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. MEAD, A MINOR, Petitioners,	)	
v.	)	Docket No.: 03-215V
SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	)	

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IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS

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

Wednesday,
May 21, 2008

The parties met, pursuant to notice of the Court, at 10:00 a.m.

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

APPEARANCES:

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C O N T E N T S

E X H I B I T S

RESPONDENT'S EXHIBITS:	IDENTIFIED	RECEIVED	DESCRIPTION
8	2356	--	Robert S. Rust Slide Presentation

P R O C E E D I N G S

(10:00 a.m.)

SPECIAL MASTER CAMPBELL-SMITH: We are back on the record for another day of hearing in the second theory of the omnibus autism proceedings to continue with Respondent's presentation of Respondent's case.

I understand from counsel that there are no preliminary matters to address this morning.

MR. POWERS: That's correct, Special Master.

MR. MATANOSKI: That's correct.

SPECIAL MASTER CAMPBELL-SMITH: Mr. Matanoski, call your next witness.

MR. MATANOSKI: Thank you. At this time we call Robert Rust.

SPECIAL MASTER CAMPBELL-SMITH: Good morning, Dr. Rust.

And who's going to conduct?

MR. MATANOSKI: Ms. Esposito will be.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

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

Whereupon,

ROBERT S. RUST

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

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

Dr. Rust, just a reminder, we're going to ask you to speak up so that we can make sure that we hear you across all of our microphones.

THE WITNESS: I'll do my best. My students tell me I mumble.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

You may proceed, counsel.

MS. ESPOSITO: Thank you.

DIRECT EXAMINATION

BY MS. ESPOSITO:

Q Please state your name for the record.

A Dr. Robert Rust.

Q What is your current position, Dr. Rust?

A I hold the Worrell Chair in Neurology and Child Neurology and Epileptology at the University of Virginia where I'm the Director of Child Neurology and the Co-Director of our Epilepsy and Child Neurology Clinics.

Q Your CV is on file in both of these cases as Respondent Exhibit JJ. But I'd like you to briefly describe your educational background, starting with college.

A I went to separate universities and received a degree in 1970. Went to graduate school at the

University of Virginia, taught overseas, returned to do research at the university and to go to medical school there, finishing in 1981. Then did my residency training in pediatrics at Yale University; my training in neurology, child neurology, developmental neurochemistry, neonatal neurology, at Washington University in St. Louis.

Q Have you had any additional training beyond that?

A Well, every day is a training experience for most of us. That would be chiefly what I have.

Q Do you hold any Board certifications?

A I'm Board Certified in Pediatrics and in Neurology with special qualifications in Child Neurology.

Q Have you served on the editorial boards of any journals?

A Yes, I have. I don't know the exact number, but I think it's six or seven, something like that.

Q Can you list some examples of the journals you've served on?

A The Journal Of Child Neurology; Pediatric Neurology are among those; several neurochemistry journals. Those would be the important ones.

Q Have you served as a reviewer for any

scientific journals?

A I don't know how long the list is at this point, but it seems to me it must be 16 or 18 journals. Something like that.

Q That you currently serve on?

A When they send me a paper, I, yes.

Q Are you the author or co-author of any peer-reviewed articles?

A Yes. I believe it's about 50 or 51 at this point.

Q Can you name some of the journals that your work has appeared in?

A The Journal of Child Neurology; I'm going blank on this point. Neurology, Green Journal, Blue Journal, all of our neurology journals I think are the major ones that I have papers in, reviews in neurology. A number of different journals.

Q Have you also written any book chapters?

A Yes, chapters and reviews I think number at this point a little over 50.

Q Can you please describe your current responsibilities at the University of Virginia?

A Well, as I mentioned, I run the Child Neurology Division so I'm responsible for running our training program in child neurology as well as our

clinical programs, caring for children. I'm co-director of our clinical programs in child neurology and epilepsy, so running our out-patient division as well as our in-patient division in Child Neurology. I have a fair number of responsibilities as far as education, things outside of neurology, including pediatrics, developmental pediatrics, psychiatry and those would be the important ones.

Q Do you conduct any research?

A Yes. I've conducted research throughout my career.

Q What is your primary research area or areas?

A The interests are pretty broad and cover a considerable portion of child neurology. Autism, for example, is a great interest that we have ongoing projects in autism, in headache, in behavioral disturbances of children and their treatment, of a broad variety. Epilepsy and ataxic conditions of children, degenerative conditions of children. Quite a few different things that we have ongoing at this point. The EEG aspects of both neonatal neurology and of autism, we have an ongoing project with regard to the EEG of individuals with autistic disorders.

Q And do you also have a clinical component to your work at the University of Virginia?

A Quite considerable clinical component. That includes both my own practice at the university as well as the clinics that I run for our residents. Again, that's residents in neurology, pediatrics, developmental pediatrics, and psychiatry, all rotate through my clinics.

We have outreach clinics as well in Southwest Virginia for the medically underserved, and that's both children and adults that we care for in those clinics.

Q Do you diagnose children with autism?

A Yes, I certainly do.

Q Approximately how many times have you diagnosed a child with autism in your career?

A I can't give you an exact number, but I'm sure that it's many hundreds.

Q Today, approximately how many children would you say you are currently treating? Children with autism?

A I don't know the answer to that with any accuracy. I suspect it's somewhere between 80 and 100, something like that. There may be a few more. Some patients I see infrequently, patients that I've seen at other institutions than my current one. Patients sometimes will come a distance to see you, so

I have I think a fairly large number.

Q Do you speak in the field of child neurology?

A Yes, I do.

Q Are you going somewhere tomorrow to do that?

A Tomorrow I'll be flying to Japan for the 60th meeting of the Japanese Child Neurology Society and to be a Visiting Professor.

Q Dr. Rust, do you have an opinion as to whether the Thimerosal in vaccines causes autism or autism spectrum disorders?

A Yes, I do.

Q What is that opinion?

A I don't think it has anything to do with these disorders.

Q At this time I'd like to go through your PowerPoint exhibit. This is going to be Respondent Trial Exhibit #8. We've got copies.

(The document referred to was identified as Respondent's Trial Exhibit 8.)

SPECIAL MASTER CAMPBELL-SMITH: Just a reminder both to counsel and to Dr. Rust, when you begin to refer to the slides, if you would indicate by number the slide to which you're referring.

THE WITNESS: Yes, Special Master. I'll try to do that.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

BY MS. ESPOSITO:

Q Dr. Rust, we're going to move to Slide 2 of your PowerPoint where you define autism.

A The definition of autism has changed considerably over the last 80 to 90 years, an interval during which we've understood that there is a separate class of disorders with some unifying features that are important unifying features and these are the things that we call pervasive developmental disturbances that the Court has heard a great deal about, and it certainly at this point knows a great deal about.

The interesting things about autism are many, including the fact that these criteria have become increasingly refined. This has been very important to us in terms of several different things. One is understanding how prevalent the condition is, which has changed as we revise criteria. Another thing is as we refine our understanding of the condition in terms of its clinical manifestations, it's one of the most important ways in which we can come to some understanding as to what its causes are.

And then equally importantly, understanding what its clinical course is.

We haven't fully understood this and perhaps don't to this day fully understand what goes on with children with pervasive developmental disturbances, but they're not static conditions nor is life. And the individuals with pervasive developmental disturbances grow and develop as all the rest of us do and we need to sort out the aspects of that development that are normal to the aspects of that development and those that are not, and especially those that cause an individual and the family of that individual to have the considerable difficulties that can arise in the setting of pervasive developmental disturbance.

It's very important that this is an age-dependant syndrome. It tends to arise at a given age and to have then an ensuing development that we're increasingly defining. This has helped us to understand a good deal about when the condition arises and what the approximate causes may be, and also to understand what type of a disease it is. So these diseases fit into what we call systems diseases, and we've got several different kinds of systems diseases but the ones we're referring to here are the ones that

cause a change in development with deterioration of function. These can happen in various ages in life and these tend to happen very early in life. We have other diseases that can come on at other ages that also involve what we call systems.

So this is not an issue of brain injury from trauma, it's not an issue of toxic injury to brain, it's an issue of how a system that's determined genetically doesn't develop properly and this can happen --

Has this gone away again? Maybe I should use this one, I don't know.

(Speaking into a different microphone).

As we increasingly understand how the brain develops, which is another thing that we haven't known as much about in the past as we know currently, the diseases where something's gone wrong in terms of development help us to understand what normal development is all about. We're coming to understand that in normal individuals brain development takes places over at least three and possibly four decades. At these various stages, genetic signals turn on and turn off in normal individuals, going through stages that may be more or less functional. Adolescence is one of those phases where important things happen for

people, but some of them are dysfunctional, as we all know as parents. Yet that's part of normal development.

But at each of these stages what's happened is that brain systems are being replaced. So we can see degenerations occurring at any of these various stages and we're defining more and more of them. In some of our degenerative diseases we see stages at which an additional developmental deterioration may take place which has something to do in these instances with a genetic signal that's meant to speak to each of these successive phases of development. This is a very important area of what we understand about pervasive developmental disturbances.

We presume that the substrate for these conditions is neurobiological and it has to do, as I say, with signals, these complex signals that help us to develop our brains in a most beautiful and complex way that sometimes goes wrong.

So we need additional refinement of our definitions. We continue to do this as I'll emphasize in some of my slides.

This is a question of time spent more than anything else, I think. When my career started, when we saw the occasional patient that we diagnosed autism

in, we went to see that patient because we thought this was a rare condition and because we defined it so narrowly and because we asked so few questions. Really every successive year in my career, since I see a great many patients with these disturbances, the number of questions that I ask gets longer and longer.

With this we begin to understand more about what defines these diseases and what the characteristics are, and it allows us to understand the successive phases of disease development. We can't do this without spending time, and we used to not do this. And the time spent, of course, as the other very important aspects of allowing us to help the families of individuals that have these conditions and explain what we understand.

Early in my career we oftentimes provided a definition for something we couldn't treat and then felt very uncomfortable with the fact that we didn't have a treatment. Those patients would return for follow-up, wondered what we were doing.

I've come to understand, again with time spent, that there's continual alleviation of senses of guilt; continual explanation to take place; and continual refinement of our understanding of what the successive phases in these conditions do for families

and what tolls they take.

As well, questions come up to us with these conditions that the families oftentimes don't ask unless we wait and spend time with them. They often involve things like genetic counseling, which needs to be readdressed and readdressed with these conditions.

It allows us, as well, to define individual sub-syndromes so that we can come to a better understanding of what really causes these things.

So this is defined by a triad of deficits.

I can go to the next one, if you don't mind.

Q Right. On Slide 3 now, you have the three areas I think most of us are familiar with, but can you briefly touch on what those are?

A This is one of the most important and early recognized things was that this is a disorder of verbal and non-verbal language development.

The onset of language is something we've only come to understand carefully over the last 15 to 20 years with the work of Prechtl and other people that have done ultrasonography in children in the womb and have identified the fact that our gestural language comes on before we're born and stays with us throughout life.

Differences that may be observed in

individuals that have pervasive developmental disturbances because it's this gestural language that tends not to develop, and that's the earliest part of our language development. So pointing being a very important aspect of our recognition of autism.

Oftentimes we begin to define the disease as children don't develop the language that should come on in the second half of the second year of life. But as we go back and wonder about gestural language, we find that so frequently children that seem to have had the onset of their disease at the end of the second year of life have in fact lacked the gestural component of language from very early on.

So this is a system that's involved in language, and it's very widespread in the nervous system, and it lateralizes from one side typically so that we specialize in one hemisphere.

And both with language and as well visual aspects of autism. One of the things we're coming to understand is this lateralization which should occur very early doesn't take place. So that understanding not only using our own gestures, but understanding both the gestures and the facial expressions of other people is something that is a primary aspect of another kind of communication, understanding what

other people are trying to tell us by their facial expressions.

There is increasing understanding that this occurs because of a lack of lateralization of these systems, the lack of subspecialization which should take place in the first and early second years of life.

Q And here you're talking about the disturbed social interaction, the second --

A We're talking about everything including not only interpretation, so the interpretation of both the gestural or the visual or the facial language of others, but we're talking about people with autistic disorders having some difficulty in providing the same kind of facial expressiveness as gestural expressiveness is lacking as well.

This plays a terribly important role in social interaction and social integration of individuals with disorders that involve autistic features and is an isolating aspect of this that has social consequences that we don't fully understand. Because another aspect of these diseases has been, and this is something that took 30 years of being interested in these diseases for me to come to appreciate at this point, but we've tended to come to

conclusions about what's going on in the minds of individuals with autistic disorders and we actually don't always really know what's going on.

So some of the interpretations that we provide about why people do particular things with autistic disorders are probably entirely unsatisfactory. We need to come to understand these things better. This includes interpreting features of a person's performances. Anxiety for example. Because it draws our attention sometimes when an individual seems to be more active than others, and we don't pay as much attention during those long intervals when individuals are not so active, or more withdrawn.

But we can't ask the questions that are important here to understand these things well. So we've made the mistake over a long interval of time of assigning from our own perspective things that are probably not true about autistic individuals. We're perhaps getting better about this over time.

Q Let's move to the third area on your slide.

A The third area is restricted imaginative and behavioral repertoire. We interpret this with regard to childhood play where activities of childhood play oftentimes seem to us very restricted as compared to

other children.

Again, we can't pass a judgment as to whose world is better. We just know that most of us are in a different world. The behaviors get interpreted as representing things that they don't necessarily represent such as mental retardation. But a child we consider normal in their play in the first year of life and in the early second year might involve picking up a hammer and banging with it or picking up a truck and running it around the room and trying to make noises. Very frequently one of the things we find in our careful histories in children that have had language regression in the end of the second year or not developed language, either one of those are possible. We find that children tend to concentrate on very tiny details of those trucks or cars. They'll pick them up and turn the wheel. Put it right up to their eye as they do this, and watch it spin around. This of course is a very different behavior.

One of the things we talk about or ask families about in order to confirm the features of an autistic disorder have actually come on much earlier than the readily recognized language disturbance.

Repetitive behaviors are part of this as well. But again, this is something we're beginning to

understand in a broader context because we know that people that are otherwise normal have repetitive behaviors and we need to try to understand the context in those individuals as well as in individuals with autistic disorder.

Q Let's move now to Slide 4. Can you explain what this is?

A What this is a representation of is the manner in which the data that we have is not necessarily very helpful, especially the data that we've gathered in days when we didn't have very good definitions and when we didn't segregate our patients very carefully. So this is a common figure to represent, commonly available, to represent what the substrate for autism is.

Many presumptions are involved here, and many problems with definitions. So we used to include children with all kinds of autistic manifestations in a general category, and we now know there are symptomatic autisms that ought to have their own particular category because although they have features of autism they may be quite different in terms of their substrate.

We need to leave open the possibility that in fact those children will have injuries that are

similar to those that occur developmentally in both categories -- the symptomatic patients with another process than autism and those that don't have that.

So in the known etiology category which has shrunk as we've taken patients away from this, we now know that children that are born very prematurely and children that likely have injuries to the cerebellum, a very important area in autistic neuropathology, that leads probably in the ensuring development of the cerebellum to a systems problem with the connections between cerebellum and brain stem. Those very premature children who have autistic manifestations add a clue to what goes on in autism itself.

So although there is this category, we've tended more recently to consider in the way in which we segregate out autistic disorder from most symptomatic causes where we have another defining characteristic. We think perhaps 10 to 15 percent have an identifiable cause.

The importance of recognizing this as well is something that as you spend more and more time with the families of individuals with autism you understand is a very important thing. Families are facing, as we describe to the families, and as they come to understand better than our description as time goes

on, we know that they're facing an extremely difficult time in their lives. There are rewards, of course, with any child, with whatever their disabilities. But as with some other conditions that we treat, families trying to cope with these things, not having an adequate definition of why the child is having these behavioral things and what has caused the guilt that families often feel is something that we want to alleviate.

So we need to understand what the actual causes are, and properly define them as time goes on. I can give you an example of a child with autistic features, and this child had Rett syndrome which has many autistic features and shares neuropathological aspects of autism, very informative for us in that regard, who came to me at 32 years of age and represented another important feature of autism and Rett syndrome, the fact that there are increasing numbers of different types of these disorders.

The family asked what was wrong with their child who could speak, and because of gestural and because of visual issues in a child that could speak, usually not thought to represent Rett syndrome, we thought that's what was going on here.

We had a tussle with the insurance company

in order to get testing for this child, and in fact it was declined. The family finally agreed to pay the expense of this test, as many families of children with autistic disorders agree to pay considerable amounts of money for testing and treatments, many of which are not useful but they want to do something for their child.

We found this was Rett syndrome. When I told this to the family and asked the insurance company will you pay now? They said no. The mother said it's all right. It was worth it because I always thought, because I smoked a little during the pregnancy, that my child had Rett syndrome.

So we have many instances where children have the wrong proximate cause identified and guilt associated with that. The more we can understand that these disorders that have so characteristic a developmental pathology and a systems pathology are in fact genetically determined, the better.

Q Let's move to your next slide, Slide 5, understanding complex disease.

A These are complex diseases. As I say, we only gradually and I think with increasing velocity of what we understand about them, because we know really how to do these things better than we used to, get

better clinical descriptions. It has to be exceedingly detailed. We need to set apart some conditions where we can find a genetic clue, and having done that can see to what extent those genetic clues inform us about the rest of the autistic spectrum.

This can only happen, as I mentioned, with time spent. If I have a family that's coming to me and I know in advance it's an issue of autism I see them the last patient of the day, I set aside two hours, and then go on as long as the family needs to talk about these things because generally families haven't had the opportunity to spend this much time and it's important not only for the families but for me and for our understanding of these diseases.

So we get more and more information and we ask more and more questions.

We try to compare these diseases then to similarly well described and better understood conditions. Again, amongst these, one of the most important is Rett syndrome which has such distinctive features that share so many characteristics of autism. We understand a great deal now about the cause of that disturbance and how it develops over time.

We understand as well as we do in autism,

that there are set intervals during which we can see additional periods of deterioration of function that are determined by a genetic code problem.

We then develop hypotheses about these conditions and then we try to design the best possible sort of experiments. We design also retesting in terms of getting more clinical history, and we try to understand what's going on. We do careful analyses of the increasingly abundant literature on these subjects and then we execute the well designed scientific investigations and among them, perhaps we don't live in a golden age just now, but we live in a golden age of science. There are so many techniques available to us in which we can do experiments to actually prove what may or may not be going on. There are many bad experiments and observations, but we try to make those better.

Q Doctor, when you said "we" do these experiments, who do you mean by "we"?

A I mean the medical and scientific community. There are both clinical aspects to this and basic science aspects to this. I've engaged in both of those things with regard to elements pertinent to what we're talking about today.

Then we need to always have the willingness,

once we've done these experiments that prove or disprove hypotheses. Hypotheses are a dime a dozen. Anybody can make up an idea about what's going on and try to string it together in ways that can be very destructive. We need to do the experiment and see whether we can either refine that experiment or abandon that hypothesis based on those conclusions.

Q Let's move to Slide 6.

A We have the opposite way of doing these things and some very good scientists have been caught up in these things. Perhaps not so many people in the court know the great astronomer Tycho Brahe from Denmark. He made wonderful observations about planetary movement. He was an important astronomer in the days of Galileo and Copernicus, but he had a fixed idea about the universe which was of religious proportions. He thought that everything moved around the earth. In trying to prove this he adjusted his own observations and those of others with very complicated explanations for why a particular observation might be seen, mathematical observations that altered orbits of planets and so forth. This is what we call a preconception fallacy. Sticking with something and making what becomes an increasingly complicated explanation because you have just one

thing in mind.

One thing that can happen with a preconception fallacy is that you might be able to substitute other things into this framework as time goes on, once you've got the complex framework. Now Tycho Brahe stuck with the idea that the earth was at the center of the universe, but we've seen many examples and continue to see them where people get so attached to a complicated explanation without scientific validation that they can substitute one thing after another into that framework. We've seen that with autism, for example, with the substitution of infections, of toxins, and other kinds of things.

But we can go back further than that and see the other destructive elements of this approach because in the 1950s when we really had the first advances in trying to get more information, there was really very little information about autism together, the preconception fallacy was that autism was a result of a refrigerator mother. This lasted, our understanding of these things, for 15 to 20 years, where as so often happens we blame the mother for so many things, and mothers are so frequently willing to take on blame for things if they can't find some way to blame their husband.

But this was a very destructive thing. Especially conditions that arise early in childhood, including autism, but ones for whom the mother wondered, as the mother of the child of the 32 year old young woman with Rett syndrome, wondered whether something she did during pregnancy caused this problem.

So we've got to be very careful to test these hypotheses because they have a lingering negative effect on parents that want to do so much for their children and want to understand what they had to do with the arousal of those conditions.

Q There is a simplicity to it I think you demonstrate in Slide 7. Let's move to that.

A This is one of my great teachers and a great scientist with whom I hope to describe some work that we did some time ago in his laboratory. But what he taught me early on was, because he talked about proving things by what we call P values which show how repetitive an experiment might be.

If it's the wrong experiment, it doesn't prove a thing. You have to have a good idea in the first place, you have to have the best possible experimental things. And what Dr. Lowry said, it's not whether you can do the same experiment over and

over again, but Oliver Lowry, who is the most cited scientist in the history of medicine and science said was that in adjusting our experiments carefully to what we do, we always find that we have as a result something that's elegant and simple as our explanation for things, and we begin to take some wonder at the way in which things go right, and some further understanding in the way that things go wrong.

He says that this is often an unexpected conclusion, as has been true of our understanding of the developmental aspects of Rett syndrome and our increasing understanding of autism and related disorders. It's satisfying because of the simplicity and not because of this garrulous kind of complexity that tries to prove a point that's preconceived.

Q We'll move now to Slide 8. The pathophysiology of autism.

A Well, as I mentioned, we can identify a cause, a genetic cause in perhaps 10 to 15 percent, having set aside other kinds of causes into separate categories. But we have those cases where there are symptomatic prenatal influences that are also thought to have a genetic aspect to them. But an occurrence of something else that happens during a particularly vulnerable phase of genetic development, Congenital

Rubella, is one of those things.

So we know that it is possible for infection under a very specific circumstance and with very specific pathological observation that are repetitively observed and are systems observations, not a more generalized toxic effect, or not a more generalized inflammatory effect.

So in Congenital Rubella we have just such a condition. As we began to understand that that was the case, and as we developed vaccines, that particular condition has now been eliminated as a cause of tragedy for children and families.

But we now know about other conditions where the pathology is very different, where we don't have a developmental aspect to it, and a particularly tragic example of this is congenital mercury exposure, about which I'll say something where we have not a systems disease, but a disease that causes a non-systematic pathological result as we see not only in congenital mercury, but as we see in measles occurring later on in life than in this very vulnerable prenatal period of development where so many things are going on.

These are all conditions which have a very strong, so far as we understand it, genetic and epigenetic component. They produce highly consistent

syndromes, even when we don't have a specific cause identified. We have Rett syndrome where we do now know why it is that it's mostly a disease of girls, and yet we've now come to understand that boys in a very vulnerable period prior to birth can in fact have Rett syndrome because of a mixed aspect of vulnerability that's genetic and developmental.

We now know that male autism is also a consistent syndrome. Because it's emphasized in boys, we know that, and so strongly emphasized in boys, we know this must also have a genetic component to it. And we have an additional now, we understand, genetic and sexually related aspect to these conditions which is the epigenetic aspect of inheritance from paternal to maternal side with genetic imprinting.

And as we've only recently come to understand this, we're only now beginning to ask the questions in the clinic that will allow us to add that to our understanding of why individuals develop particular kinds of autistic manifestations, just as they develop particular manifestations of other imprinted conditions.

Q Let's get into the clinic a little bit and talk about the standardized checklist that you use when making a diagnosis of autism. This will be Slide

9.

A As I mentioned, the list of things I ask has gotten very long and the ones that I ask my residents to ask as well. When we don't anticipate seeing a patient with an autistic disorder and the resident has seen the patient first, they know what my checklist is because I spend so much time talking about this in terms of things that we now know, and I didn't know 15 years ago, even 10 years ago, that these were important modifiers of our diagnostic criteria, and these are important things that tell us about the first year of life, even in individuals that seem to have regressed in the second year of life.

But I reserve time for those patients as well, to see them later on, to spend the time that, as I say, is so important to talk about these things in greater detail.

We gather that information for our research, but as well the lesson of those cases is that virtually every week or at least every two weeks or three weeks in my clinic a patient comes into my clinic that comes for cerebral palsy or comes for mental retardation or some other condition and it's as plain as the nose on my face that these individuals have autism because I know what it looks like. It

just tells us that there are still very many children out there that are diagnosed as having other conditions and yet despite our awareness of autism, it's still not properly diagnosed sometimes as late as three or four or five years of life. So this is one of the most important explanations we have for what has appeared to us to be an increase in the prevalence of autism, but not an increase in the incidence of autism.

We use these checklists then to affirm the diagnosis because these are standardized checklists and they're importance is that there is an abundant literature out there that doesn't use these checklists. So it means that confusions about what goes on in autism are so dependent on long series of patients, that whatever was studied, whether it's the electrographic aspects or whether it's the pathology or whether it's clinical aspects or whether it's treatments, include a broad variety of conditions and we need to know what happens in specifically isolated conditions. So these are what we use.

They're also important because we now understand that treatment of autism is important, but that treatment doesn't involve dangerous or useless or expensive therapy. It involves dealing with this

aspect of things I referred to before which is the isolation that patients with autism experience because of communication differences. Whether they're better or worse, they're still differences. The place in which we can find these interventions are so important as we try to educate children. What we find is that what might appear to be anxiety or other things are so readily alleviated when a child is placed in an educational setting where there's understanding on the part of the educators who have dedicated their careers to teaching children with these kinds of problems, and where there's a patience and understanding. I think that misinterpretations about whether stereotypies or anxiety, which they usually are not, at least not in a severe way, and no difference than other people really.

But what a child with autism may have, and as I say we don't know for sure because we can't ask. But if we can imagine ourselves, I'm going to Tokyo, as you mentioned, where I don't speak any Japanese so I'll have people to help me with these things. I'll have some understanding of the framework there. People will be able to interpret my gestures and my facial expressions if I'm alarmed about something. But the autistic child doesn't have this opportunity.

So if I were to go there not only without language but without any of these other things, I could imagine myself being exceedingly bewildered and to have somebody that understands and can help translate and help to settle something into these thing is an intervention of great importance.

MS. ESPOSITO: I would like to make a brief request. If we could check to make sure everyone's cell phone is off, that might have something to do with the interference we're hearing.

SPECIAL MASTER CAMPBELL-SMITH: Turn off your cell phones and your blackberries as well.

THE WITNESS: Mine is off.

(Pause).

BY MS. ESPOSITO:

Q We'll go on to Slide 10, unless you have something else to say about number 9.

Number 10 is the red flags for autism. Can you describe what you see with the patients that come into your clinic?

A This is only one of many things that I now ask about, and also what sometimes they call the recognition that mothers have about things they've known are not quite normal sometimes, but other times they haven't really.

This is one of the additional problems with recognizing autism is that so frequently these children that are diagnosed late are the first child of a family. That's characteristic. When I had my first child, there were many things I didn't understand about children. My wife says there still are.

But you don't know what to expect, and we see this in a broad variety of conditions, whether it's epilepsy or other things.

