looking at this paper I realize this isn't the Pardo paper I've seen, but I'm interested to see it.

BY MR. WILLIAMS:

Q I'm sorry? I didn't hear you.

A You had asked me whether I had seen this particular Pardo paper.

Q Yes.

A And I realize the title is similar to one I have seen, but that isn't the one that I had seen.

Q Okay. So you have not looked at 424 before?

A No.

Q All right. Now let's look at Exhibit 72, which is the one I intended to show you.

A Right.

Q I'll ask you first have you read that paper by Pardo, et al.?

A Yes, I have.

Q Okay. But again it's not in your report. It's not cited in your report, is it?

A No.

Q Let's look at the diagram on page 8 then in the upper left-hand corner. Now, over in the left-hand top circle or oval they have Environmental Infections and Toxins. Do you see that?

A Yes.

Q And then they have arrows going Interacting with Genetic Factors, and you've agreed that's a reasonable hypothesis that environmental toxins would react with genetic susceptibilities?

A I'm not quite sure what you mean. React with? If you mean that there will be both, certainly. Whether you're implying a gene/environment interaction, I don't know that. There's no evidence I know of in support of that.

Q Is it reasonable to think that there could well be people who are more susceptible to the toxic effects of mercury than other people because of their genetic makeup?

A It's possible, but it has not been demonstrated.

Q Then the diagram also points over to the CNS. That's central nervous system, correct?

A Yes.

Q And it has neuro organizations, synapses and neurotransmitters, and then it points down to neuroglial activation. Do you see that?

A Yes.

Q And that points over to the release of cytokines, oxidative stress, systematic cytokines. Do you see that?

A Yes.

Q And then eventually it comes down to the autistic phenotype of regression. They list some other ones there.

Now, do you think this is a reasonable model of how some autistic children could develop autism; that environmental toxins could activate their microglia and lead to autistic symptoms of regression?

A Well, if one looks at the subtitle it's Hypothetical Interactions, and that's exactly what it is. It's a speculative portrayal of what there might be.

Some of those arrows are better substantiated than others. I mean, let me focus on one that you emphasized, neurotransmitters. One of the very striking things about autism is that unlike all other psychiatric disorders there is no consistent response to drugs that have been at least used so far that affect neurotransmitters.

So that it is very unusual with a disorder which we've agreed is likely to be a system of one kind or another that features such as neurotransmitters that operate throughout the brain are not beneficially affected by the drugs that alter those neurotransmitters, so that would be one aspect of this diagram where you have to put a major query. Many of the other arrows, the same sort of thing.

So scientists quite commonly follow the pattern of telling stories about how things might be.

That's a legitimate way of beginning in science. You tell a story, and then you undertake the systematic research to tell you whether that story is correct or incorrect.

So as a speculative story that might apply it's a reasonable starting point, but as the paper goes on if you look at the conclusions it is evident that they are putting it forward in a very cautious way, quite properly so. They're not saying it's wrong. They're saying these are some ideas that we think are worth testing. I would agree.

Q But you didn't think it was worth discussing in your report?

A I hadn't come across it at that time.

Q I would like to turn to page 17 of your report where you discuss --

A Okay.

Q Paragraph 25 specifically is what I want to blow up on page 17.

You talk about two concepts here. Biological plausibility we've already discussed, but what do you mean by biological coherence? That's an additional requirement you would impose on an explanatory theory.

A It's not my terminology. It is a way of

restating Bradford Hill's guidelines in which what he is meaning by this is that if one looks at what we understand from empirical studies of the way systems work is there a coherence in the evidence coming together to indicate pathways that might be relevant?

It is a guideline. He's quite explicit in these guidelines. These are not rules, but it is saying you need to look at the biological evidence as a whole. Is there a coherence in coming together to the same sort of answer?

Where it is then that makes it a bit more likely. Where it's leading all over the place in different directions then that makes it a lot less likely.

MR. WILLIAMS: What I'd like to show you now is sort of five or six pieces of what our experts' theory has been and ask you if it looks like it's more coherent than not.

This is a slide that we've prepared called Biological Plausibility and Coherence of Thimerosal-Containing Vaccines Regressive Autism Link, and the first point is this.

If you could pull it in, Scott?

BY MR. WILLIAMS:

Q We've seen evidence that thimerosal-

containing vaccines deliver inorganic mercury to the brain of infant monkeys. You cite that infant monkey study in your report.

A I do.

Q In fact, you state that it's interesting enough it should be followed up on, don't you?

A Yes.

Q Now, who should be doing the following up on it? Do you think, for example, that the manufacturers of the vaccines that deliver mercury to the brains of these infants have any responsibility to do studies to follow up on that Burbacher infant monkey result?

A Oh, I think I'd rather not comment on who should be doing it. What I said in the report I stick by. That's to say it's an interesting finding, and therefore it's certainly worthwhile to be followed through.

Now, in terms of the issue of a highly unusual, susceptible subgroup, the comment that I would make is a twofold one. The first is that as I understand the animal data what one is seeing is not very unusual responses in a few animals. One is seeing a response which is broadly comparable across the group.

So that in terms of evidence that mercury is

doing things to the brain, fine. I have no quarrel with that. Of course, there are other studies that show the same. In terms of an unusually susceptible subgroup, I find this insofar as it goes rather against that.

The second problem is that as the study and other studies bring out, interesting things happen to both ethyl mercury and methyl mercury and the breakdown to inorganic mercury and that one, in looking for specificity of effects, the minute you are looking to things that come up from all sorts of products other than thimerosal it becomes much more difficult to say what is causing what.

So it is an interesting study. Yes, I do think it's worth following through. At the moment I don't find that it helps me very much other than interesting bits of good science in knowing about thimerosal.

Q Well, if you can't say who should do the follow-up can you say what kind of follow-up you would recommend?

If the vaccine manufacturers on their own came to you and said we're concerned about the fact that our vaccines probably deliver inorganic mercury to the infant brains in a lot of kids and what should

we do to investigate that, what would you tell them?

A I don't do consultancies to drug companies partly because I'm not a toxicologist. That's not what I do.

Q Okay. So when you said in your report it should be followed up what did you mean? Did you have something in mind?

A There are a whole series of ways in which one might follow things through, but I think you're taking me down a road where I have ideas on the sorts of approaches, but I'm not a toxicologist and I don't wish to get involved in saying it's this strategy rather than that strategy that would be preferred.

Q Now, the next step in our coherence that I'm positing to you is that --

MR. WILLIAMS: It should say, Scott, that mercury persists in the brian. I think that got left out.

BY MR. WILLIAMS:

Q In the Burbacher infant monkey study, and I meant to have the third point be the second point, but in any event --

A I can deal with both of them.

Q In the adult monkey studies that are referred to in the Burbacher infant monkey studies

there was a series of papers that found inorganic mercury persisted in the brains of adult monkeys for years, and it provoked neuroinflammation.

Now, you don't cite any of those papers in your report. Did you go and look at them when you read the infant monkey study?

A No, I didn't because, as I say, these are studies which are at an early point of indicating that there are aspects of the way mercury operates which require further study.

I agree with that, but as they stand at the moment they don't help very much in relation to the particular hypothesis of thimerosal and autism.

Q You do agree, don't you, that there is wide individual variability in the blood and brain levels of mercury in both the human and the primate studies that we've seen?

A There's wide individual variability in almost any biological measure one cares to think about.

Q And there is with mercury brain blood levels from thimerosal vaccines, right?

A Yes.

MR. WILLIAMS: The next point, Scott?

//

BY MR. WILLIAMS:

Q The Burbacher paper says that inorganic mercury at doses only five times higher than shown in the infant monkeys ignited neuroinflammation in the brain of the monkeys. You don't disagree that that happened, do you?

A I haven't looked at that particular paper, but I see no reason to disagree.

What I would not have the expert knowledge to know is whether the five times higher is a sufficiently big difference to make one not wish to extrapolate or not. I can't answer that one.

MR. WILLIAMS: Let's pull the other points up, Scott.

BY MR. WILLIAMS:

Q Neuroinflammation has been found in almost all the brains of human autistics when it's looked for. Do you agree with that?

A No, but the point is that the number of brains that have been looked at is very small. Moreover, the brains that have been looked at are highly atypical.

That's not meant as a criticism of the research. It's simply you can only look at the brains of the people who have died, and the people who have

died are much more likely to have epilepsy and to have profound mental retardation or intellectual disability because those are the ones who die.

So it's not that they've chosen the wrong groups. It's the only groups that are available. So we have a small number of brains looked at from an atypical group.

