UNITED STATES
COURT OF FEDERAL CLAIMS

HAZLEHURST,	)	
	)	
Petitioner,	)	
	)	
v.	)	Docket No. 03-654V
	)	
SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
	)	
	)	
Respondent.	)	

REVISED AND CORRECTED COPY

Pages: 442 through 554

Place: Charlotte, North Carolina

Date: October 17, 2007

HERITAGE REPORTING CORPORATION
Official Reporters
1220 L Street, N.W., Suite 600
Washington, D.C. 20005-4018
(202) 628-4888
hrc@concentric.net

IN THE UNITED STATES COURT OF FEDERAL CLAIMS

HAZLEHURST,	)	
	)	
Petitioner,	)	
	)	
v.	)	Docket No. 03-654V
	)	
SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
	)	
	)	
Respondent.	)	

Courtroom 6330
North Carolina Superior Court
832 East Fourth Street
Charlotte, North Carolina

Wednesday,
October 17, 2007

The parties met, pursuant to notice of the Court, at 9:00 a.m.

BEFORE: HONORABLE PATRICIA CAMPBELL-SMITH
Special Master

APPEARANCES:

For the Petitioner:

CURTIS WEBB, Esquire
Webb, Webb and Guerry
155 Second Avenue North
Twin Falls, Idaho 83303
(208) 734-1616

For the Respondent:

VINCENT MATANOSKI, Esquire
LYNN RICCIARDELLA, Esquire
LINDA S. RENZI, Esquire
U.S. Department of Justice
Civil Division, Torts Branch
P.O. Box 146, Ben Franklin Station
Washington, D.C. 20044
(202) 616-4356, 4133

C O N T E N T S

P R O C E E D I N G S

(9:00 a.m.)

THE COURT: We are back on the record in the matter of Hazlehurst v. Secretary of the Department of Health and Human Services, Case No. 03-654V. Respondent to present your case, would you call your first witness, please?

MS. RENZI: We'd like to call Dr. Robert Rust.

THE COURT: Dr. Rust, I think you'll find some water there. You can help yourself, and then we'll administer the oath.

DR. RUST: Thank you, Judge. Should I stand for the oath?

THE COURT: You don't have to, but be on notice that the chair does not move.

DR. RUST: Okay.

THE COURT: Would you care to raise your right hand, please?

Whereupon,

ROBERT RUST, M.D.

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

THE COURT: Thank you.

//

DIRECT EXAMINATION

BY MS. RENZI:

Q Good morning, Dr. Rust.

A Good morning. Wrong one?

Q Yes.

A Good morning.

MR. WEBB: Excuse me. Might I just ask one thing before we begin? Both Mr. Hazlehurst, Sr. and I had a little trouble hearing the questions.

MS. RENZI: Okay.

MR. WEBB: If you could remember to keep your voice up to the extent you can remember?

MS. RENZI: Thank you. I will.

BY MS. RENZI:

Q Could you please state your name for the record?

A Dr. Robert Rust.

Q And what is your current position?

A I'm the Director of Child Neurology and Director of the Child Neurology Training Programs, Co-Director of the Epilepsy and Child Neurology Clinic at the University of Virginia.

Q Dr. Rust, you were present for the testimony yesterday of Dr. Corbier, is that correct?

A Yes, I was.

Q Is there any credible evidence that the MMR vaccine causes autism?

A No, ma'am.

Q This hypothesis has been well-studied, hasn't it?

A Yes, ma'am, it has.

Q And could you please tell us about the studies that are out there that discuss the MMR vaccine?

A There are a number of studies of varying quality that have tried to make a correlation between various factors that can include relationship to the time of vaccination. Really most of the evidence involves that, but that sort of evidence needs to be placed within the context of epidemiological studies, and the epidemiological studies have not supported that association.

Q Is there any credible evidence in peer-reviewed medical literature that MMR vaccine can cause autism?

A No, ma'am, not to my knowledge.

Q Is there any credible evidence that thimerosal-containing vaccines can cause autism?

A No, ma'am, not to my knowledge.

Q What is the basis for your opinion on that?

A The same information, the lack of any kind of epidemiological correlation. There's the additional fact that especially in consideration of thimerosal, that --

What one needs of course in support of such a hypothesis is a reasonable biological explanation. And there is no such reasonable biological explanation, and there have been considerable studies concerning mercury and its toxicity to brain, and they haven't supported that contention either.

Q Doctor, I'd like to go over your CV, which was filed as Respondent's Exhibit F. Could you briefly describe your educational background, starting with your undergraduate degree?

A Undergraduate education was at four separate universities. After completion of that, I did graduate school at the University of Virginia. This was graduate work in history, history of science and biology, in particular immunology and that was followed by several years of teaching in Europe, then several years of immunological research at the University of Virginia. That was followed by medical school at the University of Virginia, finishing up in 1981.

I then trained first in pediatrics at Yale

and then in child neurology and neurochemistry at Washington University in St. Louis. I did as well a

fellowship in neonatal neurology. On completion of that work, I remained on the faculty at Washington University before taking a position at the University of Wisconsin where I was the Program Director and Training Director in Child Neurology and Director of the Cerebral Palsy clinic.

That was followed by appointment at Boston Children's Hospital where I was again Training Director in Child Neurology, Director of the outpatient clinics among the three Co-Directors of our Intensive Care Service and other physicians during that tenure. I returned to the University of Virginia as Professor of Epileptology and Neurology holding the royal chair in those disciplines as Director of Child Neurology as I mentioned and the training program as well as their outpatient clinics.

Q And what board certifications do you hold?

A I'm board-certified in pediatrics and neurology with special qualifications in child neurology.

Q Could you please describe some of the honors and awards you have recently received or in the recent past?

A Not usually the kind of thing I say too much about. What would you like to know?

Q Just maybe a few in the last couple of years?

A Well, over the years I've had quite a few teaching awards. I have had recognition for my research in terms of fellowships and support for research programs, numerous visiting professorships and just last Saturday received the Hauer Award (phonetic) of the Child Neurology Society.

Q And what is that award? What is that in recognition of?

A It's meant to recognize the person who has made the most distinguished contributions to child neurology. It's a yearly award, and somebody is selected each year, and this was my year for it.

Q Congratulations, Doctor.

A Thank you so much.

Q Do you serve on editorial boards?

A Yes, I've served on quite a few of them. There are I think six or seven of them or something like that.

Q Could you name a couple?

A Journal of Child Neurology, Pediatric Neurology and a number of other things over the years.

Q And are you a reviewer for any scientific journals?

A I've provided reviews for I think some 20 or

22 different journals over the years.

Q Could you just name two or three of the journals that you would serve as a reviewer for?

A Acta Scandinavia Neurologicaca, Lancet Neurology, and all of the North American child neurology journals, the Journal of Neurology, Annals of Neurology, those sorts of things.

Q You've also published approximately 100 peer-reviewed articles, is that correct?

A About 50 peer-reviewed articles and about 50 chapters. That's right.

Q Could you describe your responsibilities at the University of Virginia?

A Well, I'm responsible for making sure the child neurology program functions properly and that we have everybody where they're supposed to be on time and so forth. It's our belief and some others, but for the training of our child neurology candidates, for the child neurological training of our adult neurology trainees, for the neurological training of our pediatricians, for the neurological training of our medical students at all four years of their training. I make contributions to that.

I'm responsible for our outreach clinics in child neurology in Virginia of which we have four.

I'm responsible for my own activities as a researcher and some other things I guess.

Q So you have a clinical practice in which you see patients?

A I have a very busy clinical practice and have had throughout my career.

Q How many children over the years have you treated with the diagnosis of autism?

A I must say I've not counted. They've been seen of course in two capacities: One as the person overseeing the training of child neurologists or neurologists or pediatricians, and one as a person seeing patients in the ward service as well as my own private clinic. I would suspect several hundred patients at least.

Q And do you diagnose children with autism?

A It has become a very common experience to do that, yes.

Q Why do you believe it's become such a common experience?

A It's quite clear to me based on my own career that we've become more sensitive to what it is that causes somebody to have that diagnosis, that in the past we may have assigned other diagnoses to patients, especially mental retardation, static

encephalopathy, an injury to the brain, and now we know a great deal more about how to sort these things out.

For me, over the last 15 years it's been a considerable interest to make a contribution to understanding the manifestations of children that have autism. One must dig for the diagnosis, ask particular questions, and it generates particular phenotypes or particular appearances that young men particularly but some young women as well have, which is consistent with the diagnosis of autism in several forms.

Q Have you ever reviewed videos to diagnose or determine when the onset of autism is?

A Quite a large number. That's one of the most helpful things for us. We typically make the diagnosis by observation of the child in the clinic, but in order to get some better understanding of the natural history of autism, we find that videos can be very helpful.

We're also called upon to view videos of individuals who haven't yet come to the clinic or individuals that won't be coming to the clinic because we're consulted by parents, who are entertaining the possibility of adopting a child from overseas and were

meant to try to provide them with the best information they can about the neurological health of that child.

Q In addition to the testimony of Dr. Corbier, which you heard yesterday, what else have you reviewed in preparation for your testimony today?

A Well, I'm pretty widely connected with the literature on this subject, but it's a literature that grows very rapidly and I've provided I think several lists of papers that are pertinent and was asked to pick 10 in particular, which I did, and so that's I think been provided to everybody.

Q Have you reviewed the medical records?

A Yes, I have in detail.

Q The videotapes?

A Yes, ma'am. There are many videotapes, and I've reviewed them.

Q And you've read the report of Dr. Corbier?

A Yes, ma'am, and responded to it.

Q And you responded to that in an expert report that we filed as Respondent's Exhibit E. Dr. Rust, Petitioners have put forward a hypothesis that thimerosal-containing vaccines cause autism. What is your number one reason that that hypothesis will be proven wrong?

A That we're coming to some considerable

understanding of actually what happens in autism and why this terrible illness develops in children. This has been the progress of the decade of the brain and the very excellent work of a number of developmental neuroscientists. So we're understanding this and other disorders with regard to problems in the working out of a genetic code for the development of the brain.

THE COURT: Pardon me. I'm concentrating very carefully here, and I'm having a little difficulty hearing, and I'm getting a note that there are others in the back who have indicate they're having trouble hearing. We all want to make sure we hear what's being said.

THE WITNESS: I'll try to speak up a little bit more.

THE COURT: Thank you. Is that better, Madam reporter? Okay.

THE WITNESS: Sometimes I'm told I speak too fast, so feel free to slow me down.

THE COURT: Okay.

MS. RENZI: Dr. Rust, I'm just going to back up for a second. You've prepared some slides for today, and I apologize, Special Master, we do not have photocopies of these slides for you. We will provide

them for you tomorrow, if that's okay.

THE COURT: Okay. There are copies for everybody to be provided?

MS. RENZI: We will have copies for everybody tomorrow and file them as an exhibit.

THE COURT: Okay.

BY MS. RENZI:

Q We still don't have a screen, but we will put these slides up on the wall, and if you could just go through a few of them?

THE COURT: I'm just going to ask that as you refer to this, particularly because we don't have the actual copies, you would make reference to the slide number with your comments as well, please?

BY MS. RENZI:

Q And we have slide no. 1, which is autism pathophysiology. Could you explain what pathophysiology is?

A Physiology is the way in which organ systems function in the body, and pathophysiology is a way in which their function is abnormal. It's pertinent to particular diseases, and so we like to be able to sort out how the manifestations that we see in a particular disease are explained by an adequate and sufficiently detailed pathophysiological understanding.

Q And if you could go through the points that you have on your slide, please?

