MARTHA HERBERT, MD: TRANSCENDING THE GAPS IN AUTISM RESEARCH

Interview by Frank Lampe and Suzanne Snyder • Photography by Meghan Moore

Martha Herbert, MD, is an assistant professor of Neurology at Harvard Medical School, a pediatric neurologist at Massachusetts General Hospital (MGH) in Boston, a member of the MGH Center for Morphometric Analysis, and an affiliate of the Harvard-MIT-MGH Martinos Center for Biomedical Imaging. She is director of the Treatment Research and Neuroscience Evaluation of Neurodevelopmental Disorders (TRANSCEND) Research Program.

Dr Herbert earned her medical degree at the Columbia University College of Physicians and Surgeons. She holds a doctoral degree from the University of California, Santa Cruz, where she studied evolution and development of learning processes in biology and culture in the History of Consciousness program and then did postdoctoral work in the philosophy and history of science. She trained in pediatrics at Cornell University Medical Center and in neurology and child neurology at MGH. For her neuroimaging research and its implications, she received the first Cure Autism Now Innovator Award. She is co-chair of the Environmental Health Advisory Board of the Autism Society of America (ASA) and directs ASA's Treatment Guided Research Initiative (TGRI). Some of her papers are available on her website, www.marthaherbert.com.

***Alternative Therapies* (AT):** You have a very broad educational background, including your doctoral work on the evolution and development of learning processes in biology and culture. What brought you to study and then practice medicine? More specifically, pediatric neurology and your focus on autism?

Martha Herbert, MD: My PhD is actually from a program called the History of Consciousness at the University of California at Santa Cruz. My dissertation was on evolution and development of learning processes using the texts of some social theorists, including Piaget, Habermas, and Marx. But using these texts as pivot points, it was able to be very broad. When I did my defense, my committee told me that while we are in a "history of consciousness" program where most people ignore the name, I was actually taking the name of the program seriously in what I was studying. I had a remarkable dissertation advisor, John Halverson, who's now passed away, who was able to encompass this approach and led me through a great range of readings. The History of Consciousness program at that time was a precious interdisciplinary haven, located on the magnificient and vision-inspiring campus of UC Santa Cruz, where this kind of breadth was fostered.

I had a particular interest in emotion, partly from some therapeutic processes that I had been trained in that involved catharsis. This got me fascinated with the biology of laughing and crying and yawning and fear expressions and trembling, which led me to pursue literature on these things, thinking that I wanted to do a dissertation on the evolution of emotions, but I didn't find much that was very useful to the questions I had developed from my observations and experience. I mean, there was Darwin, but there really wasn't enough of a systematic body of literature that could have allowed me to do something like that taking a dynamical approach.

While I was doing that work, I took an independent study with a neuro-linguist on the neural anatomy of emotion, and I became completely entranced with brain anatomy. It was so intricate and detailed. And it was a welcome relief from some of the more speculative work that I'd been reading in anthropology, philosophy, and psychology. I had started college years before as a biology major, and so I always had kind of a first love of biology, and getting into the brain anatomy while I was in graduate school provided me with a focus that felt like going home and, at the same time, linked to these broader questions.

I had been thinking about medical school, partly because of the science and partly because of the chance to legitimize the clinical side of this therapeutic work that I had done. I resisted this thought because I was getting a PhD and to start over and get an MD was a bit daunting. So I worked with some evolutionary biologists and comparative psychologists studying the evolution of emotion. But the bottom line was that they weren't asking the questions that I wanted to ask. So I bit the bullet and finished off my pre-med degree and got into various medical schools, and I chose Columbia.

When it came time to apply for residency, I wrote about a project I'd done as an elective about the relationship of brain and neuropsychological evaluations to brain localization. When I

Opposite: Dr Martha Herbert, shown here at her home north of Boston, believes that both the popular and professional understanding of autism is shifting to a whole-body model focused on treatment, environment, and recovery.

wrote about that interest in my application for the neurology program, my application was picked out of a pile at Mass General because the hospital had a lab that was doing exactly that.

