Transcript of Dr. Robert Hendren presenting "Integrating Treatment for Autism Spectrum Disorder Through the Life Cycle" at the 2019 Autism Summit on 11-02-2019.

Slide 1:
>> Dr. Robert Hendren: It is really a pleasure to be back home. I was born a couple blocks from here at St. Luke's Hospital. I grew up on the First Bench and went to elementary school about a mile from here on the Boise State University campus. I went to Borah. Go Lions!

[laughter]

I spent two years at the University of Idaho. Go Vandals! My parents are buried in the Morris Hill Cemetery, as are my grandparents and my aunts and uncles. This is my home and it feels very nice to be here.

I'm going to have a broad topic to talk about. Integrating treatment through the life cycle. And that's kind of what I was assigned, so that you'll find I'll go quickly through a number of things. But many other speakers, including Dr. Epperly this morning, have hit on some of those. I was so pleased as I listened to think that the primary care orientation is having this whole body think about the whole person, form a relationship, kind of basis to what's being done and you'll see that woven through my talk today as well.

Slide 2:
The... at least in medicine meetings, and I don't know if it's important here, we're supposed to give a full disclosure. What might I get money for that might influence what I'm talking about.

I do a study - I do research for Curemark, which is a pancreatic digestive enzyme, and that I'll mention. Roche, which is a new compound based on vasopressin oxytocin called Balovaptan, that I'll mention. Otsuka has a antipsychotic that I think has less side effects, or at least is thought to. That's in trial now.

I'm on advisory boards for Curemark. BioMarin does some interesting compounds that are related to Fragile X. Janssen, that both Matthew and I work, and thinking about a search engine, not directly doing clinical trials. And Axial Biotherapeutics makes a probiotic. I'll tell you more about those as we go through.

And I've written a number of textbooks, and those are the ones that I'm still getting active royalties from in the last year.

Slide3:
I hope that what we'll do today is talk about successes and challenges, and the developmental progression through the life cycle of people with developmental disabilities.

Identify and talk about, which Dr. Epperly has already talked about, comorbid medical, emotional and behavioral symptoms.

And then in the end, talk a little about what my recent passion is. Which is thinking about integrating biomedical treatments for autism into conventional, that might include conventional psychotropic medications but also other things that are sometimes complementary and alternative or supplements. And what evidence there is for that into a comprehensive program for treatment.

Slide 4:
As Dr. Epperly mentioned, we've seen an increase in prevalence in autism in the last number of years. It keeps going up and up and up. And we keep seeing more and more people. Now the difference between incidence and prevalence is somewhat important because incidence refers to the number of new cases. Prevalence refers to how many you've seen that are identified.

So we don't fully know whether, when people say, "Is there more autism?" Based on incidence we don't know. Those are really hard studies to do. You have to go into a community, identify everybody in the community, follow them along. See is there actually more new cases rather than just look at, at whether there seems to be more of it.

Slide 5:
But people give different explanations for that increasing prevalence. Some say well it's because as we move from DSM 3 to 4 to 4R and now to 5, that we've changed the way we diagnose autism. So that's led to expansion and perhaps substitution, that we used to call something an intellectual disability, and you'll find throughout my slides I use “ID” often, and that's referring to intellectual disability. But maybe we've seen the incidence of intellectual disability go slowly down, so maybe we're calling those that we were calling them intellectual disability and now we call them autism, but we don't see big changes in those.

We see others. Maybe better reporting. We identify autism more now, an increasing recognition. I find many patients in my practice come hoping, their parents are hoping, that their child will get identified with autism because they can get better services for their child than if they had a mental disorder diagnosis, or others. So autism at least in California, but I think in most other states gets better kinds of interventions as a developmental disorder than it would as another kind of disorder. So they hope that that happens.

Then an increasing acceptability. That we've appreciated the neurodiversity movement. We've appreciated that having autism isn't something that blames parents, for at least mostly I hope not, blaming parents for having anything to do with this developing.

And maybe even that we measure it in places where people have moved to get services, so we find more of it there because people have moved.

But excellent studies have said that maybe explains about 50 percent of the difference, done by a good epidemiologist. Other things that people are wondering about, and we'll talk briefly about, are things like environmental toxins. Infectious or immune vulnerability. Things that affect just so-called epigenetic process that we'll talk more about. What goes between genes at

the core of the earth if you will, and symptoms at the surface of the earth, if you will. What happens in between there that affects growth and development, and how can those factors play a role in the later development of autism.

Slide 6:
We know autism is a genetic disorder, and I don't expect you to read all the things on this slide, except to say that if you look at fraternal twins and identical twins, there's a big difference. Lots more autism in families with identical twins, suggesting there is a genetic component, not just environmental one. Or if we look at siblings, the more conservative number is four but it goes up to as high as 19 percent, especially if the births are close together. So you say you have one person with autism in the family, then you wind up with more. And I'll bet many of you have seen families where you see two, or three, or four, the most I've seen is five people in a family with autism. That you know you think, "Whoa, what happened to that?" You know how could that have happened to those people? What a, what a challenge that must be.

But we find we can find a clear genetic etiology, and at best 25 percent of people with autism. So maybe it's fragile X, and we can say it's due to fragile X. Maybe not fully, but some people say that's the explanation.