Now, whether the findings that are found are related more to the epilepsy than the autism we have no idea. With the number of brains available at the moment, it would be pretty well impossible to sort that out statistically, but clearly that will have to be done.

As I'm sure you know, there are studies both sides of the Atlantic trying to accumulate larger number of brains so that issues such as the one you mention here, but umpteen others as well, can be looked at in order to determine can they be found by independent investigators, because that's the golden rule of science.

And can they be related to the particular aspect looked at, i.e. not the mental handicap, not the epilepsy, but the autism, because the groups have mostly had all three of those, and have the right checks been done to determine whether it is a cause or

whether it is an effect of the changes that take place.

So as an area where more research is needed, absolutely I agree. In terms of what can be concluded so far, I think very little.

Q You seem to suggest that you were aware of autopsy studies on autistics where --

A Yes.

Q -- the investigators had looked for neuroinflammation and failed to find it. What study are you talking about?

A Well, they were focusing particularly on glial changes, which are the sort of characteristic changes of injury that you get in postnatal brains. They did not find that. I'm not sufficiently expert on the techniques that they used to know how sensitive they were to that.

The study by Bailey and his colleagues similarly looked and found some evidence in some individuals that were compatible with that and again left open as it were the meaning of it.

So based on a very small number of brains investigated in slightly different ways by different investigators that don't as yet end up with a coherent story, I'm optimistic that in the goodness of time

they will, but until we're there it's premature to build much of a theory on it.

Q I thought you had already told us that you didn't know whether Kemper had looked for neuroinflammation.

I'm asking you to tell me what study you're referring to where they looked for neuroinflammation in the brain and didn't find it.

A I said she looked for glial changes. I don't know what range of techniques she used. I'd have to relook at the paper. Again, I'm not a neuropathologist.

MR. WILLIAMS: And then finally, Scott, pull in the last point there.

BY MR. WILLIAMS:

Q This is the point that Dr. Courchesne and the Vargas and Pardo group have made in their review papers that persistent neuroinflammation can explain the symptoms of autism.

Do you agree with that particular point; that it can explain the symptoms of autism?

A It's a speculative notion.

Q Now, every one of these points which come out of the published literature appeared in 2005 or later.

You were first retained by the vaccine manufacturers on the thimerosal question, according to your report, sometime in early 2004. Is that right?

A Yes.

Q So when you wrote the first draft of your report none of this information was available to you?

A True.

Q But when you wrote your report in this case all of that was available to you, and yet you didn't even discuss it, did you?

MR. MATANOSKI: I object at this point. This line of questioning, Your Honor, has gone on time and again. I've let it go on, but it deserves to be commented on.

The inference here is Dr. Rutter didn't mention this because it was part of the Petitioners' case that he couldn't address. This was not part of the Petitioners' case when he wrote his report. Neuroinflammation was not their case.

MR. WILLIAMS: I don't think this is the time for argument.

MR. MATANOSKI: Dr. Deth made his theory present and known back at the time that Dr. Rutter was answering and gave his report.

This three week old theory of

neuroinflammation, I don't think that it's proper for this line of questioning to keep faulting Professor Rutter for not addressing something that he had to be somehow cognizant of before it was even presented by the Petitioners.

SPECIAL MASTER CAMPBELL-SMITH: Petitioners' counsel, how much further are we going with this line of questioning?

MR. WILLIAMS: I just want to ask him if he agrees that that is a coherent theory.

BY MR. WILLIAMS:

Q Even if you say it's not proven yet, isn't it a biologically coherent theory?

A It's a highly speculative theory, and it's not one that had been drawn to my attention at all in the case at the time I wrote my report.

So that if I was redoing a new report I would look at these papers, but I would have to, as I indicated, be very careful in indicating this is not a particular area of science on which I'm expert so I would comment on it in terms of a causal inference.

I would not be prepared to comment on the details of the laboratory features. That's not my area of expertise.

Q Are you saying you can't say whether it's

coherent or incoherent?

A It's so general that it's difficult to say anything other than it's a speculative attempt to bring a general mechanism together in terms of accounting for a specific phenomenon.

Q Coherent or incoherent? What's your answer?

A It's so vague that it's neither.

Q Let's talk about regression for a minute. You agreed I think that there have been cases -- you've said you've seen them -- where there is clear and even dramatic regression into autism of children who developed normally until they were 18 months of age, correct?

A Yes. The dramatic is unusual, but I've certainly seen many cases of regression, yes.

Q Now, you said that you thought regression was on average about a quarter of the cases?

A Yes.

Q Are you aware of the study that was done in California called the CHARGE study? It's an epidemiological study of regressive autism.

A I'm not quite sure I recognize it by that.

MR. WILLIAMS: Let me show it to you. This is Petitioners' Master Reference List Exhibit 562.

Scott, if you would just pull up the title

of the paper? We've already discussed this briefly before with another witness.

BY MR. WILLIAMS:

Q The title is Regression in Autism, Prevalence and Associated Factors in the CHARGE Study. Have you not seen this paper before, Dr. Rutter?

A I think I probably have, but I need to look through it properly to check.

MR. WILLIAMS: If you would just blow up the abstract?

I don't want to go into the details. I just want to ask him about the conclusion of the abstract here for now. Highlight the Results section if you would.

BY MR. WILLIAMS:

Q In the Results section they say that 15 percent of the combined autism ASD group lost both language and social skills, 41 percent lost one or the other, and no differences were found between the two samples of children with regression.

But do you agree that this epidemiological study conducted in California probably is the best measure we have right now of the percentage of autistic children who have both language and social skills regression?

A Well, there are other studies. I'd have to read it more carefully to say that it's the best.

It does of course come up with a combined figure of whatever it is, 56 percent, so it's actually saying over half have regressive autism.

Q But the children we're talking about in this case lost both social skills and language, and the study found that those type of children only occurred in 15 percent of the cases, correct?

A Where does the fact that we're referring only to those who lost both come from?

Q The two cases that are at issue here today.

A Oh, I see. Well, I have not looked at the individual cases so I can't comment on that.

But in the general evidence that I have seen it's not been specified in that particular way. It's talked about definite regression. It's not said that it has to be in both language and social.

Q You made a general comment on epidemiology that you thought if it was 25 percent of the population, of the autism population, that the ecological studies that have been conducted on autism rates over time compared to thimerosal vaccines would have picked it up.

Are you aware that both Dr. Greenland and

Dr. Goodman for the defense have said that if it's 15 percent those studies would not have been able to pick it up?

MR. MATANOSKI: I think that's an unfair characterization of either witness. I'm certainly sure that it isn't Dr. Goodman's statement.

MR. WILLIAMS: Well, let me ask the witness another question.

BY MR. WILLIAMS:

Q Do you know what percentage of all autism they said would not be able to be picked up if it were a certain size? Do you know what numbers they used?

A No. I have read Dr. Greenland's statement, his report. He doesn't deal with what the proportion is, but he does assume a very low rate.

But he does so without reference to the literature on the reported studies looking at regression so that he ends up with the perfectly legitimate point that if it is a very low rate it wouldn't be picked up.

Now, what rate would be picked up would depend on which study one is talking about. Obviously the smaller the proportion the less likely would it have been to be picked up. I mean, that is a general epidemiological finding, and of course I agree with

that.

I have not looked at the evidence sufficiently in relation to knowing which percentage would have been picked up and which wouldn't.

Q Do you know what Dr. Rust said about this issue as to what percent of his patients he thought were truly regressive?

A I don't think I do, no.

Q You don't know that he said that of the patients that he has in his own clinic that were apparently regressive that when he went back and looked carefully at them only 20 percent of those cases were truly regressive? You're not aware of that?

A No, but I would question the basic assumption.

The evidence to date I think suggests that regression isn't an either/or phenomenon so that Dr. Kinsbourne in his report talks about in biology continuing the usual. I don't remember the exact words he used, but something of that kind. I agree with that statement.

My clinical experience over some half a century goes along with that in relation to regression. That's to say there are some cases that

are indeed severe and dramatic. There are others where much less so and all the way along the line.

The evidence as to which cutoff you should use to identify a distinctive subgroup, I don't think we have the faintest idea where that should be. But the study here, for example, just eyeballing it because I haven't had time to read it properly, indicates that they found no differences between the two samples with regression or the children without loss of skills so that the notion that there is a distinctive group I query.

I'm not saying it's impossible, but what I am saying is it certainly has not been demonstrated, and it certainly has not been demonstrated that any group of that kind is medically different. It's a possibility worth studying, but hasn't been shown.

