

## Interview with Dr. Martha Herbert— Autism: a brain disorder or a disorder that affects the brain?

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### Abstract

Autism research priorities have been shaped by underlying models. The model of autism as a genetically determined hard-wired brain disorder, dominant in recent years, has led to a search for “brain genes” and brain alterations. But this model has produced limited results, has rested on an over-interpretation of evidence for heritability, and has also failed to encompass multiple features of autism outside the behavioral definition, including systemic physiological changes (especially, but not restricted to, gastrointestinal and immune) and the increasing numbers of cases. A more inclusive model would construe autism as a disorder that *affects* the brain, and that is the outcome of complex interactions among factors related to genetic vulnerability, environmental triggers or causes, and epigenetic changes. This model can incorporate many recent findings, and it opens the field on several levels: to broader genetic investigations (including, for example, systemically expressed genes that could impact the brain secondarily), and to study of vulnerabilities beyond genetics at multiple physiological levels. Since the behaviors that define autism appear to be produced by brains affected by a variety of biological alterations, this more inclusive model is also better oriented to encompassing autism's heterogeneity. It allows us to investigate what systems and network-level commonalities there might be among brain and body changes whose specific biological details may differ. Of paramount practical importance is that some features of systemic involvement may be modifiable. Thus, we may therefore more aggressively search for such features as potential treatment targets that may reduce suffering and improve options for affected individuals. By improving metabolic status, parameters modulating brain function (e.g., synaptic thresholds, connectivity, energy metabolism) may be affected in a favorable way. This may account for some of the growing number of anecdotal reports of recovery from autism after integrative biomedical and behavioral treatment. Moving from a “genes-brain-behavior” to a “pathogenesis (genes, environment, epigenetics)-mechanism (molecular, cellular, tissue, processing)-phenotype (behavior, sensory-perceptual, cognition, medical)” model, which not only spells out the levels of the biological hierarchy, but also looks at all these levels developmentally, is a challenge to compartmentalized science, but this is what we need if we are to translationally connect research and successful treatment.

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*Now please join me in welcoming Dr. Martha Herbert. Dr. Martha Herbert, M.D., Ph.D. is an Assistant Professor of Neurology at Harvard Medical School, a pediatric neurologist at the Massachusetts General Hospital in Boston and at the Center for Child and Adolescent Development of Cambridge Health Alliance and a member of the Harvard MIT MGH Martinos Center for Biomedical Imaging.*

*Prior to going to medical school she obtained a Ph.D. in the History of Consciousness from the University of California, Santa Cruz. She has received the Cure Autism Now Innovator Award and directs the Cure Autism Now Foundation's Brain Development Initiative. She is the co-Chair of the Environmental Health Project of the Autism Society of America. Her research program includes studying what makes some autistic brains unusually large, how the parts of the brain are connected and coordinated with each other, how to incorporate metabolic biomarkers into brain research and how we can develop measures sensitive to changes in brain function that could result from treatment interventions.*

*Today we are learning more about concepts and findings from Dr. Herbert's papers entitled, Autism: A Brain Disorder or a Disorder That Affects the Brain?" published in Clinical*

*Neuropsychiatry in 2005 and her most recent paper, Autism and Environmental Genomics from Neurotoxicology.*

*Dr. Herbert, a pleasure to welcome you to Autism One Radio.*

Thank you. Thank you for doing this.

*Dr. Herbert, how are autism spectrum disorders currently defined?*

Autism spectrum disorders are defined behaviorally—by behavioral criteria that you observe according to a set of standards that have been developed through extensive research on many individuals. But there are no biological markers. There's no blood test, there's no brain imaging test, there's no EEG that can support the diagnosis. It's a purely behavioral diagnosis.

*So how much do autism's behavioral features really tell us about autism's biology?*

Well, we really can't answer that, but I suspect that it's a pretty indirect route from the behaviors to the biology. What I mean by that is that there may be a number of different biologi-

cal pathways that lead to similar behavioral features. And you can't reason back directly from the behavior to the biology, except possibly in certain circumstances. But we really don't know because, for the most part, autism research hasn't been measuring that biology.

*Those are really good points, Dr. Herbert. Now, how many body systems seem to be involved?*

That's a very interesting question. And, you know, I'm wondering whether it's always the same thing. Certainly the immune system and the gastrointestinal system feature prominently in many individuals. However, it may be that in different cohorts, in different countries, you may see different patterns. I've heard from some researchers that there are more gastrointestinal cases in England than in the United States. And I took a trip to Cuba and I found that people at the autism schools there were talking about lung involvement which I haven't heard anywhere else. The bottom-line is that we really have very little systematic evidence on that.

*I think that brings up a really important point and possibility to mind—that because they're reporting a greater prevalence of GI involvement in England or lung involvement in Cuba, that gives us some more direction for research.*

Well, these physical phenomena are tremendous cues—clues—I mean, both. They're clues because they point; they're clues and cues because they point us in directions where we can use, if we are courageous enough to do so, the biological information about those systems to help us understand what could be driving the problems.

*Yes. And it kind of is a reminder to us, a cue as you said, to keep our thinking broad for the moment. Would you agree?*

We really need to keep our thinking broad. I think when you don't know what a disease process is you need to observe the phenomenology – which is just what... how it presents itself – very carefully without imposing models which would exclude certain factors on the basis of assumptions that maybe you haven't proven yet.

*Right. Science is supposed to go into things with an open mind and report what it finds rather than a limited presupposition?*

Right. You're supposed to describe carefully. There's a natural history phase in the early periods of the development of domains of science where you mainly describe carefully, and the systematization comes after an extensive period of careful observation. I think that kind of careful observation has been supported in autism research to a significant degree in behavior, but we need it in the whole body approach to autism as well. We need it to be systematic; we need it to be supported.

*Now, you go into a more systematic whole body approach in your paper entitled, "Autism: A Brain Disorder or a Disorder*

*That Affects the Brain?" Why is it important to make the distinction called for by that question – that title of your paper?*

I think we're oriented very much in what we perceive – by what we think. We organize the information and the information that comes in that matches the models in our minds is highlighted. The information that doesn't fit in with the models becomes background or invisible. If you call autism a brain disorder you will study the brain and you will presume without even thinking about it that the brain is the primary and maybe even the sole target of whatever it is that's causing the problem. But, if you call it a disorder that affects the brain you certainly still are talking about brain changes, but you're now saying that perhaps the brain is not the only target of the factors that are causing the problem, and that other things could be affected. And the brain can be affected even in parallel with, or even downstream of, other things that are going on in the whole body.

*What an excellent way to put it. Now Dr. Herbert, you've alluded to earlier that you think that a child can reach the final endpoint labeled "autism" in a variety of ways. So, have we found one gene, one set of genes, one set of biomarkers, one phenotype or one etiology associated with autism or specific autistic behaviors? I think what you said previously tends to preclude that?*

Oh no, we haven't found that at all. Some of my colleagues still don't really understand this issue. For example, some geneticists I know will say Fragile X is a gene problem that causes autism. It's really interesting that they will say that considering that only 30% of people with Fragile X develop autism. Such geneticists may say Fragile X doesn't have "full penetrance," but that really begs the question of what mechanisms modulate penetrance. So, Fragile X can't be a cause of autism; it can substantially raise the risk of autism and it may take not a whole lot of anything else to kick a person over into autism. But if some people with Fragile X don't have autism, then it alone can't be a cause of autism. So, that's one line of argument saying that we don't have causes. But more beyond that we have been funding and supporting a lot of genetic research, and we have found genes on most of the chromosomes that we carry. Most of them are of low effect, and most of the studies that find something of significance in genetics are then not replicated by some other group in some other place. And that doesn't necessarily mean that the first study was wrong. It might have said something somewhat meaningful about that limited cohort. But if we don't find the same thing everywhere, as we have in some more classic genetic disorders like Huntington's Disease, then we're looking at a different way that genes operate. So, this is something that's incredibly challenging because in the era of conquering infectious disease we got used to the idea that if you find the bug and you find the drug you've got the problem solved; whereas, autism doesn't look like that. It's much more complicated.