I was moved to find that the people at Mass General found my trajectory very interesting. I had a life-changing interview at Mass General in which the director of the residency program said to me, "We really appreciate your background." He said, "Molecular biology is a juggernaut. It will succeed, no matter what, but you've spent a long time, well more than a decade, working on systems approaches, and systems approaches in neurobiology will not happen by themselves unless somebody who's highly motivated takes it on. And we really want you to come and do that with us."

I was already not such a young person. My other residency interviews included comments like, "You're too old for this," "You won't be able to handle the call hours," "You're presumptuous," "You shouldn't be doing this." And here was somebody, at a remarkable institution no less, who actually recognized and welcomed the intellectual integrity of the move I was making. It was very touching to me. So I went there.

The pediatric neurology specialization made sense because my PhD dissertation had been on Piaget. And I was really interested in evolution and development. I wouldn't have had that dimension in adult neurology, though the training would have been shorter. An additional blessing was the chief of Child Neurology at Mass General, Verne Caviness, who was behind my application and my getting into that program, and who became my mentor there. He was a very brilliant, intellectual, far-ranging thinker in addition to being an incredible clinician. He had the vision to understand the importance of my intellectual background as well.

When I got there, I still really wanted to study the biology of emotion. But when I finally had enough time late in my training to attend some professional societies that focused on emotion, I found that their concepts of emotion were very static: there's fear and there's anger and there are these behaviors and these facial expressions and these brain regions associated with each distinct emotion. That was really remote from what my own thinking had been, which was that emotion is a dynamical process that involves integrating information that's disparate and maybe full of painful cognitive dissonance. The emotional processing allows you to bring different pieces together into some kind of a new synthesis. There was nothing even remotely like that in emotion research. And there was no way that I was going to go into a social-sciences emotional research field; it was completely arid, boring to me.

Meanwhile, I was handed a big pile of brain images of children with autism. I got 93 MRI (magnetic resonance imaging) scans, and I started analyzing the data. That's how I got into autism. They just basically handed me this giant pile of already collected data and said, "Do something with it." So I rolled up my sleeves and did imaging analysis and then data analysis. It took several years. As I got into the data analysis, I realized that this was something very, very different than what everyone had been telling me it was. Because the analyses that we'd initially set out to do were complete failures.

But alongside the lack of significance of the correlations between specific brain regions and specific behaviors there were other things that were crying out to be noticed—in particular, the striking and widely distributed increases in white matter volumes in both autism and specific language impairments, as well as the alterations in brain asymmetry in both conditions that were distributed very widely beyond regions "specific" for language and that were distributed in almost the same way in both ostensibly distinct conditions. These pervasive changes blew the old modular model and also blew the model that these conditions are clearly distinguishable, and I had to fight with my senior colleagues to get them to take these other findings seriously. I really came into my own integrity as I said to myself, "I'm not going to try and look for what I'm supposed to be looking for. I'm going to call what I see and do whatever it takes to say what I think about it." That's when I began to open up to the incredible challenges that autism poses to just about everything. That's how I got into autism.

AT: Were you aware of any other researchers who were translating emotional components to the physical and biological components of brain?

Dr Herbert: There may have been, but partly it was where I was looking at the time—as an academic graduate student I was looking for "scientific" and "rigorous" literature with pretty conservative criteria for meeting those bars. When I looked in the neurological literature for the neurobiology of laughing and crying, I read about things like gelastic seizures (ie, uncontrollable laughter disconnected from emotion) but not emotion as information processing. I didn't find what I was looking for either in the psychiatric or cognitive neuroscience literature I read. The closest I came was some neuroanatomical work by Sanides on the evolution of cortical and limbic connectivity that reversed commonly held assumptions about the order of evolution of primary and associational processing and commentaries upon this work, and I still hope to get back to pursuing and writing up what I found in this literature. From time to time I read about things like neurobiology of ritual trance or cathartic therapies where the questions were closer to those my earlier training and experience had posed, but there was a big gap between, say, Wilhelm Reich or Art Janov or bio-energetics and what you can rigorously support or even explain to anyone in an academic situation. There was a yawning chasm. And I didn't see bridges at that time. Then I got into neuro-anatomy, but I got into it in, again, a static framework. We were studying brain volumes as indicators of fixed brain deficits. So while it had its fascinations, it wasn't an immediate bridge. Damasio's work on emotion bridged somewhat, but by the time it appeared I was already well down this other anatomical path.