MR. WILLIAMS: You can take that down, Scott.

BY MR. WILLIAMS:

Q Now let me ask you this squarely. What is your opinion as to whether there has been any measurable increase in the incidence of DSM-IV autism over the last 20 years?

A I don't know. As a careful, rigorous scientist it bothers me that I have to say something

as vague as that.

Let me put it this way. There is no doubt, and this would be generally agreed, that there is better ascertainment now than there used to be and that that will have certainly played a part in the rise.

It's also the case, and again as far as I know nobody has disputed it, that the broadening of the concept is for real and has played a part. So the question comes then does better ascertainment and a broadening of the concept fully account for the rise? I know of no evidence that can rule that in or rule that out.

But one of the studies that I am involved with, which is the Norwegian so-called MOBAS study, mothers and babies study, following 100,000 children and mothers from pregnancy onward is looking at whether there are environmental risk factors that could be involved with autism.

So I am very heavily committed to the need to study not just genetic influences, but also possible environmental causes, but I do so on the grounds that it is reasonable with a multifactorial disorder like autism to suppose there are nongenetic factors, and it is the job of scientists like myself

to strive to find them.

I think that the evidence as to whether there is or is not a real rise I don't think is worth investigating at the present time because I don't see how you would ever know. You can't go back in history with measures that were not existent at the time.

I am in favor of research that says here is a hypothesis about something that might have caused a real rise. Let us investigate it. That was done with MMR and it was done with thimerosal, and I think it was reasonable in both cases to look at the epidemiological evidence that it was associated with a real rise.

In both cases I think the evidence is against that having been responsible for a real rise, but clearly when the suggestion was put forward it needed to be investigated, and one of the key features that is most decisive is what happens when the risk factor -- MMR in the one case, thimerosal and vaccines in the other -- are removed.

So there is a need to look at this possibility. I don't know whether there's been a real rise.

Q Okay. You said that you thought in the modern era that the prevalence estimates now are

reasonably accurate?

A Yes, I do.

Q I assume that's post DSM-IV, is that right, the modern era?

A Yes. I'm not a great adherence to official classification systems despite the fact I was involved with both.

Q But what I was hearing you say is that we can reasonably rely on the prevalence estimates in more recent years of autism.

A Yes. Yes. Not because they rely on DSM-IV or ICD-10.

Q Okay.

A But because they use standardized instruments. They look carefully at confounding factors. They use good general population samples. I mean, they as it were remedied many of the problems of the earlier research.

Whether they were helped or hindered by DSM-IV and ICD-10 is really neither here nor there. They were good epidemiologics.

Q And when did we enter the modern era?

A That's a bit like regression. It happened gradually over time.

Q Okay. We're there now. You don't know when

the studies were published that we can trust and rely on their prevalence estimates?

Studies published after 1995? Can we rely on studies published after 1995 as giving us accurate prevalence estimates?

A I as always, as any good scientist does, do not rely on the year. It looks at the quality of the research. The quality of the research in the studies done in the last decade or so are definitely higher than those.

I know Dr. Fombonne has done analyses looking at particular year cutoffs. I think that's a sensible thing to be doing, but I actually don't have much faith that that actually gets you very far. I think looking at the quality of the research is the key thing.

Q Well, I think in your report you cite to the two studies done in Atlanta, actually in the United States, that estimated population rates of DSM-IV autism, and it came out to roughly 60 or 70 per 10,000.

Is that what you believe is the current reasonably accurate prevalence estimate of autism in at least the United States?

A Well, I also pointed out that the variation

in prevalence rates even in the recent studies that rely on administrative figures vary from state to state in a puzzling fashion. I concluded in my report that I therefore don't place a lot of credence on administrative figures for true rates of incidence of autism.

So whether the true figure is higher than that -- or I doubt that it's much lower; the study at Guillain Barré put it actually higher than that -- it certainly is somewhere between the half a percent to one percent, which is way higher than the estimates of 50 years ago.

Q And the good epidemiological studies done in the last 10 years --

A Yes.

Q -- have been able to reasonably and accurately measure the prevalence rate using those instruments you talked about?

A Yes.

MR. WILLIAMS: Okay. I need to spend some time with him on the epidemiological studies. It's 1:00. I assume this would be a good time to think about breaking.

BY MR. WILLIAMS:

Q However, I want to ask you about Dr. Young's

study that was published a couple weeks ago, and I want to make sure you have a copy now. Have you read the Young study?

A No.

MR. WILLIAMS: Let me give you a copy then that you can have over the lunch hour. This is Petitioners' Master Exhibit -- no. Is this a trial exhibit? We marked it though, didn't we? No? Yes, we did.

SPECIAL MASTER VOWELL: 665. Petitioners' Master Reference List 0665.

MR. WILLIAMS: 665. I'll write that on here for you.

SPECIAL MASTER VOWELL: It's the Young and Geier study.

MR. MATANOSKI: With respect to that, Your Honor, obviously we'll see what we can do over the lunch hour, but I would like to have Professor Rutter have a chance to eat too.

MR. WILLIAMS: I don't mind taking a longer lunch. We've lost two other witnesses today. We have plenty of time.

MR. MATANOSKI: The other characterization of this study as it being out for a couple weeks I think would not be accurate. I think it's been out

for a week now.

Maybe Petitioners' counsel have been aware of it much longer than that, but as far as in front of the Court I think it was on Friday the first week. That was the first time we saw this study from Young, Geier and Geier, I believe.

SPECIAL MASTER CAMPBELL-SMITH: Right. With these representations, how long is counsel proposing for lunch? How much longer do you anticipate going?

MR. WILLIAMS: Well, it depends on how long it takes to go through this study. I think it will take a lot less time if he has a chance to read it first. I think I've probably got 45 more minutes.

SPECIAL MASTER CAMPBELL-SMITH: An hour for lunch?

MR. WILLIAMS: I'm happy to take an hour and a half for lunch to give him more time to read it.

MR. MATANOSKI: I think an hour should be sufficient.

SPECIAL MASTER CAMPBELL-SMITH: An hour? I have 1:00 at this point, so we will take a lunch break and return and resume at 2:00.

MR. WILLIAMS: Okay.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

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(Whereupon, at 1:00 p.m., the hearing in the above-entitled matter was recessed, to reconvene at 2:00 p.m. this same day, Tuesday, May 27, 2008.)

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

(2:00 p.m.)

SPECIAL MASTER CAMPBELL-SMITH: Please be seated. We are back on the record to continue the cross of Sir Michael Rutter.

MR. MATANOSKI: Your Honor, if I may just before we start the cross?

There's one matter that I wanted to clear up on the record and that has to do with Dr. Pardo because there were comments about Dr. Pardo not being called by the government today and I wanted to clarify on the record what transpired following the close of our on-the-record proceeding on Friday.

We indicated that Dr. Pardo was available to testify today and offered that he would be available for cross-examination about the contents of his letter or his report. In that off-the-record conference with the Court and Petitioners' counsel they indicated that they did not desire to cross-examine him on those matters.

They also indicated that to the extent Respondent would be asking Dr. Pardo to offer an opinion beyond what is in his letter or in his article that that would constitute expert opinion in their view and that they were entitled to a written report

of that in advance.

It was in light of those representations that Dr. Pardo is not here today.

MR. WILLIAMS: I just wish they could have told us that on Friday because when we left here Friday we were under the impression that we were not allowed to contact Dr. Pardo because they had retained him and that he was going to show up today and testify.

So we actually did a lot of work over the weekend to prepare to cross-examine Dr. Pardo, and it was only yesterday that they told us they had decided not to call him.

MR. MATANOSKI: I'm not sure what kind of work would be necessary if all he was going to be discussing was his article, which has been referenced numerous times by Petitioners' counsel and their experts, and his letter, which is a page and a half.

SPECIAL MASTER CAMPBELL-SMITH: Any further comment, Mr. Williams?

MR. WILLIAMS: No.

SPECIAL MASTER CAMPBELL-SMITH: Thank you. To continue the cross, please.

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Whereupon,

MICHAEL L. RUTTER

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

CROSS-EXAMINATION RESUMED

BY MR. WILLIAMS:

Q Dr. Rutter, before we get into the ecological studies that you cite in your report and a couple controlled epidemiological studies of a cohort nature, I wonder. Do you know why we don't have any randomized control trial data on thimerosal vaccines and outcomes?

A As far as I know it's not been proposed so that --

Q You didn't know that there actually was a randomized trial in Italy that was done where a few thousand kids got thimerosal-containing DPT vaccines and several thousand kids didn't; they got nonthimerosal-containing vaccines?