A Well, what we do know about autism of course is it's highly age dependent with regard to its manifestations. It's a collection of clinical entities, some of which have already been explained on the basis of particular single genes, but others that likely involve as well the epigenetic effects of other aspects, especially the sex of a person and some aspects of pregnancy in some instances.

We feel that autism is likely the result of a number of different genetic problems. Not all those genes represented in every individual, not all those abnormal genes, but these may provide some subtle differences between patients and certainly provide differences that are not subtle, and that's the time of onset of disease, which is likely the result of a combination of influences.

We know for example that there are patients that have manifestations of autism at birth, and they must very carefully be sorted out in those patients from other entities, from static encephalopathy, which simply means a patient who has had an insult at one time in their development. It's not going to come again, but it leaves its own often tragic footprint on

the

patient.

It takes some time during the first few months of life to sort that out, and as the child acquires additional skills, and as their nervous system develops, we can see what does or doesn't develop in the way in which the program development of brain and nervous system should take place. We see another interval then after birth at about two and a half or three months when a good deal more in the way of cortical activity of the brain comes on.

At that point, we can see more about a child's activity and interests in response to surroundings, many of which things are again built into the genetic code of the child. It's a curious thing that in fact the cortical aspects of brain function are really not online to a considerable extent, or one might say hardly at all online when a child is born even at full term.

So, if we see a baby that's had a stroke involving both hemispheres where virtually all of the neocortex, virtually all of what we call the forebrain, and this is all the parts of the brain that represent the human potentials that we all cherish for our children and for ourselves. Nonetheless, a child born without some two-thirds of the brain oftentimes

appears perfectly normal to examination.

It's only when at two and a half or three months those cortical centers are meant to take the place of deeper centers in the brain, and not only meant to take the place, but have no choice but to do so, and the centers that are deeper go offline. That's the point at which we see abnormalities. It's often hard to convince parents and grandparents that their child has such an injury because of that, but then we see that at two and a half or three or four months.

Obviously, a child is called on to do more things, interact with their surroundings during the second half of the first year of life, and that's a period during which we can see additional changes. Many children to which we give the diagnosis autism have that diagnosis during that first year of life, and these are the babies that can fit into several categories of congenital autism. During the second -- am I speaking loud enough?

Q I think so. Okay

A During the second year of life, we see another large and strikingly homogeneous population of patients, of children with autism, and this is the category that is either a degenerative or acquired

form of autism, a

regressive form. It goes under various names, and very typically we see that progression some time between 12 or 14 and 26 or 27 months. As we look back at those children in terms of gathering additional history, we find that they've already had manifestations of the illness.

In most instances, the distinction between the congenital and the regressive form is in a sense artificial because children typically don't have normal language development, typically don't have normal interaction with their surroundings, even if they fit into this acquired form. There are however a great many patients that do have a perfectly normal history so far as we can determine, and then a sudden deterioration.

So, it seems that that's a point at which additional genetic signals have come on board that are meant to take the place of preceding signals. The cortex of the brain and the -- what we call a fiber pathway, so the cortex consists of the thinking cells, and their supportive cells, the neurons and the astroglial cells and other kinds of cells that function together in a very complex way and talk to each other with various pathways.

They talk to themselves in the cortical

layers in which they find themselves. All of these cells have to migrate from deep in the brain to form the cortex, which is the outer part of the brain so this is as if you have a coating on the brain in which all these cells finally find themselves and talk to one another with an exceedingly complex system of fiber pathways or connections that we call axons and dendrites.

They also talk to the layers beneath and talk to the other areas in the cortex so the cortex is subspecialized. It's a remarkable miracle that these cells arrive where they need to be in most individuals and function in a way that's distinct, one area from another, to do all the things that we can do. This not only involves single areas, but connections between areas that's exceedingly complicated and coming to be far more well understood than it was even five years ago.

Then the two sides of the brain have to talk to one another, which they do through large fiber pathways from one side to the other, so we know of neurological syndromes where the disconnection between the two sides of the brain accounts for problems. We know of those where the communication between one or another subarea of brain is interfered with, and we

know of those where the organization of activity even

in the tiny small area where initially the neurologic task is undertaken in those small areas.

Things can go wrong with communication as well. The understanding of this is proceeding at a remarkable pace with what we need to have in the way of science. We need to have first a hypothesis that makes sense biologically and neurologically, and then we need to have the observations of one group and then another group validating the first group.

Then additional points made as we go back to the patient, or if we go to an experimental model to prove that these things in fact can be replicated in either circumstance. We usually observe things we hadn't observed before because of what we've learned and then make an understanding of the particular syndromes far more complicated, far more sophisticated and in fact in the long run far more simplified in that we can fit so many things together.

That is the period that's pertinent to this particular case, but there are other intervals. In little girls with Rett syndrome, they have an additional period of deterioration at five or six years of age. In children with autism, there's an additional period of deterioration in the teenage years and so forth that are at various other

stages, so the general concept I hope I've made reasonably understandable.

Influenced not only by genes but by epigenetic influences. These can include environmental influences, usually deprivation being the most important one where children don't get sensory input, sensory experience. The sex of the child is very important in several different ways. The sex of the parents may be important in the newly understood system of parental imprinting for diseases.

So a disease that has some autistic manifestations, Angelman's syndrome is one where the effect of one parent's genetic contribution may influence the outcome. The syndromes are highly consistent and readily recognizable. We need only watch the child for a few minutes typically to come to some conclusion about whether that child has autism in the second year of life or the first year of life.

Rett syndrome is the same thing, and the clinical differences between these are often striking as well, particular ways of dealing with the environment.

Q Doctor, if I could just interrupt? What is epigenetics?

A Epigenetics are those influences that play a

role in the working out of what the genes are trying

to do, and it can as I mentioned be deprivation. It can be a negative influence of something in the environment. That can be during the pregnancy in particular with reference to autism, it's a time during which infections may play a role, and rubella is the classic one.

Now, a child with rubella encephalopathy has striking autistic manifestations, but those children differ from other individuals with autism in that they have other abnormalities, other areas that are afflicted by the infection and so they can be set apart from other kinds of autistic syndromes. The sex of the child or the maternal hormones may also play a role. These are things we're coming to understand better, but this is an area that one might call a work in progress.

Q And when you say environmental influences, do you mean things such as the introduction of toxins?

A Yes. It's possible that toxins may play a role in injuring the developing nervous system, and there are quite a few examples of this. Again, they usually have a particular syndrome with appearance, so with reference to mercury, for example, and I'll say something more about this, there's a particular appearance of the children that are injured by

intrauterine mercury.

Unfortunately, because of blood flow to baby and other kinetic considerations, and by that I mean other ways in which substances move from one area to another and cross various membranes and become concentrated there. If a mother has a considerable amount of mercury in her system, that mercury actually gets concentrated in her fetus resulting in mother having less of a mercury burden and the child having more.

Tragically, when that happens, we do see children that are severely afflicted with manifestations that only superficially resemble autism. In fact, the children have what we call a static encephalopathy with neurological problems and things very different from those in autism that interfere with their communication with their surroundings.

Q Can autism be caused by a toxic insult?

A You can produce again a child's interference with surroundings that may appear like autism, but we don't have in fact a good example of a toxin that produces something that is the same as the syndrome of regressive childhood autism. I'm not aware of a toxin that produces the phenotype that we in fact see.

Q What are the core features in autism that

you would not see in a brain injury that is caused by trauma or toxic insult?

A It's a very complex thing autism in children. The regressive form has its own set of peculiarities that I mentioned are so characteristic from child to child. Children don't have all of them necessarily, but they have very many of them, and these represent probably the preservation to some extent of skills that come online very early for the child and are not replaced by skills that are at the higher level.

So with many children, who have regressive autism or high-functioning autism or other types of autism, we see things that we have described as splitter skills. We may have a child that has little or no language or at least little language who then has an astonishing capacity to deal with numbers or to know a great many words in lists. It's likely that that capacity to gain knowledge about lists of things is a way in which we initially learn our language.

Ninety-five percent of children acquire nouns predominantly, lists and lists of nouns that they can use to name things. And we see in autism some individuals that -- I had a patient who knew every name in the phone book this big. If I asked him

the phone number for any patient in that book, he

would immediately give it to me very rapidly in a strange way, so there's a strangeness that accompanies these kinds of skills and probably because we learned certain kinds of social skills and things as time goes on.

And probably part of this is genetically determined and part is experiential. He would give those things to me very rapidly. The idea that because of his capacity to memorize, he might find useful employment was one that we explored, and it did not work out as it often doesn't because of the very complex aspects of the strangeness, I guess you might say, associated with autism.

Of course, we say strangeness because we're different from the children with autism, and perhaps if they were the dominant group of people, they would think us strange. But nonetheless it does appear strange, and the quality of strange is the way in which we help to make the diagnosis. Parents, if you ask them does the child do something strange, and they'll give you a list of such things, they're often the same list.

The parents are often gratified by the opportunity of trying to explain these things. They're often taken to task by other parents or

cousins or aunts or something else or people in the supermarket when their child is having difficulties in that setting and told why don't you discipline your child more properly or something like that. I provide my parents with a little card that says you don't have any idea what I'm dealing with here, so please shut up.

It's important for the parents to have that kind of support I think with my signature on it. The long list includes odd things. Children that cover their ears when the vacuum sweeper is turned on, so sensitivity to loud noises. This sets most autistic children apart from those with deafness, who go and hug the vacuum sweeper because they're actually hearing a sound and gratified by that.

There are peculiarities about eating. Foods are allowed to go to room temperature rather than being hot or cold. Oftentimes, it's fright related to people wearing masks to people wearing hats. There are other kinds of things, and it's a long list, and it's not always gathered on every patient, but it does help to demonstrate both the fact that this is likely almost entirely genetically determined because we have things that are so true from patient to patient.

That's the way in which we can understand

those things. Toxic influences or injuries or infections produce a wide variety of changes typically, and that's not what we see in regressive autism. Does that answer your question? I apologize for the lengthy answer.

Q I believe it does, but what wouldn't you see in a toxic injury that you would see in autism? For instance, in this case we know from the videotapes and from the testimony on Monday that you weren't here that Yates knew his alphabet and his numbers, but had no expressive language.

A Well, one must be cautious about --

THE COURT: Pardon me. I think what might be helpful is if Dr. Rust would address the phenotype first and then distinguish it. It might actually be more helpful if he would address the regressive phenotype first.

THE WITNESS: That seems right to me as well. I think that's the best way to do it.

THE COURT: Okay.

BY MS. RENZI:

Q Is there another slide that we should --

A Yes. There are several.

Q Okay.

A Perhaps if I could go through the slides and

then add what needs to be added?

Q That would be fine.

A Thank you. The second one, the features of classic or regressive autism. As I mentioned, the classic type are those children that were improperly characterized a long time ago by Bruno Bettelheim as being children that didn't respond to their surroundings because of mother not raising them properly, the so-called refrigerator mother.

It's an example of the many blind alleys and inappropriate and injurious ways in which the understanding of autism has worked its way out over the last 40 or 50 years, but Canner described these children, who from very early on, are not normally responsive to their surroundings. This is meant to be set apart from the regressive form, but as I mentioned, as we look back a videotapes of children that can be said to have suddenly regressed, we find features that are not typical for children in many.

I mention both of them at the same time because there is an overlap between these two things, but with the regressive type, you have the second phase of regression taking place, so the onset is typically before three years of age. It typically is between about 15 to 24 months, but the broader

interval would be something like 12 months to 28 months typically.

These children have severe verbal and nonverbal language impairment, and to speak with regard to the current situation, one must be careful again about making judgments based on videotapes rather than on -- I guess they're not videotapes, but CDs or whatever they are, rather than seeing the child and doing the kinds of things we do to confirm the diagnosis.