Or there's a variety of other kinds of genetic causes that are associated but if we're going to say, "Can we find one, or two, or five genes?" We can't. We find there are hundreds of genes, and the genes interact with each other, and interact with the environment to create sometimes what are called de novo mutations, meaning they didn't come from parents who had autism. The parents didn't have any of those autism genes, but the kid did. So something happened that changed the way that gene expresses itself. That then leads to that gene being different.

It makes it a challenge to say, "Can we use precision medicine if we only use genetics to decide how can we target treatments?" So we'll talk about other ways that we can think of that happening as we go along.

Slide 7:
And when we talk about the environment, there's no smoking gun. There's no thing that we can say, "Ah, that's what causes autism." But there are there are lots and lots of theories. Things like prenatal or perinatal exposure to viral infections like rubella. You have rubella in the mom during pregnancy, there's a higher incidence of autism in the offspring. Valproic acid, if you take that during pregnancy. Or there were studies too looking at thalidomide, remember was given for morning sickness, and maybe for anxiety. These kids had little flipper arms, but if they took thalidomide during the end of the first trimester of pregnancy, higher incidence of autism.

But then the ones that are proposed go on and on. Mercury and fish, mercury and dental amalgams, lead, environmental toxins, vaccines, lack of vitamin D. If we have time, I'm good, I'm going to leave the vaccine thing for a side, for a while, but I recently gave a talk at a psychopharmacology conference in Las Vegas, there are a couple thousand people. At the end, the respondent, somebody another doctor that I knew who hosted the conference who's to ask

questions, and her first question that she had from the audience was, "What do you think about giving kids vaccines? I thought, "Oh my God Ann. How could you start with..."

[laughter]

for my first one?" If we have time, I'll tell you how I answered it.

[laughter]

Parental age, the older males particularly have a higher incidence of autism. People think that has to do with as you grow older your body absorbs more and more toxin, environmental toxins. Those get stored in germ cells that then get passed on. It also seems to happen with younger moms, very young moms, and with older moms.

Maternal metabolic conditions. Influenza and fever during pregnancy.

Air pollution, the closer you live to a big highway that has diesel exhaust, the higher your incidence of autism. The closer you live to places that spray pesticides, the higher incidence of autism. If you live downwind from a coal burning plant, higher incidence of autism. Coal has a lot of mercury in it. So there are certain environmental associations but not things that we could say absolutely cause and effect. We know that this leads to autism but we have an idea of what might be thought of as risk factors.

Slide 8:
So when somebody says, "What causes autism?" There's a kind of simplistic way that we can say, "Well we know the first hit comes from a genetic neurodevelopmental vulnerability." Some people have more of it, some people have less of it. Especially if we consider those de novo mutations that might play a role.

But the second hit comes from an environmental stressor and an interaction between the two. So the vulnerability plus something stressing in the environment leads to the problem.

And the third hit comes if we think that autism is a hopeless condition. That we can't help it get better. And then we say as we used to generations ago to parents, "Prepare to put your child in an institution. There isn't much that we can do." And sure enough when these kids learn from other kids with autism about socialization, and they didn't develop very good socialization skills, but when they learned from people that were typically developing, or people that could help them learn that reciprocity they could do lots better. So it's not nearly, you know, the kind of bad outcome kind of thing that was thought of generations ago.

Slide 9:
So I've alluded to this already, but the idea of thinking about autism as it's like a slice through the center of the earth. Some of you know my wife is French, and she has a home in Paris, and our daughter went there to go to college. And she met a French guy who's from Alsace. And they said, "Let's go visit my parents." And we went to Alsace, and you might recall Alsace is in the north German side of France. And, and so we went there and they said, "Let's, you want to

go visit some wineries?" I said, "Yeah that sounds fun. I'd love to go to some wineries." And as they went to each winery, they talked about their terroir. The way that their wines were made so fabulous because of the terroir. And they talked about the glacier that came down through Alsace that carved out the land, you know that made this valley. And then they talked about how that led to differing amounts of clay, and ash, and sand, and other things that went into their soil. So he said, "That's part of what gives us our terroir." But it's not just that. It's also the amount of sunshine, and the amount of rain that we get that leads to these great grapes that we're able to grow. That's part of our terroir, but that's not all. It's also the souls of the people that are tilling the soil that makes our terroir.

And I thought, "Well you know that's the way kids grow healthy brains." All of those things are important in thinking about the full picture that goes from symptoms, but down to the bottom at DNA. And for many years we thought by making a good symptomatic diagnosis we'd figure out how we were going to treat something, like doing the DSM. Well when that didn't work we said, "We're gonna find the gene and then we can go down to the DNA and then we'll find out how to figure it out." And really we found the action is what's happening in between.

When I first talked about this, and I was at the MIND Institute, I said to one of our researchers, Sally Rogers, who was one of the three people that developed the Early Start Denver Model, I said, "You know the problem Sally with what you're doing is you're working on the behavior, just on the surface of the earth. We need to figure out how could we make the ground healthier. How could we make things work better so that kids could do better?" And Sally, if you know her, is a clear critic, she said, "You know Bob you're wrong."

[laughter]

She said, "If I get these kids young enough and I do a targeted kind of intervention, I can resculpt their neurons. I can change those things that are happening down at the center of the earth." And so I put the arrows along the side saying that's true.

We can, through a variety of ways, but what the rest of my talk is going to talk about is to say, "Let's try and do this at all levels. Let's not do it at just one level. Let's treat the whole body. Let's find a way that we can do everything we can to make the body as resilient as possible. To be as healthy as possible."