Other than that trial, are you aware of any other randomized trial on thimerosal?

A No, I'm not aware.

Q In your opinion, would it be ethical today to do a randomized control trial on American children

with thimerosal-containing vaccines for half of them and thimerosal-free vaccines for the other half?

A Well, I think it would be ethical in the sense that there are known demonstrated risks associated with thimerosal.

Whether it would be sensible given the lack of evidence to spend time and money and resources to do a randomized control trial I doubt.

Q There was never any suggestion that thimerosal improved the immunization effectiveness of the vaccines, was there?

A No, no, no. It was a preservative.

Q Are you aware of any epidemiological study done to look at the association between thimerosal-containing vaccines and regressive autism?

A Not as such.

Q Let's talk about the Verstraeten study. You mentioned it in your direct, and you discuss it in your report.

I think you said one of the strengths of that Verstraeten study was the large numbers of children that were --

A Sure.

Q About 140,000 children in that study?

A Yes.

Q Do you know what Dr. Verstraeten himself has said about that study in the published literature?

A Yes. He has said that he regarded it as inconclusive.

Q Well, let's see if that's exactly what he said. Let me show you Petitioners' Master Reference No. 19. I'll give you a copy.

A Okay. Thank you.

Q Now, this is the letter that Dr. Verstraeten wrote to the journal in which his study had been published, correct?

A Yes.

MR. WILLIAMS: I don't know if we know the date of this letter.

Scott, do you know the date of this? It doesn't have a date on this page.

THE WITNESS: It followed shortly after the article.

MR. WILLIAMS: Yes.

THE WITNESS: I don't remember the exact date.

MALE VOICE: April 2004.

MR. WILLIAMS: April 2004 is the reference. If you would highlight the top right-hand column, the top of the right-hand column, Scott? Yes. Maybe a

little bit further down there. Blow that up.

BY MR. WILLIAMS:

Q Do you see where he says: Surprisingly, however, the study is being interpreted now as negative by many, including the antivaccine lobbyists. Now, is your characterization of this study as negative?

A As I said, he describes it as inconclusive, and he does so because of the wide confidence interval.

Q No. I'm asking what your characterization of it is. Do you think it's a negative study, or is it an inconclusive study?

A The studies can't be divided up quite like that. What you have to ask is is there any evidence from this study and others using a range of strategies that is in support, and the answer is no. This is not in support.

Q He goes on to say: A neutral study carries a very distinct message. The investigators could neither confirm nor exclude an association, and therefore more study is required.

Do you agree with that; that more study in this Vaccine Safety Datalink database is required?

A At the time that that statement was made

that might be correct, but since then we've got a number of other studies, all of which failed to show any association, so I would no longer regard that as appropriate. This was four years ago, remember.

Q That's right. Did you know that in 2006 the NIH convened a panel of experts on autism and epidemiology to consider whether additional studies within the Vaccine Safety Datalink could and should be done that would be informative on the question of the association between thimerosal vaccines and autism?

A No, I didn't know that.

MR. WILLIAMS: You didn't know that? Well, let me show you that briefly and ask you if you agree with their recommendations. This is Petitioners' Master Reference List 553.

The rest of us have seen this before, Doctor, so let me just represent to you that that is the signature on the first page of the Director of NIH, and it was in October of 2006 when this was released.

If you could just pull up, Scott, the highlights that we had in there on what the committee recommended be done?

BY MR. WILLIAMS:

Q You haven't seen this report before, Dr.

Rutter?

A No. No, I haven't.

Q It says that one possibility that generated support by the panel, and they're talking about possible studies that could be done, was an expansion of the VSD study published by Verstraeten.

By expansion I think it's fair to say they were talking about both an expansion of time forward to the point where a lot of the children had not been exposed to thimerosal, as well as an expansion geographically to additional HMOs within the system.

Because I think even one of the criticisms you made of the Verstraeten original study was that it only had three HMOs in it, and one of them was very small, right?

A Right.

Q So would you agree with this expert panel in October of '06 that it would be a good thing to do to expand this Verstraeten study timewise and geographically?

A You've got to remember I come from the U.K., and with the availability of funds in the U.K. I would have to say there is not sufficient evidence in my view to justify spending British money doing an expanded study.

I realize the U.S. has much more money and if in its wisdom wished to expand, fine, but the situation now I think is where there are sufficient studies with different strategies coming to the same conclusion that I wouldn't want my taxpayers' money used in that way.

MR. WILLIAMS: You can take that down, Scott.

BY MR. WILLIAMS:

Q Let's turn to your discussion of some of these ecological studies you mentioned. Now, the Heron study you discuss on page 44 of your report.

A Yes.

Q That was one of these prospective cohort studies, correct?

A Yes. Correct.

Q Now, you said in your report, and isn't this a fair criticism of the study, that it didn't have autism as an endpoint, right?

A Uh-huh. Correct. Correct.

Q We have to have an audible answer for the record.

A Oh, I'm sorry. I'm sorry.

Q I knew what you were doing. The audience didn't.

It also was a fairly small study, right? Only 14,000 children.

A Yes.

Q You wouldn't be reasonably able to detect a change in the autism rates among that small group of children, would you?

A Well, in that it's a single cohort you couldn't look at change anyway. You could only look at associations here.

Q But the confidence intervals would be enormous, wouldn't they?

A Yes.

Q Right. And yet you think that you can take that study and add it to the rest of them and it gives weight to them nevertheless, right?

A I didn't give much weight to it, as you will realize from what I've got in the report. There are too many limitations on it for me to wish to place much weight.

I note that it is a good epidemiological study. I have no criticisms on that, but the reasons you've given -- that there isn't a specific focus on autism and its sample size is on the small size, studies of this kind -- I wouldn't place much weight on it and I didn't.

Q Now, on page 44 of your report in discussing the ecological studies in general in paragraph 75, and let's just pull up paragraph 75 of your report and discuss it for a second.

You're talking about one of the limitations in the cohort studies is that there is little variation in the total amount of thimerosal received.

A Right.

Q Why is that a weakness in the cohort studies?

A Well, because the opportunity to find an effect is of course very much related to the degree of variation in what is your independent variable so that to go to an extreme you can't look at the effects of thimerosal if everybody gets the same dose at the same time.

By extending that argument a little bit further if the variation either in the timing or in the dose is very small the chance of detecting an effect is equally limited.

Q Now, if you tried to solve that problem by combining a group of children who were exposed to thimerosal in say years one, two and three and then thimerosal is removed and now in years five, six and seven you have no exposure, don't you still have a

problem because you're not measuring the rates at the same point in time? Isn't that also a weakness in the study?

A I'm not quite sure what study you're referring to, so I'm not -- I mean, has anybody done that?

Q I thought you cited several studies that had done that in your report. The Scandinavian studies that looked at a point in time when thimerosal was in the vaccines and another point in time when it was out.

A Yes.

Q My question is doesn't that though add some potential confounders that wouldn't be there if you could look at different doses at the same point in time?

A No. But as I tried to point out, each of the designs has got its own particular strengths and limitations.

The advantages of the ecological designs looking at time/trends comes especially because their one big strength is that there is a firm prediction of what should happen when thimerosal is discontinued. That's its strength.

Its limitation is that you can't look at it

on an individual case basis. If you look at the cohort studies you have the opposite set of strengths and limitations. There you can look at it in terms of what the individual has received and you can control for confounders much better because you have individual data, but you can't look at changes over time.

So this comes back to the main point I was trying to make in my report, which is that you're foolish always to rely on one single type of design. The strength comes from looking at a number of different designs, each of which have particular strengths, but equally each have particular weaknesses.

Now, if a varied range of designs give you a varied set of answers then you are in difficulty in knowing what to conclude. If, however, despite their variations in strategy they come up with a broadly similar answer that gives one confidence that the positive or negative conclusion as the case may be is more likely to be solid.

Q Let's turn to the Young-Geier study.

A Okay.

Q Which is Petitioners' Exhibit 665.

A Yes.

Q Now, this study has 278,000 children in it, correct? Right?

A Something like that, yes.

Q Much larger than the Verstraeten study?

A Yes.

Q And much larger than any of the other ecological studies that you cited?

A Yes.

Q Isn't that a strength of the study?

A No. Let me talk about the study in a bit more detail. Quite frankly I think it's a poor study, and it's a poor study for several different reasons.