But, in viewing the videotapes in this instance, language development was abnormal prior to 12 months, at least based on what I saw in the videotapes. It may have been something that was not captured, but not only expressive language, but the kind of language we provide in the way of facial expression. This young man didn't have the typical array of facial expressiveness that one sees in normal children at 12 months.

Based on the kinds of tasks the child is meant to do whether being with other people or whether being videotaped himself, his facial expression again was not normal. There were only a few smiles, and even at 13« months, the child was still using utterance such as mu mu mu, which is an utterance that

extinguishes typically at about seven or eight months in 75 percent of individuals as they replace that kind of utterance with other things with their first words, so we see that fairly frequently.

Then there's a very sudden, sometimes overnight, and sometimes over weeks, regression that children experience and where the child really changes remarkably and where parents tell us that it's not the same child that they had before. Likely, as I mentioned, this is because of replacement of more primitive systems of wiring with more sophisticated systems of wiring and some things going offline, but the pattern is fairly consistent.

And so, its language impairment, it's social impairment, restricted interests and repetitive behaviors. Those are the things that are part of this syndrome, the kinds of repetitive behaviors that we look for typically at the outset are limitations in play where a child may tap at a drum, for example, and seem not to be paying attention to it for an interval and then go off to do something else.

May use objects inappropriately, may pick up small toys and run them back and forth on the carpet, which is a quite typical behavior. A little bit later on, typically but sometimes quite early

flapping activities, spinning activities and so forth come on as well, so that's the syndrome that we're talking about here. If I can have the next one?

THE COURT: Thank you. Before we leave, the reference that you just made was to slide no. 2. To proceed.

THE WITNESS: Thank you, Special Master.

BY MS. RENZI:

Q Now, Doctor, we're on slide no. 3.

A As far as heritability is concerned, although again all the details aren't worked out, this is strikingly one of the most heritable severe neurological disorders that we're aware of. It may occur on the basis of quite a long list of genes at least being isolated. This is still something of a work in progress, but the concordance between identical twins is quite high and between siblings a reasonably high risk also for autism unfortunately.

So with fraternal twins or with siblings of a first child with autism, there's a risk of something between 10 and 27 percent for some kind of autistic syndrome. This needn't necessarily be classic or regressive autism. It may be other things that fit within this general framework, high-functioning autism being one of them. Probably certain kinds of OCD.

This, what we call the autistic spectrum, is not as well-defined or refined as we really need for it to be, and this is the reason that we go to such painstaking detail to get all the characteristics either prior to the child coming to us or when they come to us, so we have a list of some 40 things that we want to know about. The reason for this is we want to make sure that we're not jumping to conclusions.

A great deal of jumping to conclusions regarding behavior of humans has been made in medicine and science for a long time, and that includes the last 20 years, and so people do make long lists of those that are said to have this or that label in terms of their behavior, and this needs to be carefully worked out, but it does appear as if features such as anxiety, features such as restriction in interest and so forth are part of families with children with autism.

It's not known yet whether this is a combination of the genetic problems, whether it's what people call gene dose, meaning the amount of that gene that's expressed in the child because genes are turned on and off in the developmental process, and it may account for some things coming on earlier than others. The best evidence for this is related to Rett syndrome

where we now see a very wide set of diseases that go under that heading of Rett syndrome.

The point is that it's clear that there's a heritable aspect to this that this quite striking and supports the idea that the chief abnormality and the probably the abnormality is sine quo none, the thing that has to be there, is a genetic defect and other things are not necessary for it to express itself in that way. The risk of classic autism in siblings is 20 to 50 times higher than it is in the general population, and so as I mentioned it's a highly heritable condition. I can go on to the next one.

Q Now we're looking at Slide 4.

A So this is one example of a gene that's of great important because this, as with so many other genes, there are incredible numbers of genes that contribute to the making of our brains and our nervous system, and these genes account for the extraordinary things that we can do with our brains, and this is one of great importance. It codes for a protein that initiates some cascades of cellular development. There are plenty of other that do this and probably plenty of others that account for autism.

This one is particularly an interest to people now because of its contributions perhaps

to several different diseases or several different kinds of things in the body, so cascades of signaling take place where one gene turns on and another and another and signals and multiply themselves. You make material in the cell that moves to other parts of the cell, that talk to other parts of the cell, and with this you get cells that multiply and become more specific and more sophisticated themselves.

So there's replacement, for example, of neurons with other neurons and replacement of connections of neurons with each other, and this in fact continues through the first three decades of life, at least, and in fact some of this takes place in adults as well, so it's cells that multiply. They grow connections with other nerves, touch them and talk to each other.

This is becoming a more complex thing in science as time goes on. They differentiate over time. They may remove some of the connections and replace them with others, and this may have -- probably has something to do with environmental influences, so this becomes an epigenetic phenomenon as well. If you don't use a portion of the system, you may lose its function.

This is exemplified by a young lady in 1956,

who was seen at UCLA, whose parents had shut her in a closet for the first 11 years of her life with only a tiny crack of light showing, and the opening of the door to bring her food, and her visual system developed improperly. And she had manifestations that were suggestive of an autistic syndrome probably because the experience was necessary for the system to develop properly and therefore did not take its opportunities to develop.

So we have that kind of acquired epigenetic effect as well. The patients -- the young children that have the CC phenotype of this have a markedly increased risk for autism, so that's a question of gene dose. They got two copies of an abnormal gene and more autistic manifestations. The next one then.

Q Doctor, if I can just interrupt, could you define how you are using the term "environmental."

A Environmental refers to everything that a person experiences from the time of conception. It includes all those things that take place in the womb and thereafter, which do influence our development and do influence the way in which we function. Some of those influences are transient in the sense that if we have something bad happen and become depressed, we're generally able to snap out of it and move on to

something else.

With enough of those events, some people find it more difficult to recover, but there are some kinds of genetic influences as I mentioned with the little girl at UCLA that if again the opportunity for a system to come online. And what happens probably in the brain is the same thing that you or I do when you learn something. If you want to learn the piano, you can't learn it without sitting at the keyboard, we have to sit there and practice and learn things, and the nervous systems lays down tracks to do this.

So, if you learn to play a piece of music well, the system then takes it offline in the neocortex and places it online in the cerebellum in the back of the brain so that people that learn the song reasonably well find if they try to think about what they're doing instead of allowing the cerebellum to be on autopilot, they stop and can't play and have to go back somewhere and start over again.

So the pattern has been transferred to another part of the brain. This is what happens with all of the automatic tasks that we learn. If somebody practices the piano more and more and becomes a professional, the cortex comes back online so that people can in fact pay attention to what they're doing

because additional connections have been made, so experience and environment in those ways modifies what we do, and it's a very important thing.

That is one of few tools we have with children with autism where we're trying to make them as functional as possible to find the right way to approach the things that they know about and can do and make connections to other things. This idea has been around for 150 or more years. Madame Montessori put it best when she said our job is to find the little glowing embers and to blow on them and make them burn brighter, and that's what we try to do with children with autism.

We're trying to make connections in new areas so that they can function better.

Q So, Doctor, you're not using the word environmental in the same way Dr. Corbier was using environmental factors?

A I believe he used it in the setting of exposure to toxins or potentially toxic substances or things that potentially cause inflammation. That is part of the environment, but it's a very tiny part and not in fact pertinent to this particular set of diseases.

Q Thank you.

A The next one?

Q And we're looking at pathology of classic regressive autism, slide 5.

THE COURT: Thank you.

THE WITNESS: So the next step for the neurologist, once we've defined something clinically is to see where it is in the brain. We do this on examination by finding things that are wrong and knowing where they are in the brain and seeing whether they all seem to be in the same location. That's where we start. And for a very long time we then looked at the brain itself when the opportunity arises to see what we can find in the way of abnormalities.

And in fact, with autism, this opportunity is there, and very important pathological analyses have been performed on children with autism, most especially the work that Dr. Baumann started back in the late '80s with Dr. Adams and other in Boston and identified by making very thin sections through entire brains that the critical pathological change in autism is in a structure called the amygdala, which sits deep in the brain, and is a very, very complex organ that connects what we call the limbic system.

This is the part of our brain that has to do with fight and flight and strong emotions, sexual

activity, other kinds of things. It's the thing that motivates us. I suppose the most amygdaloid complex is now known to have something to do in fact with alertness, of great importance to know about that. It connects with the basal forebrain and with the forward parts of the brain, which as they mature provide us with ideas about what we ought to do and restraints on what we do.

It connects with the thinking portions of the cortex with slower connections with the thinking portions. This we think somehow explains that particular disease that we all run into whether for ourselves or others called adolescence during which these connections are just maturing and people are a little more impulsive and more likely to be swayed by emotion perhaps than later on. Older adults are not immune to that either, but the amygdala seems to be the critical place here.

Then selective changes in what the amygdala connects to, and this is an extraordinarily beautiful part of working out of the pathology of this condition because in the brain these exceedingly complex connections through five layers of neurons, one to another and to other portions of the same side and other side of the brain and brain stem into the body.

All of these things organize themselves into mini columns.

These are areas of columnar structure talking to each other in a particular portion of the brain and to other minicolumns laterally and to other parts of the brain. In looking at these minicolumns, there are particular areas. Autism is not a condition that can happen anywhere in the brain. It happens in very specific parts of the brain as I've said here, and this dysgenesis is found in brains of people with autism.

We see not only the column itself being abnormal and its connections being abnormal, but thickness of the cortex over it, it may be larger than it out to be, and then the thing that you wouldn't necessarily think to be true but is true is the abnormal tissue is actually thicker than it ought to be. When we cause injury to a tissue, we make it smaller because we cause cellular elements to be disrupted and killed.

In this instance, it's larger, and during brain development in the first year and a half of life, lots of areas of the brain become larger than they will be in time because they've got all those recruited neurons that are excited about doing

something and are not yet connected with each other, and once they do connect, some are eliminated, and so this enlargement becomes something that's smaller and more compact, very much like the way in which electronic devices have become smaller.

I reckon you can say that first they were huge and didn't do very much, and then they become smaller and more technical and do a great deal. These are very specific changes of dysgenesis that are found, and especially it involves connections that we call GABAergic. I apologize for all the technical terms, but there are no others to take their place, but what I can say about the GABAergic system is that this is a system that controls things.

It makes some things that we don't want to happen less likely to happen, and with these particular what we call synapses, connections taking place in the brain, this controls things like epilepsy and convulsions and abnormal electrical surges in the brain, so in a sense it's kind of like the way in which we control electrical systems with different insulation and other kinds of corrections.

This likely accounts for the very common problem in autism of abnormalities of EEG that we see in an overwhelming number of children with autism,

usually not associated with epilepsy until later on in life, and again that has to do with the working out over time of vulnerabilities to dysfunction. These changes are identified in specific areas of brain pathologically, especially its some frontal areas and in several portions of the temporal lobe.

I can show you a picture of those in a moment, but what we see in the brain itself is underneath the cortical margin, which is the outside of the brain, underneath it is an inner layer and an even more inner layer, and it's the inner layer that becomes too large and too thick and too unwieldy and doesn't do its job quite right, and the layer under that that tends to do its job appropriately, even though there are some problems that we can see when we look clinically at patients, so this volume increases.

This is a characteristic thing. It's characteristic of particular brain regions, so again the idea that autism can happen because of injury anywhere in the brain is quite wrong, and persons who would maintain their position perhaps don't look carefully at patients. I can't say. The inner bridging area, which is this inner area looks more normal, and again these changes are in specific areas of the brain.

If I could have the next one? I lost track of the number I'm afraid. I'm afraid I don't have a pointer. I perhaps should. Does anybody have a pointer? I could walk over there. Is that permitted in the courtroom?