*So, getting back to what you said about Fragile X, it sounds as if every time there is a genetic possibility for autism to occur or something that may help it along, it won't necessarily occur.*

*So if there's a relatively high percentage of children with Fragile X who also have autism or children with Down's syndrome who also have autism, that may help it along but every time there's a genetic possibility it doesn't mean that autism will occur. Is that all right?*

That's right. Genetics is not inevitability. Genetics is risk.

*Ah. Wow! Well put. Now, how has the mainstream perspective to date framed the research agenda?*

There's the triad, the three behaviors that define autism. This is the language: "Impairments in language, in social interaction, and a tendency to repetitive or restrictive behaviors." These features seem to many researchers to be so precise that it's hard for them to imagine that there wouldn't be precise determinants of such features to be found in the genes or in the brain.

This is ironic in that if you actually hang around with the children you can formally construe children as meeting those criteria, but in fact each child does it in his or her own way. There's a lot of variability between children. So, the idea that these things are precise and uniform isn't really accurate.

But let's say you believe that this is precise and uniform. What you will then do is design a research program to look for genes that affect specific brain regions that are implicated in constructing the behaviors that are, as it described in the definition so to speak, going wrong in autism. And that's what people have been doing. And I still talk to researchers who think they're going to find one set of genes for language and corresponding brain regions, one set of genes for social interaction and corresponding brain regions, and similarly for the repetitive and restrictive behaviors.

And actually there are a lot of us who don't look at it like that at all, but that's what the research has been like. I started that way. I had brain data and I got a federal grant to compare the neuropsychological deficits in behavioral data with the brain volume differences in specific brain regions. And I worked and worked and worked, and—my goodness—it wasn't there. That wasn't what was going on. There were other things going on but that wasn't it. So, I evolved away from that point of view. Other people haven't evolved away from it quite as much as I have. But, there are also many others who have evolved away from it. So, this is a – there are quite different sets of perspectives currently coexisting in the field.

*You mentioned Dr. Herbert that genetics wasn't "equated with inevitability." – it was equated with risk. Are there environmentally responsive genes that are also related to risk to disease vulnerability?*

Well that's a very important question. The National Institute of Environmental Health Sciences has an Environmental Genome Project. They're studying variations in genes that are associated with how we respond to influences from the environment. These influences could be chemical, or stressors, or infections, or other such things. We have a lot of variability between us in our genetic underpinnings for this. Enzymes and response systems can work more slowly or more quickly and this may have something to do with the environments in which our an-

cestors lived... where there's a lot of ecological variability from region to region in the stressors that our ancestors faced, and that may have selected for different types of genes in different individuals... that's one possible contribution to differences among us in environmentally responsive genes. Also, environmentally responsive genes to a significant extent have more variability than other genes because all of these need to respond to environment sets that are different in different places.

If you are in an environment where you face a certain kind of metabolic stressor or an infectious stressor you will be more likely to be able to handle that better, but then the gene that gives you that ability may also confer other side effects that can cause problems, particularly, when you're in a different environment where the stressors are different. So, this is a way of thinking about genes, which relates to our history on the planet that also relates to the fluidity with which we interact with our world. You know... we're constantly metabolizing things and responding to things. And there's a great deal of difference. There are differences up to 10,000-fold in how fast people can metabolize and eliminate various toxic chemicals.

*Wow.*

So that's an enormous difference between individuals. So then an exposure that one person can take in stride perfectly well can be a real problem for somebody else.

*Well, it sounds from what you're saying, Dr. Herbert, as if this lends to taking a more common sense approach. Certainly what you said seems prudent and logical. It sounds as if things to which we're exposed is not a "one size fits all" formula and that, in general, we've best be careful about what we expose people to, in the meantime, until we know more.*

I think that's right. I think that what we're coming to is in 21<sup>st</sup> century medicine and biological science the problem of individuality and the problem of complexity. We're finding that the genome differs very much from person to person, and we don't yet know how to really turn that into a comprehensive program of prediction and treatment. But we know that that variability is critical. And in a population there can be a substantial minority who have greater vulnerabilities.

And this leads to something called the "precautionary principle." The precautionary principle is a basic principle for policy with regard to innovations including chemicals and new technologies, which says that we should prove things safe before we implement them. The current standard is more a risk-benefit analysis approach where you calculate up the risks and compare them with the benefits, and where you presume safety until danger is proven. So, you do not have to test things as exhaustively in a risk-benefit approach as you would have to test them in a precautionary principle approach before marketing innovations.

So we have, you know, several thousand chemicals introduced to the market each year and we have many chemicals that have been around for a long time even before the regulatory apparatus that we now have was introduced. So I think we have something like 58,000 chemicals about which there's almost no testing data – but that they were "grandfathered in" because

they've just been around. And that's a problem because what we're finding is that not only are there differences in vulnerability from one person to another person, but we're also finding that there are different levels at which chemicals can impact you. At a high level a chemical or a metal, or whatever, can kill a cell, but at very much lower levels, thousands – sometimes even many thousands – of times lower exposure level, a chemical can imitate one of your body's own hormones or signaling mechanisms and change the way the cells in your body communicate in a manner which is not what the body would have done on its own.

So all of these things are incredibly complicating the way we need to be thinking about environmental risk, and then you add that to the differences in vulnerability, and we have a very, very, very different situation than what we thought we had in the 50s and so forth when we could go around saying "better living through chemistry."

*I think you've just given us some incredibly important insights, and I think you've made a crucial distinction in talking about the significant minority who could be affected and the "precautionary principle." Let's talk about twins for a moment. Although a strong genetic contribution has been suggested for monozygotic twins, what do percentages of monozygotic twins affected tell us about the possible role for environmental factors.*

You know it's really interesting that many people, even some quite knowledgeable about autism, quote the concordant figures in a somewhat inaccurate way. "Concordance" means that if one twin has autism the other twin will have autism. But there are different levels of concordance. One level of concordance is that if one twin has autism the other will have some features of autism, but not necessarily the full syndrome. A more stringent way is if one twin has autism and the other twin also meets full criteria for autism. So, many people will say there's a concordance level in identical twins – monozygotic twins – is 90%, but that's somewhat misleading, because there is a 90% on average concordance among studies but it is only for the broad spectrum autism. So if the first twin has full autism, the second one is only required to meet that weaker criteria, to have some features of autism. The concordance where both twins meet full criteria for autism disorder is 60%. So that means there is a large genetic contribution, but that still leaves 40% unexplained. And that probably has something to do with environmental factors which kicked one twin over the edge into autism but didn't do that to the other twin in the non-concordant 40%.