Slide 10:
So when you say, "What's the center of the earth?" "What are those processes that are the epigenetic process?" There are things like immune abnormalities and inflammation, oxidative stress, free fatty acid metabolism, the microbiome, the gut, the microglia and astrocytes. All of those and we'll talk about some of them.

And I don't know if there's a way that people have access to my slides? Can they, can you get my slides? They sent them to Richelle.

>> Richelle Tierney: Yeah I'll have them posted on our website.

>> Dr. Hendren: Okay, because I drill down on this now but as I talk, but I added some slides at the end that if you have an interest in knowing more you can get to those.

Slide 11:
So I'm going to come back to that, but we're talking about autism through the life cycle.

Slide 12:
So when we think about brain growth and development we know that this prenatal or the parental history and early development experiences affects the epigenetic information. It does that through things that we call methylation and chromatin patterning. That's the next step after the DNA gets laid down. Histone acetylation, non-coding RNAs, mitochondria but they're all that that, layer that on my diagram went from genes up to mRNA and then went on up from there. Those are things that affect the way genes express themselves.

And that these things can be affected not only by the DNA, but they can be affected by things that get passed on that are even in that next layer. If your, if your grandmother smoked, the effects of her smoking can be seen in you or in your offspring. Skipping even a generation and going on. Where we can see those effects that get passed on. We've learned that everything isn't determined solely by that DNA code, but why the way DNA expresses itself.

Slide 13:
So we thought about that, and thought are the things that we could do that it can improve the perinatal experience. That could make the outcomes better. And we searched MEDLINE, which is a compilation of all the articles that have been peer-reviewed and in reputable journals, looking for risk factors. And then looking that might have things that might improve the outcome. With the goal of saying, "Is there anything that we could do for high risk pregnancies or high risk parents?" Especially parents like we've talked about, these that have one, or two, or three kids with autism, And I find a lot of parents that have had one child with autism will come in and say, "You know we're not sure we want to take the risk of having another child with autism." Or, "Is there anything that you could tell us to do that could improve our odds that things are going to be better than this."

So our review, which was published in Medical Hypotheses, last, or this year, was in agreement with other reviewers that support the possibility that maybe we could do interventions that could change outcomes.

Slide 14:
And the risk factors include those things that we've talked about, like maternal infection and inflammation, environmental toxicants, air pollution, pesticides, so on down the list.The SSRIs, there's a big question whether that really works.

There have been recently some interesting studies talking about an increased risk of both autism and ADHD in moms that took acetaminophen during pregnancy. They don't say as a

result of that they should be told never to take acetaminophen, but they might not use it in huge amounts. At least that seems to be an issue or a problem.

Slide 15:
What things might be protective? Folic Acid we know helps a lot with neural tube closures. And we primary care physicians, OB-GYNs, advise parents to take, moms to take folic acid, but it's remarkable how many don't. And in a study that was done at the MIND Institute looking at the incidence of autism among moms that took folic acid and moms that didn't, there was much less autism in those moms that took folic acid during pregnancy.

There are also some suggestive studies looking at omega-3's, vitamin D, antioxidants, iron, especially in older moms and moms that might be iron deficient.

Choline. And a developmental pediatrician and that I, I think was innovative as a person who does lots of autism. She has 340 kids with autism in her practice. And she had lots of moms coming to her saying, "What can I do to improve the odds that my next child won't have autism?" So she told these parents to minimize toxicant exposure.

Was an interesting study done of OB-GYNs asking them, "How many of them talk to their patients about whether they might be exposed to toxicants in their practice and how many, or in their work, in the things that they did, and how many of them really did anything to kind of suggest that they get out of that environment?" It's a really small number, like 20 percent. They asked, "How many of you think that exposure to toxicants might increase the risk of birth defects or of other kinds of problems?" Up around 90 percent. They said, "How come you don't talk to people?" And they say, "Well we're not sure enough about the evidence, and we don't want to worry them unnecessarily. But the notion or idea of saying, "Do you work in a plant, do you work, do you work near where pesticides are being sprayed? Do you work near a highway that has lots and lots of diesel dust?" You know just to say, "Maybe we don't know, but maybe you could avoid, you know going there." And usually most employers, many employers, will think about helping that not happen.

But she minimized toxicant exposure, maximize breastfeeding. Stretching out to two and a half to three years. Gave probiotics, did nutritional counseling, not necessarily casein, gluten-free but just making sure that they were eating well and healthy, limited antibiotics, and minimized the use of acetaminophen. And in a number of cases between 2005, and this zero, but 2005 should have been to 2013, she had zero new cases of autism.

And I saw her a couple weeks ago at a meeting. I said, "You know, I still really like that study. How is that coming"? She said, "You know, to tell you the truth, we still don't have any new cases of autism in these moms that have been following this program." Now that's not, you know, the kind of science that we base a recommendation on. To say, you know, this person did this in their practice. But it's interesting. You know it kind of makes you think, "Are there ways that we could work together to think about how to improve outcomes?

Slide 16:
There's a group called P2i, preconception to infancy, that's been trying to do this in a larger way. They arranged with China for all of us to visit there last year to talk to China about, you know, the amount of pollution they have. They don't acknowledge it, but if you've been to China, and I've been a few times. The air is, sometimes you can't even see across the street, and you imagine, what does that do? But to say are there things that we could do to push back, not criticize, you know their pollution, but to make them healthier. So we gave a series of presentations at Beijing University about how could we make these interventions. Everybody liked it, but so far nobody's funded it. So we'll see what happens.