THE COURT: We don't have a microphone.

THE WITNESS: I see. Well, let me try to describe it.

BY MS. RENZI:

Q And we're looking at slide no. 6, Doctor.

A Okay. You can see this brain, it looks like a cauliflower. This is what brains look like when you cut through them. It's been cut through in a coronal plane here, and as you can see as in every brain almost there are these areas in the middle that have a waterlike substance in them that's perfectly normal to have. We need to have that. On the outer side of this, you can see that grayish area. That's the cortex of the brain, and that's again where all of the thinking cells find themselves.

There's a slightly lighter subcortical layer, and throughout that cortex are all these layers that I talked about are very, very carefully arranged connections of neurons. Then as you see in the frons of this thing, you see something. It's a little

brighter white, these little fingers of white matter that go into the gray matter, and that's the outer white matter layer, and underneath that is the inner white matter layer.

It's that outer layer that represents the problem together with the cortex at least to autism with very specifically distributed abnormalities. There are other kinds of brain problems that can lead to difficulties in all these areas, but they don't look like this clinically, and they don't look like this pathologically. This is a specific entity. If I could have the next one?

Q And this is slide no. 7.

A Pathologically these are the cell losses that occur, and they're in highly selected areas in the brain, and these tend to be what we call evolutionarily advanced architecture of the brain, things that in our species and other species have learned over time that these happen perhaps by chance or by intent of some kind we don't understand, and as they develop, they get retained because they provide advantages.

These are the particular frontal associational areas that seem to be involved. These are the areas that are involved with recognition and

appreciation of certain kinds of things, recognition of faces being a very important one, retention of that memory of faces. This is also probably epigenetically determined as well, because women have a tendency to take -- it's quite striking when you study it carefully.

Normal women take inventories of what they see and retain that information in relationship to the environment. Men can walk into the same environment and not retain the slightest idea of what they've just seen. I don't think I need to convince you of that. There is a tendency on the other hand for even perfectly normal men to have restricted interests, and I don't think I need to convince you of that one either.

This has to do with the important male theory of brain with regard to autism and perhaps some aspect of the effects of testosterone and other things on brain development very early on and not later may have something to do with that. I mention again that these terms are big and fancy, but dysplastic meaning improperly formed, and axodendritic meaning the cell body of the neuron and its connections to other kinds of cells have either axons or dendrites.

Long connections we call axons and shorter

connections we call dendrites that cause the system to communicate. I want to point out very particularly that not only are these specific areas that I've mentioned here, and it's hard to remember these things, but these are the areas that make the amygdala, B1 frontal associational areas, superior frontal gyrus and other areas, but the areas don't matter insomuch as saying this is very particular.

It's not what you see if somebody has mercury or if somebody has arsenic or any other kind of toxin. It's not what you see after encephalitis. It's not what you see after acquired brain injury. This cannot be the way it is without having its basis in a developmental process. There's no other way in which this inducted change, things touching one another and having the first events take place. The only possible way in which this can take place is by the unraveling of genetic code.

You lose large perametal neurons, and I'll emphasize it's the large ones, the things that used to be called Bett cells and other kinds of things, but it's the very large ones, and you lose some small neurons in the limbic system, and that's the thing I told you about that has to do with emotions and connection with our surroundings in an emotional way.

You lose these GABA projections.

This is what I talked about in terms of something that exhibits some control over the system, so it may have something to do with outbursts that are seen in individuals with or without autism because they can't always exhibit the equanimity that's necessary. We must be very careful about this because individuals with autism are individuals.

They're people like everybody else and are subject to emotions like everybody else and must be subject to frustrations based on the limitations that's placed on communication and other kinds of things. We don't fully understand it, but we do see those kinds of outbursts, and very importantly a quite significant loss of what we call Purkinje cells, these are in the cerebellum, the back of the brain, the coordination part of the brain. It does other things.

It has to do with language and music and other kinds of things. It's a very important center, but those cells are lost specifically and very characteristically, so this is the pathology. Highly characteristic so that a person who cut through the brain in these serial sections could identify the disease on the basis of the pathology, not necessarily looking at the patient to come to that conclusion.

The next slide?

Q We're looking at slide no. 8.

A The results we can begin to sort out, and this is what we do in neurology. We try to gather information that makes sense and is proven. We put that together. Then to go back to the person with the disease and find out what they have that can be explained in that way, and in doing that, we try to find ways in which we can make things better. There are plenty of things we don't understand.

There are plenty of things we don't even know the pathology of, but these kinds of observations help us to find ways to treat individuals and maybe we'll come to the point at which the salvage of these pathways with genetic treatment might be undertaken, so reduction of functional boundaries in the minicolumns and reduced these association and integrative capacities.

So, that this I believe explains very convincingly the fact that an individual with autism may in a restricted area become very interested in that problem and acquire enormous facility with that particular thing. There's oftentimes a repetitiveness to that, and it's something we can take advantage of therapeutically.

Music being a very important preserved area in children with autism and adults with autism where we can use this as a calming effect and use this as something that a person enjoys and that something that a person gains greater sophistication with over time. It's a way of communicating. It's guerilla warfare in all of our patients, but this is a particular kind of guerilla warfare where we're trying to do something better.

But this is what's lost, the integrative part of it where things cannot be made to have the same response that perhaps that a person with this preserved architecture might have. So excitement, overplay and activity, losing interest in one and moving onto another in a systematic way are things we don't see in autism, and it's almost certainly the result of this loss of integrative capacity.

That doesn't mean there aren't other strengths, and one of our jobs as neurologists is finding the strengths of our patients as well as the deficits. Reduced higher level conceptual capacity is a characteristic of autism in patients with high-functioning autism. It's oftentimes the conceptual understanding of the other person. We don't fully understand the child with autism, and autistic

patients.

Patients with autism don't necessarily understand the social context as readily as we do, and so in patients with high-functioning autism, you may see patients that get very close to other people, in their face as we call it, not understanding that important boundary, who may not appreciate how another person is thinking about things, and this is a spectrum that falls into the normal population.

We've all observed people, who don't have other features of autism, but who just don't get it as far as the other person's point of view is concerned, and it may be that there -- and I think there's excellent psychological information to suggest this is more of a problem in men than in women looking at normal populations of men and women. But there's probably something that's right about people who jump to conclusions at the right time as compared to those who wait and think about it longer.

There's a reduced conceptualization as I mentioned. Abnormal sensitivity to certain stimuli, and this is so characteristic that we almost always have the report as I mentioned that a child would cover their ears at certain loud noises, that a child will have difficulty with certain kinds of sensory

stimulation, mixed textures that they're eating in foods.

They'll have other kinds of sensory experiences that others don't have, waving hands in front of the eyes, or even feeling the hands move. A child with autistic movements of the hands usually doesn't look at them, but has that and we don't understand why, but it's so characteristic. Then increased risk for seizures or for -- and outbursts of behavior, which come on very early in autism, unfortunately. The next one.

Q This is slide no. 9.

A This is the architecture we're talking about. It's quite beautiful and complex, and this doesn't even do justice to it with the overlying blood vessels that you see there feeding these regions of the brain and then these connections that are so extraordinarily elaborate between portions of the brain and that not only developed in the womb and the first year of life and the second year of life, but at least down to the third decade of life or even fourth decade in some, including some repair taking place into the 60s or 70s. The next one?

Q This is Slide 10.

A These are some of the areas. It doesn't

display very well, but we see a region with a circle around it that involves facial perception. I know that it's hard for me even as a neurologist to think that we can reduce human beings to electricity in connections, and I'm a strong believer in Wordsworth saying that man is greater than he knows, but we do know that certain things --

THE COURT: Pardon me, Dr. Rust. I'm sorry. Just so that we can orient to the slide, you're talking about the circle on the slide?

THE WITNESS: Yes.

THE COURT: This is slide 10 in Section A?

THE WITNESS: Yes. I'm sorry. That's right. In Section A and in Section B, and what you can see inside that circle again this is an area that's involved with face recognition. What can be measured here is perhaps a surge of connections that take place as recognizing a face causes us to think. The more work an area of the brain does, the more blood flow goes to that region, and you can see in a normal control individual on that side, you can see those yellow and red things inside the circle.

That's activation of this very particular area that's involved in autism. It's abnormal. It doesn't activate, and you can see with same face

recognition task, the individual with autism on the other side doesn't have that activation. And the same can be said of other areas, and these are represented in the green here, but they include two portions of what we call the temporal lobes.

If you look at the side of the brain here, this is the outside, just a drawing of the brain, the part that sticks down below there is called the temporal lobe. That has a lot to do with hearing and recognition of things we hear, and you can see two particular areas there that are characteristically involved in autism. You've got that inferior frontal gyrus that is one the same slide over on the far side, and you can see several other areas that are involved.

These all have names. These all have their very particular architecture. These particular areas are different than the area next to it. They have specified functions. These are the areas that are abnormal in autism, so it is a specific syndrome. There is no way in which a toxic event can produce this combination of changes. There's no way in which an inflammatory event so far as we currently understand can produce this combination of changes.

There is a tendency of certain kinds of infections or inflammations or toxins to go to certain

portions of the brain, and there is an increased vulnerability of certain portions of the brain. But this varies from individual to individual, so if you look at one brain and another brain and another brain, you'll see some similarities, but you won't see an overlap that's so dramatic as it is in autism. This overlap is seen in autistic individuals.

Those lower brains represent autistic activation, areas that don't activate properly. The next one? All right. So this is meant to be compared to something else, and autism or at least the injurious effects produced by organic mercury have come up here in this trial as they do elsewhere, and we do have pathology in that condition as well. I'd say at the outset the children who have been injured by large amounts of methyl mercury do not have autism.

They have a combination of findings that are consistent with what we call a static encephalopathy. It has its own characteristics. It's tragic when it occurs, blindness and abnormal hearing that deprive the child of sensory input that may produce to the casual observer or the untrained observer the appearance of autism, but it's far from the fact you see as well malformation of limbs.

You see injuries to brain, so the usual

thing is to injure the visual cortex and the auditory cortex vision and hearing. It usually spares the large neurons. The large neurons in the cortex are exactly those that go wrong in autism, and the small neurons are spared. These are the sensitive cells. They're the wrong ones for autism. It does not produce the same appearance clinically.

You also damage not the outer laminae, the outer portion of the brain, the outer white matter, but the inner white matter and the deeper cortical laminae. This is a different pattern from what's seen in autism. It's virtually the opposite, and you injure the cerebellum, the organ that I talked about, but you injure it in a very different layer, a very different part of the cerebellum.

It's the most extraordinarily complex thing the cerebellum, and the Purkinje cells are characteristically spared. They don't get injured. It's exactly the thing that goes wrong in autism, the Purkinje cell injury. It does not happen in mercury toxicity, even in these little babies who had more mercury than anybody else again because it was concentrated in large quantities from their mother into the babies and again spared the mother's lives.

Because of that, mothers that had similar

burdens of mercury would survive if they were pregnant, but produce a tragically injured baby. This was all despite very uniform distribution of -- Dorothy Russell, a superb and marvelous neuropathologist, who did these studies after Minimata Bay carefully studied the amount of mercury you found throughout the brain. It was uniformly distributed, so it's not that you're only getting mercury one place or another.

It's throughout the brain, and therefore all of the things that could have gotten injured in autism, could have gotten injured because there was plenty of mercury there to injure these other kinds of cells, far more, extraordinarily more, 10, 12 digits more of concentration than we might see from very tiny amounts of mercury exposure. It didn't injure the areas that are involved with autism. It did injure other sensitive areas, and in fact it was difficult to get into the brain.