There's a further point that needs to be made about twin studies, which is that all the twin studies that are quoted for these figures were done quite a long time ago, the latest being in the 1980s. And that's before all of the reports of increasing numbers started to come in. So we don't even know whether the children we're seeing now have the same biology as the children on whom these twin studies were performed. We just don't know. So, these studies may not even apply so strongly to the population coming through now.

*Now is that another important reason for the CAN's AGRE program, Autism Genetic Resource Exchange?*

Oh absolutely. We need to collect information on more recent people in order to figure out what the genetic features are and we need to have substantial other data, not just genes, but a lot about what's called the "phenotype." The phenotype is a word from biology that describes what the person is like and that includes everything from behavior to biology.

*Is there a genetic overlap between autism, Tourette's, and autoimmune disease?*

Oh, it's interesting, there's a lot of work that goes on in autism research on what's called "comorbidities." So many of the psychiatric autism researchers will study overlaps between say autism, obsessive compulsive disorder because of the possessiveness, tic disorders, because of the repetitive movements, and so forth. But Kevin Becker who's a scientist at the National Institutes of Health did a very interesting study where he overlaid the genomes—the areas of the genomes on the different chromosomes where findings have been identified, and he did it for autism, Tourette's, and autoimmune disease. He's also done it in other areas like diabetes in other papers. He found an enormous amount of overlap to the point where you wonder what is it that, given so many similar genetic vulnerabilities, leads one person to be autistic and another person to have Tourette's. Because it looks like there's a whole set of shared vulnerabilities. And in other work that Dr. Becker has done – he has a very interesting paper called, *Common Variants, Multiple Disorders* – basically showing that a whole set of genes can contribute, presumably through vulnerability-type mechanisms, to dozens of diseases. These genes are not specific for any one disease. They set you up for something more generic. Autism, Tourette's, and autoimmune disease all potentially have immune system contributions. So that may be one piece of this. I don't think they really fully understand all of it. But, we are learning these days that inflammation is a common feature in an incredible range of diseases that we didn't appreciate before. Even heart disease and obesity have a substantial component of inflammation.

So, I think that our ideas of what causes disease and what is specific about a disease definition are going to have to undergo a substantial change. This is something that an area called "functional medicine" talks about a lot. It talks about the differences in function and highlights how blurry the boundaries are between disease entities and how much overlap there is in many of the biological or pathophysiological features underpinning what goes on as a person gets worse in many of these disease processes, including autism.

*Now, so Dr. Herbert where do you think that the direction of gene research needs to go?*

I think the geneticists are having trouble understanding that they need – that their data in itself is not going to be able to answer that much. Genetics needs to be placed in the context of more of biology. I wrote a paper about this a number of years ago called *Genetics: Finding Its Place in Larger Living*

*Schemes* and, in autism, people in genetics are beginning to figure out that they need good phenotypic data, but all they're looking at this point is psychology. It's amazing when you know that genes code for proteins and they also – there is also regulatory function in DNA, but particularly we know from high school that genes code for proteins; that you would think that that would make geneticists interested in finding out about the proteins in the individuals that they study because that's the stuff that's closest to what the genes do. But it hasn't occurred to them to measure that.

Another thing is that genes code for is enzymes, and enzymes work in pathways. And yet almost no one in genetic research is choosing the genes to look at on the basis of biochemical pathways. Jill James has a new paper coming out (it's been accepted and it's in press in the *American Journal of Medical Genetics*, which is a wonderful thing; it's a very good journal)[ed note: this paper appeared in print in December, 2006] talking about genetic vulnerabilities in the folate, methionine synthase, transsulfuration pathways related to glutathione production and protection from oxidative stress. She has an extensive discussion in this paper of how some of the different mutations in those pathways can relate to each other. Interestingly, the paper doesn't have a lot of references to other people who think like that, that is, in terms of linking mutations and biochemical pathways. I spoke with her and she said that the reason is that not that many people are doing it. Also interesting is that I spoke with an old mentor of mine, now in his seventies, at a later date who said that several decades ago the linkage of genetics and biochemical pathways was routine, but the biochemistry seems to have gotten lost since then. I hope that changes.

*Absolutely. Might my multiple genes impact the same mechanism?*

Absolutely. First, there are many genes in any given biochemical pathway. Second, any one of those genes may have more than one mutation that can affect its function. So, absolutely. Every time you have an enzyme, you have at least one and possibly multiple genes involved in shaping that enzyme and shaping the things that modulate it. So an enormous number of genes can converge on one pathway.

If you have problems in more than one gene on a pathway, those things can add up together: And this is what Jill reported in her paper: that any one gene on some of these pathways would confer a mild, modest increase in risk, but if you have two of them your risk for autism could potentially go up a lot.

I'm being generic here; it depends on which combination. Also, some of these genes are what you call "high frequency low penetrance genes." "High frequency" means that they're very common in the population. And "low penetrance" means they don't do that much all by themselves. So some of these genes you'll find them in 16% of the general population and maybe 25% of autistics. So 16% – but it doesn't give you autism, it just sets you up a little bit for a greater risk.

*Excellent point. That's very important. Now let's look at your paper entitled, "Autism and Environmental Genomics."*

*What resources and databases did you look at that were taken into account for the paper?*

Well, what I did was I said that I wanted to find out whether the environmentally responsive genes that have been identified by various groups are localized in areas of the genome that have been identified as containing genes that are relevant for autism—the genome hot spots so to speak. So I took those hot spots and I looked to see what genes from these databases were in there. And the databases I used were three: The Environmental Genome Database; Seattle SNPs, which is an inflammatory gene database; and the Comparative Toxicogenomic Database, which is a small database. I started this because my feeling was that every time I read a review of autism genetics I saw that the authors were making an *a priori* decision—a decision ahead of time—that the genes that were going to be important were ones that would have some kind of direct relevance to something in the brain like a receptor or a neurotransmitter. And I thought, "Well, that doesn't make sense. Because what about inflammation? Or what about problems in other parts of the body that could secondarily impact the brain or that could impact the whole body and not just the brain...? Like various metabolic factors?"

I hypothesized ahead of time that I would find a lot of genes just from doing this overlap that nobody had ever thought about in relation to autism because they were biased just to thinking about brain mechanisms and not mechanisms in other parts of the body, and that's what I found: that there were just a lot of genes that you can uncover like that that people haven't thought about. Now that doesn't mean they're all relevant. Many of them may just be coincidentally there. But the point is that I think we need to be thinking beyond the brain. I'm saying that as a brain researcher. I am a neurologist and I am a brain researcher, but I'm also someone who is forced by my clinical experience to think about the whole human organism – I mean, as a pediatric neurologist, we deal a lot with metabolic disorders and from that you learn that when you have a problem in metabolism, it affects things in many parts of the body and not just the brain.

The brain is easily targeted because it has a lot going on. But it is very rarely targeted all by itself.

*So this is a systemic approach?*

This is a systemic approach. So my training in pediatric neurology is a big part of what led me to think about this as a systemic problem and not as a brain problem.

*Okay. Now do I have this right? If there are genes that are involved with the immune system or metabolism then those could be affected and that could go back and affect the brain.*

That's right. There are certain energy metabolism processes that occur in every cell of your body and they can affect your whole body at the same time. But certain cellular processes require more energy than other ones. And the ones that require more energy are going to take a hit sooner than the ones that require less energy. And we know that the brain burns up an incredible amount of energy. So, for a vulnerability like that,

the brain will get hit first. That the problem will be going on in other parts of the body and other cells where there's a high energy demand and other systems will also get hit first.