The only thing I'm emphasize in this slide is head shyness. This is not something that finds its way onto the checklist, but you find out about this after a time. The families understand this, they recognize it. This is a first year manifestation of so many children with autism whose language problems are recognized in the second year.

Q What do you mean by --

SPECIAL MASTER CAMPBELL-SMITH: I was going to ask, what do you mean by head shyness?

THE WITNESS: Thank you, Special Master.

The issue here is whether a child will permit their head to be touched, whether they'll permit their hair to be brushed, whether they'll permit the hair to be washed, let their fingernails to

be cut. We know that many children don't like that, but this little bit of head shyness is a very striking thing.

In order to affirm that this is something that sets children apart I've spent a lot of time putting my hand on the head of other children of young ages that come into my clinic. This is the only way we really know what seems to us initially to have been something special and it turns out not to be.

And this is a very special sign that comes on early, along with lack of pointing and lack of responsive smile and some of these other things.

Now a responsive smile in the first year of life is a very difficult thing to know about because parents want their child to smile responsively. They're doing so much work for the child. I know about that. I thought I did as much as my wife and she said she did a lot more in the first year. That's the good thing about breast feeding, I guess.

But at that time you get the idea that the child is smiling in response. What grandparents know, I know as a grandparent, or not yet but nearly a grandparent, but you can blow a little puff of air in a child's face and you get what appears to be a smile. This allows the grandparent to one-up the parent

sometimes, to get seeming response.

So we need to set these things apart carefully. These slides are only meant to emphasize that we need to have more about what is normal and what's abnormal and when they come on to really know when autism arises.

I would also mention this issue of non-aversive eye contact. We say a lot about eye contact in children with autism and people postulate, these are the theories again, perhaps the child is shy, perhaps the child is anxious, perhaps the child is disinterested. All of these things we talk about, but it's only really in the last year or two, and a little longer, that we begin to understand that this also is a systems problem and the issue of eye fixation and eye aversion actually become one of these issues probably, this remains not entirely proven like so many things, but we know more about it than we used to because of careful scientific investigation and because we have techniques that will allow us to look at the system which are functional MRI. This can be done in children that are not necessarily so very cooperative.

We already know that there's already a genetic distribution of gaze. That men and boys are

more attracted to a moving stimulus than girls. This is well proven in the psychological literature, although people don't seem to be clear about it or don't seem to know about it. Women tend to look at things in detail and get a system of observations about what's there. Men are attracted to something that moves. Sometimes this is misinterpreted as an aspect of attention deficit because of distractibility.

But it's a very important developmental aspect of the function of men in civilization, noting what's going to come and attack their herd of sheep in the early days, probably. But these are determined genetically and are systems issues, and the abnormalities of these things, if we can define them better, are also things that allow us to know when the onset of a developmental disturbance occurs.

Q Your list of red flags for autism I believe continues on to Slide 11.

A Yes. Again, I've talked a little bit about what people do with trucks. It's been known for a long time that personal pronouns are left out, and it's known that echolalia is an issue here as well.

Putting objects in the mouth and touching the lips not so very well recognized, but in fact the

issue of putting things in the mouth is seemingly non-discriminately mouthing them, playing with them with the tongue, rubbing them on the lips is a very striking and common thing. It might be mistaken for some odd dietary thing in individuals, but it's a very common aspect of things.

Putting lips on cold surfaces, and that sort of thing.

Q Does that have any relationship with pica?

A It can be mistaken for pica. Children have a lot of odd habits about their eating that also need to be set apart from what normal children do. So there are a fair number, a large number of normal children that eat odd things. String or sand or other kinds of things.

But this issue of putting things in the mouth, tonguing them, and keeping them in the mouth, whether they happen to be pebbles or toy objects, that sort of thing, can be a feature of autism that can be seen in some normal individuals as well.

The social scripting is an aspect of this too. Although we're only beginning to understand this better. So issues that we again assign values to anger is something that we do see, very difficult to manage in children with autism, especially once they

become adolescents. And it's one of the most difficult things that families have to deal with. I'll say something in a moment about how I try to help out with that in the clinic in the four tools that we've got for these things. But laughter as well.

We've now come to understand that some of laughter and some odd aspects of breathing have something to do in later stages of autistic disorder with perhaps the triggering of seizures that have a pleasant sensation associated with them. These sometimes, including in my own practice, have been misinterpreted as behavioral issues of a different sort and treated in the wrong way.

Q Moving now to Slide 12, regressive autism.

A I've referred to so much of this already. Children that we have called regressive autism because, again, the recognition of their condition can sometimes arise at the end of the second year. But good data, including the data that we're gathering in my clinic, would suggest that about 80 percent of these children have been abnormal prior to that time during the first year of life.

Among those abnormalities, two were things that I noted in the records of the children that are involved in this trial. One of those was what people

have come to recognize as a quite striking thing in the first few months of life, the initial rise and fall of head circumference in a child during the first six months of life, without following the growth of a child in terms of length or for that matter weight, and this is what was displayed in a characteristic way in the head circumference measurements of William Mead.

In the case of Jordan King the records reflect a parental report of four to five words that were lost at one year of age rather than at 16 to 18 months as some other aspects of the record suggest.

One only finds these things out by spending time with the family and carefully ascertaining what has gone on with the child.

Familial clustering. We do have this familial clustering where we can identify more than one child with autistic spectrum disorders. This does not distinguish classic autism, so-called, not really a useful term any more as we get to know more things from regressive, and not really a useful term any more as we know more about these things because we get the same degree of familial clustering in both those sets of disturbances.

As we look at children with

electrophysiological studies, we don't find that these necessarily distinguish classic from regressive autism, but on the other hand the data here is biased. The reason it's biased is that we've tended to do EEGs in children that have this seeming regression and possible regression and sometimes definite regression of the few words of language that they have at the end of the first year of life because we want at that point to see whether they have Landau Kleffner syndrome. We do that because we know how to treat that disorder and because we want to make it better. We want to do everything we can to make our children better, especially in this most important area of language dysfunction.

In doing these EEGs we do it and these children seem to have regressed in the same way that Landau Kleffner may have done. If we ask these children the history we find the same thing. Eighty percent of them have preceding manifestations of autism. As we try to treat it in the way in which we treat our children with Landau Kleffner, we find it doesn't work. There's an age difference between these individuals because Landau Kleffner tends to arise at three. But unlike what I think is said in Dr. Kinsbourne's report, we see it younger than that as

well. We see it at one or two years of age. But understanding the prevalence of that condition also takes seeing children with these disorders and trying to distinguish them.

Q So there is no distinct biologic process that differs autism from what could be a regressive --

A We can only formulate our biological hypotheses once we have an excellent understanding of these conditions. It's easier once we have a primitive understanding because we can jump to so many conclusions. It becomes much more difficult the more information that we gather. There is no clear way in which to say there's a biological difference between these two conditions.

We have to add the fact that with developmental systems conditions there can be different phases of regression. That's because of genetic signals that are involved in these conditions, can express themselves in successive phases of development. In the case of autism we now know that there is a second phase of regression in the second decade of life. The reason we didn't know that before is we didn't ask the questions, and because individuals with difficulties in the second decade of life were institutionalized so frequently.

We now try to find out about these things and know that that's the case.

What's probably a superb biological model for autism, in Rett syndrome we know there are at least three and possibly four successive phases of deterioration, but we find in the first deterioration in the first year of life; the second in four to six years of life; and the third in nine to eleven years of life; and perhaps thereafter.

Q Dr. Rust, are you familiar with the term "clearly regressive autism"?

A Well, I'm always suspicious about the word "clearly". It usually causes me to ask additional questions. Oftentimes the word "clearly" substitutes for proving your point. It just means this is the way it is and I know this is the case. In my experience, is another way which people try to say what's going on. But I don't think "clearly" is helpful, except to alert us to the fact that at that point once we think it's quite clear we need to ask this whole long list of questions to find out if it really is clearly a new phase of illness.

Q Let's move now to Slide 13 where you talk about personality characteristics.

A Yes. In families that have more than one

child with autistic disturbances we find other things in the extended family. These include such things as rigidity and aloofness and anxiety. They include hypersensitivity to criticism. They include the things that are listed here, limited friendships. Sometimes found in both parents, 38 percent.

This doesn't prove anything. What this tells us is we need to ask more questions. But what it does alert us to is the possibility that lesser degrees of expression of a genetically expressed condition may be causing disturbances in other family members. But then we need to go and find out in all the other people that we don't ever ask about these things, whether these things are true.

So it can lead us to the wrong conclusion unless we're very very careful about what we do. There are plenty of people with limited friendships, there are plenty of people with deficits in speech, there are plenty of people that are hypersensitive to criticism, many of them holding high office in this city.

(Laughter).

Q Let's move now to Slide 14, the heritability of autism.

A Increasing information about heritability as

we define these things better, and the degree of this increasing recognition has led people to observe that autism is perhaps among the most heritable of all neurological conditions. There are plenty that are more directly heritable.

But as regards conditions that we've come to understand are inherited, this isn't the same degree of kinship recognition that might suggest that possibility. Certainly similar to what we initially encountered as we began to study Rett syndrome, it's important for us to recognize that in 1984 when I saw my first patient that had Rett syndrome, this attracted so much attention in St. Louis Children's Hospital because this rare condition that we perhaps would never see another example of. At that point the question was, was this an intoxication because it was thought that intoxication might have something to do with that condition. That was Andreas Rett's first idea in 1965 when they recognized the stereotypies of that condition. This still lingered among the possibilities in 1984 for this rare condition.

But this is a condition that I see all the time now. It's the same inherited condition as it was. Its incidence is the same. Nothing has modified that incidence as far as we know, and --

Q You're talking now about Rett syndrome?

A Rett syndrome. Thank you for clarifying that. And I diagnose this condition now quite a few times a year.

So again, recognition tells us about things that have an incidence that we didn't recognize previously.

Q Let's move now to Slide 15, the genetics of autism.

A A genetic contribution is postulated to be involved in perhaps 90 percent. Not proven. This has to be proven. But again, the evidence is trending in this direction. Trending is another word to beware of in a paper or report because you need, again, to continually refine your idea about these things. But we know of a lot of conditions that cause single gene defects that may do this. We know imprinted conditions that may produce considerable autistic features that so closely resemble the behavioral and linguistic aspects of autism as well as electrographic characteristics, and these include conditions that are imprinted from both the maternal and the paternal side. These conditions mentioned here -- Angelman syndrome and Prader-Willi syndrome.

So we have a variety of genetic possible

explanations, and that always tells us that maybe there's a variety of gene expression, or maybe a variety of gene modification that may take place after the gene begins to express itself. This is an area of, among the hottest areas in science, progress taking place so very swiftly now as we understand how to do these things, and particularly in the setting of Rett syndrome.

Q Let's move now to Slide 16, a picture of the little girl. What's the significance of this photo?

A It's a child with Rett syndrome. It seemed to me they're particularly beautiful children. The same thing is true of the children I see with autism. I think a lovely child with so many impairments and we want everything we can do to be able to say why. We want to understand its variations and we want to be able to do something to improve communication and help these children with whatever else happens with them.

We have very few tools to do this in Rett syndrome as with autism. We have difficulty with breathing that is sometimes so similar, that is to say strange patterns of breathing. We're beginning to understand a little bit about that as I mentioned, in at least a very small subset of children with autism. But in this disorder we have so little to offer

sometimes. We try a great many things. We fix sometimes briefly, that those things help children with Rett syndrome, but so little that we can do about this condition, and we want to do it.

So we try to do things that won't cause any harm. We try to look carefully at things we thought might be helpful. We usually find out that they don't help very much.

These are children that tend to be very quiet and tend to sit quietly and perhaps get neglected in some ways. We don't know that's true either, because the parents of children with Rett syndrome, as the parents of children with autism, seem to me to be so very attentive to their children's needs in every possible way.

But it does lead to parents trying with these disorders a broad variety of treatments that are oftentimes very expensive and oftentimes particularly harmful. What I tell parents in those situations is that if it's very expensive, we would do it ourselves if we knew there was any proof it was going to help. And because we find so frequently that the ways in which these therapies are set up, sort of set up parents for the belief that it isn't going well if they're not adhering to the regimen carefully enough,

if they're not doing enough, if they haven't added enough solvents and oil extracts and hot baths and so many other things that the right combination will be hit upon if the parents spend all their time doing these things. We think that's disingenuous.

We see families bring their children back to us after treatments of all these broad varieties, whether it's hyperbaric oxygen, whether it's hydrocorticosteroids, whether it's patterning, whether it's, any number of other things. We see plenty of children that get chelation therapy. We do caution them that this is not necessarily a safe thing. There have been at least four deaths in the United States from chelation therapy. People that are practicing these things don't necessarily know exactly what they're doing.

So we try to follow up to see whether any toxicities have taken place.

But what we find in trying to be as objective as possible is that we don't see differences. Even though parents often report to us that there is some difference.

We know that we're subject to that too. We give treatments to children and think we've made a difference until we look very carefully. So it's

understandable people want things to be better, but we try, again, to keep data on this, with careful, subjective information about what's going on with the child.

Q Let's move on to Slide 17 which is focusing on Rett syndrome again.

A We now understand the genetic condition and we understand a good deal about what modifies its expression and why there are successive phases of development of this condition.

The first phase is usually five to nine months. These children, as well, have an increased, have a phase previously unrecognized of changes in head size preceding the onset of Rett syndrome, something that was overlooked until we began to look more carefully.

We also know that prior to that time, as we look carefully at the children, this is especially siblings, but we can see abnormalities of tone and abnormalities of sucking behavior. Again, oral behaviors are important in these disorders. And there are peculiarities of aversion especially in autism, an aversion that can be labeled as a GI problem but accounts in fact for most of the GI problems that we see in children with autism.

Another and probably peculiar sensory problem accounting for problems at the other end of the system as we look carefully. But issues in terms of oropharyngeal. Rejection of textures in autism. But in Rett syndrome there's not only rejection of texture sometimes, but abnormalities of sucking behavior. Paroxysmal abnormalities in the wake and sleep EEG is prominent at this phase of regression and may, of course, be seen in the second half of the first year of life in the children of autism where we do EEGs. And as I mentioned, the reason we do them in those children is not because they have seizures, it's because we wonder whether they have something that's treatable like Landau Kleffner syndrome. And Landau Kleffner syndrome is a condition that's epileptic in nature, that is caused by epileptic discharge and we know how to treat that.

But as I mentioned, we don't make, as we're trying, we have an ongoing project with regard to children with autism, but we don't make them better with regard to their language.

We do feel and have looked carefully at this, that we can make sometimes things better with regard to certain behavioral aspects and especially sleep, which is important.

Then there are, as I mentioned, ensuing phases of degeneration which can occur in genetically determined conditions, and it's possible that some of the children that have what appears to be a degeneration in the second half of the first year of life are in fact experiencing what we now would recognize as a second phase compared to the earlier manifestation, and that second phase having something to do with modification of gene expression or something else that happens at that time. But most likely that, because that's what we begin to understand about Rett syndrome.

Q We're going to move on to Slide 18.

A This slide, what it shows us is this is phases of brain development. The blue tells us about the phase at which brain development becomes mature throughout the brain.

Q In our black and white copies can you identify where the --

A I'm terribly sorry. Let me see if I have a black and white copy.

The darker things are the blue. So the more darkening you see there, the more you find the areas achieve a mature representation. This is very difficult information to have obtained, and you might

guess, as I would have thought when I was a medical student, that this represents brain development between birth and three years of age or something like that, when the head size reaches something approaching its adult size.

This is between birth and 18 years of age. We now know that this continued development of the brain takes place until at least 24 years of age, with astonishing changes. And included in that in the mid teenage years is enlargement of brain size above what happened prior to that time. That's a phase where that enlargement in brain size has to do with remodeling that takes place. This involves, probably involves, this is not yet proven but this is one of the hottest and most promising areas in developmental neuroscience, including developmental neuroscience in the second decade of life. This includes the remodeling aspects of what we've formerly regarded as inflammatory things. We've thought so often it's a negative thing, but it turns out that the systems we regard as inflammatory and the systems we regard as neurodevelopmental, work hand in glove with each other.

We've come to understand that the ways in which these systems actually communicate amongst

themselves share very important and very careful modifications, very careful protections, and are involved in the way in which the dendritic trees, that's the way in which the brain elaborates and makes connections, modify themselves for the first three decades of life. That enlargement reminds us of the fact that we see enlargement of brain during phases of development and reminds us of the fact that during this first year of life when we see enlargement of the brains of children with autism, that that enlargement we now know in Rett syndrome as well, almost certainly involves elaboration of brain constituents and including during that period not only elaboration of neurointerconnections, but a concomitant elaboration of these other cells that play a role in modifying and eliminating these synapses that we've thought about previously as being inflammatory in nature. But because these are reparative systems as well.

So this takes place for these, down to 18 years of age. We now know it takes place to 24 years of age. At each phase here we have genetic signals that turn on in order to make these elaborations and these developments and eliminations in which things such as glial system cells that eliminate the things that we don't want in the nervous system, so the brain

doesn't get so large as to become constricted inside of the skull, become very important actors. But also stages at which a particular genetic error may once again cause problems and cause a second phase or a third phase of deterioration such as this adolescent phase we see now that we recognize it and didn't before, in adolescent autism where we used to call it behavior or we used to call it rage or we used to call it anxiety. All these blunt labels that we improperly applied. Now we know it's a developmental neural problem as well. The same thing with Rett syndrome.

Q Just to clarify, for Slide 18 you're talking about Rett syndrome rather than autism?

A This is normal development I'm talking about here. And I'm talking about its relevance, its important relevance to these phases of development that take place and involve what we would regard as degeneration, or what we might regard mistakenly, if we don't look carefully at the brain as being something else such as mistaking microglial elements that are involved in remodeling as an inflammatory change, or as mistaking these neurodevelopmental changes as being something other than what they are.

This work is exceedingly tedious and so many errors have been made, and so much lack of recognition

has been made because people haven't done the sort of work that Dr. Bauman and others have done, and Dr. Courchesne and so many people have done. Not so many. A very small number. There's not much money to do this, very time consuming, very difficult. But in order to actually recognize what cells are what.

The reason we began to understand the issue of Purkinje cells first, is that they're all lined up in a row. I'll show you a picture of that. I think I've got it here. Maybe I don't. But they're all lined up in a row. You can just count them, one after another. Even at that, this was not recognized for a long time.

You get into the cortex in the areas that are so important in autism and Rett syndrome, language areas, frontal areas that are involved in modification of behavior, and you have to do such careful stereotypic analysis to know what cell is what because they overlap. And in order to understand what's a process and what's a cell and what size they are, as these studies have been done this is where we've come to understand now that there are these very important changes in the way in which the nervous system is set up in autism, in Rett syndrome, and that the same kind of microcolumnar changes, the same kinds of changes in

particular cellular systemic populations that talk to one another, that don't develop properly or may even degenerate to some extent because an additional signal that has to be turned on doesn't get turned on.

It's a wonderful thing that we're beginning to understand these things. Perhaps one day we'll be able to do something about diseases such as autism for which we haven't got good therapies other than, as I mentioned, trying to make whatever small things we can do about accommodation and learning in these other things better.

Q We'll move now to Slide 19. We'll try to pick up the pace here a little bit. We've got a number of slides to go through.

A Sorry.

Q I appreciate your explanations, but we'll try to move along here.

A I'll do the best I can to pick it up.

Q Slide 19.

A I mentioned Rett syndrome was overlooked for a long time. I mentioned, I think I've said everything that's really on this slide.

Q Okay.

A And in terms of variance, we now have 13 for Rett syndrome, all determined by the same gene with

modification. Likely some of the things we're setting apart very carefully as other kinds of disorders with autistic features, will find their way back into the family of autistic disorders such as these Rett's variants have as well, because they share the same mechanism causing the same systemic manifestations that we know are these peculiar behaviors that set autism and Rett syndrome apart from other diseases.

Q Slide 20?

A Now people are able to produce mice that can manifest so many of the features of Rett syndrome and show the same development, so we can look then at the pathology of these mice who show the same manifestations, same genes, same events and gene development that produce Rett syndrome. The same characteristic stereotypies with Rett syndrome. They're very peculiar. The child rubs their hands together so repetitively like this, that's one of the ways in which we make the diagnosis. But we only more recently came to understand that there is a gaze issue that we still don't understand.

What this is, and it's absolutely characteristic of Rett syndrome, and you can diagnose the case reliably in the office, when a child with Rett syndrome seems not to look at things, you might

call that gaze aversion, will momentarily fix you with a gaze like that, their eyes get a little bigger, and you suddenly feel like you're being stared through. It took looking at this a number of times to know exactly what was going on.

We still don't understand it, but we now know that as with autism, the centers that involve the direction of gaze are the likely explanation for this. yet again, more has to be understood about this, but it's one other shared feature of some importance that differ from each other, but maybe not so very different from each other.

We know that if you have inheritance from the father. And again, we have looked carefully at our trees to see whether these issues of strange behaviors that might suggest an autistic linkage. We don't know much about the paternal and maternal side. We need to know more about it.

But if you paternally inherit the MECP2 gene which is the thing that causes Rett syndrome, you have a loss of Purkinje cells in the same layers that you lose them in autism. We didn't know this before. And we have astrocytic gliosis as has been described in autism and can be misinterpreted as something other than what it is, a genetic expression of change in the

system with the associated modifications taking place as part of not a true inflammatory response, but a mopping up that these cells do to eliminate its synapses and other kinds of things, and in the same layers, the molecular and granular layers.

So not an inflammatory change caused by a toxin that somebody has to do something about, toxins being, as I mentioned, non-specific as far as these injuries are concerned. Typically non-specific. But in the same areas that we see in autism.

Abnormal or early development of the inferior olivary nucleus which we didn't know before about autism, but exactly the same thing that we see in autism now that people are looking for it, and may in fact, and is likely in fact associated with the language disturbance that's so much more severe in children with Rett syndrome of the early onset variety than it is in many children with autism, but identical to many children with autism. This is, I'll say something more about that in a moment.

Q Moving now to Slide 21, Rett neuropathology.

A What else do we know about it? We now know that the synapses, and this is as the cells, these neurons migrate to get to the formed layers of the cortex of the brain. You can see them represented in

this slide as those various layers there. And you can see cells that are different sizes, perhaps, as they're moving through these layers. They move all the way out to the surface and then additional layers form.

I should say in passing that this very arduous process of these cells migrating to the cortex for all of us to form our brain in this very elegant way could not possibly take place unless there were astrocytes present because throughout their lives and throughout their production of all the things, that thinking cells we think of, the neurons do, they cannot do this without astrocytes. This is a team. And neurons specialize in doing these fine functions of thinking and appreciating and being inspired in all these things, but the seemingly lowly astrocytes are packed with all the things that nourish the neurons. Without those astrocytes there, it would never migrate in the first place; and without those astrocytes there, they would never survive.

So if you try to grow neurons in culture you have to have astrocytes. We now know some tricks to allow them to grow briefly, but even in those trick cultures, you have to put astrocytes in once they mature or they'll die off. This is a very important

thing for us to know about because if we injure astrocytes, if we make them go away, neurons will not survive.

So the idea that there might be a way in which neurons would become rambunctious or get out of order or cause autism because you've injured or eliminated astrocytes is really a scientific impossibility so far as we now very well understand this connection.

At any rate, there is increased density of neurons. Many of these are small neurons. There's increased packing of these neurons. We now know this is because of the expression of a particular thing that we didn't know about before called synaptophysin. This is a particular thing that helps form these synapsis for local connections and regulate their development.

So this is true of Rett syndrome and it's also true of autism. It's the same sort of thing that happens, now that we can carefully study both things. We don't yet know about synaptophysin in autism because we don't have the same animal model to look at, and because we have so few brains that have been studied in individuals with autism.

There's less dendritic arborization as well,

and this is in selected cortical areas. Frontotemporal and visual, same as in autism. And in selected layers. The neocortical layers two through three, five through seven. The same thing in autism. And in Folium II at the cerebellum, also similar to and almost the same as what takes place in autism.

Q Let's move now to Slide 22.

A What are the functional correlates of these things that we now understand? We understand that methylation has to take place. Successive steps in expression of these genes. There has to be suppression of certain gene transcription. If you don't suppress that gene transcription abnormalities can form.

We understand that some of these abnormalities may involve, as we now understand in autism, may involve the over-elaboration of connections, too many wrong connections, so that we get not only dense packing of cells, much dense than they ought to be. Too many neurons. But we may end up with too many local connections in certain cellular layers and we know this happens in autism. And it may be that what doesn't develop as well is long arc connections. That is to say connections between regions where there's the right number, not too many,

not over-connected neurons, but these long connections which connect one small area of the brain with other areas of the brain. I'll say more about that.

We now know that suppression of one particularly important thing in Rett syndrome, the DLX5, if it's not suppressed we have disregulated expression of GABA. What GABA is, this is a very important compound to neurons. It's a highly regulated aspect of when you get too much excitation in neurons. It's GABA that turns that off. It's exquisite that you turn this down so very quickly. It also happens in astrocytes so that you can turn things up or down as far as the channels that are involved in making glutamine. At least glutamate. I'm not sure about glutamine. But this particular thing is important that these cells can make this very exquisite change. If it doesn't happen accurately then we can see conditions such as seizures which are an aspect of Rett syndrome, an aspect of autism arise because you don't suppress these cells. It takes time to happen. It's a developmental process. The more you get this synaptic activity taking place, the more you're likely to remodeling which then leads to the possibility of having seizures.

But there's one very important thing to know

about these elaborated local and, as we now know, especially from functional studies, these under-elaborated, what we call long arc connections, one small area of the brain to another area of the brain.

If you have over-elaboration, I'm going to point out to you that this is a theory. I've warned you about theories, but it can be tested as time goes on. Is it possible that one of the most remarkable things we see about children with autism is what we call splitter skills. They're isolated areas of such remarkable function. You all know about individuals who can hear a piece of music and then play it on the piano. There have been people like Mozart who can do that. Some people say Mozart had autism. This is not true. It's not true. But if the music is played by individuals, at least when we've heard these things it also has this quality of strangeness that sets autism apart from other kinds of functions.

One of the things that's so striking in autism that isn't asked about, it's asked about in my clinic, is the children with autism who seem to not be paying attention or seem to have very selective gaze or seem to have many things that people can assign questions to and say what's causing it. So frequently you find, in the majority of children, that a child

with autism will go some place that they've been before, a different season, three years prior to that time, they'll look up and look at this place and say something's down there. The child with words to say these things. And the family will say I don't think so. Dad will say that, because dads don't remember these things. They don't know what's associated with other things, as I mentioned. Mom might know.

But this sort of memory, this sort of trick of memory, is a remarkable thing. It's a trick of connection between things that possibly are quite near to each other in the nervous system. Memory for words in their connection to other things we know are quite near each other in memory banks.

I had a patient who lived in a town with a phone book that big, and when he came --

Q Your fingers are about how far apart?

A Oh, I'm so sorry. I'd say that's three-quarters of an inch. I'm something of a carpenter so that's probably right. Other things I don't know about.

Green Bay, Wisconsin is where this was, and I could mention a name in that phone book, any one I picked out, and -- the strangeness was the speed. The social aspect of speed and communication, something

that's wrong in autism. If I got him to slow down, the numbers were always right. I couldn't do that. None of us in this room could do that. It's a remarkable preservation of a skill that's likely, theory, likely very close to things.