[laughter]

There's a University of Georgia Center of Excellence. I gave a talk a few months ago at an integrated medicine conference that Andrew Weil sponsors, and the medical director for that program in Arizona told me she had written a book and sent it to me on "Be Fruitful: The Essential Guide to Maximizing Fertility and Giving Birth." It's an excellent book. It's really thought out well. She's a thoughtful physician, and I would recommend that to people that are trying to think about this.

Slide 17:
So as we go on past infancy. Is this pace okay with everybody? Is it too slow, or too fast, or it's okay? Thanks. Okay good, thanks. So the majority of research, you know what the research what us researchers want to do is work on young kids. The brain's plastic, we're going to see the biggest effect. And it's kind of too bad. I was so pleased on this balovaptan study that I had talked about, and I'll tell you more about in a minute, that they they opened it up because there hadn't been anything done with adults. So we did a study of balovaptan that's been published. Saying that this thing that's related to vasopressin, seems to improve socialization. And Roche is continuing on, studying that, but that's the only study done with adults. There's one other that's in the works right now. But mainly kids, you can see the biggest effect. You can see whether you change the course of things.

Slide 18:
And there are a number of studies that are done, but the problem seems to be too, how well are we doing it, identifying that. And Dr. Epperly referred, you know, talked about this and the importance of how do we identify things early? But when we look at, at kids with infectious disease, with, with intellectual disability. That's another ID.

[laughter]

And, and developmental disorders, children with autism were younger when parents first had concerns, and first discussed them.

It compared to those with just intellectual disability. Parents of children with autism were more likely to be reassured. To say things are going to be okay. You know, let's not worry about it.

That the more proactive the provider, the better at identifying those things early on than in those that are making passive or reassuring responses. Because if a parent's concerned, well it may not be autism, it's usually something that's going to benefit from an early intervention. So it's worth considering how can you get those things happening?

And those that had the early concerns, the delays and diagnosis were common. Particularly if the bulk of the comments were passive or reassuring and for somebody living in Idaho, I think about what if you live in Sandpoint? Or what if you live, you know, in any of those other small communities that we all love to go to when we go fishing or hiking but, you know, how do people get in and out of those? And then how do you get out of a mountain range to the nearest place for you, even if the miles aren't that far? So trying to make those needs for improvements in primary care.

Slide 19:
Then you say, "Is it too late?" And by the time you get to adolescence and adulthood to make any kind of difference?

Slide 20:
There are some studies, and I just mentioned one, but there are a number of others saying that the brain is still changing by the time we get to adolescence. And that we can make changes that show things make a difference.

There have been some interesting study of PEERS, which is a group treatment of teaching socialization to kids that have been done with children, but now adolescents, and recently with adults. And we just did a study at our school, that I'll tell you about in a few minutes, looking at, at PEERS can make big differences in how kids are doing, even in adolescence or in adulthood. And there are other interventions that we can do that can make a difference as well. So it's not ever worth saying, "It's too late, or there isn't any more that we can do to make a difference."

Slide 21:
The thing that's sad, I find for adults, especially as they get to be around 22, they kind of fall off a cliff. There's a sense that the resources that are available to help them aren't there as much. So only about one-half of young adults with autism have ever worked for pay. When they do, it's making far less than people even with similar kinds of disabilities might be making.

There was an interesting article in The Wall Street Journal last Saturday that some of you might have seen, that was talking about a program at Microsoft, and the way that they had of helping to interview people on the spectrum that was sensitive to how they express themselves. So that they could bring them in to, to jobs if they were qualified, rather than do one quick interview that just didn't go well. And then they don't really get in, and can't keep going on with that.

Slide 22:
Another challenge though is primary care for adults with autism. Many primary care, or I don't know if Dr. Epperly would agree with even with saying most primary care doc's are not trained to work with people on the autism spectrum. They've been, they, and it's a whole different thing that they're working with because the challenges are not just in one area. Like, say you have a developmental disorder that makes it so you have motoric difficulties. You have one area of difficulty and here we have multiple accesses spoken language, written communication, performance, daily living. All of those things that, that need to be addressed and thought about by the primary care physician.

There's also an increased rate of chronic medical illness that you've heard about already, and other kinds of symptoms that could be a little bit of a surpriseto the primary care physician. There's also many times the need to work with the whole family. If you're thinking about working with an adult, you think that adult comes in to see you. But in this case the whole family comes in to see you. And you're thinking about, you know, who do I talk to, who do I have a right to? And have the parents had this child conserved? What, what are the all the legal kinds of rights that need to be thought about? But you're also thinking about, "How do I communicate in a way that works for everybody?" "That respects this person with autism and their individual rights, but respects the parents who want to do the best they can for their child." So it's a, it's a trickier kind of circumstance that I think is often richly rewarding and a pleasure to be able to join a family and be part of that family. But I think people need to be trained to know how to do that.

So children, or youth 11 to 22 with autism were thought to thrive less well than even those just with intellectual disability and the biggest difference seems to have to do with socio-communicative ability and school participation in terms of how that outcome goes.

Slide 23:
So as I move right along. I'm moving into comorbidity and interventions, but I can go fast through this because you've already heard some of these.

Slide 24:
But I'm going to go back to the terroir model to say once again as we think about these levels where can we make an intervention?