*Okay. Now, you mentioned a SNP. What's a SNP?*

A SNP is a Single Nucleotide Polymorphism and it's a change in a particular part of a gene that is a variant of the standard genetic code in that area.

*Now, so you compared these three databases. Can you explain in more detail the kind of overlap that you found?*

We didn't compare the three databases. What we did was we pooled the genes from all three databases and looked at how many of them landed in regions of the genome associated to date with autism, as determined by the start point and the stop point of the autism associations on each chromosome. And that's something that you can do with a computer. You have the locations – so we had the genome areas and that's like a link on each chromosome. We have 23 chromosomes. And then for the three databases we have from the Human Genome Project the location on each chromosome where that gene lives. So we could just use the computer to determine how many of the genes in the Environmental Genome Project and the Seattle SNPs Inflammatory Gene Database and the Toxicogenomic Database actually are found inside areas that have been identified in genome scans as probably containing genes that are relevant to autism.

So it was an overlap where one piece of data was the parts of the chromosome and the other one was the addresses of the specific genes. And out of that we found, I think it was, 147 genes and you can go into other databases and see which ones have been studied for autism when we found that a majority of them had not been.

*What is a linkage region? How many of those did you look at?*

I don't remember the exact number. A linkage region has to do with an area of the genome that seems to be more – where something is going on in relationship to autism. And it can be quite a long region and then what happens is after you identify that region you have to go on a hunt for what specifically within that region is going on. And that's where your *a priori* assumptions, the models in your head, get involved, because there's way too much to look at in there. So in the earlier stages of studying linkage regions people have picked out candidate genes based on the models in their head. And if you have a model in your head that autism is a brain disorder you're going to pick out brain genes. But if you have a model in your head that autism is a disorder that affects the brain then you're going to pick out a broader set of genes, not only ones that would directly affect the brain but also ones which could affect the brain in a number of other manners.

Also you should know that linkage regions differ—the linkage regions identified in one study are not always identified in another study. And the problem then becomes “is one wrong and the other right?” Or is that a reflection of the great hetero-

geneity in autism, that is, the variability that could be in part regional as well as just random?

*And you said that you found many, many genes that were of interest but had not been studied before?*

There are genes that could potentially be relevant. In order to prove that any of them would be relevant, you would have to do a lot more work. All our group did was do work in bioinformatics with databases. We did it mainly to show that the biases that have, to date, been informing the choice of candidate genes and the way people narrowed down these huge domains in order to make them tractable, to be able to work with them—that the biases have been toward brain genes and that actually we could be missing some very important things if we don't broaden our perspective. So the take home message is to broaden the way we think about genetics.

*Okay. So, this supports studying genes sensitive to environmental influences and sensitive to changes in physiology.*

That's right. It doesn't prove any one gene is right. It just supports a broadening of our emphasis.

*Yes. Now, is this kind of gene sensitivity or adverse interaction necessarily limited to the prenatal period?*

I don't think so. I mean we don't really have strong proof that autism is a purely prenatal disorder. I think there's plenty of evidence to say that there's vulnerability before you're born. We know in animal models that animals who are impacted by infection *in utero* can develop a larger brain after they're born. We know that animals that are affected by infection *in utero* can develop behavior problems after they're born. There are a lot of reasons to believe that there can be *in utero* vulnerabilities, but there's no reason to think that it can only be *in utero* or that vulnerability and damage stops at that time.

There are changes that go on in brain metabolism that continue over time that could be relevant. And that's something that's really important to think about. The evidence arguing for exclusively *in utero* prenatal changes in humans is pretty slim. It's rested on interpretation of data from analyzing tissues from brains of individuals who have died, looking at it under a microscope with various stains and techniques. And you can interpret some of those findings as being evidence of prenatal changes and they may well be. However, some of these changes could also be interpreted as results of things that took place in the early postnatal period. So there hasn't been consensus that these changes exclusively point to a prenatal origin, and there also is a growing body of other changes that people are identifying which look like they most likely occurred after birth.

*Okay. So, you would still be curious about what caused the postnatal changes.*

You certainly would. And you also have to be sensitive – when you're looking at the brain of a person who died who had a diagnosis of autism; first of all that person is going to be at least three, or four, or five years old, usually substantially older.

So you're not looking at their brain during the time when the autism emerged. You're trying to be like Sherlock Holmes or some kind of archaeologist and figure out, from what you're looking at, how it got to be that way in the past. So you really make inferences. It's not direct – you're not catching it in the act, you're catching it way, way after the act. Once you start getting into that kind of reasoning, there's a lot of room for different interpretations. So what happens is, you report the data, you report the phenomenology, you report what it looks like—that's the "results" section of a paper. And that should be objective without interpretation, although it's often colored by your interpretations (that is, what you observe and what you don't notice)—but you're supposed to check your presuppositions at the door for this part.

When you get to the discussion section you try to put it together into some kind of a story. And that's where your biases really come strongly into play. And so it's no surprise that a lot of the controversy occurs around the interpretations. I mean there's also controversy about methods of how you do things, and that's important. But what I'm trying to say here is that we're doing this by reason – it's like going to a crime scene after everyone is gone and you find a few snippets of hair and a little bit of blood and you try and figure out what happened. It's kind of like that.

*Well, I understand that the M.I.N.D. Institute's Autism Phenome Project is going to be studying younger children. So it sounds to me as if you may see advantages with that.*

Absolutely. Actually I'm aiming to do that, too, and I'm actually going to be collaborating with them. But I really love those people and I'm eager to have the kind of work that they do be replicated in other centers. So I'd like to be a part of that as much as possible.

*Just brilliant people, and it's good to know that our children have brilliant dedicated researchers like the people at the M.I.N.D. Institute and like you working on these things every day for them. So, Dr. Herbert in summary, what are the advantages of a genetically-influenced systemic model of autism and a systems framework?*

Well, the advantages are that you are more open to the variability in the data, you can see more possibilities, and really the biggest thing is that if it's genetically influenced and environmentally modulated or triggered, there's more that you could do about it, particularly with regard to treatment. And if it's systemically involved, then you take seriously the things that are going on in other parts of the body, and if you can affect and improve the metabolic status of system-wide metabolic problems—or all problems affecting particular systems such as the gut—you may be able to improve the status of the whole person and also of the brain.

*Great. So, a biological systems approach lends towards identifying disease mechanisms that may be treatable and it optimizes our chances for identifying treatment targets?*

That's right. And I think that's the most important thing. I mean why are we doing all this? The reason should be to help the people who are affected. To help the people who are affected overcome problems which they don't need to have. There are people in the neuro-diversity end of things who argue that autism is a difference and not a disease, and there are many marvelous things about the way autistic people perceive the world. But that's a different category of existence than the problems of physical illness, self-injurious behavior, behavioral inflexibility and inability to talk that many autistic individuals suffer from. And when you have an individual who can't talk and has a lot of other problems with physical coordination and all sorts of things—that may be a difference, but if it's a difference that responds to treatment and gives the person more ability to self-regulate and control what they do and have more choices, then that's something I favor, obviously.