What about these other skills? Social interaction of language. Social interaction of gesture, which is motor, which is ataxia, which is the cerebellum, which is different motor systems. Language itself, broadly expressed in the nervous system. Lateralized in normal individuals, less lateralized likely in autistic individuals. These are the long arc connections that we know now from functional studies are not expressed in autism as they are in normal individuals. Another aspect of brain development.

So chromatin folding, other kinds of things here. I won't go into detail. But the last of these is that we now understand that this ramifies itself to issues of brain energy which we're beginning to understand better. And one might in fact mistake this for mitochondrial disease. But in fact it does have one aspect of mitochondrial disease, and that aspect is what we know is wasteful energy expenditure.

So if one were to find something that might

suggest mitochondrial disease in autism, one would anticipate from the comparison that this disease, so similar to autism, that it might have exactly the same genetic basis, exactly the same expression, in the same complexes as we might see in autism if this is true, and it probably is in Rett syndrome. It's testable.

Q Dr. Rust, we're going to move along through a few more slides. Can we move up to Slide 25?

A Can we go back to the prior one?

Q Slide 24.

A This is what I'm talking about. This is, you can see, those are blood vessels, the large ones. But you can see the connections, those long arc connections are the things that seem to be trailing down there in the illustration here. Those are the things that we know from functional studies are reduced in autism.

Q Slide 25 now, the neuropathology.

A Neuropathology. Again, we've got that early increase in brain weight that we talked about. We've got expression in particular brain areas that are systemically connected areas. Just as I mentioned to you the connection between brain stem and those Purkinje cells that have, as we now understand and

never understood before, something very important to do with language development. We've got the amygdala which Dr. Bauman's elegant studies, again done very carefully where you looked in this very complex organ that sits at the base of the brain, connects with all of these areas that have to do with certain kinds of impulses, certain kinds of behavior aspects, have to do with language, have to do with so many systems. This amygdala is connected with so broad an area of the brain.

What you found there is this increased packing of small neurons. Just the same thing. It has to be measured very carefully so that if you don't do that you're going to overlook it and you're going to come to the wrong conclusion about what's going on there. But this again is the same issue. The same sort of packing that interferes with the long arc formation and suggests local connections are overly abundant into which we can get into trouble.

Truncated neuronal dendritic arborization, just like Rett syndrome, and the increased density of small neurons, just like rett syndrome.

Q If we can go to Slide 26, some other observations you have.

A These have been put together more recently,

especially in the work of the Courchesne laboratory in California, to the identification of these organizational structures that are called microcolumns. These are the sorts of things, we have the right number of local connections, the right number in a columnar organization of long arc connections connected with other areas of the brain, and this happens wondrously and fortunately in most of us; and unfortunately and tragically in a small number of individuals with Rett syndrome or autism.

This is what I've already spoken about. For example, again this issue of gaze, and people have made many observations that I think are really, they're probably based on not seeing enough children with autistic disorders and they probably are not reading enough in depth about what really is going on in autism. But what we find about gaze problems was all the silly things we might say about them, is these really do have something to do likely with, especially distinctive gaze abnormalities as we see in Rett syndrome and autism. The connectivity of these microcolumnar things with centers at a great distance from where we have problems with packing and these sorts of things.

Q The next slide, Slide 27, pathology of

autism.

A In autism we see the same thing, a selective cortical microcolumnar dysgenesis as in Rett syndrome. We see increased thickness as in Rett syndrome. We see GABAergic loss, the same thing as in Rett syndrome that I mentioned in Rett syndrome has to do with the failure to suppress. Not to express, but to suppress a particular gene. There are many many genes that have to be suppressed so that they don't express themselves. This is true of cancer, and it's true of Rett syndrome. So we protect ourselves from things because of the way the system developed.

Increased outer cortical radiate white matter. This is another feature. But despite what some people have said about inflammatory disease in white matter in autism, it isn't a feature of the pathology of autism.

So what we have is an increase in the density of outer cortical radiate white matter and inner bridging/sagittal white matter. These are terms that don't mean anything to anybody in the room but me probably. But what this tells us about is the very same thing I've been trying to talk about, this whole issue of local connections versus distant connections. This very same issue of over-dense packing, over-dense

connection between local things, under expression of things that suppress that locality, and the ways in which these things express themselves. We can in fact see especially bridging areas that carry lots of fibers that go all around the brain as being too small. Another area where errors have been made. I won't go into that right now, but I'll just acknowledge the fact that this has to be done most carefully and that's it.

Vision, hearing, peripheral nerves in the pathology of autism are uninvolved. Very importantly, uninvolved. Normal vision with regard to the visual apparatus. Abnormality of these long arc connection systemic functions about vision. So normal hearing.

SPECIAL MASTER HASTINGS: Doctor, let me interrupt and ask, when you use the term autism in the title for this slide are you now referring to the narrow category of autistic disorder, not all pervasive developmental disturbance? How are you using the term?

THE WITNESS: Thank you, Special Master. I apologize. That's a very important question that you're asking.

With the studies that are so important to us which are the Bauman studies and others since that

time, this is very scrupulously and carefully limited to children with autistic disorder. So it doesn't include these other disorders. I'm comparing them to something that's been set apart because we know the genetic cause which is Rett syndrome. But in making the comparison of the pathological findings between those two conditions because they so strikingly resemble one another. To imply with I think some reason that one might regard the autistic disorder as being a genetic condition because of, again, increasing numbers of comparison that are so similar in terms of manifestations, clinical course, and pathology. So that's a very important question.

If we included all those other disorders we would get exceedingly confused about these things. In addition to that the age of the patient and other things must carefully be defined, because as I say it may be a developmental pathology.

So this is autistic disorder.

SPECIAL MASTER HASTINGS: And let me also make a comment here. I take it so far what I've heard from you, and I've been listening as hard as I can, you're giving us a lot of background on Rett syndrome and now you're moving into autism and sort of how it works.

I would just like to emphasize that we have a particular theory of causation of regressive autism that has been put forth by Petitioner's experts, and I gather you're giving us enough background so you can then explain to us why you think that theory is incorrect. That seems to be where you're going here.

But I guess what I'll say is, you need to give us enough background that we can understand your theory. So far I've been pretty overwhelmed with a lot of detail that I have really, as yet, no idea how it relates to the theory that I heard from the Petitioner's expert. So if you can, as best you can, focus on giving us what we need to understand without giving us everything you've learned about autism in your long career. I don't think I'm going to be able to absorb all of that.

With that, I'll turn it back over to you.

THE WITNESS: Thank you, Special Master. That is the direction you anticipated where I was heading.

BY MS. ESPOSITO:

Q Dr. Rust, you've got a copy of the handout in front of you as well, correct?

A I do. I think all I'll say about this complex slide is --

Q That's going to be Slide 28.

A Slide 28, thank you so much. Is that particular areas are involved. These are areas that have a particular brain system with which they're involved. These particular systems almost certainly, and we know in some instances certainly, have particular genetic expression that develops them. It's the same in so many ways to Rett syndrome that we now understand is a genetically determined developmental condition that explains the abnormality of development, and so this is the similarity between the two things.

The other reason for mentioning these particular focal areas is that I'll want to compare the ways in which this startling contrast with what may be seen either in inflammatory illnesses, although there's a broad variety of things, but especially with regard to mercury.

Q I think we can move through a number of these slides at this point.

A Again, this is what things look like. We can go on from there.

Q This being Slide 30.

A Again, this is a system thing that we now understand are connected to one another.

Q To the extent we can minimize it, let's go through --

A I will say one thing about this slide.

Q Slide 33.

A It's one of the reasons that it's difficult to avoid some complexity. But if you look to the left hand side, you've heard about Purkinje cells, I reckon. That's what they look like.

This is the point that I made with regard to them being lined up one after another so you can count them. This is one of the reasons, even though it was overlooked, is one of the things we now recognize as being a hallmark of Rett syndrome, genetically determined, and of autism that most of us presume is genetically determined.

SPECIAL MASTER CAMPBELL-SMITH: Dr. Rust, when you say these are the things that are lined up, you're referring to the bulbus-like figures in the left hand picture?

THE WITNESS: Thank you, they are. That's right. They have that sort of appearance of a narcissus bulb, something like that.

Next to it is actually a representation of a Purkinje cell.

I want to stress something about the

complexity of this and it's the reason I've said so much. One Purkinje cell has probably 175,000 synapses and probably 350,000 inputs. The nervous system is very complicated. It's remarkable it doesn't go wrong any more often than it does, but in order for this development to take place you need exquisite regulation of this abundant amount of regulation and you need genes that turn on and off at various stages, and you need cleaning up of the debris. That's what the immune system does.

It may do other things, because there is increasing evidence that the immune cells that have been talked about here in terms of possible inflammatory cells have a role almost certainly in the normal development of a system, and if one doesn't be careful about what one calls those cells, one can mistake the presence of those cells, once one looks carefully enough to find them, as evidence of inflammation.

Q Dr. Rust, if we can move up to Slide 45, we're going to skip a number of them.

A May I look through them?

Q Sure. The Special Masters will have copies of the slides to review on their own later.

SPECIAL MASTER CAMPBELL-SMITH: Let me point

out that if it is a slide that you think is pertinent to your discussion and explanation, we would rather have our review of the slides with you, Dr. Rust.

THE WITNESS: Thank you so much, Special Master.

If I were to try to put one sentence to each slide, would that be useful?

SPECIAL MASTER CAMPBELL-SMITH: In your own judgment. But I'm saying if it is germane to your opinion and you really want the best understanding of the slide it is best for you to review them rather than a take-home course.

THE WITNESS: Could we see the next slide, and I'll try to do this quickly.

BY MS. ESPOSITO:

Q This will be Slide 34.

A All I'll say about this slide is that there is a significant peculiarity with regard to the reaction to drugs on the part of children with autism. This is especially true with children with autistic disorder, carefully defined, and this speaks to systems problems. It tells us we must be very careful in treating children with autism, but again it's evidence that we've got to be careful what we do for children with autism. With our treatments, limited as

they are, we must be very careful about what we're doing. We sometimes significantly over-estimate what we're doing for a child, but we've become much more careful about that and we're very concerned about a number of therapies being added to this without that same degree of oversight.

Next slide.

The systems have something to do with other things we see in children with autism as in Rett syndrome. These involve a lot of neurotransmitters. I won't go into them in detail, but these are all systems diseases. And these systems diseases, connections of various parts of the brain with neurotransmitters are diseases that we characteristically have come to recognize as diseases that are genetically determined.

SPECIAL MASTER CAMPBELL-SMITH: This is on Slide 35?

THE WITNESS: Slide 35, I'm terribly sorry. And not features of what we find are environmentally injured brains.

I mentioned the environmental aspect of autism that's very important. That's the aspect of communication and the aspect of understanding. That's very important for us to know about as an

environmental aspect of things.

I mentioned about this, and we can go on.

This is the way in which we look at these systems.

BY MS. ESPOSITO:

Q This would be Slide 37.

A Slide 37. Again, this new technique that we now have of functional MR spectroscopy. We didn't have this before. The more we do in children with autism the more we find that these are systems that are going wrong. Developmental systems that are going wrong, and this is not the way in which we see systems, we don't see these system problems in toxicity and we don't see these system problems in inflammatory disease.

SPECIAL MASTER CAMPBELL-SMITH: Let me ask on Slide 37, you have circled areas up in the A portion that are red. Will you discuss those later? Is that something you need to draw particular attention to?

THE WITNESS: What I'm identifying here is the absence of expression, the open circle, in the child with autistic spectrum disorder. Of particularly important expression in the cortex of the brain, an area that hasn't developed properly.

SPECIAL MASTER VOWELL: Doctor, while we're on this slide, you made the statement that systems problems are not seen in inflammation or toxic insults. So is what you're saying that the systems problem has something to do with development, or that toxic insults or inflammation doesn't target these areas? I'm not sure I understood what you meant.

THE WITNESS: Yes, Special Master, and it's important for me to add that this is with regard to the complexity of these identifiable systems problems and our increasing understanding of these techniques of where these systems are and what they connect with.

With toxicity or inflammation, the effects, first of all, are all at once and nothing first. They take place when the exposure takes place or the infection takes place, and that's that. They affect the system based characteristically on the types of cells, no matter where they're to be found. So they may affect neurons no matter where they're to be found. That's typically the case in these kinds of conditions.

Sometimes there's a greater vulnerability of a particular area of the brain but the system doesn't have the same problem so we don't see the same thing in toxicity or inflammation.

SPECIAL MASTER VOWELL: And by systems, you are referring to how different parts of the brain interact with one another as opposed to a specific part of the brain that controls a specific function.

THE WITNESS: Yes, Special Master, that's exactly right.

SPECIAL MASTER VOWELL: Okay.

MR. MATANOSKI: Special Masters, I suggest at this point so that we can perhaps move along a little more rapidly, if we could take our, I don't know whether you were planning on having a break this morning or not, if we could do that, then perhaps Dr. Rust could look through some of these slides and decide which ones were appropriate to comment on and we can move on after we come back.

SPECIAL MASTER CAMPBELL-SMITH: The morning break would be a 15 minute break.

MS. ESPOSITO: That's fine.

SPECIAL MASTER CAMPBELL-SMITH: Maybe we'll push that just a little bit further for ease of reference.

My clock is showing about five of noon, so 12:15, if we could come back? Do you have a different time? There's another watch that says 11:48, which puts us --

MR. POWERS: That's the consensus watch.

SPECIAL MASTER CAMPBELL-SMITH: The consensus watch makes it closer? Well then 15 minutes which will bring us back at noon. We'll do that.

MS. ESPOSITO: Maybe five after?

SPECIAL MASTER CAMPBELL-SMITH: Five after. I'll let somebody with a more reliable watch get us back here at five after.

(Laughter).

Thank you. We're in recess.

(Whereupon, a short recess was taken).

SPECIAL MASTER CAMPBELL-SMITH: Please be seated back in your same spot because we got the microphones to work.

Just a quite note, looking ahead, recognizing that Dr. Rust has limitations on his schedule, thinking that we'd go as long as we can before we try and take a lunch break, but recognizing that the local cafeteria closes at 2:30, our thought was we might try to break about 1:45 for lunch.

Those of you who have more accurate time pieces might want to try and flag my attention as we're getting close. Just to be put on alert about that's our preliminary thought for schedule.

MS. ESPOSITO: Okay.

SPECIAL MASTER CAMPBELL-SMITH: Ms. Esposito, you may continue your Direct Examination.

BY MS. ESPOSITO:

Q Dr. Rust, we're going to move to Slide 41. I believe you had a brief comment about the hyperactivity note at the bottom of the slide.

A Yes. Again, I've said perhaps too much about systems, but these are some examples of them.

These kinds of behaviors that we see that are so very peculiar in children with autism are things that an inexperienced observer might mistake as hyperactivity, anxiety, other kinds of things, I've already mentioned that issue of label. I think it's important to bring this up within the context. I'll be commenting on Dr. Kinsbourne's report, but there is a considerable emphasis placed on these as manifestations of a hyper-excitable state in the nervous system and I'd simply say it doesn't make sense to me to put things together in that way. It's certainly not in keeping with the data that I'm aware of or my experience in the clinic with considerable numbers of patients. And these kinds of behaviors, as I already mentioned, melt away so dramatically in the setting of families that show understanding and educational settings, and yet some things persist.

They need to be separated from one another and to cull themselves, whether it's anxiety, hyperactivity, hyper-excitability of the brain is far beyond what we know about these things.

Q We're going to skip a few slides, but we'll move up to Slide 45. Can you explain to me what this is? It says, "To whom it may concern".

A The preceding slides concerned some of these peculiarities of behavior with the emphasis on how these are almost certainly systems related things, differences of behavior. If children were autism were most of the people in the world, we might look peculiar in that setting, but nonetheless, this is the way things are.

Because of these things, because of lack of understanding, when I see a family with a child with autistic features I give them this card. This is so they can show this card to people in the supermarket, or they can show it to Uncle Ed or they can show it to whoever it is, that tells them they don't understand how to care for their child. It's important to know that all of us have difficulties understanding autism and it's important to know that people sometimes try to intervene in children with autism and not understand what they're doing, so this is what this

card is all about.

MR. POWERS: Excuse me. I have a question for counsel and for the Special Masters. Are the slides that are being skipped, are they being withdrawn from the exhibit? How are we handling that?

SPECIAL MASTER VOWELL: I certainly have questions on some of them that I intend to go back to, if that helps you.

MR. POWERS: Okay. And I would too. I just wanted to get clear that what we see here as this exhibit, even though it's being perhaps skipped on Direct testimony is remaining in the record and there's an opportunity for Cross on this.

SPECIAL MASTER CAMPBELL-SMITH: Yes.

BY MS. ESPOSITO:

Q We'll move now to Slide 49. Talk about methyl mercury intoxication. Can you explain to me what we see in methyl mercury intoxication?

A We have a good deal of information about methyl mercury because of the tragic experience in -- could we go to Slide 48?

Q Slide 48, okay.

A We know about this condition because it was so carefully studied pathologically, clinically, and all other ways. This is a young child that had methyl

mercury intoxication. As was typical in these cases, it was a disease that occurred prenatally, thought to be the case because of the concentration of methyl mercury being much higher in the fetus than it was in the mother, with observations that the pregnant mothers of children in Minamata Bay were not affected by the methyl mercury intoxication in the same way other individuals that were not pregnant were. The tragic consequence, despite the fact that the mother didn't have disease, was a child with severe neurologic disease. Children as in this instance cared for by their mother throughout their ensuing life.

Q And Minamata, was that a congenital mercury exposure?

A This was, again, the children manifested this condition, or fetuses during the period that they were exposed. Again, the thought is that the fact that the mothers were less likely to have poisoning and manifestations was because of concentration of the toxin in the baby.

This suggests to us, for which there is additional evidence, that a very high dose was necessary. That the mother could be protected, yet exposed to the same waste material that had the methyl

mercury as long as the toxin was concentrated in another individual. And the fact that this affected children in the prenatal environment as compared to children that were post birth, again is interpreted as because of concentration.

So people do have some ability to withstand this toxin unless exceedingly high concentrations are achieved.

Q I think on Slide 49 you describe what methyl mercury intoxication actually looks like.

A The clinical aspects of it are these. Severe visual and hearing deficits, as I mentioned. These are not features of autism. Severe central nervous system and motor dysfunction. Not a feature of autism. In fact motor function in autistic individuals is oftentimes quite dramatically excellent. Severe peripheral nervous system sensory dysfunction. Not a feature of autism. And limb deformities. Not a feature of autism.

Q Slide 50, the pathology for Minamata Bay.

A Almost exactly the opposite of what we see in autism. The large neurons that seem to be less well represented in autism are spared as are the deeper cortical laminae. This is not, as I was trying to emphasize in the preceding slide, an example of

systems dysfunction or remodeling. It's a matter of toxicity and we don't see the same system problem. We see the central nervous system relatively spared because of blood-brain barrier, and the deficits tend to involve peripheral nerves more.

Sparing of Purkinje cells. Very importantly, which we know are exquisitely sensitive, seemingly, in autism. And this is despite a relatively uniform distribution of mercury in the brain.

Q Let's move to Slide 51.

A If an injury is produced to the brain as is suggested in these cases by inorganic mercury, the pathology and the dose required one must presume to be exactly the same as that in these methyl mercury intoxications if the emphasis is placed, as it appears to be, in Dr. Kinsbourne's discussion on inorganic mercury and its accumulation in the brain. Because both methyl mercury and ethyl mercury break down to inorganic mercury. There is a small difference in terms of concentration that is nothing like the difference in concentration that's observed in Minamata Bay disease where prenatally the children seem preferentially to accumulate mercury.

Q Dr. Rust, we're going to move now to a

discussion of the two children in these cases. We'll start with William Mead. We're going to break from your slide show for the time being.

Do you agree that William Mead has autism?

A Yes, ma'am.

Q In your opinion was William's autism caused or contributed to by his receipt of Thimerosal-containing vaccines?

A No, ma'am.

Q Can you explain that?

A I've tried to explain it in the preceding information. He doesn't have a disease that has the clinical aspects of mercury intoxication. It's a disease that has all of the features and manifestations that we know in autism and find in great measure in Rett syndrome that we know is a genetic disease.

Q In your report on William Mead you discussed the significance, and in your testimony earlier today, you discussed the significance of William Mead's enlarged head circumference. There was an issue last week as to the citation for that head circumference. I'd just like to clear that up with you at this time.

The reference in your report was William Mead Exhibit 3 at page 34. This is what's on the

screen right now.

Can you tell me what this exhibit is?

A That's a representation of length and head circumference, and I thought it was at birth.

Q Let's look at William Mead Exhibit 1 at page four. Can you tell me what this is?

A I apologize for the error of citation. This is the important illustration of head circumference crossing centiles. This is quite unusual during the first three or four months of life.

Q What was blown up here is the head circumference over the first few months of life chart.

A This is what I believe I represented in my report. The 60th rising to the 97th percentile, something like that, and then declining thereafter.

Q Dr. Mumper had suggested that William's large head size was just in correlation with the size of his body, that he was just a large baby. As a pediatric neurologist, is that your understanding of what happened here?

A No, ma'am. We see this rise being out of proportion to the increase in linear growth of the child.

Q Is there a point on William's growth chart for his head size that's particularly telling to you?

A The high point of these charts, if people are not used to looking at them, represents centiles for growth parameters. We use these as things that may help us to detect the cause of a problem. But in addition to the increase, the even more telling aspect of this is the ensuring decline because there isn't anything that can compress the head and cause this change as time goes on. We see rather an initial increase with the ensuing decline in size suggesting that something developmentally has gone on. If one were to have a hemorrhage or hydrocephalus one would see further increase, and it's this decline that takes place afterwards is the thing that we see in children with autism in the first year of life.

Q And by decline, you mean that William's head circumference came back towards the mean?

A As you can see, it continues to grow but the rate of growth violates the centile.

SPECIAL MASTER CAMPBELL-SMITH: And that is represented by the circles that are on the arcs.

THE WITNESS: Yes, Special Master.

BY MS. ESPOSITO:

Q Dr. Rust, did you find any significance to William's numerous sicknesses during his first few years of life?

A They didn't seem to me to differ in any quantitative way from other children. Is there a specific you'd like to ask me about?

Q Just the round of the antibiotics. I believe in your report you stated that there were six rounds of antibiotics that William was on, I believe you said from 1998 to 1999. There may have been prescriptions for more. I believe Dr. Mumper had said there were nine antibiotics given in the first two years of life.

If it were nine, or even a few more than that, would that be unusual in your opinion?

A Based on the clinical descriptions and based on what we know about variation in practice in the community, very little can be made of the number of antibiotics given for what are largely or perhaps entirely viral illnesses. Ear infections come from a variety of causes but almost all are viral. Some practitioners will provide more antibiotics and some will provide less for those things. Some don't provide any at all. So the comparison of children getting more or less antibiotics is a parameter we can't interpret because it's based so much on the practice of an individual and because we know that most of these illnesses are viral and not responsive

to antibiotics. That's what I'd say about that.

Q Dr. Rust, you had already discussed pica a little bit. There's some evidence in the record, both from the medical records filed and from Mr. Mead's testimony last week that William may have put marbles, gravel in his mouth, and had some other, there's some other mention of pica in the record. Do you find that significant in his case?

A As I mentioned, these peculiarities of mouthing objects or putting them in the mouth, or rubbing them on the lips are very common in autism. But we do find the same things in some otherwise normal children.

Q Dr. Rust, from your review of the records is there any evidence that the biomedical interventions performed on William treated his autism?

A No, there's no evidence that there was an effective treatment provided.

Q We'll go through some of those in a few minutes.

In Dr. Mumper's report she infers that William's teeth grinding is a sign of mercury intoxication. What significance to you place on the teeth grinding?

A We have a fancy name for it. We call it

bruxism. Bruxism is so characteristic of Rett syndrome as to be almost universal. In autism we see that very commonly. We don't know the significance of it, but we find it far more often in autism than in some other settings. It's not a sign, to my knowledge, of mercury intoxication.

SPECIAL MASTER CAMPBELL-SMITH: Dr. Rust, I'm going to ask you to spell your fancy name.

(Laughter).

THE WITNESS: I'm terribly sorry. I hope I can. B-R-U-X-I-S-M.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

BY MS. ESPOSITO:

Q We're going to move now to some of the facts specific to the Jordan King case.

Do you agree that Jordan King has autism?

A Yes, ma'am.

Q In your opinion was Jordan's autism caused or contributed to by his receipt of Thimerosal-containing vaccines?

A No, ma'am.

Q Is your reason the same as what you gave earlier?

A Yes, ma'am.

Q There was an issue last week again with the

citations in the record that I'd like to clear up regarding a record which documented the timing of Jordan's loss of speech. In your report it notes that the father, Jordan's father, was the historian. The record that you cited to was Exhibit 7, Jordan King Exhibit 7 at page eight.

This is what you see on your screen right now, and Mrs. King actually came back and testified about this being her notation.

I'd like to draw your attention now, Dr. Rust, to Jordan King Exhibit 1 at page 41.

Is this the record you meant to refer to when you described that Jordan's father had said that Jordan's speech had stopped around one year?

A Yes, ma'am.

Q Did you find anything aside from this record that included some description from Jordan's father, did you find anything else concerning in the record about Jordan's speech?

A At this moment I don't recall whether there was something else. Did I cite something else?

Q I'm not sure if you did or not. I think you stated earlier today that Jordan only had five words. I think from his mother --

A Five to six, I think it said.

Q It could have been up to ten from his mother's testimony last week. Is that what you would expect in a child who stopped speaking at 18 months? Five or ten words?

A No, I think there's abnormality. That's why I mentioned the fact.

Q Would you expect more words from a child who's speaking up to 18 months?

A I think the important thing here is, as I mentioned, that he stopped communicating. It isn't the number of words. We have certain interpretations of things a child may mean to say, but the important thing is, the mention is of the change in his communication by the person who knows him best.

Q There are some notes in the record that Jordan was never a people person and he was never an "I want to be held" baby, as early as three months. Is that significant to you in terms of his autism?

A We take that quite seriously when we hear about it.

Q You mentioned earlier that some children with autism have splitter skills that are unusual. According to the record, did you find any of those splitter skills in Jordan King?

A There is a mention of the very thing that it

seems to me the sense of direction part of it was mentioned in the record. I believe I recall that. And musical abilities were also mentioned. These are fairly common areas of attainment.

Q Is that the type of skill that would be present in someone with mercury intoxication?

A As I mentioned, the hallmark includes hearing problems and motor skill problems. And these were not manifested by Jordan King.

Q There was an amino acid analysis used by Dr. Green. This would be Jordan King Exhibit 1 at page 12 and 13. Can you tell if Jordan had an amino acid disorder? I'm going to pull that up for you here.

(Pause).

A There's no data here on amino acids.

Q I think this is just Dr. Green.

A When it's suggested there is an amino acid disorder we of course always check the results of the amino acids that have been obtained in blood and urine.

Q You stated in your report that looking at those records, Jordan has no evidence of a known amino acid disorder.

A That's quite correct.

Q Does it appear to you that Jordan, through

your review of the records, that Jordan had any evidence of pancreatic dysfunction?

A I didn't see any evidence of pancreatic dysfunction.

Q Did you review the results of the various mercury tests performed on Jordan King?

A Yes, I did.

Q What, if anything, can you conclude from them?

A Mercury testing done in normally accredited laboratories was always either quite normal or in fact nothing at all was found. So quite normal results.

Q The other laboratories that did some of the tests on Jordan King, in your report I believe you said there were astonishing levels of various metals in the lab results. This would be Jordan King Exhibit 1 at page 55 was the exhibit.