It was less of it than in non-brain tissues. Mercury has a difficult time crossing the blood brain barrier, and so the brain had less than other portions of the nervous system that are outside the blood brain barrier, and so that what we call sensory ganglia that are not invested with blood brain barrier were

injured even more than the brain itself so that the children, their limb deformities, were a product of the injury to the peripheral sensory nerves. The next one?

Q This is slide 12.

A In this instance, as we suggested we have a particular syndrome that's a product of a particular neurological process or injury, and so these children tragically had visual and hearing deficits. They had dysfunction of the central nervous system motor system. What we know about autism is that motor functions are entirely preserved.

At least in classic and regressive autism, we have impairment of function to some extent in children with some other syndromes, or at least we have some strange aspects of motor function, but one of the important things to make sure of when you're trying to diagnose autism is that the motor system is in tact.

It's not being used necessarily in the same way of other people, but it is quite in tact, and yet we have a severe abnormality of motor systems if you injure the brain with mercury, and the peripheral sensory system I mentioned. I don't know whether there's another slide. I think there is. This is

demonstrating -- what the greenish

and reddish areas represent here are areas that are immature becoming mature into the 20s.

This slide very importantly illustrates I think, and many of us do, with great support for this idea that the second deterioration in higher functioning autism in the teenage years is not because of battering or bruising in life or because people are not trying hard or anything else. It's because new systems that have to come online that treat this, what we might call an illness, adolescence, it's a very important kind of illness because that's where we all get our experiences.

Don't we? We do things impulsively, and sometimes people convince us to go off to wars and things like that. You perhaps wouldn't convince a 40-year-old the same with the same readiness. These things happen 15, 20, 25 years into life when new systems come on that may account not only for what we facetiously call the disease of adolescence, but the wonder of adolescence and maybe the systems coming online account for what we call the feet of clay that we develop as time goes on and perhaps don't have that same enthusiasm. Next one?

THE COURT: Pardon me. Before we go on, the slide to which you were referring with the reds is

slide no. 13. To proceed.

THE WITNESS: A few other things could be said that I think are pertinent. There is the fact that some people have demonstrated that glutathione, peroxidasin and glutathione dismutase activities may be low. This is based on information in the peripheral circulation, and this is important to know about because it is possible that environmental influences could have some effect on the Purkinje cell loss.

I'm not entirely excluding environmental events, but these may be the sorts of things that people naturally experience, and it may be that at least this particular system has something to do with the sensitivity of Purkinje cells. It's not fully understood yet, but we must keep an open mind about these things. Nonetheless, this is pretty good information and may have something to do with a combination of genetic sensitivity and other things that happened. It may have nothing to do with it. The next one?

THE COURT: That was slide 14. We're now moving to slide 15.

THE WITNESS: People are trying to look as we know there's a great deal now of very important

information about mercury and the brain, not only what I've shown so far, but information that tells us a lot about the kinetics of mercury, a lot about its excretion. In the excellent work done in the Seychelles, the kinetics of mercury transport were worked out into a single and a double volume way of looking at these things.

That's a technical term, but there are ways in which we understand how elements and medicines and other things move around in the body, and there is no evidence that there is transport difficulty with mercury. It does as I mention get excluded from the brain to some extent by blood brain barrier, which influences the kinetics, and one of the problems with kinetic studies is when we look at a safe drug, we just give the drug to somebody and see where it gets in all the compartments.

Obviously, nobody is going to do this mercury, so these kinds of studies are dependent on knowing what the predicted mercury burden of an individual has been. It can be quite high, and as you all know in the studies of the Inuits where that burden might be quite high, there's no epidemiological demonstration whatsoever of a risk of the development of autism on the basis of that considerable mercury

burden.

Many studies that are done on mercury don't have this kind of sophisticated careful estimation, most of them probably, of the burden that's ingested. There are areas into which mercury goes in the body that are what we call sinks, areas where it doesn't cause severe injury, usually bones, hair and so forth, but it can be mobilized from these areas by chelation, and when that is done, we can estimate the body burden, but the chelation requires all of the excretion systems to be in tact.

If they're impaired or in tact, you cause injury to the individual by chelating them. This has been most carefully worked out after initial bad experiences with chelation of toxic substances. Likely, without much question I believe it's a question of the amount of mercury that produces injury to sensitive tissues as it is with virtually all toxins that we're aware of.

Some are more potent than others, but in Wilson's disease where there is a transport problem, and that's the basis of the disease, it's still the amount of copper that causes the injury. It is a dose-related effect quite distinctly dose related. It has nothing to do with the transport process itself

except to the extent that that transport takes the copper to tissues, accumulates in those tissues and causes injury.

We know this because individuals who are fed out of copper pots, such as certain people from Japan get their Wilson's disease earlier and have higher burdens of copper. Finally, because autoimmunity has been a career-long interest of mine and because I've reviewed this literature with particular care, there are plenty of papers, there are no markers for autoimmunity to suggest that this is an autoimmune condition.

I've tried to cover the waterfront as far as central nervous system autoimmune conditions are concerned, including a forthcoming book on the subject, and there is nothing to suggest currently that this is an autoimmune condition in any way.

BY MS. RENZI:

Q Thank you. Doctor, based on the pathology that you have just described in detail for autism, is there any evidence that Yates' autism was caused by mercury toxicity?

A There's no evidence whatsoever, ma'am.

Q Petitioners have also put forth the hypothesis that measles virus causes autism. What are

the problems with Dr. Corbier's hypothesis in this respect?

A Well, as far as I can understand the hypothesis, it has to do with either effects of administration of the vaccine or with persistence of measles virus in the system causing the difficulties in various portions of the body. There are a number of papers on this subject related to both nervous system and areas outside of the nervous system.

The most striking observations have I can say with confidence been thoroughly discredited in the medical literature and in medical communities on the basis of the ways in which we usually thoroughly discredit things: The lack of validation, the lack of a capacity to repeat the same observations, review of the tissue specimens and the techniques that were used to study those tissue specimens demonstrating that the methods were faulty and the observations were incorrect.

The gathering of information from nonsequential patients, demonstrating those patients in the medical literature in ways that misrepresent the manner in which those patients were gathered, failure to misrepresent economic advantage related to publication, a wide variety of things. The medical

community is relatively forgiving about some things in its community, but scientific fraud is not one of those things that we forgive.

We'd be very careful before we assign that sort of thing, but there is abundant evidence that that was the case here, and for us, it's something that we don't like because we try so very hard to do what we can for patients. We try to provide them with appropriate counseling and care. We try to provide them with an accurate explanation for why that child is afflicted with something.

We try to provide appropriate therapies. We try to protect them from inappropriate therapies. We try to make sure that our parents in trying to do something for their child about whom they're understandably upset are brought to spend money in therapies that are both expensive and potentially dangerous, so that aspect of things, thoroughly discredited.

Other attempts to look at this question remain and probably are some subareas, especially with regard to stimulation of the immune response that one must consider as possibilities, but thus far, no evidence as I mentioned in the literature to support that point of view. Insofar as persistence of virus

in the central nervous system is concerned, we have a considerable understanding of this process.

We understand especially what measles virus may or may not do within the nervous system. We know exactly what acute measles encephalitis is. It's a horrible illness, which used to cause millions of deaths every year before vaccination. Personally, I had a friend in high school, who died within 36 hours of measles encephalitis,and I've taken care of patients with measles encephalitis as well.

We also worry about the possibility that folks will not be willing to vaccinate, and these illnesses will return. We have measles that persists in the tissues and produces SSPE. This is especially pertinent to some argument that some measles acquired early in life might give rise to an illness that doesn't produce the severity of early measles in terms of SSPE.

We don't understand why the latency. I believe the other day it was mentioned one to nine months, but that's by no means my understanding of the latency. In fact, quite characteristically, the latency is between four, and in a patient I took care of, 14 years after measles in the first year of life. We understand something about why this happens,

something about the inadequacy of the immune response.

It's likely that the measles virus remains resident in the central nervous system. The measles virus in SSPE has been carefully studied. It has never been the A1 strain that's used for vaccine. It's always wild type and it comes on with an illness that once there is any suggestion of neurologic disease, the illness universally progresses to death within three years.

It's a terrible illness to follow with initial behavioral manifestations that are different from those seen in autism and sometimes are misunderstood by those, who take care of the child. Then we have inclusion body measles, which is another entirely different disease in no way to be confused with autism, so as far as virus resident within the nervous system is concerned, there is not one particle information in the medical literature or in medical experience to suggest that that happened.

As we try to keep an open mind, there are sometimes things that surprise us, but thus far people have gone at that with a will, and it's not founded to be the case.

Q Dr. Corbier yesterday put forth a profile of children that he believed you could determine that MMR

was the cause of their autism based on a profile, and that profile was normal then with regression, GI dysfunction including malabsorption and diarrhea and the onset of symptoms one to nine months following vaccination. Could you please address the doctor's profile and how significant that profile is?

A Well, it would cover virtually all of the children that I've taken care of with regressive autism in some way or another. Although, then it depends on how you define those entities. As far as normal to a child deteriorating in terms of intellectual and other functions, that covers a great many of the children that have the regressive form of autism.

As I mentioned, if you look carefully prior to that time, you frequently find things. Parents have high expectations for their children, and sometimes it's only with careful history taking we find out that there are things that they haven't done on time, but that would cover virtually all of the children that fall into the regressive category. The second portion of this was the GI complaints. Is that what --

Q Yes.

A Well, again we have a little bit of black

humor in medicine from time to time and a common saying in medicine is that one man's diarrhea is another man's constipation. It depends on what people's attention is drawn to. I'm a pediatrician as well as a neurologist. I've taken care of a great many children in my career in various settings, including emergency rooms where children come in with a complaint of diarrhea.

Children get three to five bouts of diarrhea a year quite typically, especially those that are in daycare settings because the transient of infectious agents in that way, viruses typically. Children also get diarrhea from noninfectious causes. The most common one is treatment of ear infections with antibiotics. That treatment with ear infections interfering with what we call the gut flora or the kinds of bacteria that are in the gut to producing diarrhea.

Maybe in some instances because of other effects of medication, and the medications typically used for ear infections are among those that quite commonly cause this problem, so again it depends on how you define it. Children that have autism sometimes have an element of anxiety, which we're still trying to work out, but we find an overlap

between children that have anxiety and children that

have stool retention.

Stool retention producing overflow diarrhea in lesser quantities, but more persistent than is seen without these large retained stools. This is another behavioral phenotype in children, and it's not limited to autism. If one were to try to make some sense of those things, one would have to perform careful, very careful epidemiological studies to find out if that is something that sets these children apart from other children because again it's such a common phenomenon.

I believe another thing that we frequently see is again after treatment with antibiotics we see the adventitial development of thrush, sometimes involving both ends of the GI tract, again because of the influence of antibiotics I would say, so that was Part 2. I think those are such common things that again one would be making a case that all children are having injury from something that has no basis in medical science.

Q The last one was the one- to nine-month period of onset following the vaccination.

A Well, we don't have any information upon which we can base such a judgment. But again, I think an illustrative example would be the set of information that was gathered about the second DPT

immunization.

Those immunizations were given at two, four and six months, and again there are not only autism but other conditions that develop at a certain time in the development of the nervous system characteristically.

Not only does autism develop in the regressive form in some kind of proximity to the 12-month or the 15-month or the 18-month vaccinations but so too with an even tighter correlation, a thing that we call infantile spasms, and we still call it that. Infantile spasms is a severe seizure disorder that comes on between four and six months characteristically right around four or five months.

That's the time at which it manifests itself in most children. Because the four-month vaccination was given, people understandably wondered whether there was a connection between the two things. Additionally, with the second pertussis vaccination, very frequently children get a local inflammatory reaction in the leg or the thigh that causes them to cry within the first 24 to 36 hours.