Slide 25:
How might we make those, and at a level we can think about. That outside level of behavioral interventions, family support, and structure.

The next level thinking about speech, language, OT, cognitive behavioral therapy.

The next level might involve pharmacotherapy. We'll talk briefly about that now and then we have a panel discussing it later this morning.

And then this biomedical epigenetic approach that I'm going to talk a little more about as we get towards the end of our time.

And then I don't think we're ready yet for gene modification, but certainly there is that point at the, at the gene part of what we might be thinking or talking about.

Slide 26:
We have a whole panel talking about behavioral treatment so I'm not going to go through all of these except to point out there are a number of behavioral treatments. There isn't just one. And sometimes we think of ABA as being one kind of treatment, and yet there's all of these that follow underneath it. There are people that have various amounts of good evidence for PRT. The Koegels have good evidence. Floor time doesn't have good evidence, but people that are passionate about it. TEACCH doesn't have good evidence, but people that are passionate about it. The Early Start Denver Model that has great evidence. And then what has been called Naturalistic Developmental Behavioral Interventions. And I don't know Julie if you're going to talk about all of these, or...

>> Dr. Julie Fodor: We're going to talk about [indistinguishable]

>> Dr. Hendren: Okay, good but at least that's, there's a list of those that you'll find people feel passionate about, and then you need to figure out what's the best fit for my kid. Or is there even a way that my kid progresses through these steps? That you, and that's kind of what the Early Start Denver Model says, although Sally disagreed with me on that one too,

[laughter]

but I said, "You know I think that there's a way you start off with discrete trial training, and then you get the kids attention." "You need to get an interaction. Then you work your way through it."

Slide 27:
Medical comorbidities. Sleep disorders are a big problem for families.

That occur in 50 to 80 percent. GI abnormalities. It used to be people would say, you know, GI abnormalities just because the kid with autism eats funny. And that's, you just need to figure out how to not have them eat only chicken McNuggets. We still think the two cardinal signs, you could make a diagnosis of autism if the child only ate Chicken McNuggets and they really like Thomas the Tank Engine.

[laughter]

>> Audience member: There you go!

>> Dr. Hendren: You got those first two things, you got the diagnosis! But, they still eat differently, but there is a certain way that it's more than just how they eat I think, and there

have been good studies from Autism Speaks and others. Kind of reviews looking at GI abnormalities.

Abnormalities higher than in the general population, up to about 30 percent of people. Two waves, one that occurs more in childhood but not from febrile seizures, a little later than that. Another one that happens towards the end of adolescence into young adulthood, and suggests that maybe there's a second wave of brain changes that are happening that lead to that epilepsy. Which may lead to a worse prognosis because people can die from those seizures or from things that happen when someone isn't there to help keep them from choking or other things like that.

Slide 28:
Immune disorders. These kids have more food allergies, allergic rhinitis, atopic dermatitis, autoimmune disorders, asthma. The studies show increased numbers of pro-inflammatory cytokines. And people use a variety of treatments, but don't have any great evidence for trying to treat those.

And then a higher rate of other medical conditions that I've already alluded to. Many kids with autism, you gather the history, and they say, “Yeah, he always had an ear infection. He was always having trouble.” And they get their tonsils taken out. They do other things.

Slide 29:
Mental retardation. At least according to DSM 4, are talked about 70 percent. It's probably less than that now because I think we've really expanded the spectrum to where we're seeing this whole broad spectrum of people with autism that does account for the larger numbers. Many of those people are very, very, you know 140 IQ but with lots of splinter skills and ups and downs, and how they're doing with those areas of how things are going.

Regressive autism was controversial. All kids with autism seem to show a bit of a regression around 18 months but there are some kids that seem to be developing relatively normally, and then they show a fall-off. Which is where some people have tried to say, "Well that's because they got vaccines then." But studies of vaccines hasn't said they correlate perfectly with that. But there have been studies of family home movies, a variety of other things, tracking kids at high risk that does say some kids do regress. And maybe they're a unique group. Maybe they could, maybe they're more autoimmune, and maybe there are things that could be done to treat them differently.

And mitochondrial, I shouldn't say disorders, I should have said dysfunction. Because the disorders are really, really rare. And they're really rare in people with autism. But when you look at mitochondria. Those little energy bunnies in your cell, that kind of drive you along. The, the one, the first case of vaccines that was won in the, in the Vaccine Court, for I think two million dollars, was by a doctor. Jonathan Poling, who had a little girl Hannah that got nine vaccines at one time when she was four or five. And she developed autism at that point. And she had a mitochondrial disorder that had not been previously diagnosed. And so they, the

people said, "Well she shouldn't have gotten all those vaccines. That shouldn't happen." The Vaccine Court gave him two million dollars. He donated it.

The one other digression I'll say on that story. When Jonathan came to the MIND Institute with Hannah, we talked for a while. I said, "What things have you tried for your child with autism? You know what, what kinds of treatments?" And we'd start going through this list. And we finally even got to chelation. And this guy's a neurologist. Trained at Hopkins, really a thoughtful doctor. And I said, "Chelation?" And he said, "Yeah, we've tried that." I said, "Oh my god Jonathan, I don't believe that. How could you have tried chelation for your daughter?" And he said in a way that still almost makes me choke up. He said, "You know Bob, my little girl Hannah has autism and I'm going to try everything I can to figure out how I can help her." "I'm not going to stop at anything unless I think that it's way too dangerous because I want to be sure that I've tried everything." And it's made me think ever since then about how important it is to try to work with families to help them find the right way to make decisions. To get to the right resources. To have that work out the best they can for them.