What do you find significant on this page? If you were to accept these results.

A This and other records show remarkable elevations of a broad variety of compounds including metals at concentrations that we would be very worried about the expression of the diseases that are known to be associated with those kinds of things, and it would raise the question as to how in the world this child

might have acquired that much in the way of these compounds. There are many things in the environment, but we do heavy metal screening on lots of children for various reasons and we never find anything like this except in rare instances.

I can't quite read this but it seems -- tin, for example, is shocking. There is tin intoxication. It's seen almost exclusively in people who spend their careers for long periods of time working with tin and tin becomes inhaled, especially when people are working on tin with hot torches and this sort of thing. It takes a long time to happen. It's a mid-career thing in people that get it. And children absorb tin, if they can get it, very poorly.

Tin has the advantage from the standpoint of intoxication of having a taste that people don't like. So I think people wouldn't be likely to put this in their mouth.

Q I take it you saw nothing in the records aside from this result that would make you think Jordan King had a tin intoxication?

A No, ma'am.

Q I'd like to move now to the treatment of autism. From your experience are there any treatments that seem to improve symptoms in autism?

A Yes, as I mentioned, proper understanding, improvement of sleep, sometimes we can help out with medications for others, specific indications, as long as we're very very careful about the dose, because I mentioned the sensitivity to medication. As long as we check very carefully afterwards to make sure we've achieved an affect. There's opportunity in children with these kinds of problems to multiply medication in ways which we then can't sort out disease from toxicity. What I tell families when we try something is we do one at a time, then the family takes a close look. If it looks like it's not causing any problem we increase the dose gradually so that we don't again complicate things. There's such variation in behavior in children with autistic diseases that we have to be very careful as to what the background is.

Children tend to come to us when they're having more problems. The family wants us to help. We give something and they get better and we may try to take credit for it, but behavior and many other manifestations of this disease, as with human behavior in general, typically follows what we call a sine wave. A sine wave, as you'll recall, is this thing that goes up and down and up and down like this. For all of us things get better and things get worse,

things get better and things get worse. When things are better, it's fine. If things get worse, we do something. If it gets better, maybe it's mother nature doing that. Often it is. So we need to be very careful about that in confusing us.

Then to decide whether something's really helping, after the family has looked so very carefully, and sometimes other people, what I tell the families is nothing should be continued unless you suddenly say I wish we'd done this before because it made such a difference. From our vantage point when we see children that have been treated variously we can sometimes get a sense of that as well.

Does that answer your question?

Q I believe it does.

A Can you extrapolate from a seemingly successful treatment to a causative factor for the underlying autism?

A No. I don't think so. Not in my understanding of this disease process.

Q I'd like to discuss some of the treatments that have been administered to the two children in these cases, and check to see your understanding of the efficacy of these treatments for autism.

Both of the children received IVIG therapy.

Is that known to treat or help autism?

A It's been tried, as has its cousin, corticosteroids. Typically they're tried in the setting of EEG abnormalities. We've had the opportunity to closely observe children treated with both forms of therapy without any evidence of improvement behaviorally or functionally or from the vantage point of EEG.

Q Both of the children in this case were also on supplements. Have you seen anything that indicates a supplement improves --

A I'd have to provide a very general statement. There are so many supplements, we don't hear about most of them, probably. We don't hear about when they started or stopped most of the time. So I can't say for certain. We don't have as close an opportunity to observe.

To the extent that there is data, and to the extent to which families will share with us what they've been doing, we haven't seen any efficacy for many different kinds of supplements, but I don't know whether we've seen the whole list or not.

Q What about secretin?

A Secretin has been subjected to a very careful study to see whether it's efficacious. It was

found not to be efficacious. It's a compound that continues to be studied and perhaps additional information will be found.

Q What about chelation?

A I've seen no evidence that chelation is helpful in this setting. It is helpful in some other settings. It's helpful in the case of lead intoxication at higher degrees. And as an older pediatrician when we used to see more lead intoxication than we do now, and as my clinics are oftentimes on Friday, I had some experience with the considerable pain that children would experience with chelation typically, so we'd always know that the chelation clinic was open because children would be screaming on their way into the chelation. It did help somewhat with lead and that's why it was carried on, and helped with copper as well. But in the setting of autism I've seen no evidence that it's efficacious and wouldn't expect for it to be efficacious because it's not pertinent to the disease.

There have been four deaths at least from chelation therapy, and that's probably what makes me a little irritable about the subject, in addition to the pain it causes in children.

Q Have you heard of a therapy of putting a

child in a sauna to sweat it out? Does that help the symptoms of autism?

A It's been around since ancient times, that approach to things in all cultures, and with the idea that it might be helpful whether in the sweat lodge or whatever. It does seem to be helpful to some individuals with headaches; it helps some individuals with stress and tension. I see no reason why it would help in autism because there's nothing to sweat out except perhaps some of the notions and treatments that are provided to the child.

Q I'd like to direct your attention now to William Mead Exhibit 15 at page 28. This is a treatment note from Dr. Green.

There's a note here that Dr. Green was looking at the possibility of doing a reimplantation enema, ideally with a colonic delivery system using a diluted maternal fetal supernate.

Are you aware of that as a treatment for autism?

A I'm aware that it's provided to some children with autism.

Q Are you aware of its efficacy?

A So far as I know there is no known efficacy. There's no reason to anticipate that it would because

there's no known element of the pathophysiology of autism to which it would address itself.

The approach has been around for a long time. It goes back to Roman times, as a matter of fact, for a broad variety of illnesses. It continues to be practiced regularly by some adults as well as other people in those settings. We don't have any reason to believe it's going to be helpful in any particular disease.

It used to be a regular feature of childbirth, the idea that the introitus might be wider. Some mothers were subjected to enemas for that purpose. Once it was studied carefully and found to be a silly idea, it was abandoned. That's been true of the other indications as well.

Q What about the possibility of feeding a child fermented vegetables? This is further down on that same exhibit, William Mead Exhibit 15 at 28.

A Fermented vegetables are an item of the diet in large parts of the world and is said to be enjoyed by people as well. Their benefits are unknown. When you do ferment vegetables you do have the possibility of introducing organisms, if the fermented solution is like that. Sometimes this can be beneficial and sometimes it can be a negative thing.

So many people in the room will have enjoyed and perhaps obtained some benefit from fermented hops as beer, other people wine and so forth. It also can be something that in excess can be a problem. So we've seen it go both directions.

I know of no reason why this would have anything whatsoever to do with autism.

Q Further down on that, it's still highlighted there as well. Earthworm eggs. Is that known to treat autism with any success?

A No known benefit that I'm aware of.

The Chinese botanical is interesting. We had a patient that came to us with difficult epilepsy and a Chinese botanical was introduced and we were astonished to see how beneficial it was in this child's epilepsy, so we thought we were onto something. We sent it to the laboratory and had it analyzed. It was phenobarbital.

Q What about charcoal capsules? Is that something that's been known to help in the treatment of autism?

A The same general idea about charcoal, of course, is leaching something out of the system. We don't, I don't have any reason to know that would be beneficial in autism.

Q What about oral Baygam which is an immune globulin. Do you know if that is used --

A I have no information whatever about that subject.

Q What about Valtrex, a medication?

A I don't know any reason that it would be helpful here in autism.

Q Are you familiar with Eskimo Oil?

A I don't know what you mean by that. I have no idea.

Valtrex is used for genital herpes, isn't it? I don't know why it would be beneficial in this setting.

Q Have you heard of Actos for the treatment of autism?

A No.

Q If there was a report of improvement after these treatments, would you extrapolate from that to a cause of the child's autism?

A If we definitely saw an improvement, I'd try to sort out what had happened. First you have to know what's being treated and secondly, you have to know whether anything else has been involved there. Then you have to decide what the mechanism is and then study it. So theory is one thing and observation is

one thing. Once we get ahold of something and it looks like it's promising it has to be subjected to experiments so that we can really understand what's going on. It needs to be extended to a broader population oftentimes to really see what's going on.

As I mentioned, all of life follows a sine wave, up and down, up and down.

Q Is it standard practice for a physician to recommend a product to patients and then personally sell it to them?

A In my experience this is considered to be one of the most important violations of the oath and the responsibilities that we take as physicians. We are there to help the sick; to listen without repeating their complaints; and the idea that somehow we would keep an office full of Amway products or something and sell them to our patients would be, for most of us, considered a grave violation of our responsibility and taking a grave advantage of patients. Because it trades in that setting on the prestige that we have, the reliance that the families have on us, and this is one of the most, has been since the beginning of time, one of the most grave violations of our code of conduct, codes and ethics.

Q Back to the list of treatments we have just

discussed, I take it you don't prescribe any of those or suggest any of those to your patients?

A No, ma'am.

Q Do you know if any of them are recommended by other neurologists within the American Academy of Pediatrics or other colleagues of yours in the field?

A I don't know them all. all the ones that I know don't use these things. If we want to make ourselves feel better sometimes we can bring these things up and have a little laugh about them. Then we think about the children that are unfortunately subjected to these things.

So I don't know of anybody that does these things.

Q And the reason why you don't do them is because they don't work?

A If I had anything I could do to help a child, I would do it.

Q I think you mentioned before that when you try a treatment on a child you use just that one treatment at one time, is that right?

A It can be too confusing otherwise. There are times when we do more than one thing in a child with very significant epilepsy. We may double up on anti-seizure medications. There are times when we use

more than one thing. But most of the time, especially in behavioral medicine, we need to be very careful about finding out what we're really doing.

Q I'd like to show you a statement from Dr. Green, in a letter from Dr. Green to the Mead family. This is William Mead Exhibit 5 at page 89.

Dr. Green says, "In a sense together we have to become masters of the multi-varied analysis with multiple interventions infringing on him simultaneously or nearly simultaneously."

What's your response to that statement?

A The way I use the language I'd say infringing is exactly the right word. We're infringing on this patient's opportunity to have carefully studied remedies and infringing on the opportunity of people to actually understand what in the world is going on.

Medicine has been filled for centuries with potions and toxins and other kinds of things given to children or adults or other people, for various reasons. Oftentimes in association with strange ideas people have about the gut. These have almost universally been things that resulted in no improvement and resulted probably in problems more than health.

Q Dr. Rust, you just mentioned the gut. Are gastrointestinal issues something seen uniquely in the autism population?

A Everybody has gut problems. I guess it's what it is and how much of it they have. So the data would suggest that if you look carefully, maybe as many as 80 percent of children with autism have some kind of complaint related to the digestive system. But overwhelmingly in my practice and in the data that's been most carefully gathered, that's at the top end of things, and that is the remarkable and so very uniform issue with regard to certain kinds of things that won't be eaten under certain conditions.

Q Can you describe that a little bit more?

A Food that's warm is allowed to go to room temperature and food that's cold is allowed to melt and go to room temperature as such a very frequent thing in autism. I don't understand why it is, but as I ask about it with other children in the clinic I don't find the same thing, so it does seem to be a feature that is peculiar to the autism.

There are food textures that are rejected. There are difficulties with oral medications sometimes that also are features at the top end of things.

At the other end of things we see

particularly frequent diarrhea in some of our patients. It doesn't seem to be in association with abdominal pain or discomfort, but when looked into we find that like some other children, but particularly in some children with autism, we see retention of large amounts of stool. The result of that, the detection of it can be found in otherwise normal children because they complain of discomfort. Then the investigation of the ensuing diarrhea, once you get a large amount of stool the less-formed liquid stools tend to traverse around that large amount of stool and manifest as what seems to be diarrhea. So you can again get a clue in normal children, because they tell you about the discomfort they're experiencing.

We don't get, for various reasons, some of which we know about, some of which we don't, the same complaint in individuals with autistic problems.

What we find when we find it is that the same sort of thing is often there in the child that has frequent watery stools, and it's the same feature of overflow diarrhea around that large stool producing many liquid stools over a long interval of time. It's a difficult problem to treat but it can be treated and it represents a frequently observed thing in our

gastrointestinal clinic at our hospital.

The other interesting feature about it is the feature of autistic individuals not complaining of pain. Now in those that don't have language to complain that is quite understandable. But we have these peculiar issues of pain intolerance or tolerance in autism that we also don't understand.

I've had a number of autistic children, or children with autistic features I should really say, that have broken bones and one doesn't find out until one looks very carefully.

I've had children that have had severe falls and get right back up from them. Yet on the other hand a child can have a small cut with bleeding and become so upset that they sometimes can't be calmed very quickly, or the place on another bandage on a cut or a wound can't be tolerated sometimes.

So there are unusual sensory features. And probably the prevalence of this gastrointestinal thing down below stool retention, which is really only found in about seven or eight percent of children with autism. But it recurs so much because of the flow around the stool that it does become a persistent problem with frequent stools.

Q At this time we're going to move to a

discussion of Dr. Kinsbourne's report. You can get back to your slide show.

Before we do that, though, I take it you've reviewed Dr. Kinsbourne's report?

A Yes, ma'am. I have.

Q What's your general reaction to Dr. Kinsbourne's hypothesis?

SPECIAL MASTER CAMPBELL-SMITH: And you're now on Slide 54?

THE WITNESS: Fifty-four.

BY MS. ESPOSITO:

Q Fifty-five I think has some of your response, but just off the cuff --

A I prefaced my account with the problems that we run into with deciding what the cause is in the first place and trying to fit the evidence to it. I mentioned Tycho Brahe and trying to place everything around the earth in the solar system. There's lots of this in medicine where people stick with a particular thing. And as I mentioned, one of the greatest figures in medicine and science, Oliver Lowry, said that when you hit on the right idea it's bound, as it's been my experience ever since, to be something that is simple and elegant and unexpected, or usually unexpected.

The hypotheses here are incredibly complex and awkward. They are, most of the data is either not representative of the papers that are cited as evidence or there seems to be some distortion of the data. Other things are offered far ahead of the availability of any reliable data. So there's very meager data for these things. He's not to be faulted for the fact that there's meager data because there isn't that much data, but there is more data than is cited and the data that is not in keeping with the hypothesis is not cited.

These kinds of hypotheses are relatively easy to put together. I don't know how this was put together except to say that it's awkward. But sometimes we see in our medical students, or in people putting together high school projects for science fairs, that they will go on-line and put a few words in there and come up with some connection and try to fit these things together in some way. One gets a feeling for this, but I don't know that he did it that way.

Prominent countervailing data and theories are not considered, and the idea, we know a great deal about the regulation and the interaction of the systems that are involved and referred to, and there's

absolutely no apparent understanding of the ways in which the system actually functions.

One example I already suggested, which is this absolutely necessary interaction between astrocytes and neurons and the very complicated business of counter-regulation for excitatory compounds in the synapse, and no real understanding of the architecture that's in it as far as I can tell.

There is shifting reliance on one or another portion of the data, and shifting reliance --

One convenient thing about an awkward theory like this is that once you have the idea that they give you some special susceptibility or there is some way in which some particular thing can cause a problem that it's never known to cause and hasn't been identified as causing pathologically. You can substitute one thing for another. So we now have something that seems to be a substitution for prior suggestions by various people, I believe Dr. Kinsbourne among them, that measles virus does this. That is an awkward hypothesis because we know exactly what measles encephalopathy looks like clinically and pathologically, and it's not autism.

The supportive data seemed to me to be taken out of context and seemed many times to be impertinent

to what's going on. It's data selected to support that hypothesis.

Q Moving to Slide 56. It appears you take issue with Dr. Kinsbourne's hypothesis about regression and his attempt to set regressive autism off from classic autism. Can you explain your thoughts on that?

A It's an artificial distinction except to say that in some children we see an emphasis on parents, tell us this and we believe them. We see an emphasis on something declining in the second year, but sometimes we get reports at variance with one another. But it's a small difference and once we ask the questions that I mentioned to you, our former view that there was in fact this thing as a very discreet thing has really vanished because we find pre-regression abnormalities that I've already referred to.

One thing that made these things rather different from one another is when we used to include a variety of symptomatic autisms under this heading, some of which would fall into the classic group and some of which would fall into the regressive group. Once those were separated the difference became also less distinct.

As to whether there are more overt seizures in regressive autism, we don't actually know whether this is true. There are citations to this effect. What we do know is we do more EEGs and we find more EEG abnormalities than we have recognized in younger children, but we don't do EEGs on our children that come to us with autism in the first year of life.

Q Dr. Rust, if you had let's say two six year old boys, one with what might be termed classic autism and one with what might be termed regressive autism. At the age of six, are they going to clinically present any different from one another?

A They don't look any different to me. There is some variation in individuals, but they don't look any different to me.

The other point about this, seizures and regressive things, is that overwhelmingly in my practice and that of others, seizures are not a feature of toxic conditions. Dysfunction is a feature of toxic conditions.

When we see seizures and don't have an explanation, the first thing we look for is a developmental genetically determined condition.

Richler is cited in there, there are not too many citations in there but he cites Richler's paper

about regressive autism and this is to support the statement that there are more GI complaints in autism. In the same paper Richler says the majority of regressive ASD children had clearly atypical pre-loss development. This is an example of a piece of information. If you're citing a paper, you regard somebody as authoritative in one sense, you must regard them as authoritative in others. We don't have any reason to distinguish and pick and choose. But this is what we call cherry-picking which is sometimes an aspect, usually an aspect of these kinds of hypotheses, so we need to respect the individual who's come up with something we think is important and listen to the rest they have to say because it's usually evidence they've looked very carefully. The kinds of things that were found were social and verbal IQ and language problems. That would seem to me to undermine the idea that the MMR vaccine is causing this combination of things.

Q The MMR vaccine or Thimerosal --

A Thimerosal, I'm sorry. Any vaccine really.

Q Let's move now to Slide 57, your comments on the GI system.

A These are the kinds of data that are gathered in careful groups. Really one of the leading

groups in the world is Isabelle Rapin's group. She's been interested in this since 1961 and has published extensively. Her data was what set me to thinking about these things and looking carefully at our children, and we find the same thing. The same amount of patients with GI problems. Mostly problems from above, stool problem abnormalities down below.

I think we've stolen the marks on Isabelle's, the only time I've known about doing this with her, with this idea about stool retention which we've now found in so many. We're looking carefully into this in a prospective way.

SPECIAL MASTER CAMPBELL-SMITH: Let me just ask Dr. Rust, I'm lost with the abbreviation 42 percent DD. Help me.

THE WITNESS: Gastrointestinal problems, 70 percent of children with autistic spectrum disorders, which includes as the Special Master suggested earlier, a broader variety of individuals needs to be looked at more carefully in sub-groups. But developmental delay, 42 percent have gastrointestinal problems. That's a high number. And in normal children, the control is 28 percent.

So there are lots of children with gastrointestinal problems. Lots of children that have

ear infections which are a non-specific feature not suggestive of vulnerability for autism, so many of those. But so many children get diarrhea as a result of being treated for ear infections as so many children get thrush from being treated for ear infections. Then as they're treated, because of the thrush resulting from the antibiotics, they get some thrush down below, associated with diarrhea and it gets into a cycle that we frequently see as the explanation for children that have diarrhea in the setting of normality, developmental delay or autism.

Stool pattern abnormalities, Isabelle's group found 18 percent in autistic spectrum disorders and four percent of controls.

We've looked at our children and have found a slightly smaller number than that. About seven percent of children with classic autism or regressive autism, which we can't readily distinguish from one another.

Q Let's move now to Slide 58 where you appear to take issue with Dr. Kinsbourne's statement that there was a previously normal developmental trajectory. I think you've already somewhat explained that.

A I really have. This issue of increment

needs to better refined than this. He doesn't support it with things. And it seemed to me this was set up for a particular purpose, what we call a straw man. But if it's truly the fact that incremental changes occur, then one can't exclude the possibility that we find is a probability that children have what appears to be a regression in the second year of life have had preceding manifestations of illness in the first year of life.

So this seems to be used, I don't know, I can't get into his mind, but looking at the way in which the argument is set up, this seems to be support for the idea that there's some gradual and incremental aspect to retention of inorganic mercury in the brain.

Q Moving now to Slide 59, the systems view of autism.

A I think I've already referred to this a good deal, but I think again the reason it's included here is that this is not represented in the formulation of the hypothesis. This is, the way in which most of us that see lots of children with autism or spend a good deal of our careers interested in this disorder try to understand these things and so as I've mentioned already, because the hypothesis has to do with inflammation and intoxication, inflammation of a novel

sort that we don't know about otherwise, and information about intoxication of a novel sort that we don't otherwise know about, that it doesn't take into consideration the fact that those conditions don't produce the kinds of injury or the kinds of abnormality, I should say, that involve these functional connections.

The fact that there are a greater severity of early injury in autism is suggestive to us that during those early periods of brain development where so much is happening so rapidly, that that's when much more severe illness can present itself. And since there isn't any exposure to toxins at that point it would suggest to us that again the likelihood is that the developmental aspect of the disease is what's going on here. Rapid periods of development are periods during which more severe disease presents itself, and subsequently lesser degrees of injury.

SPECIAL MASTER VOWELL: What time are you talking about with regard to that second bullet?

THE WITNESS: The intrauterine environment being the most severe interval for those things. We have numerous examples of that.

BY MS. ESPOSITO:

Q Moving now to Slide 60, autistic regression.

A Again, this seems to be at variance with the idea that there is an incremental development of disease that was asserted earlier. It's at variance with what we really now know, once we've been looking carefully about additional stages of deterioration in autism. I mentioned in particular deterioration during the second decade of life which is a very troublesome period for that. And certainly at variance with the hypothesis that then is developed later on that there is ongoing injury that represents itself not only in ongoing changes in the system, but an ongoing manifestation being the novel idea about hyperexcitability in the brain.

He does say in the same paragraph that autism may become more severe, and that would seem to me also not to be self-limiting. Then there's the issue of if the regression is self-limiting why it is that children might get benefit from chelation and other kinds of things if the injury's already been produced.

There is a false assertion that the medical literature is almost devoid of attention to the mechanism of regression in autism. There is an enormous literature on this subject and considerable attention to understanding this very important disease

and its results.

Q Moving now to Slide 61.

A There is an inaccurate statement that autistic regression is shocking. This seems to put a little emotional aspect in the particular paragraph and then it can't be mistaken for mental retardation or developmental delay. This is considerably at variance with my own experience that families do notice these things but wonder about them for some time oftentimes. These are not the sort of thing, because families do notice things, that would have been overlooked in the past. Families would either early or later have brought them to our attention.

The differences that we see in these children, as I mention now, is a long list of things we can ask about. And there are things that were overlooked in the past, but nonetheless the function of children with autism is something that we've known about for a long time. We've given it wrong labels in the past. This had to do in part with institutionalization. It had to do in part, in considerable part, with our inattention to these manifestations and our willingness to use labels inappropriately. We're far more sophisticated now.

But it does, in my own personal experience,

and in the experience of many of us, and in my continued observations about clinicians who refer patients to me, to see that we are labeling patients better than we used to and may of us believe the seeming increase in numbers of cases of autism is related to our much increased ability to diagnose.

Every year I diagnose many children with autism, as I mentioned, who have been overlooked by other clinicians as having a very obvious case of that disease.

Q Your last point there, you say there's no reason to argue that the genetic explanation is inadequate and therefore an environmental factor must be implicated.

I want to ask you a little bit about differential diagnosis. If you're trying to figure out the cause of some type of disorder and you create a list, let's say, with two items on it. And you're able to cross one of them off. Does that mean that the one that's left on the list is the cause of the underlying disorder?

A No, it certainly doesn't. It sometimes does, we get lucky sometimes, and some diseases are pretty obvious to us so neurologists take great pride in making the smallest list possible. Once they've

made the list they don't just sit back and put it on the wall. The test for it. And it's our pride that sometimes we can say something right off the bat.

It's not as if other people haven't noticed. Especially in autism, when I see a child, based on a few quick observations, placing my hand on the head of the child, then ask a few more questions, and diagnose autism, they've been through three physicians or four physicians and I ask the mother, you knew this was autism, didn't you? She says yes, she did. So the mothers sometimes know. We sometimes know because of certain clues. But if we have an idea about something, it's our obligation then to test for it. For all those things that we have tests we go ahead and do it. Some make long lists for these tests, and some make short lists.

But we don't have an explanation for many conditions. There are lots of things that we deal with every day. We don't know what causes most cerebral palsy. We don't know what causes 85 percent of mental retardation. That doesn't stop us looking for those things and it doesn't cause us to conclude that we could make something up on the spot and say that causes all of them.

Q Let's move now to Slide 82. I'm sorry, 62.

A A citation of Rutter is used to support the suggestion that awareness in changing criteria cannot account for anything like the actual rise of autism rates.

What he actually says is available data mostly prevalence, few of incidence, but no good evidence that the overall rates have soared. So this is a distinction between knowing what the real incidence of a disease is and knowing what the prevalence in our own populations, based on what we recognize as the disease is. And now we recognize more and more of it, so actually we're getting closer to the idea of what the incidence is and that incidence is higher not because the disease is increasing, most of us believe, still requires some more proof that has to be further refined, as all hypotheses do. But the evidence, as we look at it, favors this, that the incidence is higher than we thought it was because we didn't look carefully enough.

If you look at a population in the country, I don't know why Swedes do such good medicine. Maybe it's the long winters and nothing else to do, but they look at their diseases so carefully, and only a one percent rise in the incidence of autism in the Swedish

population since the 1970 data. They have some of the best data on these kinds of things.

We do have an increase in autism diagnosis as a symptomatic variety and that's related to the only very recently recognized fact that our children with severe prematurity have autism as well. It's one of the other features. They also have motor disease and other things, but definitely have features that are those that we look for in autism. It's a symptomatic variety. And because we have more children that survive severe prematurity, we see more of that neurologically handicapping condition.

Q Let's move now to Slide 63. Your critique of Dr. Kinsbourne's citation of the Herbert article.

A The cited source seems to take a pretty balanced view and says that autism is a neurobiologically based and highly genetic condition entailing the action of environmentally responsive genes. Emphasis is placed in the review on the fact that the 135 genes are involved with regions pertinent to autism and remain to be evaluated as possible causes. And the statement that it is important to consider the gene environment interaction as a possibility did not lead to the conclusion that a particular environmental influence could be found to

cause autism.

It's quite incorrect for Dr. Kinsbourne to state that in many individuals with autism there is no viable alternative diagnostic option other than the involvement of post-natal environmental insult. This is not true at all, I can say based on my experience, and to suggest the possibility, I don't know the truth of it. Perhaps he doesn't see many children with autism.

The same can be said of other processes now known to be entirely genetic such as Rett syndrome. Again, the original idea that lasted for some time that this was caused by ammonia intoxication based on a faulty lab result, based on not testing the hypothesis, and based on the satisfaction with ease of coming to the conclusion about what causes what.

Q Let's move now to Slide 64 where you discuss Dr. Kinsbourne's explanation of inorganic mercury.

A He says that it's a cause, this point, it's caused by, I think there have been prior views, is caused by inorganic mercury breakdown, a breakdown into inorganic mercury. If this is the case, since ethyl mercury also breaks down and we know what ethyl mercury looks like when it's in sufficient quantities to cause injury, we know that it takes a very

considerable quantity to do that, as I've suggested in the concentration that occurs in the fetus --

Q You're talking about methyl mercury?

A I'm sorry, methyl mercury. Did I say ethyl?

Q I think you did.