*Yes. I agree. We always want to increase health and functionality and alleviate suffering. And keep our children and everybody as safe and healthy as possible.*

Right.

*So Dr. Herbert, how many levels of mechanisms may there be leading to autism? For example, as part of pathogenesis leading to mechanism, leading to observable phenotype—are there a bunch of levels in between?*

Yes. I have a model in my paper, *Autism: A Brain Disorder or a Disorder that Affects the Brain?*, saying that we need to move beyond the “genes affect brain and brain affects brain behavior”—“the gene-brain behavior model”—to a broader framing of it which I've called “pathogenesis, mechanism and observable phenotypes.” So instead of talking about genes, I'll talk about pathogenesis. Pathogenesis is what causes something and that does include genes. It also includes environment. And it includes developmental changes, including epigenetics, which is an explosive area of research right now. So right there you're not just saying genes, you're saying a whole different set of things that go on during development.

Then, as far as mechanisms are concerned, to say “brain”—it's such a huge concept and I wanted to break it down. In the brain there are molecules and cells, and genes definitely affect molecules and cells, and so do environmental factors. There's also tissue and metabolism, which are at the level of organized sets of molecules and cells. So some of the recent findings that we should discuss around inflammation and oxidative stress in the brain—that's at the level of tissue and metabolism—changes there. And then there are the features of the brain related to information processing. How does the brain coordinate between regions? What are the circuits and how do they work? That's what cognitive neuroscientists think about. But, you know, one of the things that cognitive neuroscientists forget (or they just don't think about it very much) when they talk about neuroscience is that the brain is a wet organ of the body. The brain is not just a processing unit with a set of circuits. The wetness of it, the tissue features of it, the vulnerability to disease processes in that wet tissue affect the efficiency of brain function. And so that's where I think it's important to break out



all the different levels of mechanisms in a way that makes you pay attention to each step along the way and not just lump it together.

And finally, with observable phenotype, we have behaviors—that is what a lot of people are focused on, but there are a lot of other things in behavior. What about sleep problems? What about anxiety problems? What about difficulty coordinating movement? What about gastrointestinal problems? What about sensory hypersensitivities, sensory integration? All of these things are part of the observable phenotype. So I think it's important to have a much more comprehensive view of what we're looking at on every single level. "Gene brain behavior" is not wrong—it's just way too oversimplified and lumps together important levels.

*So how do we determine at what level there are unifying features that account for outward behavioral, physical, and sensory consistencies found in autism? Might multiple pathways funnel through final common pathways?*

Well, this concept of final common pathways is really important. I think that the idea that there could be many ways to autism has been given some lip service, but people haven't really had a grip on what it means. I think part of that is the belief that autism is so strongly genetic that the genes will tell us—will create the disorder—got people complacent thinking that genes were the whole show and the other stuff was secondary; but now that that really isn't coming to fruition, I mean after a lot of hard work they are just not finding genes by looking at it that way.

So, the genetic determinism thing breaks down and you start to have to look at multiple other levels of what's going on. So, could there be multiple different genes that could contribute in a combinatorial fashion, alongside environmental factors that affect mechanisms related to what the genes are affecting that add up together to set you up for autism. That would be at the pathogenesis level. Multiple different contributors to the problem.

Could you have different tissue and metabolic processes that could contribute? Potentially so. We've identified a few that seem to be in play in some people, such as inflammation and oxidative stress; there may be others.

I skipped the molecular and cellular level. There are a whole variety of mechanisms at the cellular level that could be involved in affecting the way the brain operates: levels of cellular energy, levels of dendrites, levels of interneurons. All these things and many more can affect synaptic and neural systems function and many of these are areas where there have been findings identified in autism. My own sense is that the recent work on connectivity problems in autism may be where there's some commonality—that is, that the different kinds of biologies converge on common connectivity problems—but even so you can mess up connectivity in so many different biological ways as I was just saying.

So, I think that this multi-leveled-ness is one of the frontiers in autism. Now that we can no longer presume that studying just one level, just the genes, is going to give us the answers we need, we have to just take a deep breath and realize that we have to come to grips with the multileveled complexity of the

organism that's affected, and we have to go back to studying each of the levels of the organism in its own terms. We can't think that we're going to understand metabolism through genes. We have to study metabolism as metabolism.

The immune system is a great example of this because much of what goes on in the immune system has so many steps between the genes and what the immune system does that there's no way you're going to predict it from genes. So, it's like we had this idea that we had the magic key to biology and that was genetics and now we're finding out, well it isn't the magic key, it's just one player and that a lot of the other levels can set the terms themselves and they aren't all bossed around by the genes.

*So, when we're looking for the causes of the outward signs of autism, it sounds to me from what you're saying as if we don't just stop at neuroinflammation, we don't just stop at oxidative stress, we don't just stop at hyper-excitation in the brain. We dig deeper.*

I think we have to keep an open mind that whatever pathway we are currently excited about is most likely an example of a broader class of phenomena, and we may find other specific mechanisms that are members of that class. And I'm always suspicious when people say that it's any one pathway. Because then I think of—even some rare metabolic disease that has more than the expected number of people becoming autistic, where there's a different biochemical mechanism. And I say to myself, that doesn't quite fit so and so's model. Not that so and so's model is wrong. It's just a very good example and it may be a very common example, but it's not the only possible way. If there's a question of how you allocate resources, so if you have a mechanism (like inflammation), which appears to be extremely common, you should study that really hard. But it may be that other pieces of this are important too.

And I think one of the big questions is how do we get more systematic about identifying various environmental vulnerability pathways that we have that could be implicated beyond the ones we've already started thinking about. By the way, there's one very important thing that I forgot to say, which is that all of the levels of causation and mechanism that I talked about all occur in the setting of developmental timing. So, if this happens to you before you're born or in your first three years of life, that's very different than if it hits you in your 20s or 30s when brain development is at a different phase. You can get a different disorder even though you've been hit with a lot of the same environmental factors and you carry a lot of the same risk factors, because your organism and your brain are in a different stage of development. So this timing feature even complicates further the multilevel complexity that we need to deal with.

*So it's really important to consider developmental windows in shaping outcome.*

That's right. But at the same time I think it's important not to talk about closing developmental windows. For example, if inflammation and oxidative stress are a chronic problem in autism, in the Vargas and Pardo paper on neuroinflammation that phenomenon was found in the brains of people who had died



ranging in age from 5 to 44. So if you have a 44 year old who still has inflammation, I would be very uncomfortable unless I said that you could still leave open the possibility that treatment might help that person.

*Okay. What do we know about whether other brain neuropathology such as brain stem anomalies and reduced Purkinje cell number occur pre- or post-natally?*

This is a complicated question. Certainly we know that the brain stem is formed very early in gestation and brain stem anomalies are associated in toxicology studies with exposures that occur late in the first month of gestation. So that is very early and many women don't even know they're pregnant at that stage. Purkinje cell dropout has been presumed something that occurs prenatally, but it's also possible that those cells could burn out early postnatally from too much excitation. And it looks like the M.I.N.D. Institute is finding immune changes in cells which are right near the Purkinje cells and there could be some interaction there that would have to be worked out. That's something that could occur *in utero*. It's possible that some of these things can occur after birth, and it's not possible to totally exclude that.