Slide 30:
So another part of the differential diagnosis has to do with all those other comorbid disorders. ADHD. About 40 percent of kids with autism meet criteria for ADHD. Many times their autism can benefit from treatment for that. OCD. It's hard to differentiate that from the OCD that's part of autism or is it really a comorbid disorder on top? Tics and Tourette's or more Overanxious Disorder. Bipolar - surprisingly there's a genetic predisposition in families with kids with autism for bipolar disorder to be in other genetic linkages in the family. Depressive Disorder, Learning Disorder, Psychotic Disorder, Catatonic Autism. That's become increasingly interesting lately with kids that move between being stiff and waxy to being very excited.

And then aggression is the main reason I see people. You know when they get to see me as a child psychiatrist it's generally because parents are concerned about aggression and how can we deal with that. I see them for other reasons, and early on too, but when they're coming to see me to talk about medications it's often that.

Slide 31:
Here's my quick summary on medications because we have a whole panel to talk about more of it later. And in that information sheet that I had mentioned that Richelle will make available in my talk. There are a whole list of medications and the indications and studies for that.

But stimulants work for some. The early studies of stimulants suggested that kids did very poorly and I can't tell you the number of parents that come in... child with autism, said, "Yeah somebody put my kid on stimulant. He got psychotic, he was just off the wall. We don't ever want to try that again." And part of that is that they, kids that are very young have more of a strong reaction. Also you need to start at a low dose, work your way up. Start low and go slow.

Antidepressants, maybe work for, for a depression and for anxiety. There have been quite a few series of studies now saying that it doesn't seem to work as well for repetitive behaviors including just a meta-analysis out in the last two weeks in JAMA.

Alpha-adrenergic agonists. Things like the clonidine and guanfacine work for some. Not a lot of studies, maybe it helps with anxiety.

Anticonvulsants. Some for mood dysregulation, but some for kids that maybe have a, have some kind of neurologic abnormalities in addition. Even if it's not a firm EEG abnormality, or others, some kids do better on anticonvulsants. We can talk more about that later.

And antipsychotics, we will talk more about later. The two with an indication, risperidone (Risperdal) and aripiprazole (Abilify) all have adverse effects. But the evidence is quite good that they work. And then there are other antipsychotics that there is more of a question about. Asenapine. Maybe there was a negative. Lurasidone. Lurasidone doesn't have as much weight gain. It's called Latuda. But we were part of the study that said didn't seem to work for autism. So it maybe doesn't have a full place to try.

Slide 32:
The ones that are worth considering. You know that that while people don't think of them as a first line is Propranolol. The work out of the Thompson Center, which I know a number of you are here involved with. Dr. Beversdorf has done some really interesting studies about propranolol that seemed to be helpful for anxiety and a variety of other things. It's worth considering. I've especially found it useful for kids that have comorbid genetic disorders like Smith McGinnis or... come to me in a minute.

Naltrexone sometimes at low doses. Doesn't make a big difference.

Buspirone, I think BuSpar is a funny, you know it's an anti-anxiety agent, doesn't have big effects. I have, some of my colleagues laugh, and say they use it as a, as a placebo. You know if they, so if family comes in, and they think they're going to respond to anything they say, "Here take this BuSpar." And if they say it works then they know that they respond to a placebo. But BuSpar does have a specific effect and there's quite a series of mostly small case reports suggesting that BuSpar might have a particularly good effect for anxiety and kids with autism.

Mematine (Namenda) is a Alzheimers medication. They did a large autism study, turned out to be negative. More because they had a large placebo effect, like up around 40 percent and then the actual response was about 60, so it didn't separate. There's some kids that do better in that.

And interesting, Amitriptyline in a low dose seems to help some kids with anxiety.

Slide 33:
For sleep my kind of formula is to go through melatonin, then go to GABA and L-theanine, hydroxyzine, clonidine, trazadone, mirtazapine, olanzapine in that order to try and help people sleep.

Skin picking, I've had some good result with N-Acetyl Cysteine up to 2,400 milligrams. Somebody had said too, "Are you going to talk about dosing?" And I said, "You know if you want to talk about dosing in the panel we'll talk about dosing for any of these things when we do that, if there's people in the audience that are interested." SSRIs, duloxitine, buspirone.

Screeching or yelping. When I found, some kids do better on divalproex (Depakote). Treatment-resistant OCD, NAC, L-methylfolate. Anxiety - gabapentin, pregabalin.

Slide 34:
And then I'm kind of heading into the last part of my talk. I feel like you're all getting tired hanging in here with me. I'm going really fast, but, and it's early in the morning on Saturday.

CAM. You know, complementary and alternative medicine is something that I think most of us, when we hear that term, we think it's, it's used by people that don't want to use real medicine. And they don't want to, so they want to avoid it and they want to do something like have them eat plants or something you know, that, that doesn't really make a big difference or work. And yet increasingly we found there are a group of people and there are a group of things that seem to make a big difference in improving the body's resilience.

And lots of people are taking, for themselves, and for their kids, those things that be called a complementary alternative. Up to 82 percent of children recently diagnosed with autism.