The children don't seem to be themselves. They seem to be sleepy and restless and so forth. Then it goes away. The way to answer this question because it was an important one -- was to take away the four-month vaccination, and the UCLA/Denmark study

did exactly that. They moved the second immunization to 10 months and then looked at the population frequency of infantile spasms.

Infantile spasms onset at four to six months was exactly overlaying the onset prior to the immunization being moved. And it was felt by the scientific and medical community that this proved that at least in most instances if perhaps all that the vaccination had nothing to do with that, so we do have things that take place in the second year of life because of the working out of a genetic code.

If you provide a wide range of possibilities one month to nine months, it becomes very confusing for us. In trying to sort out pertussis, we tried, because again we had an open mind, we tried to get the population most likely to have a cause and effect relationship, and so we considered the children that had the onset within the first 24 to 48 hours, and we considered those children that had a behavioral change as well.

That subpopulation of patients did not change whatsoever when the four-month vaccination was taken away, so the same thing is true of inflammatory or toxic illnesses. Proximity to the stimulus is very important as a starting point to come up with

epidemiological information. For illnesses that I

study that are inflammatory, we sometimes use intervals as long as three or four weeks, but not longer than that.

If we were to try to associate certain kinds of brain inflammation, for example, with colds or fevers or infections, the children have five or six of those a year, so if you said it could be anything within six months, every single child is going to seem to have had an effect, so for vaccinations you need to move that proximity up to within a very short interval so one would think something like a week or three weeks or something like that.

Such studies I believe have been undertaken and have not shown correlation with the onset of regressive autism, so that's the starting point, and so far no support for that point of view. Doing things otherwise leads to very untidy science, and we learned we didn't always do science well.

We learned our lesson about doing things well because we could waste a great deal of time with theories and other sorts of things if we didn't have rules that we followed that got us into the best possible place for coming to an accurate and honest conclusion.

Q And to follow up, this profile Dr. Corbier

said represented a genetic subset of autistic children. Is there a phenotype in autism of children that fit this profile?

A No, ma'am, there is not.

Q Doctor, now I want to move on to Petitioner's hypothesis that thimerosal-containing vaccines and in conjunction with MMR work in concert, a synergy, that causes autism. Could you please comment on that hypothesis?

A There is no I think the word plausible was used yesterday, and I'd say there's no biologically plausible information to explain why that would happen. We know something about the potential mechanisms for either one, but again when you formulate a hypothesis, you meant to do so on the basis of a current understanding of mechanisms and trying to see what might be what.

Obviously, the other approach that can be undertaken is tight epidemiological correlation between two things happening at once, but if you select things that happen during an interval during which we know a disease develops and just say maybe they're correlated and provide a wide range of possible times at which that effect is produced, the possibility is overwhelming that the conclusion of

such study will not be useful.

We have to refine things further, and there isn't any plausible explanation that I'm aware of as to why these two effects taken together would produce autism. We don't know of mechanisms whereby thimerosal could produce this injury of brain. We don't know of mechanisms whereby thimerosal that's involved even sustained in the body over long intervals could produce that effect.

That kind of a theory is one that goes under the name of a homeopathic theory. Those theories are applied both to tiny amounts of substances given in treatment and tiny amounts of substances producing an effect over the long period of time. This is a theoretical construct in one branch of medicine that's not accepted by all the other branches and has not been proven even with carefully controlled studies to be a mechanism that in fact is valid, so that's what I'd say I think.

Q Would such hypothesis be contrary to the neuropathology of autism that you described today?

A It would not be in keeping with anything I know about neuropathology.

Q I want to focus now on Yates Hazlehurst. In Dr. Corbier's report, Yates was immune-compromised.

Is there any evidence in the medical records based on Yates' first year of life, first two years of life that he was immune-compromised?

A Because of that question, I carefully reviewed the records that were made available to me, which struck me I might add as ones that were kept by a very careful pediatrician, who seemed to pay attention to the parents' complaints and concerns, recorded these in the chart and all of the other sorts of things that are typically recorded in a well-run pediatric practice.

The health of this young man during that interval appeared to me to be typical of young children, in no way different from perhaps the majority of other children that come into a pediatric practice. There are some children that have more ear infections than others, but this was not an overwhelmingly large number of ear infections here.

Ear infections we don't recognize as something that's caused by immunodeficiency in combination with problems in the gut and so forth, at least I don't, without other attended circumstances, so in children that are immunocompromised, you can see these things, but together with other kinds of manifestations. None of those were present here.

In children with immunocompromised or failure to thrive in association with ongoing gut problems, the first place one looks is at the growth curve of the child. The growth curves of this child had several important features that need to have been paid attention to, and again carefully recorded, and what we see is that this was a child whose growth picked up early in the first year of life and was maintained at or above the 95th percentile in weight throughout the intervals where diarrhea was recorded.

This is not what one finds in a child that has ongoing gut difficulties with malabsorption or gut difficulties on the basis of immunodeficiency. This is not what one sees in a child with chronic infection due to immunodeficiency, so the growth profile was not consistent. The other interesting feature was the head growth, which increased within the first three to five months to the 70th percentile.

This of course happens in many children, but it is something that we observe quite regularly in children with acquired autism or with regressive autism. It doesn't prove the case, but it's one more consistent feature, so I didn't see any evidence of immunocompromise whatsoever. Certainly nothing that would explain ongoing infections being any way other

than usual for children, and certainly something that would have nothing to do with the question of autoimmunity related to viruses.

Q Dr. Corbier also mentions the chronic lymphadenopathy that Petitioners claim they felt on the swollen lymph nodes on Yates' neck.

A I'm sorry?

Q I'm sorry. You've published on this topic, correct?

A Well, on lymph node function, the immunology of lymph nodes. That's right. Every pediatrician is familiar with the fact that lymph node swelling to a modest to moderate degree, sometimes larger, is very common in childhood. It's one of those things that we see. It's very common. It's not an aspect of immune dysfunction. It's an aspect of normal immune function. Our studies involved trying to associate the swelling of lymph nodes with the fact that they provide a regional signal to immune responses.

So we placed them, transplanted them, into pedicle grafts and provided them with stimulus from bacteria and things, and so what the lymph nodes do is if somebody gets an infection in the arm or in the neck or in the back, the regional lymph nodes swell because of the immune response. That immune response

is meant to contain the microorganisms that have come to the lymph node, and so they won't spread to the rest of the body.

It's meant to eliminate them, and it's meant as well to provide a regional signal very probably so that you can recruit additional immune cells to come to that region. That's what lymph nodes do. Because children get so many oropharyngeal infections, other infections, lymph node swelling is very common. When one is a brand new intern, when we start out, we don't know perhaps as much as we do later on.

We write these lengthy notes in our descriptions of patients, and almost all of them have the annotation shotty, meaning like little shots, and so with enlargement of lymph nodes until we get sick of writing it down because it's almost always there, so that's a normal aspect of immune function.

Q Were there any contraindications for Yates to receive his vaccinations on February 8, 2001?

A None, whatsoever in my opinion within a reasonable degree of medical certainty.

Q Dr. Corbier also relied on a 2007 article published in the New England Journal of Medicine to support his hypothesis that thimerosal-containing vaccines can cause neurodevelopmental problems. Do

you agree with this assessment of the article?

A I'd have to look at it. If you have a copy of it, I can make a comment.

MS. RENZI: Special Master, could we just take a five-minute break and then come back to that question? Or a 10-minute break?

THE COURT: We sure can. Actually, do you have much longer do you anticipate on your direct?

MS. RENZI: Maybe 10 or 15 minutes.

THE COURT: Okay. Let's do a five-minute break, and we'll come back at quarter to. We're in recess.

(Whereupon, a short recess was taken.)

MS. RENZI: Thank you. And for the record I have given Dr. Rust the 2007 New England Journal of Medicine article that's in front of him, and that was filed as Petitioner's Exhibit 48.

BY MS. RENZI:

Q Doctor, the question I asked you before the break was Dr. Corbier relied on this article to support his hypothesis that thimerosal-containing vaccines can cause neurodevelopmental problems. Do you agree that that's the conclusion of that article?

A No, I don't.

Q What does that article stand for?

A I looked at this article just after it came out, and I just wanted to make sure that I hadn't overlooked anything in it. The point of the study was to try to find if there is any association between early thimerosal exposure and neuropsychological outcomes, and it's important to do such detailed studies, and in fact the result of the study is absolutely contrary to the idea that there's some association.

It shows no association between those two things. I believe reference was made to the occurrence of tics. This is interesting but not pertinent. Phonic and motor tics are fairly common in children. It's another problem that one could wonder why we're seeing so much more of them than we were in the past, and there's no doubt that in fact it's just because things are being brought to our attention that weren't being brought there before.

Enormous numbers of children have tics, and this is a small study, and probably there's a selection bias or something of that sort that caused this particular problem to rise to the surface. Again, what we do is confidence intervals trying to see no only that we find something, that it's more common in one group than the other but that's

significantly more common, and this rose to a level

that it requires further study.

Tics are not a feature of autism. Typically, there are patients with autism that have tics. About eight to 11 percent of boys have tics at some point in their lives, a slightly smaller number of girls, at least so we think. We think that perhaps they're overlooked in girls because what brings the boys to our attention is the hyperactive component of Attention Deficit Hyperactivity Disorder. It's not even either one of those things.

It's a part of a normal human function that can cause problems, and the girls tend not to have that, so they don't come to our attention. They may have attention problems. They may have tics, but we don't get the chance to see them, so what this shows is that maybe there's something there in terms of an association, but further study is required. And it's not in any way pertinent to the consideration of autism.

The important message of this paper is in one well-performed study it was demonstrated that there isn't any association between thimerosal early exposure and things related to neuropsychological abnormalities or autism.

Q Dr. Corbier was talking about tics in his

testimony yesterday. What is a tic?

A Well, there are two kinds of tics. There's a motor tic, and there's a phonic tic. Motor tics can -- somebody, who actually has tics and are frequently associated OCD features, wrote a large book and a set of studies on this thing and divides motor tics into 56 different types and phonic tics into 47 or 48 different types. It's a common thing amongst people. It's sort of catching in that somebody has a tic, some other people pick it up.

If it persists for more than one year with both motor and phonic tics, then we make the diagnosis of Tourette's syndrome, which is generally a benign condition that's also a developmental thing. And as with other developmental processes involving the intellect and emotions and behavior of people, it has it's positive sides and it's negative sides, and it's something we're called on to address because of that.

Q And you just stated that if tics go on for more than a year, then you'd label them Tourette's syndrome. What is a usual course of tics?

A Usually they go away within a year, so the enormous number of children that have tics, people that have sat in classrooms observing children find a huge number that have tics. This is a report by a neuropsychologist as you can see reported more tics in

the girls than their parents did, and again we see that kind of bias in observation, so these are exceedingly common things.

You can see them in bus stations and with baseball players when they get up to bat. Nomar Garciaparra has the most remarkable stereotypical tics, which are quite repetitive, so they seem to have a function for people in terms of allaying different kinds of feeling that people might have and become more common when people are anxious during test-taking situations.

Q I just want to wrap with just a couple of questions on Dr. Corbier's testimony and on his report. I want to refer you, and I don't know if you have it in front of you, to Petitioner's Exhibit 26, which is Dr. Corbier's report, and on page 7 of that report he discusses the conventional view of autism. Could we hand you a copy, or do you have it with you?

A I believe so, yes. Page 7?

Q It's page 7.

A What would you like me to comment on?

Q Does Dr. Corbier accurately describe the conventional view of autism, and is there a term called "conventional view of autism?"