*So, what about the large heads and brain sizes we hear about that are often found in autism. Are those present or not present at birth? Do brain abnormalities, such as increased brain size or white and gray matter distribution, substantiate or not substantiate a strongly genetically-based model?*

Well, a lot of this is open to interpretation, but I think that there are some reasons that these phenomena could support a gene-environment interaction. First of all, it's been observed that the brains of children with autism are—at least under the age of 12—are on average larger than brains of typically developing children. Secondly, it's been observed that the rate of increase in head size is quite dramatic in the first couple of years of life... That brains are either average or below average in size—or at least the head size—because this measurement hasn't been done in brains except for one preliminary study. So you take a tape measure and you see how big the head is, and the head gets bigger and bigger in the first couple of years at a faster rate than for typically developing individuals. Then, that rapid rate sort of stops and the amount of size difference between the children with autism and the typically developing controls kind of diminishes which is kind of sign of the typically developing ones catching up in the trajectory of their increase in size.

So, that is one set of phenomena that happens after birth. There are people who say that you can still explain that by changes that occurred *in utero*. It could be that some developmental switch was turned either by genes or environment or infection or exposure or what *in utero*, and then it played out after birth. That's possible. But I also think that you can't just assume that. If you look at this phenomenon and then you tell that story about it, you're going beyond the evidence because right now we don't know what's driving the brain volume and we don't know what's causing it. When I say “driving” it, we have some evidence that the brain gets bigger because of an

increase in white matter size more than an increase in gray matter size (and of course there's the next level question of what is “driving” this tissue change in the white matter). Now in the very youngest ones there seems to be some gray matter increase, but the white matter increases more and it persists more at least in the data that we have available to date. Now gray matter is where the cell bodies live and white matter is where the axons—the wires between the cells live. That's at least the long-range ones travel and it's white because it's wrapped in a fatty substance called myelin which is an insulating substance and that's the area of the brain in my research and Eric Courchesne's research and a few others that looks like it's bigger. You know, there's been a lot of measurements in postmortem brains—brains of people who have died—that they're heavier in younger people, but to date we do not know at the microscopic level what is it that changes in those brains to make them heavier. We have not identified what cellular change makes the brains heavier. So, everything that people are saying about that is based on theory and not based on evidence.

*Now are all of these things that you just described, Dr. Herbert, common to all children or all persons with autism, or a significant minority, or a majority, or what?*

Well the large brains – if your head circumference is at the 97<sup>th</sup> percentile that means your head is bigger than 97% of the people in the population—so by definition that means that only 3% should be above the 97<sup>th</sup> percentile—well in autism 20% of head circumferences are above the 97<sup>th</sup> percentile. So that's a lot more than you would expect in the general population. And most people with autism have brains above the 50<sup>th</sup> percentile—above average. And so that's different than the distribution of the whole population where, you know, either half of them are above average and half of them are below average.

So something's going on which, on average, makes the brain bigger. However, there are many people in the population who have big brains who are not autistic and not everyone with autism has a big brain. And if you have various other comorbidities or problems you can have a small brain and still be autistic. So, it's definitely not something that either makes you autistic by definition or it doesn't—so there's something else going on. So, I just think it's a big clue about the kind of mechanisms that are targeted, but it isn't a biomarker where, if you have a big brain you're autistic, and if you don't you're not. Absolutely not. It's not that at all.

*Okay. Good point. I'd like to backtrack for a moment. We hear the term “gene expression”, so, could you tell us please what is meant by gene expression as modulated by environmental influence.*

Well, you know, we have a whole lot of genes in our genome, and we don't use all of them at the same time. They're turned on or off based on what's going on in metabolism and development and in our interactions with the environment. So, early in development you'll have genes that are turned on and later on they're turned off. When you're sick or hungry, or whatever it is, it utilizes different genes. This is an area which we're just starting to have the tools to study. But we do know

that environmental factors affect the way that genes express, are turned on or turned off, how they express themselves, and in what combinations.

*What kinds of studies—for example, thiol metabolism or organophosphate exposure in neuronal migration, or excitation and PCBs, speak to the importance of considering this?*

Well, all of the things you talk about are exposures where a particular pathway or set of pathways may be particularly important in handling that exposure. When you have these kinds of exposures, they can trigger molecular and cellular mechanisms that change processes that are going on at the moment. If you have a PCB exposure *in utero* or early in life, it can affect your brain structure and how you process sound. My collaborator Tal Kenet (along with Isaac Pessah and Mike Merzenich) has a paper submitted about this right now—we know that gene expression changes, but we don't have to know the specific character of the exact gene expression to be able to either decide that this is a problem we want to avoid or to treat the problem. You can know something about biochemistry without knowing the exact gene mechanisms. Yet even so, the knowledge that you have about the biochemistry may be enough to point you towards some kind of a meaningful biomedical treatment that will be effective in at least some individuals.

*Okay. And brain function studies—do they suggest that autistic symptoms are due to local or pervasive global phenomena?*

Well I got interested in this problem of local and pervasive phenomena because of the “big brain problem.” If the big brains have a functional significance, then it isn't according to the model that there are specific regions that govern specific functions, because the increase is all over the place. So you have two choices: either the increase mostly doesn't matter and it only matters when it overlaps specific local neural systems, or the whole way that the large brains affect function is different than a local model. And this is where you get into network theory. We've been talking systemic in the body. Yet now we're going to use systems in a different way and talk about systems theory in the brain.

If you have a network where many things are connected to each other, then as the network efficiency breaks down, those functions of the network that are most highly networked—that is dependent on the highest levels of coordination—will be the first ones to break down.

If you have a little subroutine in your brain which can be carried on perfectly well in one place, it really won't matter that much if a lot of the brain's connections are coming in at imprecise times, because this one subunit won't have all that many connections. But if you have something where you have to coordinate information from all over the place, then anything that degrades the timing or coordination or intensity of brain signaling will break down that function. And I would contend that the so-called triad of autistic defining behaviors—language, social interaction, and behavioral flexibility—which is the opposite of repetitive and restrictive behaviors—these are all activities of the brain that require enormous amount of coordination. So

when that coordination starts to break down, you're going to have to retreat into things that you can do locally because you're not going to be able to pull off the longer-distance interconnections in a well-coordinated fashion.

So if you have inflammation in your brain or a state of stress or some kind of metabolic depression of the energy that you can bring to bear on the functioning of the network, you're going to lose higher order functions first—you're going to lose their efficiency and elegance first. And as the reduction in efficiency of the network gets more pronounced, you're going to lose more, and you're going to lose other functions.

*Wow. So is that how a global problem in the brain—caused by whatever reasons—could end up affecting those three areas in so many children but for different reasons?*

Exactly. You've got it. That's it. There's so many ways that you can mess up the elegant efficiency of brain coordination. But, once you mess up that brain coordination, if you do it in a certain time period you're going to get autism. Or, if it isn't so bad, you might get specific language impairment or ADD.

This is where you don't need to have one set of genes for the language, and one set of genes for the behavior, and a different set of genes for the social interaction. It can all be what we call “systems theory emergent properties of systems dynamics—that as the systems properties degrade you get changes at the systems level and they may look like specific changes, but actually they're accounted for by widespread network problems—or, maybe a little bit of both, like widespread inflammation that's worse in certain more vulnerable areas.