To begin with, it starts off with a cohort design so that, as I understand it, they have records on individuals that they could follow forward, but they don't actually analyze the data that way. What they analyze is in terms of time/trends.

In order to do that they have to make various adjustments with the first cohort and the last cohort so that you're dealing with a strange design which is putting together chalk and cheese in the hope of gazpacho soup coming out, to use a rather mixed analogy.

Q Well, let me ask you. Do you know whether they were allowed to look at individual --

A Of course not. I haven't discussed it with them.

Q What?

A No, of course I don't know that because I haven't discussed it with them. All I've got is in the paper. So it is poor from that point of view. I think that their analytic design and strategy was not a satisfactory one.

In terms of conclusions, if one turns to Table 3 the thing that is really striking is that you have a significant effect using a fact now not in a causal effect, but in a statistical effect --

Q Yes.

A -- with a really quite heterogeneous range of disorders.

So that let's take the neuro information hypothesis as the one that we were talking about before the break is correct. It is dealing with the most significant effect on tics and on disturbances of emotions.

So one would have to suppose that if this is seen as supportive you're getting a neural effect that is going across a range of disorders of an extremely heterogeneous kind with different ages of onset, with different genetic factors involved, with different

courses, so that the very major lack of specificity would make me immediately skeptical as to what it shows.

Q But they did use control disorders of pneumonia, congenital anomalies and failure to thrive, didn't they?

A Yes, they did, but why are they there and disturbance of emotion is not there?

Q Well, the data is the data.

A Exactly. The disturbance of emotions should have been a control disorder.

Q Well, even if it had been in the controls if they found an association they would have to report an association.

A Exactly.

Q And they reported what they found.

A Exactly.

Q What's wrong with recording what you find?

A The inferences you draw from it. I mean, I don't know what the basis of the control disorders choice was, but I would have thought that anybody who knows anything about the field at all would have put disturbances of emotions as a control disorder.

Q But even if they put it down there, if they've got the data it would come out the way it is.

They've got to report what they've found.

A Yes. Exactly. And what you have to show then is that you have a fact that is even more significant for the control disorder than you do with the neurodevelopmental disorder.

The disturbance of emotions is not by anybody that I know of regarded as a neurodevelopmental disorder.

Q Well, whether they classify it as a neurodevelopmental disorder or not it's an ICD-9 code.

They look and see whether it's associated statistically with this difference in exposure, and they found that it was. What's wrong with finding that and reporting it?

A Because the postulate is that it is found with neurodevelopmental disorders and it is not classified by ICD-10 or DSM-IV or any psychiatrist either side of the Atlantic that I'm aware of as a neurodevelopmental disorder.

Q So you're not quibbling with the data that they found. You're just quibbling with how they characterized it before they started the study, right?

A Well, I quibble with both. I think changing it from what could have been a cohort design into a somewhat artificial time/trends design, I mean that

doesn't seem to be a scientifically sensible thing to do.

Q You think that they should not have looked at emotion disorders at all? They should have just left that out?

A That's not what I'm saying.

Q Well, then what are you saying?

A I'm saying that the control disorders which are defined as nonneurodevelopmental should include all the nonneurodevelopmental disorders.

Emotional disorders by the opinion of anybody that I have ever heard of either side of the Atlantic and the official classifications and the empirical research evidence is not a neurodevelopmental disorder, and therefore to include it as supportive rather than contradictory is against the strategy.

Q You're not disputing right now that that's what the data show. However they categorize it, if they look at that ISD-9 code and find these statistics they have to report it, don't they?

A That's not the point I'm making. I'll make it once more, and then I really refuse to answer any more questions on it.

The point is that they have created two

groups, one of neurodevelopmental disorders and one of nonneurodevelopmental disorders. What is wrong is that in the neurodevelopmental disorders they have included a condition that nobody but nobody would regard as neurodevelopmental. Therefore, the comparison between these two groups has to be invalid.

Q There are a lot of neurodevelopmental disorders that they don't have and they didn't look at, right? They couldn't possibly have looked at all of them, could they?

I mean, realistically in ICD-9 aren't there just pages and pages and pages of neurodevelopmental disorders?

A This is not what they've left out. It's what they've put in.

Q Do you agree that the fact that they have large groups of children with a 100 microgram exposure difference is a strength of the study?

A I don't know why they took that particular cutoff. That's not explained.

MR. WILLIAMS: Yes, I think it is if you look on page 5 of the paper in the right-hand column. Let's go through this just so we can understand this.

Just above the figure, Scott, if you would highlight the Finally paragraph?

THE WITNESS: That describes what has happened over time. Yes.

BY MR. WILLIAMS:

Q Well, what they say here, Doctor, just to summarize it, is that there was a period of time in '92 and '93 in this country when there were two types of DTP vaccines being used.

Some of them were combined with the Hib vaccine in such a way that a lot of children only got four shots because they were combined and therefore only got 100 micrograms, 25 per shot, whereas another large group got separate shots and got eight shots and got 200 micrograms.

They were able to take advantage of that large difference to see if there was any association. Isn't that a strength of the study that isn't present in any of the other ecological studies that we have?

A No, I don't see it as a strength. I mean, the problem is that unless you've got a hypothesis which says something testable about what level of exposure the effects come it is entirely arbitrary to change it in terms of what particular mix happens so, no, I don't regard that as a strength.

Q You don't think it's reasonable to look to see in a database that allows it if there's a

difference in association between neurodevelopmental disorders and a 100 microgram difference in exposure?

A What I'm saying is that it's arbitrary in the absence of a hypothesis as to what sort of level of difference matters.

So that one of the real problems in trying to look at the literature as a whole here is that there is a complete lack of specificity as to whether, for example, the European studies are relevant or not relevant because the dosage of thimerosal is lower in the European vaccines than it has been in the American vaccines, so it keeps changing as it were as to what seems to suit the case being made.

Q All right. Have you looked at the Terbutaline papers that we've discussed in this trial for the last two weeks?

A I'm sorry. The what papers?

Q Do you know about the Connors twin study done at Johns Hopkins on twins and siblings exposed to Terbutaline in preterm labor?

A I don't think I do know that.

Q You're not familiar with that at all?

A I don't think so.

Q And you're not familiar with the follow-up animal study they did that found that in animals

Terbutaline provoked neuroinflammation in the brains of the animals?

A I think that's not a literature I've looked at.

Q I want to ask you about a study that you did cite. You cite on page 41 of your report a study from Hong Kong by Ip, et al.

A Yes. Yes.

MR. WILLIAMS: If you could pull up paragraph 71, Scott, and blow up the first six or seven lines of that paragraph 71? It's coming up.

BY MR. WILLIAMS:

Q This is you discussing Ip. You say: More importantly, the basic findings with respect to a lower level of mercury in the hair of children with autism have not been confirmed in the study from Hong Kong.

A cross sectional study of both hair and blood mercury levels of 82 children with an ASD and a mean age of about seven years were compared with a normal group of children, a control group of normal children. No differences were found between either the blood or hair mercury levels of the two groups, and therefore this evidence runs counter to the suggestion of a causal relationship between mercury

and ASD.

Now, are you aware that this study has been reanalyzed?

A I am.

Q You just didn't catch that before you wrote the report?

A Correct.

Q Do you agree now that based on the reanalysis which found a positive statistical association between blood levels and autism that this study now points toward a causal association rather than away from it?

A No, I don't. There are two key things. Firstly -- I don't think I've got that paper with me. No, I haven't. Okay. If you would fish it out?

To begin with, the reanalysis by the group shows a significance level of .056, and the critique argues that they should have said that's nearly significant.

That actually of course isn't the way things work in statistics. If you're going to take a cutoff then whether it's just above the cutoff is not relevant. That is why statisticians nowadays tend to prefer confidence intervals rather than a set statistical level.

But the other problem is that the critique argues that a one-tail test should have been employed. Now, a one-tail test means that you are looking at a finding only in one direction and that if it comes in the opposite direction you ignore it.

But the problem here is that that isn't the case so that the literature now dealing with a range of studies here sometimes point in one direction and sometimes another, so to have done a one-tail test would have been statistically quite inappropriate.

So what we end up with is a study that fails to show an association, but you could argue that the significance level comes close if you like, but it doesn't point in the opposite direction.

Q Let me show you the Results section here, the first paragraph of the Results section, because I think there may be a misunderstanding. This is Petitioners' Master Reference List 423.

A Right.

Q This is the paper by DeSoto and Hitlan entitled Blood Levels of Mercury Are Related to Diagnosis of Autism: A Reanalysis of an Important Data Set.

A Yes.