A Well, I believe I commented on this section

in my own report. One person's view of what's conventional and another's may not be the same, and this arises all the time in medicine. So what we tend to do is to hold large conferences and arrive at criteria for things, and so criteria are a little bit different than conventional views. Conventional views could be an inaccurate reflection of people if they've not been assembled in one place, and in fact that's not happened.

We haven't assembled the neurological community all into one place to come up with diagnostic criteria. But we have assembled experts on the field, and there are features that people regard as being important elements of diagnosis. The view that's expressed here did not strike me as what I would call conventional, however. And I think that the views of this section are not those of most people with whom I work on autism.

Q Doctor, he follows up with the parental hypothesis, which is also on page 7.

A Yes. I'm sorry?

Q Dr. Rust, have you read the parental hypothesis?

A Yes, I read that section as well. I can't comment on it specifically because I haven't spoken to

the parents about the hypothesis, and I would just have to presume that this is an accurate reflection of the parental point of view about what's going on. It's similar to points of view that parents of children that I care for with autism have, and it's the privilege of a parent to have their view about things.

There are many aspects of this that as you can understand from what I've said earlier I disagree with, and I think it's important that these things surface in meeting with parents of children with autism so that we at least understand that we're listening to each other.

Q Dr. Corbier's opinion also rests on that there are multiple environmental factors, some of which cannot be identified, that all contribute to the development of autism. Could you comment on whether that is a hypothesis accepted in the medical community?

A Well, the emerging view of autism as I've described is the working out of a genetic development of brain that doesn't develop properly, and the degree of that abnormality helps to differentiate the time of onset of subtypes of autistic disorders and may be related to conditions that are now in the autistic

spectrum that might belong elsewhere, so we know the most about the classic autism and the regressive autism. That's our largest number of patients, and remind me what your question was now?

Q About whether there's other environmental factors along with vaccines that all contribute to the development of autism?

A I think that would represent too difficult a point of view to perform careful research on. We need to start with the most promising areas in which we can then make an observation and then try to sort out as time goes on what other things may contribute to it. It's quite clear that the genetic view of autism is going to represent the overwhelmingly most important aspect of autism.

It's also quite clear that children can have features that to various degrees resemble autism from other kinds of environmental insults, but those conditions need to be set apart for the very important reason that first of all families might not because of the question of guilt over genetically inherited disease, because of the question of what the risk for other children in the family is, future children, these need to be carefully addressed by us.

We need to set those apart from environment

stimuli that may do things. In parents that have had a child that had something that's related to an extrinsic nongenetic insult we can provide counseling that is a little different in terms of whether the family would like to have another child and so forth, so we need to make these distinctions very carefully.

If you multiply determinants, the statistical evaluation, which is the way in which we see whether things that repeat themselves that are validated in studies become very difficult to perform. Oftentimes people multiply two, three, four, five different things and say which one had something to do with things. And oftentimes those studies are done without the kind of corrections that are necessary for what we call multivariate analysis.

It's very difficult to do multivariate analysis if you don't first know the frequency of some particular problem in the environment, so that's the first step toward doing these multivariate analyses. Once you get some information suggesting repeatable observations, that's the point at which they need to be parsed out, the individual part of it then reconsidered.

If we consider a combination of things, the

//

typical outcome of that, and there have been such studies in medicine, is to generate data that's not of any value.

Q Doctor, you have reviewed the video of Yates Hazlehurst, correct?

A Yes, I have.

Q And in some of the videos, Yates has a little bit of a distended belly. Would you agree?

A Yes. There was on in particular. He was running in a diaper in something that looked like Scandinavia or something. I don't know where.

Q In your opinion, did Yates look like a child, who was suffering from malabsorption?

A No. As I mentioned, his growth and development includes weight at the 95th percentile or above in a steady way. The belly was a little bit big. It must be said that in a child that has a recent change of diet, or in a child that has stool retention or a child that's eaten a great deal of particular foods, that kind of distension typically is either gaseousness or contents.

The child with quasioko (phonetic), we think about those children as having distended bellies appear absolutely differently from what we saw in that picture there.

Q Doctor, have you ever testified in Vaccine Act cases?

A Twice.

Q And did you testify on behalf of Respondent or Petitioner in those cases?

A In both those cases it was on behalf of a child and family.

Q And why have you agreed to testify and serve as an expert for Respondent today?

A Well, I was asked, and I thought it was important.

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

THE COURT: Mr. Webb, you wanted a period of time?

MR. WEBB: I would like to have if we can about a half-hour break?

THE COURT: How long are you planning to go?

MR. WEBB: I'm not sure I'll need it all, but I need to put my notes together. On cross-examination, I do not anticipate being very long. It would be about 12:30? 11:30 I mean.

THE COURT: 12:30? That's quite an extended period time there, Mr. Webb.

MR. WEBB: Yes, 11:30.

THE COURT: Let's see. It's about seven after. We'll give you 20 minutes to collect your thoughts.

MR. WEBB: Okay.

THE COURT: Let's be back here by 11:25, and go forward, okay? We're in recess until 11:25.

(Whereupon, a short recess was taken.)

CROSS-EXAMINATION

BY MR. WEBB:

Q Doctor, would you see evidence of a relationship between vaccination and autism in a case in which a child suffered an acute encephalopathy nine days after an MMR vaccination and that encephalopathy was immediately followed by symptoms of regressive autism?

A No, I wouldn't, particularly without being able to look at the facts of the case. I think it's the overwhelming likelihood in that instance is that the child was mislabeled.

Q If there were a subclass of children with regressive autism, whose clinical profile was truly distinctive, would their clinical profile be relevant to the etiology of their autism?

A Potentially. That's why we try to designate things as carefully as we can in subcategories to see

whether there is within a larger group a smaller group that might have some particular vulnerability. But it would not include children that have the onset of their disease in the pattern of regressive autism because of an insult occurring in the second year of life, could not be because that's not the way in which the genetic code that's leading to the disorder would work its way out.

Q What is Childhood Disintegrative Disorder?

A Well, it was described a long time ago back in the '20s, and there still are occasional cases of Childhood Disintegrative Disorder that go under that heading, and we do see children that have this significant deterioration in later stages of life. It is not regressive autism. It has its own particular manifestations, and it's a different condition and one that's rare, and has been insufficiently studied.

Q Do you believe that the difference in the age of onset and prognosis in Childhood Disintegrative Disorder suggest a different etiology for Childhood Disintegrative Disorder as opposed to regressive autism?

A It's possible. As I say, it's a rare condition despite it's descriptions very long ago, and it is not autism. It is something separate.

Q Do you believe that environmental factors play a significant role in the evolution or the causation of Childhood Disintegrative Disorder?

A As I say, it's still unknown, and it can readily be set apart from cases like the present one where it's classic regressive autism. It has its own natural history that needs to be better understood. The trouble with that particular disorder is that the rare cases that are described are described in insufficient detail to know for sure what in the world people are talking about.

That goes back to Heller's original description, which is a few cases in the 1920s, additional descriptions in the late 1940s and then some subsequent cases. We need to come to a better understanding of that syndrome distinct from the current one we're dealing with here.

Q Is it an autism spectrum disorder?

A It's been included in that spectrum. There are a lot of apples and oranges in the autistic spectrum designation, and whether some of them share pathogenesis with autism or not is not entirely clear.

(Away from microphone.)

Q How much of the testimony that you shared on the anatomy of autism is based on pathological

examinations of brains?

A All of the pathology I spoke about is based on pathological analysis. The functional MR studies are based on anatomic observations in regions where pathology has been observed.

Q Do you know the typical age of the individual from whom the brains were taken?

A Yes. That's an important point. Typically, brains don't become available until individuals are much older. Autism is associated with a normal lifespan, so is Rett syndrome in most instances, and so it's not until individuals are older when the brain can be studied in that way. This is why it's been so important to observe those regional pathological observations and find out whether they're true of younger individuals, but that's what functional MR is doing in order to demonstrate that there is a consistency between those pathological observations and the onset of disease earlier. If one observes however in pathological specimens abnormal development of brain, we can generally time that fairly well because we know when these things manifest themselves, these developmental effects. And so finding dysgenesis in the brain we have an abundant amount of //

information about when the onset of dysgenetic elements take place.

As in this instance, the dysgenetic changes in the minicolumns occur early, and so they're early childhood manifestations. The somewhat dissimilar changes that are seen on the basis of intrauterine effects have to take place early as well so they can be timed with regard to when we know that normal development takes place.

Q With regard to the pathological examination of brains, is it fair to say it's often hard to tell whether you're finding the cause or the consequence of a disorder when you look at the samples?

A The important next step I think I mentioned once you observe something pathologically is to compare that to the known function of that portion of the brain and find out what period in a person's life that dysfunction manifested itself. And in doing this we find that the pathology that Dr. Baumann and others have observed is in keeping with the timing of development of regression, for example, in regressive autism. We have very sound evidence that the timing is at the time or prior to the time that the child has provided the manifestations of autism.

Q With regard to the MRI, PET scans and other

computer imaging of the brain in which you've described the pathology and the physiology of autism, what was the typical age of the persons that were scanned for those exams?

A Some early childhood scans, some older individuals were also scanned, and so additional information is likely to be necessary. But again, we know for pretty dead certain when these changes occur in terms of cortical development because the timing of cortical development and the timing of onset of dysgenetic portions of cortex has been worked out in the brains of individuals of all ages.

In large series of patients, who have had their brains examined after their death at varied ages, both from the Perinatal Collaborative Project for Small Children that died and from the older individuals for at least 50 years, more like 70 years, we know the sequence with which certain aspects of cortical development occur, and so we have a very good timeframe within which to place the timing of brain development.

Q In your opinion, what percent of the children with regressive autism have gastrointestinal problems that merit a colonoscopy? Roughly, how common is it for that procedure to be reasonably

1 necessary

for a child with autism?

A It's uncommon in my experience.

Q I'm sorry?

A It's uncommon in my experience.

Q How common is it for children with regressive autism to require pancreatic enzymes?

A Well, the word "require" is a difficult one for me. I have plenty of patients, who are on pancreatic enzymes, that if I were their pediatrician I wouldn't be giving it to them, so it's difficult to know.

Q Do you have any idea of how many children with regressive autism are prescribed pancreatic enzymes and gastrointestinal medicine designed to reduce inflammation in the intestines by a well-qualified pediatric gastroenterologist?

A Well, I know of patients that are treated in this way and have oftentimes wondered whether it's the right thing to have done for whoever did it. Usually in those instances, the gastrointestinal complaints in the patients that I've seen don't really merit that sort of intervention so far as I'm concerned, and at least as regards our gastroenterologists at the University of Virginia, I believe that their opinion is similar to mine.

Q So would it be fair to say that in your opinion the children with regressive autism, who in fact need a colonoscopy and in fact require pancreatic enzymes and anti-inflammatory medication for their intestines is rare? Small percentage?

A Well, I would say that in my experience if one were to decide that this designates a separate subcategory of children with autism, and one wished to study it, the important first step would be to have independent confirmation by other gastroenterologists that this in fact was a necessary step and was in someway justified.

At least in my opinion having taken care of a lot of children as a pediatrician, a child that's growing well and maintaining weight at the 95th percentile and having no other significant medical difficulties, it would seem to me that somebody is likely overreaching.

Q You reviewed the medical records for the February 8, 2001, doctor's visit, is that correct?

A Yes, I did.

Q Yates was ill. Wasn't he?

A I'd have to be refreshed on the details of that particular day. I'd be happy to take a look at that record.

Q Under what circumstances did you as a pediatrician prescribe antibiotics to a child with an ear infection?