*Now Dr. Herbert, I know we've talked about things like oxidative stress or neuroinflammation. You've mentioned biomarkers and metabolism. What kinds of metabolic biomarkers do we see that indicate that there is a chronic process going on with brain tissue?*

There are three in particular. The inflammation, oxidative stress, and some of the mitochondrial problems are some of the top ones—they are by no means the only ones. And I should say that, even though I started college as a biochemistry major, I'm not a biochemist. The main thing that I have going for me here is the kind of overview of how much this pulls so many of the pieces together. Jill James' work is exemplary here documenting an abnormal oxidative stress profile and also documenting that you can correct it with nutritional intervention.

We have a lot of documentation of immune problems. We have documentation of inflammation in the brain. We have documentation of gut inflammation. And the thing about oxidative stress and inflammation is they are final common pathways if ever there were any final common pathways. Because, if you get bonked by something nasty from the environment, those are two of the basic responses that your body mounts to handle it. And, if what you're getting bonked with from the environment is more than you can handle, you can have an abnormal persistence, or imbalance, or resetting of your set-points in these domains, and you get stuck in a pathological level of inflammation and oxidative stress, that it's almost like a kind of a biochemical and immune gridlock.

But you can get to that from a gazillion different kinds of noxious influences or of just being depleted when you get hit with something. So I think that's really important to remember—that these are not necessarily specific processes at all—that is not exclusively linked with certain specific diseases. And it fits again with the idea of there being a network problem. The other one is the identification of mitochondrial abnormalities. Mitochondria are little subcellular bodies in our cells that do energy processing and when you study samples collected when children (or others) are under stress (which could be sleep deprivation, illness, or even a 12-hour fast) you can detect, in many of them, signs of mild mitochondrial disorder even though, if you were to test for the genes we know about at this time associated with mitochondrial disease, you may not find any of the classic mitochondrial diseases. A person can have reduced function in one or more enzymes in mitochondrial (or for that matter other) pathways that is not enough to make trouble ALL the time, not enough to qualify for a disease DIAGNOSIS, but still enough to gum up the works if some other stressor comes along to further gum up the works.

Now we know that toxins impact mitochondria, and even in the laboratory we will use specific pesticides, for example, to block specific steps in mitochondrial metabolism. So, it wouldn't be any surprise that somebody who's exposed to multiple noxious environmental agents might get a little bit sluggish in their mitochondria. Once you have a little bit less energy, a lot of things can happen. You just don't conceptualize very well, you can have hypotonia, low muscle tone. There are a lot of things that can happen. It breaks down the system on multiple levels. That breakdown is not a big collapse. It's a depression of the system. But it has a lot of consequences in many dimensions.

*So, we see so many regressions when kids are toddlers. Could chronic tissue changes progressively overload their abilities to compensate?*

Well, there is this book out called *The Tipping Point* and a lot of people talk about "tipping points." We have this expression from time immemorial of "the straw that broke the camel's back." You can get depleted gradually, and it may have subtle effects, and it may set you up so that when you get hit with something like an infection, for example, or a major emotional stressor or say your schoolyard or your house gets sprayed with pesticide. If you're vulnerable, then you won't be able to mount a response and you could get kicked over into another state. Then, that other state could be what the autism is. And, then, the trick is how to get kicked back out of that state.

*Correct. Alright. So, again asking about inflammation and oxidative stress, if this happens early, what does it do to signaling processes and consequent development—brain development.*

Well, it's interesting that most of the people who are studying location and connectivity activity in the brain are not studying tissue. And most of the people who are studying tissue are not studying brain function and connectivity. I think that the Holy Grail in autism that would really help shift the model in

even old-model researchers is to put our knowledge of tissue changes and information processing changes together, and show what the relationship is. Then, you would get (a) people who are looking at the biology of autism and (b) the people who have been spending time on the functions of the brain, to see that it's really all part of the same puzzle.

*So, Dr. Herbert what kinds of treatments have helped children improve and what does children improving through interventions tell us about autism's etiology?*

Right now there are more people talking about optimal outcome and recovery than in the past. There is a spectrum of opinion about what accounts for this improvement. There are some people who are saying, "Oh, it's a spontaneous recovery and anything that the parents were doing is just a coincidence. We know that some children recover spontaneously." Well, if you actually look in the literature there's been almost no study of recovery. I'm actually involved in a literature review around this issue and there isn't a whole lot there.

So, for people to say that we know that there's spontaneous recovery—this is not based on careful empirical studies because that work hasn't been done. Moreover, some of the people now saying this are probably the same people who not too long ago took it as a truism that autism was incurable. There could well be people who have gotten better by themselves, although you don't really know that because we haven't studied it. They claim to – there are people who have been documented to get better from intensive behavioral therapies who didn't do biomedical. There are people who did single biomedical or all kinds of biomedical things who get substantial or entirely better by which I mean, if it's entirely better, they are really indistinguishable and some of these people you would have to test them really hard to find residual vulnerabilities. And other ones who may still have idiosyncrasies, but they are nowhere near the level of impairment that they had before.

So, in terms of the biomedical treatments, I think you divide them up into some simple categories. There is removing toxins, there's also supporting the body's own intrinsic ability to eliminate toxins. We all have that ability but it can get impaired. There's avoiding immune triggers and allergens and there's supporting the immune system. And there's avoiding stressors and building the body's reserves, antioxidants; supporting the ability to handle oxidative stress so that it doesn't overwhelm you. If you want to really boil it down to basic categories, most of the things that people are doing fall into those categories in one way or another.

*And if you can identify a child's biological issues, can you better define which biomedical and educational interventions will help that child?*

Well, the question is at what level of reliability do you want to do that? And that gets into some really challenging areas. There are a lot of laboratories and a lot of tests which try to predict what the nutritional and immune abnormalities are in children, and then healthcare providers use those results as a basis for treatment. There are different sides of this: on the one hand, it is the best we have and, on the other hand, many of

these tests are not a part of standard medical practice. Now, why are they not a part of standard medical practice? This is something that intrigues me enormously. I think one of the reasons is that what standard medical practices is based on is treating specific disease entities that you define in very specific ways. So you either have it or you don't have it; whereas, a lot of the measures that seem to be relevant in figuring out how to treat a child, or it's not just children really, but let's just talk about that for now, biomedically have to do with gradations of function. Moreover, they have to do with abnormalities that are often fairly generic rather than specific to any one disease—so paradoxically what is keeping you sick and what is treatable may well NOT be what is most specific!! Addressing gradations and generic issues: this is more a "functional medicine" approach and it's different than what we do in hospital settings and in standard hospital laboratory settings.

So, what you begin to realize when you get into this are two things: (1) the boundary between what is normal and what is not normal is not something that is absolute and set in stone—it's something which is set in relation to some questions and problems and not others, and which was set according to some populational standard, or some average at the time, or they said everybody above the 98 percentile is sick, everybody below is not. But it's not—it doesn't mean that there's really a tight boundary there—the boundaries are very blurry—you can have problems even if you are within reference range, depending on context. And (2) you have the problem of combining vulnerabilities from different pathways—how they add up to a bigger problem when you have them together than when you have them separately.

So what we are talking about is that there are profiles of problems. And that gets you into even more trouble in terms of the way laboratory values are used in academic medicine because the profiling is something which you would have to spend years and years and years studying before it could be considered validated. And many of the tests that people are using to figure out what to do next for their children haven't gone through that kind of process.