Q By the way, this reanalysis was published in

the year 2007.

A Yes.

Q And you wrote your report in 2008. You just failed to detect this?

A Well, I have read the paper. I hadn't read it at the time I wrote my report. That's quite true.

Q Well, let's look at what the P value is in the relationship between blood and mercury -- excuse me; mercury blood levels -- in autism in the Results section.

The first paragraph says: Logistic regression was performed using blood mercury level as the predictor and the autistic control group as the criterion. Results of this reanalysis indicate that blood mercury level can be used to predict autism diagnosis with a P value of .017.

Now, that's a statistically significant association, isn't it, Doctor?

A Yes, it is, but if we go on -- let me find it.

The original authors have now currently calculated -- this is the bottom of page 1310. The obtained difference suggests probably a real difference with a probability that this count is true of 94 percent, i.e. a P value of .06, misses the

conventional mark.

Given the close value, most researchers would not call this a firm rejection of the hypothesis, but might say it was marginally significant.

Q I've lost you. Where are you reading from?

A The bottom of page 1310, the top of page 1311.

Q That's about hair, isn't it? I was asking you about blood levels.

There's another exchange that I didn't want to take the time to go into about the hair levels.

A Right.

Q Dr. Aschner wrote a paper or wrote a letter criticizing this paper for not analyzing the hair levels properly, and then DeSoto and Hitlan responded to Aschner and said no, you misunderstood us. Even the hair data supports this.

I didn't want to go into this. Have you read that exchange of letters?

A No, I haven't.

Q Okay. Then let me ask you about one other study you cited in your report.

On page 40, paragraph 69, you talk about these studies of autism rates in relation to coal-

fired power plants that release mercury into the air, and you criticize the Palmer paper in paragraph 69 by saying:

There are no data on how environmental release of mercury actually gets into the body, and hence there is no way of telling whether the mercury effects should be considered likely to be restricted to the county within which the industrial output existed.

Now, do you know that Palmer has published an updated study of this same effect --

A No.

Q -- where he takes into account the distance from the power plant?

A No, I don't know that, but I will come back to similar studies in relation to lead which I was concerned with -- where are we -- 30 years ago.

The point made then was that if toxins -- in this case they were talking about lead rather than mercury -- are released into the atmosphere the question as to how they get into the body is a key feature and that if they are getting into the body through being deposited on food the effect is much broader that you'd expect from where they live.

So that doing the analysis by area actually

is not a very good way of doing it, but apart from the fact that you're dealing here with a dispersal which has got really nothing to do with thimerosal.

But my main point here is that you've got to know the route into the body to know whether the effect is area specific or not, and they haven't done that.

Q Let me show you the updated study.

A Okay.

Q It's Petitioners' Master Reference List 560. This is what they call a preedited final edited publication.

That happens with some of your papers too, doesn't it, sometimes where they release the prepublication version even before you've finally edited all the copy, and then you have a chance to correct it before it actually appears in the final journal?

A That is unusual if it hasn't gone through review before that.

There is now in many journals internationally journals that are put on line after they have gone through full review and correction before they're printed on paper. Is that what you're talking about here?

Q Well, let me just show you the paragraph at the bottom of this first page. This study has gone through peer review.

A Okay.

Q It's been accepted for publication. Then they say: As a service to our customers, we are providing this early version of the manuscript. The manuscript will undergo copy editing, typesetting and review of the resulting galley proof before it's published in its final citable form.

A Okay.

Q But the paper has gone through peer review and has been accepted, right?

A Okay.

MR. WILLIAMS: And just quickly if you go above the Methods section, Scott, on page 5 of this exhibit? Just pull up this part of the paragraph if you would.

BY MR. WILLIAMS:

Q Now, Dr. Palmer is discussing here the various papers that you discuss, the Windham study from California --

A Yes.

Q -- and Palmer's previous paper of 2006 that you cite.

A Yes.

Q And he says: The Windham study and my study demonstrated that environmental mercury pollution was associated with point prevalence estimates of autism using EPA reported mercury release data from 254 counties in Texas.

A major limitation to this study was that the cross sectional design precluded any causal inferences. In addition, exposure was inferred from total pounds of environmentally released mercury aggregated at the county level at a specific point in time.

Using distance to potential exposure sources may be a more reasonable proxy for exposure than one defined by amount totals contained within the artificial county boundaries.

So the criticism that you made in your paragraph 69 where it says that the mercury effects should be considered likely to be restricted to the county within which the industrial output existed, Palmer's group is now trying to fix that problem by measuring proximity to the source as a new variable in the study.

A Okay.

Q Do you agree?

A It seems so.

MR. WILLIAMS: In fact, he says in the bottom line of that same paragraph, Scott, or the next paragraph if you can pull it up just a little bit and highlight that?

BY MR. WILLIAMS:

Q Right above Methods it says: The objective of the current study is to determine if proximity to major sources of mercury pollution are related to autism prevalence rates.

A Yes.

MR. WILLIAMS: Now let's go to the Results section, which is on page 8 of this exhibit. Excuse me. Page 7, Scott. It starts at the very bottom of page 7. I just want to blow up that paragraph there of the results for a second.

BY MR. WILLIAMS:

Q He's talking about different models that he used, but he says right here: Model 1-A shows that environmentally released mercury in 1998 is significantly associated with autism rates in 2002. Do you see that?

A Uh-huh.

Q Is that a reasonable timeframe? Assuming that the exposure is by inhalation of mercury vapor

from these plants by infants in 1998, would it be reasonable that you would be able to pick up diagnoses of autism four years later?

A Yes, probably.

MR. WILLIAMS: Then he says that they worked with this coefficient to come up with an incident/risk ratio.

The last sentence of this page, Scott, and then carry over.

BY MR. WILLIAMS:

Q It says: The coefficient yields an incident/risk ratio of 1.026 indicating that for every 1,000 pounds -- now we're at the top of the next page. Yes, there we go. That for every 1,000 pounds of release in 1998 there is a corresponding two percent increase in 2002 autism rates.

Then they try to take into account the number of pounds, and then finally they add distance in Model 1-C. This is the point I want to make and then ask you about. It says: Adding distance to the equation in Model 1-C shows that for every 10 miles away from the source there is a decreased autism incident risk of 1.4 percent.

Now, doesn't that fix the county limitation that you were criticizing in the first version of this

study?

A Not really. If we turn to page 10 where the limitations of the study are outlined, you see several important features. To begin with, the conclusions about exposure are not based on the distance from individual homes, but from school district centroids of various sizes so that it's not an accurate distance.

The further point I made is that you don't know about the route by which the mercury gets into the body, and that obviously depends on all sorts of things and matters. What it says is the study should be viewed as hypothesis generating, not as proving anything one way or the other.

Q Isn't virtually every study hypothesis generated?

A Not at all.

Q Some studies just end the question with no further study needed?

A No. That's not the point. That's not what's meant by hypothesis generated. There are studies which as it were raise a possibility.

Let me come back to the Fenfluoramine and Secretin examples I used earlier so we stick within the area of autism. So Fenfluoramine was based on a

hypothesis generating study which suggested that Fenfluoramine, because it was known to lower serotonin levels, was a reasonable candidate for doing further studies.

That was then followed by hypothesis testing studies that were different in the sense that they first of all looked to see whether Fenfluoramine had effects on autism symptoms, so this was done in a way in which these were quantified.

And, secondly, it was done by related whether insofar as there were benefits, and there were very few. Insofar as there were benefits, was it associated with a degree to which serotonin levels had formed, and the answer is they were not.

So this was a hypothesis testing study which used an earlier hypothesis generating study in order to do it in a way which could either confirm the hypothesis or it could refute the hypothesis in the event it refuted the hypothesis, but it could have worked either way.

So it's a quite different form of study. Hypothesis generating is what comes first. Hypothesis testing is what comes next.

Q So if someone is trying to decide whether it's biologically plausible that mercury exposure can

lead to autism in some children would you have them just ignore this Palmer study, or would you have them put some weight on it?

A I wouldn't put much weight on it. I think that when you're planning a new study you look very broadly and you pay attention to all sorts of things.

No, I wouldn't put much weight on it, but would I put some? Well, yes. It's an interesting finding insofar as it goes, but doesn't take one very far, I think.

Q Do you recall there was a point in your report where you said that on the question of whether thimerosal-containing vaccines are associated with regressive autism that that question is susceptible to being studied in a rigorous way?

A Yes.

Q What did you mean? How could you study that in a rigorous way?