A I'm terribly sorry. With methyl mercury, we know what that looks like. It takes a considerable amount, as I mentioned, concentrated in the fetus preferentially, unfortunately, but once you get that amount we know what that looks like. It breaks down into inorganic mercury. And the changes and differences between these compounds at various concentrations I would not think, we don't know this for sure because it's not been carefully studied, would not produce different forms of injury because sensitivities should be the same for inorganic mercury. It needs to be tested as well.

The hypothesis that an immune response somehow changes this pathology is a novel one for which there is no information that I'm aware of, and I looked very hard to see whether that's the case.

Then assessed the ideas about the immune response itself, found that there was no support for this novel hypothesis which as I recall Dr. Kinsbourne takes credit for. And the suggestion of sub-acute

ongoing injury once he gets into this portion of the discussion seems to me completely at variance with the idea that there's a shocking suddenness and a self-limiting aspect to autism.

Q We'll move now to Slide 65 which is titled glial cells and the brain.

Dr. Rust, have you published anything on astrocytes in the past?

A Yes, I have. It's an old interest of mine, in particular the developmental aspects of astrocytes, what their functions were, how they worked biochemically, what they did in relationship to other cells in the brain. This was particularly in relationship to neurons and to oligodendriglial cells which have remarkably interesting relationships in the developing brain that I've already referred to in part.

Q Does Dr. Kinsbourne's characterization of astrocytic and microglial changes in the brain, is that consistent with what you know about it?

A Not at all. Nor is it consistent with what I know about inflammation. Inflammatory illnesses in the central nervous system have been a preoccupation of mine since the mid '80s. I've collected some of the largest collections of the known inflammatory

diseases of children, and both speak on this subject and publish on this subject. It's a difficult one, but we know a good deal about how these conditions behave, both clinically and pathologically, and we know again, increasing amounts about what astroglial cells, astrocytes or microglial cells do both in inflammation in brain injury and now this recent and very interesting business that's related to the function of these cells in brain development.

If you have injury such as you have with methyl mercury, then microglial cells appear in order to clean up the injured cells. They do that regularly. They do that in inflammatory conditions as well.

We don't fully understand microglial cells. There's still a lot of mystery tied up in them and there's still lots of things to study about them. So this novel idea is one that somebody might choose to do experiments to prove. Perhaps Dr. Kinsbourne would be interested.

One of the many explanations for the presence of microglia found in, well, it's a novel idea is what I'm trying to say.

There is increasing evidence of the presence of inflammatory cells as a very important and normal element of brain development in terms of how the brain

develops. Perhaps Dr. Kemper who knows much more about that than I do, will say something about he.

Q Perhaps he will.

Let's move on to Slide 66. I think this appears to be sort of a general response that you have to Dr. Kinsbourne's hypothesis. What about this is striking to you?

A He cites in support of sustained neuroinflammation, the paper of Vezzani and Granata. This is work that was carried on in an entirely different setting, one that we understand in an entirely different way, and for which we've had information since the late 1970s. This has nothing to do with mercury, it has nothing to do with autism, and what this has to do with is what we now understand very well about the natural activities demonstrated experimentally in terms of the development of an epileptic focus. Again, something that has nothing to do with what we're talking about here.

So their work isn't in any way applicable to what's going on here.

What we know about is that if you stimulate particularly susceptible cells in the hippocampus, this is originally the work of Tom Sutula who trained at my institution. If you for a long period of time

provide an external stimulus to neurons, so you do this by placing a wire and providing a regular pulse of current. This is not because neurons have decided somehow to take it on themselves to have impulses, because as I mentioned, there are so many exquisite regulatory mechanisms that prevent that. And they're so able and so redundant that you have to do this over and over again, the stimulus, before you can cause them to begin to break down and produce a state where the control mechanisms don't work as well and you can produce an epileptic focus. That's what Vezzani and Granata are talking about.

So there's external stimulus, not exogenous stimulus. So it just takes your breath away how this is being applied here.

It's ignored that their conclusion is that the changes are related to genetic transcriptional activation which is exactly what has come to be understood in this experimental model.

So it's the turning on and turning off of genes here once again, that tissue injury occurs, and the subsequent work by Dr. Dichter in Philadelphia and others has shown that this regional injury in very susceptible tissue with a very special circumstance not of neurons taking it upon themselves to be

excited, but stimulating them over and over again with a noxious stimulus is the failure to control highly specific difficulties in elevations of potassium.

You can injure the region with excitatory amino acids as well, which is something that Dr. Kinsbourne seems to refer to vaguely, but this is a particular thing that has a particular genetic and particular biochemical abnormalities. It's required 30 years of work for this to actually work its way out to be understood, and it's because people, when Tom Sutula had the initial idea, lots of people thought that this was a silly idea, too.

I suppose if I say this about Dr. Kinsbourne's ideas here, perhaps I would. But it takes work to prove these things. You can't just go out and say I think this is a pretty good idea. And it took ten years for Tom Sutula to demonstrate what was going on. The result of that was generating the data that I've already cited about long loop connections. Because epilepsy, when it arises, is one of those examples as well.

It doesn't reach any conclusion at all about whether the presence of cells associated with inflammatory responses, to make a point of this, is beneficial or dilatory.

Q Let's move on now to Slide 67 where Dr. Kinsbourne stated that there's dramatic support for his hypothesis.

A He cites Bailey, and they identify gliosis in brains of individuals with autism. This is a non-specific finding. Again, it's something about which Dr. Kemper knows a great deal more than I do so perhaps I shouldn't go into it, but I know that in brain diseases in particular, of a broad variety, we see these especially in some conditions that arise from a genetic vantage point. The paper said that the cause and time of onset of autism is not known, and that the finding of gliosis was an inconsistent finding, and that the cause of gliosis and brain damage was unspecified, and it specifically stated that the findings cannot be assigned to any specific possible causative event or process.

This seems to me a balanced view and cannot, in my view, be regarded as anything like dramatic support for this novel combination of toxins and inflammation as the cause of autism. They don't discuss anything about that at all.

Q Let's move down to Slide 68 with the Hurtado --

A There's this paper by Lopez Hurtado and

Prieto. Only some parts of the brain are studied and again, Dr. Kemper knows so much more about this than I do. So particular areas, these are speech areas were looked at. There was some focally increased density of glial cells noted in association with a decrease in neuron density in a particular area. Lipofuchsin was present there which is a pretty non-specific thing, and these were individuals with autism.

The age -- He states that the age of injury was seven to 44 years of age which is interesting. I don't know whether the paper tells us that there is any difference in the amount of lipofuchsin or gliosis over those ages. I don't know the answer to that. But we know that lipofuchsin which can be found in the brains of otherwise normal individuals, gradually may increase as an aspect of growth and development for reasons that aren't clear. And a 44 year old individual is quite interesting, I think, because --

Q Let's move to the next slide. Slide 69.

A Where did he get Thimerosal from?

Q Slide 69.

A We don't know exactly when he died, but one can gather from the paper somewhere in the early '60s. So where did his Thimerosal come from if he has these changes? Where did his vaccines come from? We had

very few back then. Most were not invented at that point. We had tetanus and things like that.

As I mentioned, lipofuchsin is non-specific. The changes were most striking, this is in the paper, not Dr. Kinsbourne's use of the word, in layers II, III, V and VI, which is interesting in relationship to Rett syndrome, and a genetically determined cause of autistic syndrome. Similar changes are seen in Down's syndrome. They're seen in Alzheimer and Parkinson's disease. They likely have at least in part a genetic basis. And schizophrenia which has some clinical overlap.

Q Let's move now to Slide 70. The Friedman citation.

A The following paragraph, this is Dr. Friedman and his group, says they've demonstrated ongoing active disease in the cerebral gray matter of individuals with autism.

SPECIAL MASTER HASTINGS: Can you slow down a little bit, Doctor?

THE WITNESS: I'm terribly sorry. My students tell me I do that, too.

SPECIAL MASTER HASTINGS: Especially when you read word for word from the slides, you're going pretty fast.

THE WITNESS: I'll try my best. Remind me again, please, sir.

Ongoing active disease in the gray matter of individuals with autism. There should be another quotation marks there.

To the contrary, to my reading, these are indirect imaging studies in fact, something with which I'm quite familiar. They say that there is possible decreased cellularity. They don't tell us about ongoing active disease in gray matter, and this is consistent with, as they put it, delay in neuronal development or maturation. That's something quite different from what is said in the report.

They concluded that autism manifested, and this is their quote, "abnormal developmental processes" and they say nothing more than that, by my reading.

BY MS. ESPOSITO:

Q Let's move now to Slide 71, the Vargas and Pardo citation.

A Yes. The work of Drs. Vargas and Pardo. I think they're with the Hopkins Group, concerning evidence of microglial and astroglial activation. Something again that's very new in this area except in certain kinds of diseases. A broad variety. We know

a lot about it. But the implication seems to be that Dr. Pardo notes that longstanding inflammatory changes occurred in the setting of other neurodevelopmental abnormalities, probably as part of an active plastic response without any decrease in astrocytes.

To the contrary, the stating here is with GFAP which is a marker for astrocytes and showed that they were increased and he concluded that these findings are inconsistent with the potential toxic effect on astrocytes by neurotoxins or a toxic material. The reason for that is if you have intoxication and it kills or maims astrocytes you're going to see a decline in GFAP, the marker for astrocytes.

He properly emphasizes the innate wing of the neuroinflammatory response is not associated with infiltration of activated T or B cells which seem to be the kind of process that Dr. Kinsbourne is meaning to refer to.

Q Dr. Rust, have you read the letter that Dr. Pardo wrote to Dr. Kemper?

A I did.

Q Is that included in the slide on, Slide 71? Is that what you --

A Yes. Whether at this point it came from the

paper or from the letter, I actually can't recall.

Q Let's move to 72. It's a continued discussion of that letter, or of the Pardo group's --

A He says there are a suite, I don't know what that is, but I suppose a group of elevated pro-inflammatory cytokine levels in CSF. He says this is evidence of brain inflammation.

This is a very very complicated subject. It needs to be addressed very carefully. There is balance between cytokines in the nervous system, some are pro and some are anti-inflammatory. These cytokines serve a number of different functions and these include not only inflammatory diseases, but likely aspects of normal brain development as implied.

So they are important actually neurobiologically in normal brain homeostasis, and not necessarily representative of a condition that's causing inflammation.

We find these not only in the brain but elsewhere in the body. It's easy for us sometimes if we do a large look for either antibodies or cytokines of various sorts to find these in a broad variety of diseases and we sometimes don't understand whether they're positive or negative.

Dr. Pardo appears to be well aware of the

homeostatic functions of cytokines and chemokines and mentions these and makes it clear that his studies did not confirm a toxic inflammatory basis for any of his observations, or that they represent any deleterious process, but they could as well represent a non-specific process of repair.

I believe that's from the letter.

Q I believe on Slide 73 you seem to summarize the same idea there.

A So there's abundant evidence of the presence not only of cytokines and chemokines but of specific antibodies in brain tissue and CSF in a broad variety of neurological conditions that we know to be genetically determined, Rett syndrome being one among them that's very important here. Tuberous sclerosis as well, and other conditions such as Parkinson's disease.

So in those conditions where we don't recognize anything to do with inflammation or intoxication, we have to think about these things serving some other function. And whether positive or negative, we don't know.

Q Moving now to Slide 74.

A The basic argument doesn't seem to be very helpful. He turns to Aschner's hypothesis of

astrocytic injury as a source of neuronal injury or neuronal dysfunction. This is an intermediate step in the pathophysiology of autism, so somehow the fact that the astrocytes, appreciating perhaps as I do their importance to the neurons, once they begin to fail in their function that the neurons begin to do things on their own.

So Dr. Aschner's work I don't know fully. I do know his work on manganese toxicity and mitochondria which as far as I know is not relevant to what we're talking about here.

I didn't have the opportunity to see the report for very long from Dr. Kinsbourne, but was unable to find the paper cited from the Brazilian Journal of Medical and Biological Research with regard to the argument, so I don't know what that said. With some trepidation, as I suggest, I base my comments on Dr. Kinsbourne's interpretation. He seems to implying an affect of glutamine, he says glutamine. Now whether that's just a misstatement or not, there's another misstatement apparently with regard to pyramidal cells and Purkinje cells, so this may have been a slip of the pen. I'm known to do them myself, and all of us are.

But glutamine is a non-toxic substance.

It's put into the region of the neurons so it can be taken up and changed into glutamate. Maybe I'll show that.

I want to show a little bit of my own work, but I'll go through it quickly I hope so I won't take up too much of your time. But this hypothesis is one that I think has lethal problems in terms of scientific support.

There is some basis of this on the article by Bezzi and others that astrocytic cell death is the cause of the ensuing neuronal dysfunction. And afterwards, sustained for a long term, hyperexcited neuronal state which again is at variance with the idea of all at once, nothing first, and no ensuing development of autism.

Q Slide 75 is a little more specific to the Bezzi article.

A As he reads the experimental conditions in the Bezzi experiments, as in almost all studies, as I mentioned, of viable neurons you have to have healthy astrocytes to have neurons in the first place. There are only very special circumstances where you can have neurons in isolation.

The injury here is not produced by chronic inflammation at all. It's produced by the

introduction of freshly activated microglial cells. This is a very important thing for us to know about. We know about the very important thing of what we call bystander injury.

Once you produce a specific response of some sort, you can produce bystander injury once you activate the immune system in a particular way. Therefore you can injure cells that were not initially implicated and whether this is what's going on here, we don't know for sure because additional work is necessary.

The third and final point I want to make is that the end point in this experiment wasn't glial injury. The end point was neuronal hyperexcitation -- No, it wasn't glial injury and it wasn't neuronal hyperexcitation with the proposed idea of glutamate flow, and I don't know what that is, but it was neuronal cell death. Then I ask why this might have occurred.

Q So if there were a chronic astrocyte malfunction or astrocyte death, that would cause the death of the neuron. Is that what you're saying?

A I can show you the reasons why that might happen.

Q On the following slide? Yes, sir.

To the extent we can minimize the observation -- Number 76 is the slide we're on now.

A Part of the interaction, and this is the interaction that involves glutamate and glutamine. It's highly regulated both at the level of the neuron and at the astrocyte and it's intended to provide the precursor for glutamate.

If the neuron becomes exposed to too much glutamate or contains too much glutamate, the process shuts down. It's in the way of glutamine being uptaken by the neuron. There is some emerging evidence, but very preliminary evidence, about what happens in terms of the glutamate pore. There probably is also a highly regulated situation in the astrocyte as far as release of glutamate, but it's much too early to know how pertinent that is to the proposed model of disease here.

Q Does it seem to you that Dr. Kinsbourne is focusing on the glutamate kind of in isolation without regard to the rest of the system?

A Well, he doesn't mention any of the rest of the system, if that's what you mean.

Q The next slide, is that important to your discussion here?

A Well, this is --

Q Number 77.

A -- what I mentioned about the astrocytes and this is, astrocytes early on are loaded with glycogen which is a source of glucose. We know during that interval, we have very good reason to believe I should say, know is perhaps too strong a word. But the evidence is very strong that the presence of this energy resource serves several different purposes. One is producing intermediates for growth and development in the brain; the other is glucose to support cells that don't have the capacity that astrocytes do to accumulate and utilize this primary source of energy in the brain, glucose.

Q Slide 78. What are we looking at here?

A There was mention of the sheathing that occurs with the astrocyte and the neuron. This is also a very important and new area that's progressing very rapidly. These are artist's conceptions but the information is very strong in support of these things and with regard to the functional elements that I'll mention. It's proven.

One interesting thing is that what many people call the neural synapse, and this is, we know about the synapse, but what many people call the immune synapse which is communication between immune

cells. We've always known that at least two or three different immune cells talk to each other in producing an immune response.

But there is increasingly abundant evidence that this very closely resembles what we call the neuro synapse, at least implying in a way that is a little loose so I'll acknowledge that, there may have been a very primitive association between the immune things and neurologic things. Perhaps that's why the systems we're beginning to appreciate have so much to do with one another. But nonetheless, what's shown here if you look at the neural synapse is that the attachment between two cells at the synapse, this is where the glutamate finds its way to communicate between cells, is tightly connected with adhesion molecules, but between the two neurological elements.

Small amounts of glutamate can be released in this region and those small amounts of glutamate produce exquisite signals. The receiving cell of this signal can dial up or dial down the sensitivity of this glutamate. If there's too much glutamate, it dials way down. It loses receptors and it doesn't remake them and push them back to the surface.

So this is a dynamic system that the point is, it's highly regulated. It is possible to injure

it but not so far as we know because of glutamate necessarily in flow from some other cells that happen to be in the vicinity. The usual idea here is this has to do with this tightly regulated and enclosed neural synapse.

Again, the same thing appears to be true with regard to the very same kinds of exquisite regulation to the immune synapse which is meant to bring to mind to us that the immune system very highly regulates itself, whether it's with inflammation or whether it's with the normal developmental functions or whether it's in terms of cleaning up after some injury that it performs in the nervous system.

Q Dr. Rust, you may have already gone over this, but if there were to be too much glutamate released from the end of the cell, what would be expected as regards to the neuron?

A The exquisite part of this is the GABA regulation, down-regulation that occurs so that you limit the amount of glutamate released at that point. So there's inhibition that comes in several different kinds. There's long term and short term and other things that happen. But this is involved in learning and it's involved in normal function of the nervous system, and development, and it's highly regulated.

And it's regulated at the level of the astrocyte as well, although that's an area about which we know somewhat less than we know about neurons at this point.

Q If that regulating system were not in place and there was too much glutamate, would that cause a neuron to die?

A Yes. And again, it takes a long time to do that. As I mentioned from the Sutula model and others, you have to stay at it and stay at it to cause the remodeling to produce an epileptic situation. But that's right.

Q Do you agree with Dr. Kinsbourne's statement that autistic behavior is precisely what one would expect if the brain's excitation inhibition ratio were skewed in favor of excitation as occurs in hyperglutamatergic states? Do you agree with that statement?

A Well, I'd have to know more about what he means by that. It's a rather general statement. It seems to be applied to the notion that children with autism have manifestations of a hyperexcitable state. At least that's what I recall. And I don't know that this is true at all.

I mentioned we've got to be very careful

about what we conclude about what children with autism are doing, and so I think that's a problem.

But I would go on to say that if he's referring to the fact that the GABAergic side of things is having problems, which we know happens in Rett syndrome, and may well happen in autism because the systems that are involved involve GABA, maybe that's something. It needs to be tested.

But nothing to do with the leak of glutamate or flow of glutamate that I'm aware of. What that does is produce injury. The most active cells will then be injured and die.

Q If Dr. Kinsbourne's hypothesis were true, would you expect the deficit seen in an autistic patient to get progressively worse over time, based on his model?

A Yes, because the only way we understand that model as working would be if we're causing hyperexcitation over long intervals of time, then that's the sort of thing the Sutula model involves, and what that does is remodel things to produce epilepsy or it kills cells, one or the other.

So what we would expect to see happening, as we see in epilepsy for example where hyperexcitability is an issue, we see progressive tissue injury. What

that produces is changes in motor function, changes in intellectual function, changes in other functions that the brain is intended to do, and the production of worsening epilepsy.

That's not what we see in autism. We do see some progressive issues with regard to EEG changes and epilepsy. We don't understand those things yet and we don't know whether they have anything to do with this hypothesis. But if we see that sort of worsening in other situations, which we do see in a variety of epilepsies, we call them epilepsy partialis continuum, because of the continuous hyperexcitability. What we see absolutely in those cases is progressive injury to the brain. A non-specific sort of regional injury is the typical thing that we see. And we don't see that in autism. Injury that is neighborhood injury, injury that produces clinical signs which are motor and intellectual signs, and we don't see that in autism.

SPECIAL MASTER CAMPBELL-SMITH: Ms. Esposito, let me ask. I'm getting the eyeball that suggests that we might be getting close to the hour we had designated to break. Are you at a point that's a natural breaking point?

MS. ESPOSITO: I'm very close to it.

SPECIAL MASTER CAMPBELL-SMITH: Okay.

MR. MATANOSKI: We could perhaps just break down now and then come back briefly. That way some of these slides that may not be referred to, we can turn them out. So I think this is probably a natural breaking point.

SPECIAL MASTER CAMPBELL-SMITH: Having decided that this is now a natural breaking point, we are going to break.

Let me ask if we want to do a compromised 45 minute lunch break or if we want the entire hour, not knowing how much longer Direct is to go.

MR. MATANOSKI: I think Direct is going to be probably very brief when we get back.

SPECIAL MASTER CAMPBELL-SMITH: Okay. Is that a move in favor of a full hour for lunch?

MR. POWERS: A full hour, yes, Special Master. We'd appreciate that.

SPECIAL MASTER CAMPBELL-SMITH: Okay. Then we are in recess until 2:45.

MR. MATANOSKI: Thank you.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

(Whereupon, at 1:43 p.m., the hearing in the above-entitled matter was recessed, to reconvene at 2:45 p.m. this same day, Wednesday, May 21, 2008.)

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

(2:45 p.m.)

SPECIAL MASTER CAMPBELL-SMITH: For those who are with us, please be seated. We're awaiting the return of Respondents.

(Pause).

SPECIAL MASTER CAMPBELL-SMITH: Thank you, Dr. Rust. I did notice you were adjusting, I assume turning off your electronics.

THE WITNESS: Yes, ma'am. I apologize for being late.

SPECIAL MASTER CAMPBELL-SMITH: Ms. Esposito, are you prepared to resume your Direct Examination?

MS. ESPOSITO: Yes, thank you.

DIRECT EXAMINATION (Cont'd)

BY MS. ESPOSITO:

Q Dr. Rust, before the lunch break we were going over some of the slides towards the end of your slide presentation. I believe most of those slides if not all of them related to your study that you did in 1991 about astrocytes, is that correct?

A That's correct. And other cells as well.

Q Do you believe it's necessary to go through those slides or --

A No, I don't. I can summarize it very quickly.

Q Please do.

A The idea here was to look to see how during development and with maturation cells in different sources, that included neurons and astrocytes in particular, how they expressed and utilized enzymes for various purposes to see how they interact with each other.

Now I already implied that the astrocytes are remarkably prepared to store glucose as glycogen and then to break it down and give it neurons and to other cells in order to support them when they were doing other tasks.

So basically all those slides do is to demonstrate how much in the way of this enrichment is found in the astrocytes and how little in neurons and in other cells.

So from the standpoint of supporting, providing energy to neurons so they can do their work, and from the vantage point of eliminating things that might cause problems for the neurons. And from the vantage point of the repair and synthesis and all those things that neurons do, it's the astrocytes that do that.

The implication for which there is abundant evidence is that if you damage or destroy the astrocytes, the neurons will not be able to function.

So the idea that you can somehow eliminate astrocytes and then have neurons get out of control is actually quite wrong, because in order for a neuron to become hyperexcitable, it's going to have to have additional support of energy which can only come from the astrocyte. It comes in five or six different ways. And so a damaged astrocyte is not going to be able to support that function.

So what will happen and does happen is that neuronal function will diminish and then stop. That's why we have to grow the neurons in the presence of astrocytes except in very special conditions, and even there it doesn't last for very long that you can do that.

So the point there was with regard to the idea that somehow something happens to astrocytes and caused inflammation and the neurons then go on for long periods of time being hyperexcitable, and this is not possible. That's what that information is about.

Q Thank you.

In Dr. Kinsbourne's report on page 20 he says, "Autistic symptomatology can be classified into

that which exemplifies the effects of hyper arousal and that which represents an attempt to escape from such effects or fend them off."

Do you have any comment on that particular sentence?

A It's speculation. As I mentioned, we've got to be very careful. We've made so many errors over time in trying to decide why individuals with autism do what they do. And much of the time we simply don't know. That's the aspect of strangeness that I suggested, not meaning to be disrespectful to people with autistic features, it's just that it appears strange to us as perhaps we do in return.

But to first of all presume that this represents a particular state of arousal or state of anxiety or state of something else is something we can very easily make an error concerning. I think that these kinds of judgments and speculation and theorization about these things is best made by people who see a great many children with autism because somebody that sees one or two is going to be in the same situation as the person who might accost a family about their autistic, the child with autistic features, and they present my card saying you don't understand what's going on here. So that's what

that's all about.

And we don't know that these are hyperexcitable states, and we don't know that it's some particular difficulty about dealing with stimulation. We catalog and collect these things and try to understand them and we try to understand which are any different than what we might see in other individuals and which are age related.

But this merges into the dangerous territory of speculation based on perhaps inadequate information. The more individuals you see with autism not only the more you can refined you get about what you're saying, but the more appreciation and wonder you have about what they can do well and that sort of thing.

Q On page 22 of his report Dr. Kinsbourne says that "Over time stereotypies lower neuro excitation levels."

Do you agree with that statement?

A There's not one shred of evidence to suggest that that's true. We see stereotypies in perfectly normal children, and they can be quite complex, and we don't have any idea why they happen. Those are children whom we can talk to about it.

All of us have little ticks and things we do

when we get anxious, and it's possible that anxiety is an element. We just don't know that.

But anxiety, there is a sympathetic discharge that comes with that that involves one particular portion of the brain in individuals that are so anxious that their heart rate goes up and so forth, and other systems respond.

To say that somehow this, which again is brought on episodically, might represent the result of an ongoing inflammatory state with hyperexcitation with the loss of regulation, meaning it should happen all the time and should not be related to a particular episode with whom someone is dealing, seems to me to not make any sense.

So as long as we see that you can have a cause and effect as in all human behavior, then the probability there is the regulatory mechanisms and systems and reactions are all in place. Some people have higher gain on one system or another system than somebody else. And again, individuals with autism are individuals. We don't see a uniform presence of stereotypies, we don't see a uniform presence of heightened states. We see variations just as we do in the folks we call normal. And yet our attention is drawn to the children that are doing something that's

troubling to us or to the family.

A long view on individuals with autism will tell you that they are individuals. What we put together is a system of problems that are so uniform with autistic individuals, but there are other things going on.

Q I believe we may have been over this, but I want to be very clear. If inorganic mercury is the cause of this process that Dr. Kinsbourne is proposing, and if inorganic mercury accumulates in the brain over time, would patients with autism be expected to get progressively worse over time if this hypothesis is correct?

A That seems to me to be what he's talking about in one portion of the report. In another portion he seems to imply that this happens once and that's it. So I think those are at variance with each other.

But if the implication is that we have steady accumulation of a toxic element that's setting off this reaction, one would anticipate that the stimulus would increase over time and that would be a steady process of deterioration in function and one would think that in such instances where we have other examples of things that cumulate and cause problems

you'd have progressive loss of function of some one or another sort or many sorts.

So it would be a progressive course of deterioration that one would anticipate seeing with this model which is quite at variance to what we see in autism. Because as a rule, depending on what the state of a child initially early on, as a rule individuals with autistic features improve over time. This is quite striking and there are still considerable problems, but there is steady improvement.

Because that improvement is especially with regard to educational goals and language doesn't necessarily, often doesn't keep up with the increased demands made on a child, then we may see things that seem to fall away. But if you look closely and if you talk to the families, you find out that the child is making progress. This is important, a positive side with all children to find out about. It's disappointing that it may not be as quick or that interventions to achieve it may not be as good as it might be.

But the general course is variable, but we also see children, whether they have something that appears regressive or whether they have something that

appears to be classic autism, we see children, for reasons we don't understand, that get almost or sometimes entirely better at four or five years of age. That again includes children that have a regressive appearance.

I don't know how that can be accounted for in the hypothesis because it's much more readily accounted for by the tripping of a switch in the developmental cascade which is fortunately moving in a direction of recovery rather than not.