Another problem is that academic research, for example, into nutrition, has been involved in generating the standards that we have, like recommended daily allowance, that are oriented toward avoiding really awful diseases of deficiencies like scurvy and beriberi. But, in functional medicine, we're not talking about that. We're talking about individualized differences in nutrient needs relating to individuality both in our genes—how fast or slow the genes allow various processes to occur for example—and also to the environmental influences that may have further speeded up or slowed down our various pathways.

When you get a laboratory study, there can be a confusion because the way that people are using laboratory values in functional medicine and in biomedical approaches to autism, which is a kind of functional medicine, are really different than what my colleagues use in academic medicine. And I think that needs to be put on the table. A lot of the attacks on the way that the integrative biomedical people are using laboratories are based on a lack of understanding of all of these problems and a pretty much complete unawareness that these things are problems, or that there are rationales for integrative approaches.

But the thing is that they are not just problems for autism biomedically, they're problems for 21<sup>st</sup> century individualized medicine. That's where we need to go for all of things that people are promising that the new technologies can do—like pharmacogenomics and so forth. And so we are going to have to break out of these old models of narrow use of lab values and standardized cohorts and we are going to have to move into individualized profiles and interpreting trends and using our best judgment. And that's what integrative health care providers at least aspire to use the lab for.

Part of my next project is to get much more systematic attention paid to all of these levels around biomarkers. Particularly, I would like there to be a more systematic approach to measuring biomarkers relevant to treatment so that, for example, if you apply for a federal grant in autism they want you to take some genetic samples. Why shouldn't they also want you to take a metabolic sample?

One of the reasons that we do not do that now is that people have not really thought about it. Another one is when they do think about it, they don't know where to start. And I think one of the reasons for that is people have been spending so much time looking for genes that they just haven't thought that much about metabolism. So, I think the whole medical research enterprise has a lot of catch up work to do in metabolism and physiology.

*What great points Dr. Herbert. So, if we regard autism as in part a metabolic or environmentally modulated syndrome and if we address environmental factors and gene environment interactions, might autism be preventable, treatable and reversible?*

Well yes. Preventable, treatable and reversible – that's it. That's the new autism policy model—the horizon—that we need. Critical, critical, critical. If we have vulnerabilities that we can identify before they have hit the tipping point and we can support the body's resiliency so the person doesn't tip over into this metabolic gridlock, it looks like in at least many cases we could prevent autism. So if somebody's oxidative profile is slipping into the danger zone and we get them on antioxidants, could we prevent autism? Maybe—it seems plausible to me, enough so to merit really serious and expedited investigation.

If we know that certain people are going to have a harder time with certain exposures, can we identify that and avoid those exposures—seems plausible to me.

If we know that certain pathways are contributing to the gridlock that contributes to autism and we can support those pathways and get them out of gridlock, could we reverse autism? That would seem plausible to me.

We have to work on that. We need to make those things that could really prevent, treat and reverse into central priorities for where we invest our social and scientific resources in autism.

*Yes. And I hope for the children and families and everybody's sake and society's sake that we do it in a timely manner.*

It's not just autism, as I was talking about earlier with Kevin Becker's work on common variance and multiple disorders.

*You're right.*

These pathways are going to affect a whole line of other disorders, too. So whatever we learn that will help the children in autism, it's like a greenhouse of investigation—it's going to help a lot of other people as well.

*Absolutely. I've read a great quote of yours that I'd like to share with listeners now: "A further consideration is that given our limited understanding of the biological mechanisms underlying the autism behavioral phenotype, we cannot exclude the possibility that the alterations in signaling and connectivity, for example neurotransmitters, most proximately associated with observable atypical behaviors may themselves be networked with or downstream of alterations associated with genetically modulated environmentally responsive vulnerabilities." That's a pretty powerful quote Dr. Herbert.*

Well that's what we've been talking about.

*Yes. It's a good summary.*

I've been going around giving this talk "is the brain downstream." It really upsets some of my neurobiology colleagues. I had one graduate student tell me, "But I went into neuroscience because that's supposed to be where it is 'at'—the center of everything! How can it be downstream?" But, you know, actually it's cool when it's downstream. You still get to work on it. And it's also wonderful to have it be part of something larger and more integrated.

*Yes.*

It's just in its full ecological context.

*Yes. And if we don't study gene-environment interactions might we even be faced not only with the impairment of our views but also with our adults being struck down prematurely?*

Well, gene-environment interactions affect everything. I mean Alzheimer's disease, heart disease, and cancer, and more. That's what's going on. I mean really it's a sociological problem why we're not studying this. And I think it has to do with belief systems that all of this chemical stuff is basically safe, that mommy and daddy in the regulatory systems tested everything so we don't have to worry, everything is okay and we can just go about our own business – but this belief structure is changing. I think there are a lot of barriers to studying gene-environment interaction and one of them is this complacency that we had in the 20<sup>th</sup> century—that if it didn't kill you, it was safe. And that you could study one thing at a time. This was the basis of regulatory standards, which are now being challenged by a series of emerging scientific findings. One of them is something I discussed earlier, which is that extremely low levels of various chemicals can hijack you body's signaling mechanisms.

Another is that low levels of chemicals in combination can have effects far greater than either one alone and also novel

effects that either one alone would not have had. And we don't know very much about how this works with lots and lots of chemicals and combinations. There have been a growing number of body burden studies. You can go to [www.bodyburden.org](http://www.bodyburden.org) to see it for adults and the same group has recently done it for newborns. How many chemicals in our bodies are we walking around with? Not at levels that would kill us, but traces of these things. And when you begin to realize (1) that low levels can impact our signaling mechanisms and we were talking a lot about signaling mechanisms and (2) that they can act in combination, we realize that we have this enormous problem and that it defies the ability to get precise answers. We have 58,000 unregistered chemicals. Among the top 3,000 that are produced in the greatest quantity, if we were to study those in combinations of three for combined effects, that would take 85 billion tests. But there's no way we're going to perform 85 billion tests and that would just be for combinations of three, not for combinations of 250 or 2,000 or whatever it is that we are walking around with.

So, basically what's going on is that we're not going to be able to have treatments precisely targeted at specific exposures. All the more so because the timing and the context of the exposure affects things, and there will be great interindividual differences there. So, that's where a medical approach to this problem is better off targeting final common pathways; targeting the much smaller number of ways that the body has to handle this stuff. We don't have a separate biological mechanism for each chemical that the chemical industry has invented, or for each metal, for each infection. We have a much smaller set of mechanisms and many of these can be nutritionally supported. And we also need to learn that if there's anything we can do to avoid excessively overloading these mechanisms, we should do that. So we should avoid toxins that we can avoid. We should avoid junk food that we can avoid and so forth because we have enough things that we can't avoid that there's no point in adding things that we can avoid.

*And again, in summary Dr. Herbert, where should the focus and direction of autism research be?*

Well, first, autism is biology—and an ongoing biological process, not a prenatally hardwired state. Second, autism is a preventable disorder, it's a treatable disorder, it's a reversible disorder, it's a product of gene-environment interactions where intervening in the system, in any one of the number of places, can help well-being. And, third, we should be looking at all those levels and we should be working on prevention, on educating the public to understand that improvement is possible; that you should go for the best possible outcome in every child; that you should learn where the points of intervention are. And finally, that we should get a grip on all the different things that we are doing on our all too fragile planet that have been causing unnecessary harm to our children and other living beings and our biogeochemical cycles in this and many other ways.