A Can you direct me to --

Q Well, I thought I could. I frankly can't now find -- let me see if I can find the quote.

A Here we are. Paragraph 92.

Q Okay.

A So what I say -- let me read it out because it's quite short. I say: It would have been possible

to test the regression hypothesis in a vigorous way. Actually that should mean rigorous. A typo that has escaped my attention.

Q I read it as rigorous too.

A For example, cases involving regression and those apparently without regression could be compared blind the knowledge on regression on the presence of multiple congenital physical anomalies because they will have had to have arisen prenatally.

The advantage of such an approach is that it would not be reliant on anyone's recognition of the behavioral changes in the first year of life. The same thing could be done in relation to head size.

So those are two strategies. They're not the only ones, but the point is that having had an exploratory approach put forward that suggested something what you need to do is think what design can I use that could either prove or refute that hypothesis, and that's what singularly has not been done, but it could have been done.

Q And are you critical of the families that have brought these claims for not having done such studies?

A I'm never blaming the families because when orthodox medicine doesn't have answers that will bring

cures to their children they look around for possible explanations. They look around for people who have things to offer. No, I don't blame the parents at all. It's the scientists.

Q Just one last quick topic, Dr. Rutter. You started working for the vaccine manufacturers on the thimerosal litigation you said about four years ago?

A Yes.

Q And then you say in your report that you started working on the MMR litigation a year before that?

A Yes.

Q Is that about right?

A Yes.

Q So probably sometime in 2003?

A Probably. It must be something like that, yes. It may have been earlier.

Q Now, in 2005 you published a paper in the *Journal of Child Psychology and Psychiatry* on the effect of MMR withdrawal in a population in Japan.

A Yes.

Q Do you remember that paper?

A Yes.

Q Now, I don't know what you did, but there is no disclosure on the paper that you had already been

retained by vaccine manufacturers to work on the MMR litigation, even though the subject of the paper is MMR. Did you make a disclosure about that?

A Presumably I didn't as it isn't in the paper, but of course I hadn't completed a report at all, and the data were all collected and analyzed by Honda, not by myself.

Q Didn't you just testify recently in a hearing in the U.K. against Andy Wakefield where the issue is whether he had made a proper disclosure of his conflict of interest?

A I did indeed, but that is in somewhat different circumstances in that he was presenting results of his analysis on his cases and claiming a particular causal effect.

MR. WILLIAMS: Let's introduce the paper into evidence. It will be Trial Exhibit No. 10.

(The document referred to was marked for identification as Petitioners's Trial Exhibit No. 10.)

THE WITNESS: It's a much more indirect connection, but if you're suggesting that it would have been reasonable that I had made that act (phonetic) I wouldn't have any objection to that.

I mean, it didn't occur to me at the time and there are reasons why I think it wasn't directly relevant, but there was certainly no attempt to conceal it.

BY MR. WILLIAMS:

Q You think you're not as tempted by conflicts of interest as other scientists?

A Some are. Some aren't.

MR. WILLIAMS: Thank you.

SPECIAL MASTER CAMPBELL-SMITH: Any redirect?

MS. RICCIARDELLA: Yes.

SPECIAL MASTER CAMPBELL-SMITH: Let me clarify. Did Petitioner intend to introduce that last document as an exhibit?

MR. WILLIAMS: Yes.

SPECIAL MASTER CAMPBELL-SMITH: Okay.

MR. WILLIAMS: As Exhibit No. 10.

SPECIAL MASTER CAMPBELL-SMITH: No. 10.

MR. WILLIAMS: Yes.

SPECIAL MASTER CAMPBELL-SMITH: Okay.

MS. RICCIARDELLA: Can we take a 10 minute break, ma'am?

MR. MATANOSKI: The only reason for our asking for that is there are two papers that Professor

Rutter was asked to look at, and we just want to have him have a chance to look through them -- he hasn't seen them before -- in case he has any comments that might be enlightening for the Court.

SPECIAL MASTER CAMPBELL-SMITH: Let me take a look and see what time we're actually at just for the record.

We are just about at 3:00, so let's go until 3:10.

MR. MATANOSKI: Thank you.

SPECIAL MASTER CAMPBELL-SMITH: Thank you. we'll take a brief recess.

(Whereupon, a short recess was taken.)

SPECIAL MASTER CAMPBELL-SMITH: Please be seated. We are back on the record for the redirect of Sir Michael Rutter.

MS. RICCIARDELLA: Thank you.

REDIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Professor Rutter, at the beginning of your cross-examination Mr. Williams put up a Power Point slide that had listed six or seven points that Petitioners' experts have made in this litigation, and I believe he had it under the title Biologic Coherence. I can't recall the exact language.

Did any one of those points, the six or seven points that were listed, change your opinion in this case?

A No.

Q And one point stated that there is a wide variability in individual blood and brain metals of mercury. Is this indicative of anything?

A No. As I mentioned at the time I think, huge individual variability is a feature of almost anything that one looks at with human beings.

So that, for example, the range of when children's teeth come through is very variable. The age at which people reach puberty is very variable, but that doesn't mean that there is some interaction with an environmental factor. Variation is part of the biology.

Q Now, Mr. Williams was also asking you about inorganic mercury persisting in the brain. Is inorganic mercury specific to vaccinations?

A Not at all. It applies to a wide range of things like dental amalgam, for example, so that once one moves to aspects of mercury that are not specific to thimerosal then one is moving into a range of studies that are concerned with mercury as a possible risk factor, but not necessarily thimerosal.

Q Now, you were asked a lot of questions about studies that have been done pertaining to neuroinflammation and its purported role or association with autism.

What causal inferences can be drawn from any of these studies that were discussed here today pertaining to neuroinflammation?

A Well, none. They are hypothesis generating, if you like, so they are putting forward speculation suggestions.

As I indicated, a beginning of much science comes from telling an imaginative story as to what might be the case so they do that, but they don't demonstrate causation at any sort of level at the moment.

Q You were also asked some questions pertaining to head circumference and autism. What are the head circumference findings that are unique to autism?

A It is the normal head circumference at birth and the increase that takes place during the preschool years. It is a very characteristic feature.

As I indicated, it does vary from child to child, but it is something which is quite unusual in relation to other neurodevelopmental disorders.

Q Now, you were also shown a study by Mr. Williams. It's a future or current study. They're currently recruiting participants that are looking at minocycline to treat childhood regressive autism. Do you recall that line of questioning?

A Yes.

Q Does this study establish causation at all?

A No. I mean, the study hasn't been done for starters, but it falls into the group of things having a parallel (phonetic) with Fenfluoramine and secretin that might result in something of interest, but hasn't been done.

It is in any case an apron study so that even at completion it will still be rather inconclusive, so, no, it doesn't take us one stage further at all.

Q You were also asked whether it's possible that individuals could be susceptible to mercury, and I think you said it was possible, but not established. Is that correct?

A That is correct.

Q Based on what's known about exposure to mercury, have we seen any evidence of a hypersusceptibility to mercury?

A No. I mean, the experimental studies that

have been done have tended to show results that apply to a group as a whole rather than, if you like, outliers with a very unusual response.

The studies have not been sufficient in number or the subjects sufficient in number to rule out the possibility of a hypersusceptible group, but they certainly don't point to that being an issue.

Q You were also asked a question with regard to whether in your opinion you think that further resources should be used to conduct a follow-up study of the Verstraeten study, and you said no.

Is it just an economic consideration, or are there other considerations at work as to why you would not recommend any further such studies?

A It's a question of one wanting to put one's resources into things that are likely to pay off, so let me answer it a somewhat different way around.

We've talked primarily for obvious reasons about the hypothesis that thimerosal is a causative factor, but in the course of doing that we've touched on various studies that have looked at mercury as distinct from thimerosal.

The evidence that is worthwhile doing further research on thimerosal I find unconvincing. I wouldn't put much money in that direction. I'm much

more neutral or positive, however you like to look at it, about the effects of mercury coming in other ways.

So we know that mercury in high dosage is a neurotoxin. For example, I mentioned the Norwegian study. I'm not one of the principal investigators, but I am on the advisory group for that study, and it is looking at a range of variables during the prenatal and early postnatal phase that might be relevant, and obviously mercury in fish is one of the things that is being looked at, so I definitely don't rule out the possibility that mercury might play a role.

The evidence is weak. On the other hand, it's not so weak that it isn't worthwhile taking it further forward. It's not the only hypothesis being examined. Indeed, there are quite a range of them. There are a range of biological measures being taken to try and get a tight hold on this.