The reason that family members give for that are that they're concerned about the safety and adverse effects of prescribed medications. And then when they go see their, their doc, their regular physician, they find that they're not very knowledgeable about that. And it's very hard for families I think, to feel like they go see a non-traditional practitioner who tells them, "Here, try these things but don't go see that traditional doc." "Because he or she doesn't know what they're talking about, and they'll just say, 'don't do it .'" And the traditional doc will say, "Don't go do those things, because there's no evidence that they make any difference." And parents are left in the middle to say, "How do I decide? What do I try?"

And so I think it's really incumbent upon primary care docs, psychiatrists, others, to know enough to not just shut them down saying, "That doesn't work." But to say, "Let's examine the evidence." Or, "Let's think about what's safe to use and not safe to use and what kind of risks are you willing to take?" For my friend Jonathan Poling he was willing to try chelation. Others may say, "No, one kid died from chelation." And except they used the wrong kind of chelator in that kid. But you'd say, "I want to be sure I go see somebody who knows what they're doing." So we need to be knowledgeable resources.

Slide 35:
Those are all the things that I think are being affected, or at least thought of as being targets. We've already talked about some of those for these people.

Slide 36:
But we're increasingly finding subsets of people with autism have things like intestinal inflammation, digestive enzyme abnormalities, metabolic impairments, oxidative stress, mitochondrial dysfunction, immune problems.

And in many cases we can see improvements in those with a combination of nutritional recommendations, prescription medications, addressing underlying medical conditions, and that way treating the whole body. Treating all the things that we can see that might be playing a role.

Slide 37:
Those that I, I could, I could give you a huge list of complementary and alternative treatments, but if we're talking about those that have some evidence. Melatonin, good evidence. Three to nine milligrams, two to nine milligrams. Helps people fall asleep initially. And there is now a new formulation of melatonin that's a slow release. Which you'd say, "Wait, if you're resetting the body's clock, how does that work?" But the people who manufacture it say, "Melatonin isn't released just in one single burst, it's released in a big burst and then slowly goes down over the night time." So they're following that and that helps people sleep through the night.

Omega-3, not hugely strong evidence but good evidence, in a number of reviews, including one that we did, suggest it works.

Vitamin D3. Methyl B12. We did two studies of methyl B12. The first one, you know when Ron had alluded to the MIND Institute. When they interviewed me to be the Executive Director, they said, "You know we want you to leave no stone unturned about what might cause, or how you might treat autism. We want you to do good science, but keep an open mind." So I went to a few meetings. I said, "You know what can I do to treat, you know, what kind of treatment could I do? A randomized control trial and see that this really worked." They said, "Chelation." I said, "No I don't want to do chelation." I said, "You know that's just too hard and too controversial. And then you have to have people on a casein, gluten-free diet first, and blah blah blah. That's... what's next?" And they said, "Methyl B12." I said, "Okay." I knew somebody that could do methyl B12 biomarkers very well, Jill James. There was a way that we could do Methyl B12, and we found a way to kind of change the way that whether someone could see the syringe where you're giving this subcu injection. The first study that we did at the MIND Institute when I was stlll there. The second kid that came in was one that just changed my mind about all this. He was, it's a kid that had autism and seemed in a fog, and just seemed out of it. And the second time he came in, his eyes were clearer. He looked at me. He, it's the first time I thought he'd ever seen me, you know. And it was like there was this kind of awakening and his parents were ecstatic. They said, "You know it's not like his autism was over." But they said he's more present. He seems more with it. He seemed healthier in a certain way. And a number of kids in our study showed that improvement. I'm not saying Methyl B12 is for everybody, but it made a big difference for these kids. And based on that we got a larger, much larger grant from Autism Speaks. And we did a larger study that we've published, that was a more randomized

control trial, that showed a difference in how these kids did, and showed the changes in their biomarkers of oxidative stress that correlated with their improvement. But the sense that a veil had been lifted off this kid was something that was powerful to me. To saying, "Are you making this kid more resilient? Are you making them healthier?"Are you taking something away that helps them do better?"

NAC and acetylcysteine, some interesting studies, not all conclusive, Vitamin, mineral supplements. The diet, the microbiome. Pancreatic digestive enzymes. Balovaptin. CBD and THC. And I'll mention CBD and THC again in just a minute.

No I won't.

[laughter]

I didn't have that. So Rhonda was asking me about that yesterday, about CBD, THC. You know when you review the literature, and you maybe saw, just you know an excellent review of all the CBD studies, THC studies, just published in the last couple of weeks. Saying we don't have enough evidence to say anything about whether this works or it doesn't. And if we look at the evidence, we'd say we're premature to be thinking it works for everybody. There aren't good studies in kids with autism. And we don't know anything about dosing and safety. We do know something about long-term use of CBD, THC in people whose brain is still developing. And in fact it suggests that are bad effects long-term that are permanent in the developing brain. But there is increasing interest in the cannabidiol system. And the role of cannabidiol in autism that suggests there might be some rationale behind this. I have a number of patients that come in, and in California it's legal over 18, under 18 I still need to write for it. But I do and I'd send them to a dispensary that I'm familiar with. You know, I don't know how they dose. I call, they want me to call. Like there's usually psychedelic music playing in the background.

[laughter]

"Hey man, you know...

[laughter]

But some of these kids seem to do a little better. And some of them don't. I'd say maybe of 20 kids that I followed so far, I'd say half did a little better, continued. Even less than that half are still taking it. But many of these kids were on multiple psychotropics. Had lots of aggression, and other things. And the CBD helped. So I'm, I'm not opposed to it at this point. I'm keeping an open mind. I'm hoping that somebody does good studies so that we know more about it.