SPECIAL MASTER VOWELL: Dr. Rust, when you say they get better, you are saying get better in the absence of the therapies that you indicated there was no support for.

THE WITNESS: Entirely in the absence of those therapies, yes. Thank you.

BY MS. ESPOSITO:

Q On page 23 of his report Dr. Kinsbourne states that his hypothesis is presented in light of advances in the science of autism. Do you find that his hypothesis is at all consistent with the science of autism?

A No, I don't.

Q Dr. Rust, to conclude here, I'd like you to summarize your main criticisms of Dr. Kinsbourne's

theory. If you could distill them down into a few main points, what are your criticisms of his hypothesis?

A Well, I suggested at the outset that awkward theories that put things together in a strange way that nobody has anticipated, and where most of the elements are either made up or drawn in odd ways from other people's observations, tend to be wrong. And it especially tends to be wrong when the hypothesis is so broad that at the center of it the thing that's alleged to be the cause could be anything that you want. It could be a measles infection, it could be a toxin, it could be anything that you want to put in there, you just have to make slight adjustments. This is why I provided the example of Tycho Brahe and the universe. That's one part of it.

A second part of the criticism is that so much of what's said doesn't make scientific sense. This is a grave problem because as I've suggested, there is no apparent understanding of what advances have been made over some 30 years now, and whether those in the last year or two might have been overlooked. But especially with regard to the impertinence of the epilepsy aspects of this, these don't make sense. So there's that problem as well.

There is the inconsistency in the theory with regard to implications in one place that this happens and then it's over; and the other that it's a progressive set of issues. There is what I regard as cherrypicking, picking little pieces from the paper and ignoring the rest of it and in some instances I think misrepresenting what the paper says.

There is, especially with regard to describing children with autism, a very striking failure to understand exactly what goes on in those children, and the very willfulness to assign as the person who happens to be walking by a child with autism in a supermarket, to assign what they regard as being the reasons why a child behaves in a certain way.

So these are the things that I find problematic.

MS. ESPOSITO: Thank you.

SPECIAL MASTER CAMPBELL-SMITH: Petitioner's counsel, you may conduct Cross.

MR. POWERS: Thank you, Special Master.

CROSS-EXAMINATION

BY MR. POWERS:

Q Good afternoon, Dr. Rust. My name is Tom Powers. I'm one of the attorneys representing the

Petitioners generally, but also particularly William Mead and Jordan King in this matter.

A I'm very pleased to meet you, sir.

Q I'm pleased to meet you too.

MR. POWERS: Just as sort of a housekeeping matter, the slides that we ended with before the lunch break that were then referred to in summary, are we referring to slides that sum up a paper that you did in 1991? What slides were those? I just want to make sure that we're all speaking the same language about what was summarized in terms of the exhibit number.

THE WITNESS: Yes, sir. Oh, you want to know the numbers of them?

MR. POWERS: If you can give me the beginning page number of what Ms. Esposito and you were describing as a summary that you were not going to get into in detail.

SPECIAL MASTER CAMPBELL-SMITH: We concluded on Slide 78, if that's any guidance.

MR. POWERS: That was my understanding too. The first slide that I didn't hear testimony about specifically was Slide 79, the carbon nanotubules slide.

THE WITNESS: You're very observant. That slide concerns another way in which we seem to be

understanding that these cells communicate with one another, and this is a very new thing here. It's that there are not only these synaptic communications and not only pores that are various regulated, but there may be these very tiny tubules that allow cells to speak to one another.

BY MR. POWERS:

Q Let me interrupt you.

In my questions to you I'm going to ask you specific questions and I'm going to ask you to answer the question. My only question was, is Slide 79 the first slide in the series that you meant to summarize in response to Ms. Esposito's question when we came back from lunch?

A I left that out of my summary.

Q Okay, thank you.

Dr. Rust, if I recall you appeared as an expert witness in an earlier case in the autism omnibus proceedings, is that correct?

A Yes, sir. I think that was case number two.

Q That was a case where the young boy's name was Yates Hazlehurst. It was a hearing I think in Charlotte, North Carolina in October last year. Does that sound right?

A I had forgotten it was October, but it was

in Charlotte.

Q That hearing was about the idea that Thimerosal exposure combined with MMR exposure could result in the features of autism. Does that comport with your recollection of the theory?

A Yes, sir. It sure does.

Q The theory in that case also specific to the measles virus is that the measles virus could serve as a source of inflammation in the brain and that subsequent neural inflammation would express itself as symptoms of autism. Is that a fair summary of your understanding of what the case was about?

A That's my recollection.

Q In preparing for that case I know Dr. Kinsbourne was not a witness in that case. In preparing for that case did you have an opportunity to review Dr. Kinsbourne's expert report from the Cedillo matter, another omnibus autism proceeding that was conducted in June of 2007?

A No, sir. I didn't.

Q Did you receive and have a chance to review a transcript of Dr. Kinsbourne's testimony in the Cedillo matter in advance of your testimony in the Hazlehurst matter?

A No, sir. I didn't.

Q Between the Hazlehurst proceeding and the preparation of your expert report in this case, are you aware that there was yet another MMR/Thimerosal combined theory case heard? Are you familiar with that?

A I don't know anything about it.

Q So do you recall seeing anything that would have been a reference to the Snyder case, an expert report from any of the Petitioners' experts or a transcript of the testimony in a case captioned Snyder?

A I don't remember anything. I forget lots of things, but I don't think so. I'm sure the lawyers would know.

Q And I'm not going to ask them because they're not there on the stand, so this is all to the best of your recollection.

So you didn't see any of the materials as best you can recall that might have been generated by the Petitioner's side in these cases up until the time you completed a report in the case that we're here for today. Is that right?

A Except for the Hazlehurst material. I have a hard enough time getting through what's given to me anyway. I don't look for extra trouble.

Q I want to walk through some of the things that you talked about in your slides today. One of the first things I wanted to inquire about if I can find my page here, is on Slide 12. To make things a little easier for the court reporter, I'm sticking right into the slide presentation that's Respondent's Trial Exhibit 8. This would be page 12 of Exhibit 8.

I don't think we have that slide loaded in our computer right now, so I'm going to have to just refer to the paper. As long as the Special Masters have it and you have it. Do you have it in front of you there, Doctor?

A Yes, I do.

Q I notice at the top where it says regressive autism there is a claim here that 80 percent, it says, "80 percent retrospectively abnormal." Eighty percent of what?

A Eighty percent of children that I encounter and some other people have encountered.

Q What other people?

A I can provide a citation, but not off the top of my head now. I perhaps should have done so. But we have our own ongoing study of this so it's about 80 percent --

Q This ongoing study, who does this involve?

Who's the "we" involved in the study?

A Myself, a resident, and a medical student.

Q Is this a study that has been submitted for publication?

A No, sir.

Q Is this a study that's been subject to peer review?

A No, sir.

Q Do you have anything here today that you can show the Special Masters to describe the methodology of this study, the sample size, cases, controls?

A Nothing today, sir.

Q Are there any other things you would rely on aside from this unpublished, un peer reviewed anecdotal description that you've given that would support this figure of 80 percent of autistic children are retrospectively abnormal?

A I believe I could provide you with a reference from the literature. But I can't do it right now. I'd be happy to do it in the future.

Q Do you anticipate having an opportunity to further testify in these cases and provide the information you're not providing here today?

A I don't know what's going to happen in the future.

Q If 80 percent are retrospectively abnormal, that means 20 percent of them are not retrospectively abnormal. AmI doing my math right?

A Yes, sir. That's what I would arrive at too.

Q So that 20 percent of the people, even in retrospect, and looking -- I'm assuming you're consciously looking for early appearances of abnormality. Am I right about that assumption?

A Yes, sir.

Q So even with looking hard in a population of children, in 20 percent of the people who present as regressive, you don't find any early abnormalities, correct?

A That's correct, sir.

Q During the proceedings MyLinda King and William Mead testified. Were you here to hear their testimony?

A No, sir. I wasn't.

Q Did you listen in on the dial-in line to hear their testimony?

A No, sir. I don't know how to do that.

Q Did you download the audio file that was available to listen to their testimony?

A No, sir. I didn't.

Q Have you ever met the parents and taken a history from them?

A No, sir. I haven't.

Q You described early in your testimony spending time with the family and asking a lot of questions is critical to assessing the symptomology of autism, wasn't that your testimony?

A That's correct, sir.

Q It's particularly important in trying to identify retrospectively the possible appearance of early symptoms. You emphasized that point, did you not?

A Yes, sir. I did.

Q So with respect to these two families, that opportunity is something that you never took advantage of. Again, didn't appear to hear them live, didn't listen in live, and didn't listen to the audio download. You never had a chance to ask those questions, right?

A Well, I wouldn't have the opportunity to ask those questions because I'm not their physician, of course.

Q But you would have had an opportunity to hear the history as it was presented under oath here, correct?

A I suspect I would if I knew how to do it, but I don't.

Q Also on the same slide, number 12, there is an electrophysiological profile. And they say in Cross-Examination you're never supposed to ask a question you don't know the answer to, but in this one I've got to. What is that? What is this profile that you're talking about?

A It's an over-blown way to suggest that EEG is what we do. Some people have done other things than that. But as I also suggested, the problem with observations of that sort is that we tended to do EEGs more on children that have a seemingly regressive form of the disease than others. So it remains a soft piece of information.

Q Whether it's a soft piece of information or not, is this a piece of information that appears in the peer reviewed published scientific literature?

A Yes, sir. There is at least one such citation. I think more than one.

Q Any clue off the top of your head what that might be? I'm not trying to quiz you, but having the science in front of us to evaluate is important. I'm just trying to figure out where it is here.

A You're quite right in emphasizing that

importance. I should have done so, but I didn't.

Q You also say that the ensuing course does not distinguish classic from regressive. That's the last point on the same slide.

Is what you're saying here that assuming there is a regression and looking out into the future, if you look at sort of the end points a few years down the road of classic versus regressive. Are those the two things you're comparing?

A Yes, sir.

Q You're saying that the end point at any point in time post-regression, you really don't see a difference in the outcomes. Is that a fair summary of what this is meaning?

A Yes, sir.

Q What does distinguish the regressive versus the classic is what happens before the regression, isn't that right? I mean that's the definition of regression. You have different beginning points in a classic case and a regressive case, correct?

A As I mentioned, 80 percent of the children that seem to be regressive have a beginning point that's quite similar to the ones that are classic.

Q Let's focus on the 20 percent that don't. The 20 percent that make the difference.

In the 20 percent that don't show those abnormalities, what distinguishes them is what happens before the regression. Is that a fair statement?

A Not necessarily. So to presume that something happens and then there's an ensuing event is a dangerous thing to do, unless you have a reason to think that something can cause something or know that it can.

Q I'm not talking about causation, you're actually putting the cart before the horse that I'm trying to ask you about. Isn't it true that the difference between, the distinction between regressive and classic is that in regressives there's a course of normal development before the regression? Isn't that the distinction?

A As I say, in 80 percent of the cases that I see, it's not normal development preceding it. So the 20 percent seem to have had a perfectly normal development before some change that might occur in the second year of life.

Q Turning to page 13, Slide 13. We talk about multi-incidence autistic families.

In the two families here have you seen any evidence, and we're talking about the King family and the Mead family. do you see any evidence whatsoever

of multi-incidence autism spectrum disorders in either one of these two families?

A I'm not aware of any history of that sort.

Q And when you say you're not aware of, you reviewed the medical records, correct?

A Yes, sir.

Q You reviewed the therapeutic and treatment records, correct?

A Yes, sir.

Q So are you aware that in either one of these families there is any, this is the parental testimony, that there is no evidence of autism or autism spectrum disorder in either side of either of these two families?

A No, sir. I'm not.

Q Do you know, do William or Jordan, either one of those young boys have siblings?

A I don't recall. I know I knew when I looked at the records, but I don't recall at this point. I know they're about ten years old now, but I don't know whether they have siblings.

Q I can tell you, and honestly you can trust me on this one, William Mead has an older sister; Jordan King has a younger brother. And as far as you know there's nothing to indicate that either one of

those siblings has any neural developmental disorder at all.

A I'm sure I must have noted that in the records, but it didn't stick in my head I'm afraid.

Q So you didn't see anything in the records, and certainly nothing that you noted in your report. I'm asking because I didn't see it anywhere in the report.

A Didn't see what in the report?

Q You didn't see anything that would suggest there was familial --

A No, sir. I would have noted it had I noted it.

Q There was also a discussion about how often regressive autism early symptoms are missed in families where the child, the subject child, is a first born. Do you remember that testimony?

A Yes, sir. I do.

Q Are you aware that William Mead was the second born child in the Mead family?

A You've just told me that. I'm sure I must have noted it when I looked at the records, but I see so many records.

Q How many records of children did you review in preparing the report? You say you review a lot of

records. How many medical records did you review in order to prepare your testimony today at all? I mean obviously you're looking at the King and the Mead records, but did you look at other medical records to prepare for your testimony today?

A I look at dozens of medical records every day, that have nothing to do with the case, of course.

Q That's what I just wanted to make sure of. We're not talking about other records that might involve other children here.

You mention on page 15, there's a genetic contribution, and I'll pause for a second so folks can get to page 15, on the genetics of autism.

There is a genetic contribution of greater than 90 percent. What do you rely on for that figure?

A Well, I put a question mark as to whether that's true or not. This has been asserted by people but it remains to be proven. This is one of those points that needs to be proven.

Q One of the ways one can determine genetic contribution is through studies of twins and siblings, is that correct?

A Yes, sir.

Q There have been studies that have been published of both monozygotic and dizygotic twins.

Are you aware of those studies?

A Yes, sir. I am.

Q Based on your familiarity with those studies, what is the concordance rate generally among, and we'll first talk about monozygotic, are those identical twins?

A Yes, sir.

Q If you're looking at monozygotic identical twins, what's the concordance rate of autism in those studies as you understand them?

A I don't have that figure in my head this afternoon.

Q How about dizygotic fraternal twins?

A It's smaller then monozygotic.

Q Do you have estimates? At any point do they approach greater than 90 percent?

A No sir.

Q Do you know how close to 90 percent they get or don't get?

A I don't recall.

Q No idea?

A I have an idea, but I don't recall.

Q And there's no citation to put any number on this. It's just a question.

So on the first point, the question mark

should be after the statement that says genetic contribution greater than 90 percent. Is that where the question mark should be?

A Well, I thought it covered the subject to put it where it was.

Q I couldn't tell. I just want to be clear so I'm working with the right information as you presented it.

In these studies that show concordance rates, can you describe for the Special Masters the specific chromosome sites or the specific gene locations of these abnormalities that would contribute to the appearance of autistic symptoms?

A There's a fairly long list of genes that will produce autistic symptoms. I mention several of them here. Particularly Angelman syndrome that has such striking autistic features, and as well Rett syndrome that I emphasized this morning.

Q And if you look at the known specific genetic defects, about what percentage of total autism cases can be ascribed to the known specific genetic anomalies?

A What I mentioned was that identifiable causes are seen in perhaps somewhere between eight and 12 percent.

Q So that would mean that 88 to 92 percent do not have identifiable causes?

A Yes, sir. Not yet anyway.

Q Exactly. We're talking about the state of what we know right now. So 88 to 92 percent that are supposedly genetic, we don't know what those are right now.

A Yes, sir. Just like cerebral palsy and mental retardation.

Q It's also mentioned here about dysmorphia. About three-quarters of the way down. What is dysmorphia as you mean it to apply here?

A Dysmorphia is unusual features of appearance. Things that, as you examine a patient, may set them apart from other individuals. This can be in the face or it can be abnormalities elsewhere in the body.

Q By these, I want to make sure, again with my lay person's understanding, these are like the finger digit ratio discrepancies and facial features, things like that?

A It's other things as well. In autism, for example, it's length of fingers and other kinds of things.

Q In either William Mead's case or Jordan

King's case, did you identify any dysmorphic features that would be consistent with how you're using the term here?

A I didn't see them. But according to the records there were no such features.

Q In fact Jordan in particular got a very thorough genetic workup. Do you recall reading that in the record?

A Yes, sir. And in addition I was able to see both gentlemen on tapes. I didn't see anything.

Q So no evidence of dysmorphic features whatsoever as far as you could see.

A Not where I could see or what I could read from the record.

Q Let's turn to page 17, Slide 17. This is a slide entitled Rett syndrome.

In what gender does Rett's syndrome appear?

A In either boys or girls.

Q Is there a difference in the distribution of Rett syndrome across gender?

A Yes, sir. It's overwhelmingly girls.

Q When you say overwhelmingly, about what percentage of Rett syndrome children are girls versus boys?

A So far as we currently know, it's well over

95 percent. The issue as to whether boys with mental retardation are under-diagnosed is something that people don't know the answer to.

Q When you come down under here, there's a first point, phase of apparent regression, usually at five to nine months. Then there's a little note under there that says "closer look". Preceding abnormalities of head size. What's being discussed there?

Actually, before I even ask that, this is Dunn, Brain Development?

A Yes, sir.

Q Is that a peer-reviewed, published journal article?

A Yes, sir.

Q It's not just an abstract that was presented as a poster somewhere?

A It is an abstract because of the S preceding the 38.

Q Okay. I'm sorry, so it is or it isn't?

A It is an abstract.

Q It is an abstract. So is the full text manuscript of this yet peer reviewed and published as far as you know?

A No, sir. It's not.

Q It's not. Okay.

So in this unpublished, non-peer reviewed citation, what do you mean when you say "preceding abnormalities of head size"? Or what did they mean as you understand it I guess is the better question.

A Right. Rate of head growth was what Davis Dunn had mentioned in this particular abstract.

Q And what was the rate of head growth that's being described?

A Heads were smaller, and then accelerated in their growth.

Q I'll break it down. How small did they start off? Over what period of time did they get big? And where did they end up? Does that make sense?

A It does make sense. I don't know that I can provide an exact answer to that. But typically it was over a matter of months. That's what they were talking about, because most of the girls had their regression at, as I say, five to nine months, somewhere in there. But what centile and so forth, I don't recall.

Q These were all girls in this study?

A All girls.

Q The end point of tracking the head circumference, how far into their lives did it go?

Did it end at the nine months that's being referred to here? Did it extend out beyond that? What's your best recollection?

A My best recollection is that it continued until sometime after the child was diagnosed, but not a long time.

Q Do you know what the mean age of diagnosis was?

A I don't remember. It seems to me it was the second half of the first year of life, but I don't remember.

Q I'm sorry. The second half of?

A Second half of the first year of life, but I don't remember for sure.

Q I want to turn to page 18. You've got a slide that talks about the cortical development through three decades. If I recall, you were talking about some genetic errors when you were discussing this particular slide. You were talking about how genetic errors can switch on and off at all these different stages of brain development.

A Both are possible. People think particularly about the failure to switch on at a particular phase, or a failure to cause a particular gene that might cause problems to turn off or to

modify the product as expressed by a gene. Those are the kinds of things it would cover.

Q Gene expression, and particularly if it's a functional expression, can gene expression be influenced by environmental factors in general? As a general proposition?

A It's possible.

Q So it's possible that once's genetic predisposition one way or another can be affected by an environmental intervention at some point where that gene's going to be expressed, correct?

A There are examples of exactly that.

Q So at least at that level you would concede that there is, or agree. I don't know if it's conceding. Agree there's a gene environment interaction that can determine physiological outcomes in human beings. Is that correct?

A If you change it to maybe, I would both agree and concede.

Q So it's possible.

A Anything is possible, sir.

Q I don't want to make it, we're not pulling it out of the blue. You would agree that there is a scientifically reasonable basis for concluding that there are gene environment interactions that can

determine somebody's physiological outcome. You would agree with that.

A You have appropriately qualified what I said.

Q So for example, obesity. Are you familiar with research showing that obesity often has, appears to be, an association with some genetic contributing factors? Correct?

A It's an interesting question. There is some of that, and some is environment as well.

Q Right. Because even if you have a genetic predisposition to obesity, if you're deprived of food you will not have your genetic obesity coding expressed as obesity, correct?

A That's correct, sir. yes.

Q I want to turn to page 20. This is the Rett knockout mouse. Quite the photo. It's like a diving board mouse, as best I can tell there. That's the page that we're on.

A I had hoped to be able to click it on and show you, but I couldn't get it to work.

Q So this idea of a knock out. Can you explain exactly what that refers to? It doesn't just mean that the mouse is going to land on its head. You're talking about something else, and I was

wondering if you could explain it a little bit.

A Nowadays people can take a particular genetic segment and inter-collate it into the genome and cause the expression of that. This has become a fairly easy thing to do, apparently.

Q And so this fairly easy thing to do, that's what happened with the mice and that's where people identified this particular genetic anomaly in Rett's, is that correct?

A No, it was identified previously, and then once they knew what it was they could put it into the genome of mice. That's what was done.

Q Has there been a similar knockout gene identified for any other variation of an autism spectrum disorder as far as you know?

A I believe that there has been for other diseases that have autistic features. I could not give a list of them to you just now, but I'm pretty certain that there are others.

Q And these are for autism spectrum disorders. Is that your understanding? That people have developed knockout genes that when they're inserted into somebody's genomic material would produce symptoms of autism spectrum disorder?

A I think it's likely, but I can't tell you

for absolute certain. These things happen in the hundreds every day, apparently. But it's likely that there are such things out there.

Q But if this happened you don't have any evidence here that you could bring to the Special Masters or to share with us?

A Well, I could do so if I had the time to do it, or the opportunity. What tends to happen is that once a particularly important example of a disease process renders it a knockout mouse, folks tend to gang up on that model both because of the expense of the initial development and because the idea is that they can jointly and together provide much more understanding. That's what's happened with Rett.

Q The citation here to Watson et al. Do you have an exhibit number to that so that we could refer to it and we could refer the Special Masters to the text of that somewhere in Respondent's list of materials submitted for this hearing?

A The entire citation is there.

Q My question is can you give us the exhibit number where it appears in the record of these proceedings?

A I don't know anything about an exhibit number.

Q I ask because I looked on the list that the lawyers for y'all's side of the case provided and I didn't see this cited and I didn't see an exhibit number, so I thought maybe you had that. But you don't?

A No, sir. I wasn't asked for one.

Q Let's look at page 22. This is a slide that's entitled functional correlates. I just wanted to ask, what do you mean by functional correlate? What are you correlating a function to in this slide?

A Some of these sentences or these observations correlate things to a mechanistic sort of thing, so that's what it's intended to say. In fact you're quite right in saying I haven't correlated in the way we usually do that, some clinical thing to it.

These are really correlates between a gene issue and the particular problem that may be experienced as a result of it.

Q And again, I've asked this question on a number of slides but I'm just trying to interpret this material. On this first bullet point, methylated cytosine-guanine dinucleotides, are you intending here to report an observation of your own? Or is this a report of something that's appeared in the scientific literature?

A This has appeared in the scientific literature.

Q Where in the scientific literature?

A This observation should be from the Greenberg Lab or from Baylor. I don't know which one.

Q I saw something in here about the Greenberg -- Here it is on the next page, page 23. The Greenberg Lab. That's the page that we're on right now. It looks like there's some sort of bench research experiment going on.

A That's correct, sir.

Q And it's being conducted by a lab at Boston Children's which is Boston Children's Hospital?

A That's correct, sir.

Q Is this information that has been published in the scientific literature?

A Yes, sir. It has.

Q Where has that been published?

A I'm afraid I don't have that information in my head. It's easy to come by.

Q Can you describe the experiment that they were doing here?

A What they did was to look at genetic expression to see what happened in the knockout mouse, is my recollection. They found a target site for

activation that was associated with abnormal dendritic arborization in the experimental model.

Q And was this in mice or rats?

A I think it was a knockout mouse. I couldn't say absolutely certainly, but I believe that's what it was.

Q And it was to determine whether inserting a particular piece of genetic material into a mouse would do something about the dendrite?

A That's the importance of a knockout mouse. It's to really understand the mechanism of the disease. And the importance of these observations was to show how genetic expression could produce such a wide variety of changes and how these changes take place over time.

So the message of these sequential slides was to suggest that in development we can see various things that happen that both determined how the pattern of onset's going to be and what might alter that over time.

Q You mentioned things, certain things happened over a certain period of time. In this experiment, what things happened over what period of time?

A My recollection is of the development of

abnormal dendritic arborization. The period of time that it took is something I don't recollect. I thought I was giving too much information but I wasn't giving enough, apparently.

Q Was there an effort in this experiment to correlate what was going on in these mice to human behavior?

A The importance here was, first of all, because the knockout mouse does manifest features of Rett syndrome, these include isolation, they include gaze issues, they include stereotypies, features that we see in Rett syndrome, quite strikingly. So the issue here was to understand what sequential events might account for abnormal development.

Q So it was the same type of mouse using the same genomic knockout material that was used in that, several slides earlier with the head diving mouse?

A That's my recollection. Yes.

Q Let's turn to page 25. There is a heading at the top that says "Autism: Neuropathology" and there's a note that says "n=5". Now typically when one see n and a scientific reference that's the number of subjects in a study?

A It says nine, I believe.

Q Nine, I'm sorry.

A That's the number of subjects in this particular study.

Q What were the subjects?

A These are human brains.

Q And neuropathology, are these autopsy studies?

A Well, people don't volunteer their brains for these things.

(Laughter).

Q I understand. But there are sometimes people who have head surgery for strokes, and you can take biopsies, and I don't want to be presumptuous. So these are autopsies and there are nine autopsied brains.

A Yes, sir.

Q How old were the subjects at the time that they died?

A Most, and I can't tell you specifically in this study. You're keeping me on my toes. But people don't tend to die of autism, so these tend to be older individuals.

Q Now what study was this?

A I think this was Dr. Kemper or Dr. Bauman, but I don't remember for sure.

Q So if we wanted to analyze and have a

conversation with you about the methods and the number of subjects and information about the underlying pathological results, we don't know what paper we can refer to to have that conversation with you?

A It's likely that you could have an even more stimulating conversation with Dr. Kemper.

Q So odds are it's Dr. Kemper?

A I think so.

Q I think we'll have a chance to have that conversation tomorrow with Dr. Kemper.

A I anticipated that you would.

Q But on here there's no citation and there's no description of the methods or the data analysis involved in that study, correct?

A No. Next time I'll have to double the amount of information that I provide and keep people enthralled.

Q Page 27. This says "Pathology of Autism". I want to make sure I'm tracking this correctly. Earlier you were talking about Rett's. On this slide are you making a distinction between the pathology of Rett's and the pathology of autism?

A This is the pathology of individuals with autism.

Q Does it include people with Rett's?

A I don't believe it does.

Q Does it or does it not? You prepared the slide and you knew what you were saying. So does it include people with Rett's or does it --

A I don't believe it does.

Q Okay. Is this referring to the same study that was referenced that you think might have been a Dr. Kemper study?

A I think this is Courchesne from California.

Q I'm just trying to follow what we're -- It's not that you have to provide all that information in here, but if we at least know the citation we can then be looking at the methods and all. You don't have to explain it in your testimony, but it's very helpful to be able to analyze what you're saying with reference to the underlying literature.

So you believe this is one of Dr. Courchesne's?

A I believe that's right.

Q He's got a number of papers that are out there dealing with, as you know, the brain pathology of autism. Do you know particularly which publication you're talking about here?

A I'm afraid I don't, and this may, it does represent I think a sampling from several different

sources.