But we do need to be concerned with possible environmental causes of disease and so I would put that on the list of possibility.

Q You were also asked a couple questions or more than a couple questions about the individual epidemiological studies that you cited in your report and discussed during your direct testimony.

Now, you were asked about the individual

studies, but is that a proper way to look at the epidemiology that has arisen in this area?

A No. One needs to put them together. I was explaining referring I think to my Academy of Medical Sciences report that in science you need to not only combine multiple studies, but you need to combine multiple research strategies and that the strength of findings is very much influenced by doing that.

It's very rare to find a study that on its own changes things completely either for or against. It has to be taken as a whole.

Q You were asked a couple questions about the DeSoto paper, which is Petitioners' Master List 423. Do you have any further comments about that paper?

A Yes. I was taken to task in referring to differences where I was told we're dealing with hair mercury and I should have been focusing on blood, but as far as I can see, reading the paper carefully, what I was talking about is what I said I was talking about, i.e. findings on blood levels.

Q Okay. You were also asked a series of questions about the Palmer study.

A Yes.

Q A recent study. Does that study speak at all to the issue of whether or not thimerosal in

vaccines causes autism?

A No, because again I draw the parallel with the Norwegian study. It is dealing with a more general issue as to whether mercury in its various forms through various routes may be causing risks.

At the present time we don't really know enough to know whether they do or they don't. I do see that as worthwhile, but because it is looking at pollutants from factories the connection with thimerosal is indirect to put it mildly.

A further issue in relation to the question of the tightness of the association is that I note now looking at the paper more carefully that they make the point about you really need to take account of wind patterns and rainfall and so on, and they weren't able to do that at that time.

So it's an interesting hypothesis generating study, but in itself it doesn't take us very far on mercury generally, and it doesn't really take us anywhere in relation to thimerosal.

Q Finally, Doctor, Mr. Williams asked you about your participation in the Honda paper --

A Yes.

Q -- which I refer to as the Honda study.

A Yes.

Q The study in Japan looking at MMR. He drew the analogy to your testimony in the United Kingdom that you've given in the General Medical Council with regard to Dr. Andrew Wakefield.

Do you have any comments on the analogy that Mr. Williams was drawing?

A Yes. The situation is really a very different one. With the benefit of hindsight I can quite see that it might have been prudent to have made that overt, although it is well known that I had played that role.

The difference is as follows: The British law is that the responsibility of an expert witness is to the Court. It is not to whoever has called you. That is a difference, I realize, from the American system.

So that it is not a conflict in that sort of sense, and indeed to get back to the lead situation that wasn't a Court case, but actually I came out saying there was sufficient evidence that lead was damaging, that it should be withdrawn.

So with Wakefield the situation was that he was funded to do the study. He was funded in relation to litigants. Many of the cases involved in his study were involved in the litigation, so there was a very

direct involvement which he concealed.

My involvement with the Honda study, first of all I wasn't funded to do it. It was not my analyses, and I was an expert witness who was never called. So certainly I had no intention of concealing it.

Perhaps I should have made it overt, but it is fundamentally different from the Wakefield situation where there were direct financial issues involved and direct involvement of litigation, direct involvement of the cases in the litigation with the study.

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

SPECIAL MASTER CAMPBELL-SMITH: Re-cross?

MR. WILLIAMS: Just one.

RE-CROSS-EXAMINATION

BY MR. WILLIAMS:

Q In your work on the MMR vaccine starting in 2003, it was the British Government that was paying you?

A No.

Q Who was paying you?

A The drug company was paying me. So that the way that it works is that obviously somebody has to be

paying. There are situations where the Court pays directly, and I have campaigned for some years, unsuccessfully regrettably, that all expert witnesses should be called by the Court and not by one or the other side.

At the moment they have to be called by and therefore paid by, but you have to abide by the rules that you actually are not responsible to the lawyers who call you. You are responsible to the Court.

Q But your bills were submitted to Glaxo?

A Yes.

MR. WILLIAMS: Thank you.

SPECIAL MASTER CAMPBELL-SMITH: Anything further?

MS. RICCIARDELLA: No.

SPECIAL MASTER CAMPBELL-SMITH: Do my colleagues have any questions?

SPECIAL MASTER VOWELL: No.

SPECIAL MASTER HASTINGS: Yes, I do have a couple.

Doctor, I wondered if you had any more comments to make on the Young, Geier & Geier study that you were given before the break. Did you have a chance during the lunch break to read the full article?

THE WITNESS: Yes, I did. Not a lot to add. As I say, I think it's a poor study.

It used a database that could have been used for a conventional cohort study, but it was analyzed on a time/trends basis, and they put cases in inappropriate groups.

SPECIAL MASTER HASTINGS: All right.

THE WITNESS: So there are a lot of other things that could be said, and doubtless Dr. Fombonne will go into some of those details, but on those grounds alone I do not see that as a study worth very much.

SPECIAL MASTER HASTINGS: All right. And just one other perhaps it's a short series of questions, but you were asked by Mr. Williams about the Petitioners' theory of neuroinflammation being caused by inorganic mercury as a potential cause of autism, and you indicated your view that that was basically a speculative theory.

Now, as I look at that theory there are really two parts of it. First, that inorganic mercury can cause neuroinflammation, and, second, that neuroinflammation can cause autism.

Do you see either of those two parts as more potentially meritorious than the other, or are they

both equally speculative in your mind?

THE WITNESS: Well, good question. Let me think for just a moment how I can most helpfully respond on that.

Information is a very nonspecific sort of process, so it's a bit like a fever. So the number of medical conditions that cause fever are enormous, anything from an infection to cancer, and so there is indicating a nonspecific response to something going wrong.

So the question in terms of inflammation here is is it more than that? So the notion that inorganic mercury might cause neuroinflammation I don't find a particularly startling theory because it's at the very general level.

In terms of application to thimerosal, one has to move beyond looking at a general bodily defense mechanism, which is what information is about, so that again if one takes fever and infections as an example you need the inflammation as it were to gear up the body defenses to deal with the infection.

So it's a good aspect, if you like, because it's part of the body defense processes, but once one moves to the situation as to whether thimerosal is causing this you've got a series of different

propositions that have to be added in.

To begin with, is thimerosal having an equivalent to the inorganic mercury that is being shown in some of these more basic science studies? The answer is yes, it might be, but the minute you do that you of course have to recognize that mercury comes from many different sources, and therefore there would be the additional requirement of sharing that in this case it did come from the thimerosal, not from the factory up the road or the amalgam in the teeth or so on.

Then you've got the further problem that if you are dealing with something which is occurring throughout the brain you've then got to explain why it leads to the particular kind of pattern that you find with autism.

And by that I mean not just the symptoms -- that's one important part -- but also the increase of head size during the preschool years, the particular kind of social cognitive abnormalities that are encapsulated by theory of mind and so on. There are a whole range of things.

So the notion that neuro information or oxidative stress plays a role, you are picking on a mechanism that we know is very widespread and so the

challenge really is it's not that the idea itself is ridiculous, but does it apply in these circumstances to this outcome. That's where the speculation comes in.

SPECIAL MASTER HASTINGS: All right. Thank you. Nothing further from me.

SPECIAL MASTER CAMPBELL-SMITH: Have these questions provoked any questions from counsel?

MR. WILLIAMS: Not from Petitioners.

MS. RICCIARDELLA: No, ma'am.

SPECIAL MASTER CAMPBELL-SMITH: I think that concludes our testimony for the day. Thank you. You're excused from the witness stand.

THE WITNESS: Thank you.

(Witness excused.)

SPECIAL MASTER CAMPBELL-SMITH: And as currently advised, we are to resume hearing from Respondent's witnesses tomorrow at 9 a.m.

Are there any further matters from counsel that you believe we need to address this afternoon before we go off the record?

MS. RICCIARDELLA: Not from the Petitioners.

MR. MATANOSKI: No, ma'am.

SPECIAL MASTER CAMPBELL-SMITH: Thank you. We are adjourned until tomorrow.

(Whereupon, at 3:35 p.m., the hearing in the above-entitled matter was adjourned, to reconvene at 9:00 a.m. on Wednesday, May 28, 2008.)

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REPORTER'S CERTIFICATE

DOCKET NO.: 03-584-V, 03-215V

CASE TITLE: In Re: Claims for Autism

HEARING DATE: May 27, 2008

LOCATION: Washington, D.C.

I hereby certify that the proceedings and evidence are contained fully and accurately on the tapes and notes reported by me at the hearing in the above case before the United States Court of Federal Claims.

Date: May 27, 2008

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