A I probably did it much less often than some other pediatricians and as often as many pediatricians, which is seldom. Almost all of the time inner ear infections in children are caused by viruses and almost always occurring in association with coryza and other upper respiratory illnesses, and almost all of the time they get better without antibiotics, and almost all of the time parents don't give the full 10-day course of antibiotics, so it's an overtreatment issue.

Q I'm trying to understand. Was your practice different from that of some pediatricians?

A I'm sure it is. There are people that do all kinds of things in the world.

Q Under what circumstances would it be appropriate for a pediatrician to give a child antibiotics for ear infection?

A If they felt that there was puss in the inner ear, if they felt there was considerable amount of detraction of movement or interference with movement of the drum, that could be considered in those instances. If the child had high fever and one

were concerned about the possibility that that's a manifestation of a bacterial illness, it could be considered there as well, but most of the time it's virus.

Q I'm trying to get the sense if you can, and maybe my question doesn't make sense, and tell me if it doesn't, would the child's illness need to be more than mild? Would it have to be at least a moderately severe ear infection before antibiotics should be considered?

A Well, pediatricians used to puncture the eardrum, even in cases where there's a considerable amount of reddening, in order to obtain some material to do a slide and so forth, but puncturing the ear drum of a child that's struggling and so forth is an awkward procedure, and many people settle with the fact that if the child seems more ill, perhaps we'll give some antibiotics.

Antibiotics are not entirely safe, but generally safe, but overuse of antibiotics contributes to other problems downstream, so the evidence would be that in most instances, even in a child that has a fever of a fair degree, that the virus is causing the problem, and that antibiotics are going to play no role in treatment. The one instance I suppose

when I do end up thinking antibiotics are more appropriate if the child has a runny nose with purulent discharge form the nose.

That's bacterial overgrowth in a viral situation. Whether the antibiotic plays any role in making that better is not clear, but it's one of the times when I'll give antibiotics.

Q In your commentary on the description of onset of Yates' autism in your report, why did you omit the reference to the records that describe his regression as beginning at 12 months of age?

A My comments were on Dr. Corbier's report chiefly, and that's where my attention was directed.

Q Do you know or by his reputation Dr. Zimmerman?

A I don't know Dr. Zimmerman.

Q Do you of his reputation as a physician, who treats kids with autism?

A I've heard of him

Q Did you review Dr. Zimmerman's report concerning the onset of Yates' autism?

A I believe I did.

MR. WEBB: That's all the questions I have.

THE COURT: Ms. Renzi?

MS. RENZI: I have no redirect. Thank you.

THE COURT: I do have a few questions, Dr. Rust. You had referenced several times in your testimony and on your slide classic regressive autism. Are you using that term as meaning one in the same thing?

THE WITNESS: Thank you, Special Master. I would like to make that point clear. We distinguish the classic form, which has it's early onset from the regressive form, typically in the second year of life, and the hyphen that I placed between those two designations was meant to suggest that as we look closely, we see typically that there are some abnormalities.

I wouldn't say typically. I wouldn't say it that strongly. We can only do this in instances where a family can provide us preceding videotapes or CDs, and they can do that increasingly for us because so many tapes are taken of babies, and when we look closely at those tapes, we see children that aren't entirely normal, oftentimes even prior to the point at which the parents have really noted a significant change in the child.

They're not entirely distinct from each other these two categories, but they are distinguished from one another very reliably by the fact that

children are not so severely impaired as those children we call classic autism.

THE COURT: You also reference in your expert opinion, you use the term CPRL, Conventional Peer-reviewed Literature?

THE WITNESS: Yes.

THE COURT: Would you describe what your view of CPRL is?

THE WITNESS: Yes. I made the term up I'm afraid, but it was the best way I can deal with mixed literature on the subject, and the term conventional is used in other ways in Dr. Corbier's report, and so perhaps I'm imprecise in a way too, but I really do mean something specific by it.

What I mean is the medical literature where the process or review of articles is undertaken by known experts in the field, who read those articles carefully to make sure that the method of the research, the manner in which it's carried out, the appropriacy of that manner and the interpretation of results are all done with the care that we need in papers that are brought to our attention.

There's so much in the medical literature. It's overwhelming to all of us to keep up. It's very helpful that this well worked out process of review is

there so that we at least are starting with those papers that have adhered to what are the usual standards. They now involve not only knowledge on the part of the reviewer, and not only a very careful review by several, two, three, four, five reviewers sometimes, but then the process is very important.

Providing that information to the author of the paper so that in papers where there are problems, but there's a kernel of information that's of some importance or information you can't get elsewhere that those papers be improved and then published, so there's that teaching aspect of critical review and catching any mistakes and catching any things that are mislabeled, all those things are done by the careful reviewer.

That's the point at which it then enters the large collection of medical literature where we know that there are some journals that are more reliable than others. We keep up with those more closely than others. It doesn't mean we ignore a paper that happens to be somewhere where it is less impact, especially if that's an area there aren't so many papers.

It allows us to get on with the process of keeping up and revising our opinions and knowing that

the information from which we're spending what time we have is time comparatively well spent. There is yet another aspect in that especially over the last 10 to 15 years the peer-reviewed literature has taken excruciating pains to make sure that there's no conflict of interest on the part of those publishing the papers, and that they're not in any way going to gain financially from the report that they're providing.

All this must be attested to by the authors of the paper that all of the authors have participated appropriately and that the methods that are described in the papers are ones that they would stand by in a courtroom if they had to, to say that this is what they've done, so that's why we rely on that literature.

THE COURT: Dr. Corbier relied on a number of articles in support of his -- I believe his characterization were several, several studies support his propositions. What is your view of those articles?

THE WITNESS: Well, he obviously spent a great deal of time thinking and worrying about this case, and if something has come to his attention that I'm not aware of that would alter my opinion, and I

know he's said he's going to provide those articles. I'd be very happy to review them to see if there's

anything that would cause me to think otherwise. It's terribly important in medicine to keep an open mind.

If you don't, you're going to miss something, or you're going to continue to practice in a way in which things are not quite correct, but I would say that for 20 some years now, I've tried to keep up with this as with other literature and to have a reasonably comprehensive view of something that's very important to me. I would be happy to look at anything else that anybody would like to bring to my attention, however.

THE COURT: One final question. You referred very early in your testimony to the spectrum of autism disorders. You've clarified your reference to classic versus regressive. What neurological disorders do you think properly fall within the range of autism spectrum disorders?

THE WITNESS: Well, a wide variety of disorders have been placed there. Some just go under the designation of autistic spectrum or other diseases that seem to have autistic qualities to them. This has not been a very helpful approach in my view. The labels that are applied are oftentimes inaccurate and sometimes we're missing something. There's a problem with applying a label to somebody.

If we know exactly what we're talking about, applying that label is appropriate. There are times when labels related to autism and autistic spectrum disorders are provided in the medical community for the sake of provision of services. This is in instances where children require the understanding of patient teachers, who give the student who's having difficulties special time.

I think that many, if perhaps most, teachers do this anyway, but there are particular skills that are required for students that have behavioral issues in relationship to other things. And sometimes we know that the teacher that has those special qualities that make them a teacher of children with autism will give them that advantage, so I must say that sometimes we apply these labels imprecisely for that reason.

On the other hand, children get labels related to their behavior, their development, their capacities and their capabilities in ways that I think are not helpful. We have an overlabeling of children in general nowadays with all kinds of initial disorders. And so I've become increasingly careful about the labels that I apply to children because it doesn't help to have them in a category, and that's what I'd say about that.

THE COURT: With that said, your focus in terms of what would be regarded as autistic behavior would turn on the core features that you addressed earlier?

THE WITNESS: Yes, that's exactly right. With the categories of classic autism and regressive autism being very distinct, very carefully worked out, very, very repetitive in terms of the combination of symptoms and signs that are present in the children. And there are still other things to look at and are being looked at, and then the children that get the Asperger's designation, which is applied more imprecisely than the other disorders, but is one that is very distinctive. Then there are other things that are found within the spectrum of disorders that probably are separate illnesses, and so we use other labels for those.

THE COURT: Thank you, Dr. Rust.

THE WITNESS: Thank you, Special Master.

THE COURT: Have my questions triggered any questions from counsel? Ms. Renzi?

MS. RENZI: No, thank you.

THE COURT: Mr. Webb?

MR. WEBB: Well -- two to four.

//

CROSS-EXAMINATION (RESUMED)

BY MR. WEBB:

Q Several times in your testimony and in your slides, you listed classic and regressive autism. Are they the same thing in your mind?

A No. They're different from one another. There just happens to be an earlier onset of some of the features of regressive autism of indistinct onset, which is a little different than what we usually have designated as the onset of regressive autism.

Q In your opinion, are there different genetic or environmental factors involved in the causation of classic as opposed to regressive autism?

A I don't think that environmental factors are involved at all in any way, and I can say that with 99 percent confidence I believe, but with regard to the cause, it could be different genes. It could be different genes, it could be a different combination of genes. It could be gene dose such that some children have a greater dose of the genetic problem. We know that that's true with the CC Med problem with genetic determination of autism.

The more copies you get, if you get two copies instead of one, you have earlier onset of manifestations, so there are without doubt genetic

determinants for the onset of these things. It is possible that dose of other things that are

experienced in the childhood environment in the uterus play a role, and this may have to do with imprinting or with hormonal effects in keeping with the currently very interesting, but as yet unproven, set of hypotheses that surround the male theory of mind approach to autism.

As was mentioned, one intrauterine infection produces something that resembles autism, and that's congenital rubella, but that illness as well can likely be distinguished from classic autism even though its onset of manifestations is after birth.

Q And several, if I recall correctly, several of the slides that described pathological and physiological characteristics of autism had that classic and regressive autism label on them. Were the examples studied systematically classified as either classic or regressive in the studies?

A Yes. Dr. Baumann's studies have tried to distinguish the patients on the basis of time of onset of the illness.

Q Where any of those studies cited in your report?

A No, I don't believe they were, but I could provide those citations.

Q In fact, your report didn't go into much

1 detail on the anatomy or physiology of autism. Did

it?

A I was asked to address Dr. Corbier's report, and that's what I did.

Q You weren't asked to give a report that would give a preview of the testimony that wasn't a direct response to Dr. Corbier?

A That wasn't my understanding of what I was meant to do.

MR. WEBB: That's all the questions I have. It was more than four. I apologize.

THE COURT: No worries. Ms. Renzi?

MS. RENZI: I have no followup. Thank you.

THE COURT: Thank you, Dr. Rust.

THE WITNESS: Thank you, Special Master.

THE COURT: You're excused.

(Witness excused.)

THE COURT: I think this leaves us with our day today, and we are to anticipate a 10:30 commencement time. I'm anticipating a late arrival of Drs. McCusker and MacDonald this evening. It is further my understanding, brace yourselves, that tomorrow may be our longest day yet.

We're anticipating the testimony of both Dr. McCusker and Dr. MacDonald and any concluding statements that counsel wish to make, and I've ceded

our courtroom for Friday, so we'll run through until 9:00 p.m., if that's required and possibly walk out with the sheriffs tomorrow evening. That will be our thought, so until tomorrow, we're in recess until 10:30. Thank you.

(Whereupon, at 11:55 a.m., the hearing in the above-entitled matter was adjourned, to reconvene at 10:30 a.m. on Thursday, October 18, 2007.)

//

//

//

//

//

//

//

//

//

//

//

//

//

REPORTER'S CERTIFICATE

DOCKET NO.: 03-654V

CASE TITLE: Hazlehurst v. HHS

HEARING DATE: October 17, 2007

LOCATION: Charlotte, North Carolina

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: October 17, 2007

Mona McClellan
Official Reporter
Heritage Reporting Corporation
Suite 600
1220 L Street, N.W.
Washington, D.C. 20005-4018