Q And your slide is a sampling from several different sources?

A Yes, sir.

Q At one point, what I wrote down as you were describing this, one little note I made is you were having a discussion about long connections versus short connections in the brain?

A Yes, sir.

Q As the early brain develops, say the first couple of months after birth, is it fair to say that the axons of a lot of the neurons are actually migrating and making connections to the brain?

A As the neuron migrates to its ultimate place it leaves a trail behind it and then these things are modified over time. So the cells begin to talk to one another and there's arborization that takes place, and elimination of arborization with development. In addition to those changes there's a development of these long connections.

The state of that information is particularly advanced with functional studies. What you I'm sure understand is that this is very difficult work and that's why there are so many papers out there that one must wonder a little bit about and it's the

reason you're asking where it came from, and it's the right thing to do.

So in terms of the notion about long connections and short connections, this is a summary of a considerable amount of information. It's far beyond the stage of being made up, and it's far beyond the stage of being entirely theoretical because it is in keeping with what information is available.

Now different areas of the brain are different from one another in terms of how you study them. There is particular ease with studying the cerebellum and its connections and there's a great deal of difficulty in studying things like the amygdala or cortex. And the observations that are made, as I say, are very tedious, and rewarding when they're done. And yet more information needs to be obtained.

Now more --

Q Let me interrupt you. I think you're getting a little afield from the question I had here which is about axons and whether the long connections and short connections involve the development of axons throughout the brain. So I'll ask that question again.

Is there anything about long connections and

short connections that involve the movement of axons of neurons throughout the brain?

A Well the axons don't move around the brain. They develop and lengthen. That's a simpler answer than I thought you were asking.

Q Yes, it was that simple.

A I'm very relieved.

Q My understanding is that astrocytes, astroglial cells, play a really important role in the movement of neurons throughout the brain, is that correct?

A They don't move throughout the brain. They move in a particular trajectory. This can be interrupted or changed by events such as damage to the brain early on. But I showed a slide but perhaps didn't convey the fact that that migration is along the radial glial fibers, so these, the route that's assumed is one that's supported by a glial element that then involutes and so the stretching out is along that sort of thing. There's division at the inner areas, and then the cells form different from each other and migrate.

Q Are you referring to the radioglia that start early on? Do the radioglia then evolve into astrocytes or astroglia?

A No, those radioglia involute with time, so we have other cells as well.

I wish the medical students asked questions like yours. This is a very interesting subject and I'm glad you're interested. But cells that divide divide in various ways at the initiating zones that are deep in the brain and we end up with a variety of cells that are involved in the migration.

Q You mentioned that this process can get interrupted and it can get interrupted by events. What sort of events can interrupt this process of neuronal migration?

A The important observations were made in the mid 1920s by Pierre-Marie, and then in 1949 by, I'm blocking on his name now. Wonderful. A Russian neuropathologist. But where a stroke could cause, early stroke could cause migration to be abnormal, and associated tangles of cells that don't get where they need to be. This can happen for other reasons too, and it can happen for genetic reasons too.

Q And actually a stroke is a good example because there are a number of things that can cause a stroke, correct?

A There are quite a number of things that can cause a stroke.

Q Sometimes a stroke can be caused by an AVM, an arterial venus malformation. Is that correct?
A Sure.
Q And an AVM often is a congenital condition, something that one is born with.
A Yes, sir, it may be.
Q A percentage of the people in this room are walking around healthy with AVMs in their brains, correct?
A I'd hate to worry anybody about it.
Q But it's true, isn't it?
A The numbers would suggest that perhaps nobody in this room.
Q But if there were just a few more people we'd be bumping up against that statistic.
A Yes, sir.
Q Now strokes can also be caused by non-congenital factors. Head trauma, correct?
A That's possible.
Q Hypertensive events?
A That's a more common cause.
Q Drugs and toxins that can cause ischemia or acute hypertension, those can cause a stroke, correct?
A Yes, sir.
Q However that stroke is caused, whether it's

congenital or environmental, it can interrupt a migration of neurons at a key point in development if it happened, correct?

A Well, a good many of those things would be off the list as far as being causes for migrational problems.

Q But they could cause problems in the brain, correct?

A Yes, but not migrational problems.

Q And if you look at the pathology of a stroke. If one was to look on biopsy, for example, post-surgery of a stroke, and one saw blood profusion and dead tissue in that pathology, you can't necessarily tell from that pathology whether it was an AVM that caused it or if it was a toxic exposure. You can't tell necessarily what caused it just based on that pathology, can you?

A Oh, you usually can.

Q You can't always though, can you? Often the stroke wipes out the evidence of its own cause.

A Well, chiefly that's because we can't look. We don't go in and biopsy or anything like that, so we have imaging that will tell us something. It's the imaging that leaves us with some uncertainty. The clinical situation may then be helpful to us. But

there are many times when we don't really know what brought on these things.

Q So my question again is, you cannot necessarily tell from the pathology post-stroke what actually caused the stroke itself?

A In the instances where you do have pathology, usually you can. I'd say the overwhelming number of times you can get some idea about this, and that's because the only way you're going to get at it is because somebody's died from a stroke. So you'll have a considerable amount of information.

Q But unless they die from the stroke you're not going to be able to get that information?

A Fortunately for the person who didn't die, and unfortunately for the progress of science. The former outweighs the latter.

Q Understood. Particularly if you're in that situation yourself.

SPECIAL MASTER CAMPBELL-SMITH: Dr. Rust, I just want to ask, the particular trajectory to which you referred along which neurons moved, is that reflected on your exhibit Slide 77, to the left of the page? Is that the diagram to which you were referring?

THE WITNESS: Yes, Special Master. That's

exactly right.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

You can proceed.

BY MR. POWERS:

Q That slide, just to jump ahead then. Eventually I'd be getting there but it's good that you raise it. At the top it says brain surface. And for the record and the reporter, we're on page 77. It's the panel on the left. The top of the slide says "Astrocytic Glycogen".

Is the top where it says "brain surface", is that the cortex?

A Well, the layers, the evolving layers of cortex here.

Q So the process you're describing here is brain development as the cortex is building?

A That's correct.

Q At about what time in life would be captured by this schematic diagram? Of a human life. I assume we're talking about humans in this diagram.

A It would be true of other species as well. This is sort of an artistic representation. It doesn't give us all the information we need. It's intended, well, the pictures on the other side are intended to show us the accumulation of glycogen which

is so striking in these astrocytes, and it was used for a long time to identify the radioglial fibers so people would know where things were migrating. Nobody seemed to care much how it got there or what it did, and that's why I started doing my work.

Q Again, please, I'm not trying to nag, but focus on the question.

Is there a period of time in a child's life that you believe is captured by this schematic? Is this prenatal? Is it gestation week 40 through month two? Can you put some timeframe on it? That's all I'm trying to figure out.

A This is relatively early brain development. But as I mentioned, brain development continues to take place in terms of at least changes in arborization and that sort of thing for as many as three decades. This slide likely represents very early childhood.

Q Postnatal?

A Or prenatal.

SPECIAL MASTER CAMPBELL-SMITH: Would that be neonatal?

THE WITNESS: Neonatal, prenatal or postnatal.

BY MR. POWERS:

Q On page 37. Page 37 is the page you had referenced before and it has graphic representations here. I just wanted to first get oriented as to exactly what we're looking at.

It looks like a cross-section of brain. On the left panel as one looks at it it's a control; and on the right it's ASD. What kind of image is this again?

A The image that you're seeing there is an MRI scan. The top.

Q Is this a functional MRI?

A This is data generated for a functional MRI.

Q Excuse me?

A It's data generated from a functional MR spectroscopy.

Q And can you describe again, because I just missed it, what these circles are? There's a circle on the control and there's a circle on the ASD. What do those circles represent?

A These are areas of activation given a particular task. I can't recall what the task was, but they're simply representative of a body of information that's been generated to show that with a particular task, a very isolated task, you may see activation in a particular brain area. And a co-

activation in other areas. So these represent activation in regions in the temporal lobe and the inferior frontal lobe, and so forth.

Q Do you know what activities are being measured in these slides?

A This represents increased brain activity. It can be gotten by functional imaging or it can be gotten by PET imaging. So there are several different ways to look to see what tissues are activated.

Q And I guess what I'm trying to get at is that there's a difference -- I shouldn't assume this.

Is there a difference in the activity as captured by the MRI in the control brain versus the ASD brain?

A Well the circled area that doesn't have activation as a target for a particular task is what is being shown there.

Q Is it the autistic brain that has the lack of activation?

A That's right. That's what's intended to be represented there. There's, of course, a lot of work in this area, and the slides merely are meant to show that we can actually look at the systems related function with this technique. It's not something I do, but it's something that people can do.

Q Is this electrical activity? Or is it something like a hemodynamic MRI where you can see sort or blood flow to an area?

A For PET it's blood flow increases that are done.

Q Okay.

Do you know if these are boy or girl brains?

A I'm afraid I can't tell you, either for the control or for the autistic spectrum disorder. The likelihood is that they're age matched boys.

Q Do you know if either one of these particular, either the case or the control, had epilepsy?

A I can't tell you the answer to that.

Q Do you know if the ASD brain, if that was a child who had regressive autism?

A I can't tell you the answer to that, too. Although this kind of data has been generated for -- Well, I'd better be careful about this one. I know it's been generated for autistic disorders, but I can't tell you for sure whether people have been careful about that distinction.

SPECIAL MASTER CAMPBELL-SMITH: I just want to be clear, Dr. Rust. You used activity a couple of times, and activation. These are two presumably age-

matched children, possibly boys, a control and an autistic, who are doing the same activity.

THE WITNESS: That's right. These tend to be very very specific tasks that either individual might be able to perform, and I don't know what the task was here.

SPECIAL MASTER CAMPBELL-SMITH: In the autistic child, what we see in that sort of gap area that you addressed, the more open area, more white area in the black and white slide, is a lack of blood flow, as you further described?

THE WITNESS: In these studies, I can't tell you for sure. Typically with these kinds of studies one could compare blood flow to areas that are designated, not with a PET scan but with imaging studies, so that you co-register, is what people call it, to get one area. Then you can put it on a picture where you can show where it is on an image that people can understand more readily.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

MR. MATANOSKI: If I may interrupt, just for a housekeeping matter.

Mr. Powers, you got a copy of the color slides, right? Are you working off that now?

MR. POWERS: I am not. I'm working off my

marked-up copy.

MR. MATANOSKI: In the lunch break we were able to get color copies. I know we gave you one, but you're working off the marked up copy. I was just wondering if it was easier for everyone since these particular slides that we were just referring to were color slides, and we don't have it up on the monitor right now. but we can bring it up. If it will be easier, we do have the color copies.

MR. POWERS: I didn't have any other questions about that slide. I don't know if the Special Masters need --

SPECIAL MASTER VOWELL: I don't need a color copy.

SPECIAL MASTER CAMPBELL-SMITH: I don't need a color copy.

MR. MATANOSKI: We were going to take care of that matter after, substitute them.

SPECIAL MASTER CAMPBELL-SMITH: Thank you. We're just dealing with gray right now. Different shades.

(Laughter).

MR. POWERS: A little bit of black and white, but a lot of gray.

BY MR. POWERS:

Q I'm going to put the slides aside for a little bit and ask you a few other questions here.

There has been discussion about William Mead's head circumference. You had one citation in your report that you're now saying it's a different piece of material that you're relying on, a different piece of evidence. What I want to ask is, do you recall from your review of the medical literature what his, not percentage, but just what William Mead's head circumference was at birth?

A I think it was reflected in the 38 week mark on the other piece of information. I don't remember, but I think that's right.

Q Scott, if you could pull that up. We might even want to just use Exhibit 1, page 3.

SPECIAL MASTER CAMPBELL-SMITH: I think that's Exhibit 1, page 4.

MR. POWERS: Exhibit 1, page 4 is the birth record. I was trying to go from memory and it doesn't always work, so I sympathize with the doctor up there too.

BY MR. POWERS:

Q With Mr. Graham's assistance, we've determined it's Exhibit 1, page 31.

Dr. Rust, do you see that on the monitor in

front of you there?

A Yes, sir.

Q We're going to blow it up for you. If you could focus on the upper left hand highlighted area. You see this is William Mead's birth record. It talks about his condition upon admission.

Do you see the line where it says HD? I'm assuming that means head?

A Uh huh. Yes, I do.

Q There's a 14/36. Would that be 14 inches or 36 centimeters?

A It could be, sir.

Q So 36 centimeters. Do you know where at a gestational age of 39 weeks, which is what his growth chart showed, do you know what percentile that would place his head circumference?

Now you've said he started off in the 60th percentile.

A Yes, sir.

Q Are you familiar with Dr. Menkes' Child Neurology textbook?

A I'm quite familiar with it, sir.

Q I don't know if we can put this up on the chart, but on page four of the 7th edition of Dr. Menkes' Child Neurology book it actually shows a head

circumference chart.

Can we put this on an overhead?

Maybe there's an easier way. I wonder if I could show it to the witness and you can identify where this would be in terms of percent.

SPECIAL MASTER CAMPBELL-SMITH: Hold on for the document camera.

(Pause).

BY MR. POWERS:

Q So Doctor, if we were to look, 36, 34 is the median is that correct?

A Yes, sir.

Q And 36 is about one full standard deviation above the median, is that correct?

A Yes, sir. It is.

Q So one full standard deviation above the median, that would place his percentile more in the 80 percentile than it would in the 60 percentile, correct?

A If it were a reliable measurement.

Q If what was a reliable measure?

A The measurements provided here.

Q But we're assuming, you were not relying in any other measure, were you, in your review of the medical records and your formation of your opinion

about his head growth?

A There's a particular problem with head circumference at birth.

Q What is that particular problem?

A A child's just passed through the birth canal, so we find that those measurements are unreliable for us. There can be edema, there can be overlapping sutures, and that sort of thing. So for a variety of reasons the child during the first few weeks after birth will begin to express a head circumference that's more reliable for us.

Q His trajectory of head size, if you're saying he started at 60, so where in the peer review published medical literature do you extrapolate backwards from something that you just said is roughly in the 80 percentile to something that's in the 60th percentile? Can you direct us to where that backwards extrapolation would be made?

A It was in the head growth chart.

Q I'm just trying to figure out where the 60 percent comes from, because that just doesn't appear in the -- When you look at it and compare it to what's right there in Dr. Menkes' textbook.

A We had an illustration of the measurement. I thought we used it during the testimony. It was the

60th percentile.

Q So it is your testimony then that you believe he was in the 60th percentile.

A As I mentioned, we don't rely on the head circumference at birth because there are so many features that influence that. The child has passed through the birth canal. This can produce edema and other changes. Elongation and other kinds of changes that make the head circumference at birth unreliable for us.

Q But in your expert report you describe that he went from 60 to 95 percent in the first four months of his life, and you implicated what sounded like a very serious list of medical problems that might be indicated by that.

Do you recall describing that in your expert report?

A I don't think I implicated a serious collection of things, but at least I don't remember it, but the trajectory is important for two reasons. First of all, again, we can't rely on the birth head circumference because of the fact that it's after a period of trauma that the child's experience. So what we look for is both the rise and the fall.

There are a number of serious things that

can cause the head circumference to continue to enlarge. We've tended not to worry about that too much until it's greater than the 95th, 100th percentile, and even there we sometimes follow it for an interval.

But more important to us is the unexplained decline after that time. So it's this hump of up and down which doesn't correspond to the child's growth in other ways. And children have no reason to have their head get smaller. There's no explanation for such a thing physiologically. So we see an increase and then a decrease.

Q So again you're sticking to the testimony that despite whatever it says in the Menkes chart and on the first medical record, that it was at 60 percent.

A Again, we had a measurement that was at the 60th percentile. That's what I'm relying on.

This seems to me it was at a one month, or something like that. It looked like it was oriented around one month after delivery on the head circumference chart.

Q You're not saying that this number, this 36, was one month after birth.

A No, sir. This is at birth, I presume --

Q I'm just trying to keep track what record you're talking about.

A That would be a very slow nurse.

Q Way beyond the standard of care.

A Yes, sir. But diligent, nonetheless.

Q Let's go ahead and pull that slide down.

In your experience can an encephalopathy result in autistic regression?

A I haven't identified such a thing in any of my children.

Q Are you familiar with any pediatricians who have diagnosed a child with encephalopathy followed by regressive autism?

A I don't know of particular cases.

Q Have you reviewed the literature in order to identify any cases like that?

A There's something I might have overlooked, but it's not been my experience. The definition of autism in those cases is very important.

Q If the definition was regressive autism, would that be significant?

A You have to know what criteria they used for that diagnosis.

Q You mention in William Mead's records pica, that you recall something in his records about him

eating things that were not typically food. Marbles, I think it was. Do you recall at what age --

A Marbles or stones. I don't know which one it was.

Q Or maybe both.

A It could have been both.

Q Do you recall at what age that behavior was noted to have occurred?

A I don't recall, sir.

Q Do you recall that it was after one year of age?

A It seemed to me that it was around one year of age but I don't know that for certain.

Q But you can't describe anything in the medical record that you base that statement on in your direct testimony?

A I believe that's the only basis that I might have had.

Q You also mention in Jordan's records that you notice what you call splitter skills. What splitter skills were you referring to again?

A That was the musical interest and so forth. So these are the things that were described.

Q When did they emerge? Do you recall?

A I'm a bit confused, because a case that was

withdrawn had so much music in it. I can't remember for sure.

Q You're the one who's testifying on these individual cases, so I honestly don't know what you were relying on, so that's why I'm asking you these questions.

Do you recall that Jordan King's household, both parents were musicians? Does that ring a bell?

A I think I do know that.

Q And that Jordan King helped actually build marimbas which are a musical instrument the family played?

A Now I remember. That's right. Yes.

Q So that's the child we're talking about. That's Jordan King.

Q What about his musical skills do you recall in terms of what skills he acquired and when he acquired them?

A What I recollect is, again, there's another child that was in this, a child that had lots of music I think. But it seemed to me both the interest in music and the interest in performing music was something quite striking. It has to be interpreted within the setting of opportunity and other genetic things, which is the genetic capacity to do music, but

at least it represented the possibility of a splitter skill.

Q The question was do you recall when he acquired those skills?

A It seems to me it was quite young. It seems to me it might have been at the end of the first year or second year.

Q Did you discuss splitter skills in your individual case report in Jordan King, as best you recall?

A I don't remember whether I did or not.

Q Do you recall sitting there, or do you have any notes that could direct us to the records where you identified splitter skills and the time that they appear?

A It seems to me it was based on videotapes.

Q Do you have any notes about what you were referring to in the videotapes?

A I do have some notations, I believe, in my office but I don't have them with me.

Q So as you sit here today you can't direct the Special Masters to anything in the record that's been developed in this case identifying what skills might have appeared, when they appeared, and the progress of those skills over time? You can't

identify any of that for us?

A Splitter skills have to be placed within a context, too. And musical parents and so forth could have another, both genetic and opportunistic aspect to it.

Q I understand that. But I'm just trying to get the functional, the evidentiary context I guess is what I'm looking for.

A Yes.

Q And there's nothing that you can illuminate beyond what you already testified to on Direct, is that correct?

A Just my memory.

Q Are there environmental cases of some cases of autism that you're familiar with?

A There are prenatal ones.

Q Right. So that would include Thalidomide? Is that a recognized prenatal cause of autism?

A It doesn't really produce an autistic syndrome. It produces limb shortening and motor problems and other kinds of things.

Q So your testimony based on your recollection of the literature is that Thalidomide prenatally is not associated with autism?

A People have described an association, and

the question is whether that's accurate or not. I haven't looked at that carefully enough to know for certain.

Q So you don't have an opinion one way or the other other than you know other people have proposed it.

A It's on the list of things that people talk about. They don't talk about it, it's listed in books, et cetera.

Q Terbutaline exposure, prenatally?

A I believe that's right.

Q Valproic acid exposure prenatally?

A That's questionable. What we tend to see with valproic exposure prenatally are problems of the neural tube development.

Q Would you describe those problems as manifesting symptoms of autism once the child is born?

A I don't know that in a carefully examined child with criteria applied, that that would be the case. We can see some significant brain problems in children, but it tends to be a neural tube problem.

Q Maternal rubella. Is that associated --

A That's the most important one. It was a considerable problem until the vaccine became available.

Q How about postnatally? Viruses that are involved in the appearance of autism after a child is born. Are you familiar with any instances of those?

A Not in my personal experience. Again it's the issue of autistic features, or features people might mistake for autism in association with infections. So I'm not aware of such things.

Q Borna Virus, for example. Is that anything you recall from the scientific literature that's been associated at least with the appearance of autism in children postnatally?

A Borna Virus is one of those funny things. It appears in several settings. I've never seen a case. I don't know, not having read the particular cases, whether these are autism or not.

Q How about malaria? Childhood exposure to malaria and associations with autism. Are you familiar with any literature on that subject?

A I'm quite familiar with the literature on childhood malaria or early infantile malaria. And it doesn't produce autism.

Q It does or does not?

A It does not. It produces severe encephalopathy.

Q Is it an encephalopathy that can later

present with the symptoms of autism?

A Autism should be excluded in such cases because of the severity of the motor sensory and intellectual problems.

Q Are there any other either prenatal or postnatal environmental exposures that you would associate with the appearance of autism?

A I suspect there may be one or two other prenatal ones. I'm not aware of postnatal ones.

Q Would you agree that in genetic predispositions or genetic susceptibilities can interact with environmental exposures to produce autism in some number of cases?

A I don't know that, other than in the prenatal situation, that that happens.

Q In 2007, I think it was in April. April 17th, April 18th, 2007, the Institutes of Medicine hosted a two-day meeting in Washington, D.C. on environmental implications in the development of autism. Are you familiar with that meeting?

A Yes.

Q Did you attend that meeting?

A No, sir.

Q Did you receive any of the materials after that meeting?

A I reviewed some of the materials after that meeting.

Q I think the IOM actually put the proceedings together in a book. They didn't do a report, but they assembled things in a volume for distribution. Did you review that volume?

A No, sir. Certain excerpts from it, but not the entire thing.

Q Do you recall what excerpts you reviewed?

A This was some time ago. What I read, what I can tell you was what I read suggested that it's very important for us to look more carefully at the possibilities and there was a considerable amount of reflection on whether or not there might be the sort of things that you're implying, the interaction of genes and environment after birth. And people said as they have frequently, with some importance, we need to look.

Q And certainly it's a viable enough possibility, scientifically and medically, that it merits attention, or that it merits a look, as you say. Is that correct?

A That's exactly what I said earlier today. Theory is one thing, and doing the work to find out whether it's true is another.

Q In your discussions of regressive autism, ultimately do you believe that there is a regressive sub-type of autism? By that I'll define a child who does not have, even retrospectively, any abnormalities, who then develops at some point in the second year of life, the symptoms of autism. If that's the definition of regressive autism, do you believe that that sub-type of autism actually exists?

A I don't have any such children in my large population, but I/'d have to qualify that by saying that in the years, in the more distant past when I didn't ask enough question, it's possible I saw such a thing but didn't recognize it.

But as I've carefully paid attention to the children, I haven't seen a meaningful distinction between the two groups.

Q One of the articles that the Petitioners filed here, is Petitioner's Master Reference 154. And we're going to put that on the screen. We're going to look at page two -- Well, I'll give the Special Masters both references.

The exhibit reference is page 19 of 23 on Exhibit 154. The text is page 284. We're going to go to page 19.

If you look, there's no way to read it right

now. We're going to blow it up. If you look at the bottom quarter of the page there's a paragraph that begins with italics, Rutter, down lower than that. And if you look at the last two sentences of that full paragraph, --

A Which page is that, sir?

Q It's page 19 of the exhibit. If you look at the bottom right hand corner of the pages, Doctor, you'll see page 1 of 23, 2 of 23. This is page 19 of 23.

A I have 154. Does that mean something to you, sir?

Q That's the exhibit number. And if it helps, if you look at the top left of each page there's the actual manuscript number. The one I'm looking at is 284.

A That's what I'm looking at.

Q Okay.

I can tell yo, this was a symposium that was recorded in 2003, and it involved a lot of experts on autism who were meeting and speaking.

By any chance, did you attend this in 2003?

A No, sir.

Q And the paragraph that begins, "rutter", is I assume Sir Michael Rutter?

A I would presume so.

Q At the bottom there's a discussion going on here among the participants about regressive autism. He says, "There is convincing evidence that there are other children who are perfectly okay for the first 18 months or so. What is the implication of this difference and how might this be tackled?"

Would you agree or disagree with Sir Rutter about that there is convincing evidence that there are children who are autistic but are perfectly okay for the first 18 months. Do you agree or disagree?

A The example he provides is a home movie. These can be helpful to us, but it's certainly not the only thing that we need. We need to ask a series of important questions, as I mentioned to you. So I'm not convinced by this observation. Had I been there and had I been motivated to do so I would have asked what questions were asked of this family.

Q He says the home movies are just an example, because earlier on in that paragraph he says that it's well documented that in perhaps a quarter of cases there is regression. Do you agree with Sir Michael that in about a quarter of the well documented cases there's evidence of regression?

A I've tended to rely on my own experience in

these matters, especially when I've devoted the attention that I do to these things, and to say I don't see it, but perhaps it happens in Britain. I don't know.

Q Fair enough. I was just asking if you agreed with his observation and your answer is that in your experience you do not agree with his observation, is that fair?

A It's not been my experience.

Q Have you reviewed the scientific literature to explore this issue of whether or not regressive autism can appear after a sustained period of completely normal development? You've described your experience, but have you reviewed the literature to see what other people have assessed in terms of this phenomenon.

A I have, sir. It hasn't been comprehensive, but it's been a pretty wide review.

Q In talking about astrocytes, shifting gears again, going from regression to astrocytes. Astrocytes among the functions they perform in the brain, do they absorb excess glutamate? Extra cellular glutamate?

A They do. It's a very important function. And then they recycle it as glutamine.

Q So there's sort of a cycle there and the astrocytes are important to mediating that cycle, is that right?

A They're in the midst of at least eight or nine cycles of that sort.

Q Another thing they do is they, as I understand it, generate glutathione as an antioxidant for use by the neurons.

A Or themselves if they need it.

Q My understanding also, and correct me if I'm wrong, is that the neurons typically don't produce very much if any of their own glutathione, is that right?

A Nor do oligodendrocytes.

Q Which is another form of the glial cells.

A Yes, sir.

Q Oligodendrocytes, those are the glials that do the myelin sheathing, correct?

A Yes, sir.

Q So you has astrocytes, oligodendrocytes, and microglia.

When you say oligo in some of your slides, are you talking about oligodendrocytes?

A Yes, sir.

Q Okay. I'll use that term. It will be a

little bit easier.

So the oligos deal with myelin sheathing primarily. Is that their main function?

A That's their main function, that's correct.

Q And the microglia serve as the part of the brain's innate immune system, sort of the phagocytes or macrophage function in the brain.

A Many of us feel we haven't begun to understand the functions of the microglial cells because they're so various, and especially in their pathological expression in conditions where there are various kinds of inflammation. We don't yet understand exactly what they do some of the time, but yes indeed, they're involved not only in innate but reactive immunity.

Q And in some of the research that's looking into those there's particular focus on the effect that metals have on microglial cells in the brain. I think it's University of Southern Mississippi, they're looking at molybdenum. Are you familiar with any of that work?

A I thought that work was out of Tennessee, but --

Q Tennessee, yeah. And manganese is being looked at.