The Balovaptin I'm excited about. This is the Roche study, and it's been published. And there's a reference to it in the information that I have.

Slide 38:
This is my final segment.

Slide 39:
This is our lab and we work at a school called the Oak Hill School, which is in San Anselmo. We have built an outcome study into all that we're doing at the school.

Slide 40:
And we're trying as much as we can to use this as a medical home. To make the school a medical home. Where we can work with parents and the teachers, and trying to think about educational, medical, everything that can wrap around this child and measuring then the effects of those interventions through the, the outcome study that parents and teachers fill out. And our goal is to increase biomedical resilience. To make these kids healthier, and then pushing back, and to develop new and effective treatments.

Slide 41:
We thought about what can we do that could be a biomarker for our outcome. Genomics, too far upstream you're not going to change genes. Transcriptomics, even proteomics, not far enough downstream. We think it's metabolomics, but look at the metabolic outcomes.

Slide 42:
So we did a study with... hope I didn't do something bad...

Slide 43:
With actually sulforaphane, which is a concentrated broccoli sprout extract that was developed to treat oxidative stress in cancer. And they did a few studies suggesting that it worked. And it particularly worked on heat shock. People that had abnormalities of heat shock protein. And heat shock protein is something that correlates with fever and kids with autism sometimes show improvement or worsening when they have a fever.

So an interesting researcher thought maybe I could try sulforaphane. Randomized control trial showing kids did better. So we said, "Okay, let's do that with our kids." We had 15 kids come in, using metabolomics as an outcome measure, showing significant improvement in the, in the kids but not randomized, not controlled. But there were 77 urinary metabolites that correlated with these improved changes. The oxidative stress at the top, but sphingomyelin is something that has to do with the protective white matter sheath that we see around nerves, and we see in the white matter in the brain, seemed to show improvement. Suggesting maybe a difference for Sulforaphane.

Slide 44:
And we've done this study now with folinic acid. We're getting ready to publish those results. CM-AT is the pancreatic digestive enzyme that I hope we can do next. We have other studies that we're doing, looking, using this model.

Slide 45:

Last three slides. The... I think of autism as this veil that comes over the person that's, that's underneath the veil. There's a way that I think, I have huge respect for the neurodiversity

movement. I think that people who have autism should have every bit of respect that anybody has, and that we should respect their, those things that they have. I'm not sure that... I respect their autism, but it doesn't mean I don't want to treat their autism. It's like saying somebody has diabetes. I want to help their diabetes get better, but I still can love them just as much with their diabetes.

So for this I think about how we talk about an autistic person. Don't like that phrase. You're not an autistic person. You're a person with autism. And so this person is underneath this veil. And part of our goal is to lift that veil. To help so we can reach inside, and put our loving arms around that person to pull them out. The people that I've come to know with autism, are, you know, I like those people. There's that person in there that I get to know. And sometimes people just see the autism. And they see that's the whole person. I think it's more trying to see the person underneath. Saying, "How can I make them as resilient?" Just like I would for anybody else in a family practitioners' practice, or any other way that we're doing things. But to lift that veil so that that person can emerge as much as they can.

Some part of the veil might be part of them. There are certain ways of shaping the world that people with autism have. That I appreciate. That, I think as you know, I learn a lot from that and I enjoy that. But there are some things, like a hand clapping, no eye contact person that doesn't have any communication skills. But I'm just not going to say, "No that's okay." I'm going to say, "I'm going to try and make that as well as I possibly can."

Slide 46:
So I'm going do that by trying to treat this with an integrated approach. By thinking about treating everything that's medical that might be involved and thinking about ancillary speech and OT, using all the things that we can in a behavioral approach. Treating associated symptoms and if necessary using pharmacology.

Thinking about biomedical treatments. I use melatonin commonly for sleep disorders. I suggest to parents that they consider adding omega-3 and vitamin D3. If child has a lot of GI problems, I think about probiotics and digestive enzymes.

But I think the key to all of it is building personal relationships and resilience. Trying to say, "Form a relationship and join this family.' Enjoying this person who has autism, and help them all be as resilient as possible.

Slide 47:
I'm going to pass on this one because my time's up.

Slide 48:
At the MIND Institute we had an art competition before the building opened. And we had people from all over the world with neurodevelopmental disorders send in their artwork. The youngest was three, the oldest was 87. We had a juried panel that went through them, based on age, and picked out 70. They're now hanging in the MIND Institute.

This one's my favorite. It's called the haircut.

[laughter]

And this boy, who was five at the time that he drew this picture. And I still see this boy, he's still in my practice. And he's now 28 I think. And his mom said... So if you look at this, getting this haircut. The guy up at the top you can see with his scissors. The bee is probably the buzz of a razor cutting his hair. And you can see how he's feeling about it. She said that whenever he was in a really uncomfortable situation he always tried to show an escape route. And you can see this little door on the side.

[Audience murmurs "Ah-ha"]

That's his escape route from this uncomfortable situation.

I hope that by treating the whole body. That by helping people be more resilient. That by keeping an open mind, and considering all the things that we can do to help people be more resilient. That we can help people escape from the downside of autism, and enjoy being fully them, including being full of, for them, if part of them is autism. Except that I think the core of them is not autism, the core of them is them. So I hope that, that we can help people escape in that approach. Thank you.

[applause]