A Manganese has been looked at, especially those heavy metals with regard to extrapyramidal diseases.

Q Mercury has been examined, at least in primates, correct?

A Yes, sir. It certainly has.

Q Are you familiar with the studies that have been subject to an awful lot of conversation in these hearings so far, the adult monkey studies by Dr. Charleston and Dr. Burbacher and their group in the University of Washington?

A Yes, sir. I certainly am.

Q Is it your understanding of those studies, involving again the adult monkeys, that upon administration of methyl mercury, those studies showed that inorganic mercury was deposited in the brains of those adult monkeys after exposure to methyl mercury. Do you recall that?

A Methyl and ethyl and inorganic itself were administered.

Q We're talking about the adult money studies. I'll represent to you that the adult, because this is again, really, it's not a quiz. I just want to get your understanding. The adult money studies were methyl mercury and inorganic mercury exposure. We're

not talking about the ethyl yet that will come with the infant monkeys.

A Certainly I know that inorganic mercury in particular was administered intravenously. And that's right.

Q Your understanding would be that the methyl mercury that was administered to the adult monkeys eventually ended up, some fraction of that, in the monkeys' brains as inorganic mercury, Hg++. Is that your recollection?

A They're not the only people to have demonstrated that. And as I mentioned in my discussion, methyl mercury and ethyl mercury both go to inorganic mercury.

Q The inorganic mercury in the brains of those adult monkeys tended to, it was predominantly found in microglia and astrocytes, correct?

A Yes, sir. That's right.

Q It was found in neurons but at much much lower levels than in the glial cells, correct?

A Yes, sir.

Q And they found pathological evidence of activated microglia.

A Yes, sir.

Q Proliferation of microglia.

A Yes, sir.

Q So that means both the microglia that were there had changed shape, they sort of had that amoeba shape, and their morphology actually changed, and they could see that, correct?

A Yes, sir.

Q And there were more of them. So when I say proliferated, there were actually more of them and they were in a different shape than they would have been when they were quiescent, correct?

A That's correct.

Q The astrocytes showed evidence of inorganic mercury content and the numbers of astrocytes in the later exposed groups were lower. Do you recall that?

A I don't recall that piece of information.

Q But some of the astrocytes in some of the monkeys showed decreased numbers of astrocytes at the end when the monkeys were sacrificed.

A It may be true. This is a difficult problem, though, in terms of counting numbers. We talked about this in relationship to markers such as GFAP. But I don't remember that at this point, but I'm sure it must be true if you say so.

Q If only everything I say can be so reliable. I try to do the best I can, but that's what we're

talking about with these studies.

Now in the 2005 monkey study, is this the one in your recollection that involved the infant monkeys where they got Thimerosal containing vaccines? Do you remember that study by Dr. Burbacher?

A Yes, sir. I do. I don't remember all the details, but I certainly remember the study.

Q Would you understand that study to show that ethyl mercury exposure via Thimerosal containing vaccines resulted in the deposition of inorganic mercury in the brains of the infant monkeys?

A Yes, sir. I do recall that.

Q Do you also recall that a greater fraction of ethyl mercury ended up as inorganic mercury in the brain than did the percentage of methyl mercury end up in the --

A By a factor of 2.1 to 1 or something like that. Yes.

Q So in the adult money studies, inorganic mercury in the brain was associated with an inflammatory process of some kind.

A That's the right way to put it.

Q Then in the infant monkey study, and I just don't know if you're following the progress of the work that the group is doing, but only half the brains

were actually examined in the paper that came out in 2005, and the other half of the brains, there's been testimony about this. I don't know if you've heard any of the testimony. That they're looking to identify whether the inorganic mercury from the Thimerosal containing vaccines in infants ended up in particular cells in the brain. Are you aware of that anticipated publication?

A No, sir. I wasn't aware of that.

Q So the adult monkey studies and the baby monkey studies together, if this other study came out showing that the inorganic mercury derived from Thimerosal containing vaccines actually ended up in glial cells, particularly astrocytes and microglia, that might provide evidence of a neuroinflammatory process at least in an infant primate. Correct?

A As I say, of a process, what that's caused by and what it's directed at of course is unknown.

Q Would you agree that neuro inflammation is being considered as a possible cause of some forms of autism in some children?

A I'm aware that is among the things that Dr. Kinsbourne has considered, for example.

Q Would you agree that it is among the things that the Vargas/Pardo/Zimmerman group at Johns Hopkins

is considering?

A It is one of the things that they have considered, that's correct.

Q And they're considering it seriously enough that they're even looking into potential studies involving the administration of anti-inflammatories as a therapeutic response to the possibility that neuroinflammation might be associated with autism symptoms. Is that correct?

A I hadn't been aware that they planned to do that, but it seems like a very interesting thing to do.

Q You mentioned in one of your early slides, it wasn't a reference to a particular study by Dr. Courchesne?

A Yes, sir.

Q But I did want to refer to one that has been introduced into evidence here, and this is Petitioner's Exhibit 104. Again, I don't know if you've listened in on any of the proceedings, but if you have this is another one of those studies that has been cited and discussed several times.

If you look on the monitor, do you see a paper there called "Autism at the beginning" and then it goes on with a longer subtitle?

A Yes, sir. I do see it.

Q We're going to look to page 584 of the text there. For the transcript and for the Special Masters, this is page eight of the exhibit. Text page 584 of the study.

If you can find that page, Doctor, and then look up to me so I know that you've found that page. Okay. And I'm going to quickly ask you to look back down at the page and look at the bottom right hand corner, the last full paragraph. And it goes on to the next page. From page 584 to 585, or from exhibit page 8 to exhibit page 9.

A What am I meant to do?

Q We're going to pause here for a technical moment to get this in front of you so it's readable.

What I'm going to do is ask you to read that and I'm going to have a question for you.

A I'd have to start before that, of course.

Q I'm just going to -- Wait until you hear the question. You may be able to answer it just based on this section.

A Am I meant to read or listen to it?

Q Have you had a chance to read that highlighted paragraph?

A No, sir. I just got it.

Q Okay. Go ahead and read it.

(Pause).

A I finished that portion,sir.

Q Okay. So my question is, do you agree that some of these neuronal changes that take place in the brains of autistics, might be as Dr. Courchesne says, citing to the Vargas group, are these things that could be triggered by adverse events such as those that ignite the neuroinflammatory reaction? Would you agree with that statement that adverse events such as those that can ignite neuroinflammation can explain some of the pathological changes in the brains of autistic people?

A Well, it's one of several possible explanations.

MR. POWERS: I have no further questions.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

Any Redirect?

MR. MATANOSKI: Yes, there will be. But if we could take the afternoon break at this time.

SPECIAL MASTER CAMPBELL-SMITH: It's getting close to time. I have 4:36. How long would you like?

MR. MATANOSKI: Five after? would that be permissible?

SPECIAL MASTER VOWELL: A half hour?

MR. MATANOSKI: I'm sorry, I meant to run to the next five.

SPECIAL MASTER VOWELL: I'm glad I'm not the only one that has trouble with math.

(Laughter).

SPECIAL MASTER CAMPBELL-SMITH: Fifteen minutes. Let's, if we round up to 4:40. Let's come back at 4:55. Just shy of 5:00 o'clock.

MR. MATANOSKI: Thank you.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

(Whereupon, a short recess was taken).

SPECIAL MASTER CAMPBELL-SMITH: Please be seated as quickly as you can.

And just a housekeeping note that during our break, if you might step away from the microphones it's like backstage. Excitement and revelation on the microphones. We're still live. So just a note to all, stay away from the live microphones during recesses.

SPECIAL MASTER HASTINGS: Unless you want your conversation to go --

SPECIAL MASTER CAMPBELL-SMITH: To be broadcast.

SPECIAL MASTER VOWELL: Broadcast to us back in Chambers.

MR. POWERS: Is this a podcast --

(Laughter).

SPECIAL MASTER CAMPBELL-SMITH: Ms. Esposito, are you ready to conduct Redirect?

MS. ESPOSITO: Yes, thank you.

REDIRECT EXAMINATION

BY MS. ESPOSITO:

Q Dr. Rust, if Dr. Kinsbourne's hypothesis is true, would it apply to regressive and classic autism alike?

A It certainly should. It perhaps should apply more to the classic variety because it does seem to be greater early vulnerability.

Q When you said before that you did not see a meaningful distinction between the classic and regressive autism, and this was in reference to the slide that opposing counsel put up from Dr. Rutter, can you explain what you meant by that?

A It's what I discussed earlier with regard to the early history of the child and the ensuing outcome and the appearance of the child at a particular age. There is a difference, of course, because the parents are telling us that the child's lost skills and that seems to happen at a variety of ages and with no clear association with any particular life circumstance.

So there are children that seem to lose something that they acquired previously.

Q You were asked about the Charleston adult monkey study. Do you recall that?

A I was asked about it, yes.

Q In that study there were very large doses of inorganic mercury given to the monkeys, is that right?

A They seemed to me to be very large, and not only very large but given very repetitively over a long interval.

Q Do you recall if there were any clinical symptoms that resulted from the monkeys being given large doses?

A So far as I know there are no description of any clinical deterioration in the monkeys until the time they're sacrificed.

Q Nothing that resembled autism that you recall from that article?

A No. I don't think there was anything.

Q If you could assume that inorganic causes of glial activation would deposit, let me rephrase that.

If there were other exposures to mercury in a patient's life, if they're otherwise exposed to different types of mercury, would you see any difference in the glial activation from one type of

mercury over another type of mercury?

A No. The difference demonstrated in those studies with regard to the amount of mercury accumulating over a short interval, I might say, in those studies, from the breakdown of ethyl as compared to methyl mercury, I think it's 2.1 to 1 or something like that. Given the doses it's not particularly meaningful. It's a difference, but it's perhaps not a meaningful one. Then the question is if we waited over a longer interval, since the presumption would be that methyl mercury taking a little longer to break down would ultimately equal the deposit of the inorganic mercury, it shouldn't be any different. And we also had the additional important contributions environmentally to all of us with regard to mercury.

So in comparison to those environmental and especially in comparison to the amount of mercury in vaccines, for example, the doses given, especially to those adult macaques were astronomical and daily for I think three months.

Q If one were to suppose that inorganic mercury were the cause of autism, could you say for a certainty that it was from the vaccine or any vaccines given to that person?

A No, because again we have these other

exposures.

Q With regard to the Vargas article, do you know if that group concluded that neuro inflammation was the cause of autism?

A No, they didn't. They simply described a change that they observed by somewhat indirect methodology and whether that was of a response that was protective or a response that was something other than that is not known.

But one certainly must think about the possibility that if it's representative, an issue where the nervous system was being challenged in some way, it might well be protective. It could be related to architectural changes, could be related to other things. So there are lots of possibilities. Maybe more refinement in technique is very important in those kinds of studies, as with others.

MS. ESPOSITO: Thank you.

SPECIAL MASTER CAMPBELL-SMITH: Any Recross?

MR. POWERS: No Recross.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

I believe my colleagues have some questions.

SPECIAL MASTER VOWELL: I do, and I'll try to be clear, Dr. Rust.

If we take your figure of 90 percent

concordance in identical twins in terms of autism in one twin and significant autistic like symptoms in the other twin even if they don't reach the diagnosis of autism. That's the 90 percent figure from your slide.

THE WITNESS: I think the 90 percent was referring to a genetic contribution estimated.

SPECIAL MASTER VOWELL: Okay. and we've heard in other testimony or in articles that we've read, a concordance, a different concordance, but let's say there's a 60 percent to 90 percent concordance rate. Those seem to be the ranges we've heard.

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: How do you account for the other ten percent, if we're looking at what appears to be a strongly genetic explanation?

THE WITNESS: That's a very important question. One would expect to see the disease express itself in both children.

SPECIAL MASTER VOWELL: Like Huntington's, for example.

THE WITNESS: With identical twins. That's right. That's typically the way things present themselves.

So it's a little puzzling, as I, it's more

than a little puzzling, and it's an important question. Other factors seem to influence risk and perhaps they're not yet fully understood. If the genetic trait were to come from a particular parent, one would still presume that the imprinting effect would be the same on both children. If the genetic trait were passed on to both children by the same father.

There can be some differences in gene dose between children as I understand it. It's not an area I know a great deal about.

SPECIAL MASTER VOWELL: So we should address this to a geneticist, perhaps.

THE WITNESS: I think you'll get a more reliable answer.

SPECIAL MASTER VOWELL: Let me just ask this question, and you may not know.

I understand that Rett's is a genetic defect.

THE WITNESS: Yes, ma'am. Yes, Special Master.

SPECIAL MASTER VOWELL: Ma'am is all right.

You've drawn parallels between brain abnormalities in Rett's children and behavior in Rett's children and behavior in brain abnormalities

and ASD kids, among many other parallels you drew.

THE WITNESS: Yes, Special Master.

SPECIAL MASTER VOWELL: Is Rett's 100 percent concordant?

THE WITNESS: I believe that it is, but I'm not sure. It's another important question, especially relative to the prior question. But I believe that that's true.

The counseling in these matters is done by geneticists and I may be wrong on that point.

SPECIAL MASTER VOWELL: Assume for the purposes of this question that the loss of language or the loss of words is real in some percentage of what we call regressive autistic children. What would account for that loss of words? Is there anything you are aware of?

THE WITNESS: It would seem to me, it's the same thing that accounts for it, it's likely to be something similar to what accounts for it in Rett's syndrome because that's what we see in the little girls as well.

SPECIAL MASTER VOWELL: The loss of words.

THE WITNESS: They have words, and then they disappear overnight. Or seemingly overnight. That's among the things that the model, it is hoped will give

us some understanding of. But it's quite a striking phenomenon, so it does happen in Rett's.

SPECIAL MASTER VOWELL: But we don't know yet what causes it in Rett's.

THE WITNESS: Not so far as I know. It's an area developing so rapidly that almost by the week or the month we get something new.

SPECIAL MASTER VOWELL: You talked about the phasic, the sine curve of the generation. Do you have any idea what generates that?

THE WITNESS: I probably was saying that confusingly. I was speaking about life itself. It goes up and down. We see this all the time, whether it's headaches or epilepsy or behavior or other kinds of things.

The point I was trying to make there is that when the problems are great and we start some treatment and they get better, we're willing to take the credit for it. And then when they get -- We see this in epilepsy all the time. Things get worse and we give a higher dose and they seem to get better. We do this for a while, and then we see the pattern goes on even when we're at high doses.

This is not everybody, but it's some people. Then we begin to realize that sometimes life just does

that and perhaps we shouldn't take credit sometimes.

So certain treatments if administered to somebody, even if we think it's outrageous and is outrageous, it may appear to produce an effect that's valuable. Then if we see that it comes and it goes like that, whether it's our orthodox treatments or the ones we regard as unorthodox, we really need to sit back and figure out what it is we're really doing with those children. Then we need to assign, in a carefully designed group, the odds of making a child better to say look, we really know what we're doing with this because we can so much increase the likelihood this child will not have this or another problem.

When we do such studies, such as we do for drugs for very severe epilepsy, this is a particularly important comparison that we see with one of the worst kinds of seizures that occur in early childhood called Lennox-Gastaut. We see about a 50 percent likelihood that a very good drug is going to decrease the number of seizures meaningfully. In those studies a placebo does so in about 15 percent.

So we've got to be careful in two directions. One is we've got to consider the possibility that something outrageous might be true,

and we've got to consider the possibility that whether it's our treatment or other people's treatment, the report of improvement may simply be related to this change over time.

SPECIAL MASTER VOWELL: My question was a little different than that, but let me follow up on that.

When we're looking at something like Lennox-Gastaut, we're looking at a discernible event, a seizure. In most cases you can tell whether someone is having a seizure or not, particularly in that syndrome, correct?

THE WITNESS: Yes, Special Master.

SPECIAL MASTER VOWELL: It's not the type of seizure you need to put them on an EEG in order to see it.

THE WITNESS: That's correct.

SPECIAL MASTER VOWELL: And we have a placebo effect there.

THE WITNESS: We seem to. Again, whether it's things going in the opposite direction or things are just getting better for that child, which is the likely explanation.

SPECIAL MASTER VOWELL: And when you are dealing with more subtle behavioral concerns, then you

introduce an element of possible reporting bias.

THE WITNESS: It makes it very troublesome. There is some reporting bias problem likely when we're doing those seizure studies and somebody's hopeful for an improvement and the counting of seizures may not be quite so diligent. We don't know that to be true, but we do see this in terms of treating behavior for children with early childhood behavior disorders, attention deficit and so forth. We seem to see more positive reports when the teacher's aware of the treatment as compared to not being aware of the treatment. Everybody wants them to get better.

SPECIAL MASTER VOWELL: Let me go back to my earlier question then. What I heard you say in the Hazlehurst trial was something to do with switching from one part of the brain to another at various types of -- In other words when we're born our brain is functioning at a very primitive level. Other parts of our brain come on-line as we grow. That I think is illustrated by your slide that took the brain from birth to --

THE WITNESS: Exactly.

SPECIAL MASTER VOWELL: So is that considered one of the explanations for loss of skills or regression?

THE WITNESS: It is. The idea that, and that was the point I was attempting to make. We have these ensuing signals that over time turn on or turn off a particular gene. For that matter, that responsible turn-on other sorts of things. It happens, such as activation of cells that are formed in the elaboration or elimination of arborization or connections of various sorts.

So these things, some of the most striking observations have to do with this issue of brain growth at different intervals and why in the world that's taking place.

I mentioned that with regard to autism in the first year of life. Wonderful studies that were done quite a few years ago showed that with early adolescence brain size increases rather dramatically within what space is available in the skull at 13, 14, 15 years of age, followed by a stage during which that then goes away. This is likely, all the developmental changes that mark adolescence, the good and the bad of it, and things get reorganized and arranged. It may take some kids longer than others, but things come back on-line with regard to different kinds of control and so forth, and people discover what they want to do in the mean time, so that goes way back to studies at

the NIH that Charlie Kennedy did back in the '70s.

SPECIAL MASTER VOWELL: Does this switching have to have an external trigger? Can the trigger be in the gene itself?

Obviously in adolescents you have some triggers, hormonal changes that may influence that or may not. But I'm looking at, thinking of Huntington's where there does not appear to be an external trigger. It appears to be an internal trigger.

THE WITNESS: That's a very correct observation.

Things such as hormones can play a particularly important role. So hormonal changes for women in the second decade, aspects of immune function, brain function and vulnerability may change with regard to the endocrine axis changes and do change in favor of having the ability to have children. This is a change in both the immune system and endocrine system.

AS to whether external things modify these things, this is very tantalizing for people to understand. We know that with regard to the visual system, visual stimuli in training the system. It not only can train it but it can change the way it functions based on visual changes.

So if somebody puts on glasses that invert their vision and keep them on, the system will turn it back over again, so something happens to modify and we don't understand it. It's been known for a long time.

Functions that are apropos of the particular developing system likely can make a big difference. We know this with regard to music so children that have musical experience to a considerable degree before eight or nine years of age, have enlargement of the plana temprali on the non-dominant side, which is the enlargement that accounts for perfect pitch, which is a mixture of probably both of genes and experience.

So some kinds of things can do this, but it's probably not every environmental stimulus.

SPECIAL MASTER VOWELL: And I have one final question. You talked about several treatments for autism that are touted on the internet or other places that you do not consider effective. You consider there is no evidence for them to be effective.

THE WITNESS: Yes, Special Master.

SPECIAL MASTER VOWELL: You did not address one that we've heard a great deal about and that's the gluten-free, casein-free diet.

THE WITNESS: Yes. It's been around for quite a while. This is related to the recurring issue

of leaky gut, and called various things over time. The concept largely dismissed by specialists in the area, but the gluten-free diet is tried for these things.

We know a little bit about gluten as causing neurological problems very rarely, and we know that there are occasional individuals that develop unsteadiness because of gluten. And we know there are some people with migraines who have a worsening migraine with gluten. But with a gluten-free diet in those individuals, we've tried it. We never see the headaches going away entirely and we don't know whether the modest improvement that takes place is pharmacological or psychological. But we do know that in certain individuals we can see some unsteadiness.

Still there are people that might argue we don't know this for absolute certainty with regard to gluten and ataxia, and they'd be right. We don't know for absolutely certain.

SPECIAL MASTER VOWELL: It sounds like you're not rejecting that one out of hand as having some impact on neurological improvement.

THE WITNESS: My own experience has been that we don't see any benefit in the cases that come to me, which has never included one of those cases

where ataxia seems to result from --

SPECIAL MASTER VOWELL: I think that's all my questions. Thank you very much, Dr. Rust.

THE WITNESS: Thank you very much, Special Master.

MR. POWERS: I did have a follow-up.

SPECIAL MASTER VOWELL: I think we've got some more questions.

MR. POWERS: I'm sorry.

SPECIAL MASTER VOWELL: I'm not the only one with questions this time.

SPECIAL MASTER HASTINGS: I just have a couple. One was a follow-up on your description, I think you called it a sine curve, the curve in response to Special Master Vowel's questions, you mentioned that that's the way life goes in general.

Did you also say earlier that that applies to the symptomology of autism? That there are natural fluctuations. Was that the implication of what you were saying?

THE WITNESS: I raised the analogy with regard to treatments and whether they're effective, but I think as with all people, individuals that have autistic features, have things that go up and down over time. This can be a very difficult problem,

especially in the second decade of life with regard to how we treat things. Adolescents, on top of other things, seems to make some management problems so very difficult. And because we still have a great deal to learn about what's going on at that point without coming to some really glib conclusion about why these things happen.

But it seems to me that they do go up and down. So we're especially helped by the fact that the mothers, typically the mothers of these individuals, become so very good at sorting things out, and very observant. So often as with many difficult problems, the fathers end up leaving.

We try to map these things out over an interval so we can see between the mother and myself, if we're really making a difference, if we're making things worse, and see where we get.

Sometimes we need to bring the young man into the monitoring unit to see whether we can identify something electrical or something else that might be causing problems. And in that way we've come to have some better understanding of certain things that happen.

SPECIAL MASTER HASTINGS: The other question, I want you to clarify for me, in Slide 56

and probably a couple of other slides in that same range, you used the term "classic autism". Tell me what you, how you define "classic autism".

THE WITNESS: Typically we define classic autism as a child that manifests the disease from early on, and typically in isolation from a particular identifiable cause. Those are the children that we tend to call classic. They've been called that because they have so many features that satisfy the diagnostic criteria. And because they haven't experienced an obvious regression.

The difficulty with those children, since we're identifying them very early on, is it may be more difficult to identify something regressive in the first year of life, although I don't think it's that difficult usually.

SPECIAL MASTER HASTINGS: Let me interrupt you because I think you answered the question. You're making a distinction there between classic versus regressive. Someone that didn't regress.

THE WITNESS: Yes, Special Master.

SPECIAL MASTER HASTINGS: Are those both subsets of autistic disorder? The narrow category?

THE WITNESS: Yes, sir. That's how they used.

SPECIAL MASTER HASTINGS: Thanks. That's all the questions I have.

THE WITNESS: Thank you, Special Master.

SPECIAL MASTER CAMPBELL-SMITH: I think my range of questions has been touched upon.

Thank you, Dr. Rust.

THE WITNESS: Thank you, Special Master.

SPECIAL MASTER CAMPBELL-SMITH: Mr. Powers?

RECROSS-EXAMINATION

BY MR. POWERS:

Q Just a couple of quick questions, Doctor, to follow up on what Special Master Vowell was asking about with triggers. The finely tuned sequence of genetic on and off switches that are going on.

In that finely tuned orchestration of genetic signals, is it possible for environmental factors to interfere first with the activation of the gene's message itself? Is that possible? Can an external factor switch off a gene that was going to switch on, or switch on a gene that was going to switch off at a particular time? Can that happen?

A This is the sort of theory that's raised with regard to rubella embryopathy.

Q Can it happen?

A It's possible. And the same thing with

regard to cerebellar abnormalities in premature children, also prenatally.

Q An extension of that question would be assuming the genetic signal goes at the right time, whether it's an on signal or an off signal, there's going to be something physical in the body reacting to that. Neurons migrating, for example.

Assuming the genetic signal gets sent, can an environmental factor intervene to prevent the genetic signal from being effectuated physiologically?

A I don't know of a particular example, especially after birth. It's possible, I reckon,but usually those kinds of interferences, when we understand them, have to do with some post-transcriptional modification that also seems to be explained by the working out of a genetic code.

Q And its potential effect on any symptoms would depend on the timing, I assume. So that if there was a signal that was going to turn an event in the brain on or off at a particular time, if there was an environmental effect that interfered with that, the symptoms might be different depending on when that happened.

A I think that is possibly correct.

MR. POWERS: No further questions.

SPECIAL MASTER CAMPBELL-SMITH: Thank you.

Any further questions from Respondent?

MS. ESPOSITO: No, thank you.

SPECIAL MASTER CAMPBELL-SMITH: any further questions?

I think that concludes, Dr. Rust, you may be excused. That concludes our proceedings for today.

(Witness excused).

SPECIAL MASTER CAMPBELL-SMITH: Mr. Matanoski, are we schedule for tomorrow to hear from two witnesses?

MR. MATANOSKI: Yes, ma'am, we are.

SPECIAL MASTER CAMPBELL-SMITH: And we're on a schedule to commence again at, returning to our 9:00 a.m. time?

MR. MATANOSKI: Yes, ma'am, we are.

MR. POWERS: A quick question. I don't know if the doctor would be included in the first question.

One, the reference in the slides to one of his articles, a 1991 article? I've looked at his report, I can't see it cited. And we looked through the Respondent's exhibit list and don't see any article with Dr. Rust as the lead author cited.

So we would just request that the relevant article that's addressed in the slides be filed and

give us a chance to take a look at it.

Also, we conferred about his yesterday or the day before, we requested that Professor Rutter's books that are cited in his report substantively be produced so that we can review those in preparation for his cross-examination. We haven't seen the books yet. We just wanted to see when we would expect to see those presented for our preparation for his cross-examination.

MR. MATANOSKI: As to the former issue, we'll be happy to get Dr. Rust's article. The reason why it wasn't submitted was that it was responding to the late-developed theory here.

Now with respect to books mentioned in Dr. Rutter's report, we're trying to track those down. To the extent we do obtain them we will be providing them. Of course we received notice of this matter over the weekend, and that's made it a little, as opposed to at the time the reference list was provided. Those were textbooks or books, and rather than trying to reproduce entire books we were, I guess one would figure, just as with Dr. Greenland's Modern Epidemiology, we didn't expect that to be produced by the Petitioners.

But we are trying to obtain them. However,

there are many, and we don't have all of them unfortunately.

SPECIAL MASTER VOWELL: All right then. Since I'll be presiding tomorrow, may I inquire as to how long -- We're not going to have another short day I hope tomorrow.

MR. MATANOSKI: No, ma'am. I don't believe so.

SPECIAL MASTER VOWELL: All right.

MR. MATANOSKI: Thank you.

SPECIAL MASTER CAMPBELL-SMITH: Anything else?

We are adjourned.

(Whereupon, at 5:25 p.m., the hearing in the above-entitled matter was recessed, to reconvene at 9:00 a.m. on Thursday, May 22, 2008.)

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REPORTER'S CERTIFICATE

DOCKET NO.: 03-584V; 03-215V

CASE TITLE: In Re: Claims for Vaccine Injuries Resulting in Autism Spectrum Disorder or a Similar Neurodevelopmental Disorder

HEARING DATE: May 21, 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 21, 2008

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