AT: Has your affiliation with Harvard been a boon to your work as a researcher?

Dr Herbert: I got into the residency program at Harvard, and I never left. I went to Mass General, which is a premier teaching hospital at Harvard Medical School, to do my neurology training, and

I've been there ever since. Mass General has a marvelous aristocratic tradition of graciously persistent inquiry and discourse, and I was privileged to learn from some of the senior people in the department who had so deeply shaped the field. I was hired by Harvard to be a trainee, and then I stayed. I stayed in the imaging analysis lab, and now I'm doing all kinds of other things, too. Certainly having this affiliation increases my profile. As for the environment there, it's tolerant in many ways, which I cherish, and there are remarkable people at Harvard, MIT, and other places to talk with, but it's not nurturing. So you can think broadly, but as a researcher you have to kind of make your own way.

I've recently been shifting my work. I received a generous grant from the Nancy Lurie Marks Family Foundation to acquire an EEG (electroencephalogram) machine in the last year and a half. This happened because my mentor, Verne Caviness, and I agreed that my white matter findings in my imaging work raised the question of whether there were associated functional changes, and the way to measure that was through EEG coherence. It's a complex process to initiate a new research program at this point, but I'm doing it with the help of skilled collaborators. As it happens, I think that EEG research will over time be much more amenable to picking up the process kinds of phenomena that were interesting to me in the first place. At the same time, the work that I did anatomically gave me the opportunity to deal intimately with brain structure and then brain tissue. My research program now is trying to keep those different dimensions of it alive in the same research program with the people doing each piece talking with each other, as opposed to having them be separate silos. That's what the TRANSCEND research program is about.

AT: Is the TRANSCEND program the first of its kind in approaching autism and these other neuro-developmental disorders in an interdisciplinary manner?

Dr Herbert: Yes, probably—at least in the way we're doing it. In the brain domain in autism and neurobehavioral conditions, you have a predominance of the gene-brain-behavior model that says, "Oh, it must be genetic, and therefore the gene directly affects the brain, and the brain causes the behaviors." Then there's another part of brain investigation done by neuropathologists, who look at brain tissue in people who have passed away, where they have the resolution to look more at the level of cellular biology and chemistry. There's a little bit of chemistry in brain imaging if you do spectroscopy, otherwise not. And then there are people who do pathophysiology, such as biochemistry or immunology, which is more often than not systemic rather than brain-based.

In much neuroanatomical work in autism, interpretation of data has focused on identifying clues that could suggest developmental processes that might have gone awry, that would in turn point to potential genetic mechanisms. I spent a long time trying to do this myself, and I have written a series of literature reviews and read most of what has been there to read. But my work over the years has led me to question the strongly held assumption that autism is a neuro-developmental disorder that is wired in before you're born, a "static encephalopathy."

The "static encephalopathy," hard-wired assumption is certainly entrancing. It sort of makes sense because after all, autism does start early, and it sure seems like a life sentence. Even so, I began to realize that there are alternatives to the ways some of the findings being used to support this idea are being interpreted. For example, some brain studies looked at tissue in people who died and saw cellular changes that looked like they probably happened before the individual was born. But this was an interpretation of the arrangement of cells. One example is tightly packed cells in the limbic system; another example is changes in the brain stem. These brain tissue changes were found in less than a dozen brains each. So on the basis of a small number of brains, global inferences were made that this must have all happened in the third to fourth week of gestation or the 30th week of gestation. This interpretation became a "fact" that actively blocked funding of postnatal processes in autism—I have watched this blocking occur in grant review processes.

Now we're finding changes in the brain that appear to have happened after birth. I found white-matter enlargement that was consistent with what other people were finding, which was that in autism the brain on average gets bigger *after* the child is born. This is one of the things I found that was outside of the model I'd started with. Subsequent work has found that there is a massive brain growth spurt in the first 2 years *after* birth, where the rate of growth of the autistic brain—and this may be a subgroup, but it's a substantial subgroup—shoots up and the brain gets way bigger by the time the child is 2 than in an average 2-year-old. And then the growth rate slows down relative to children without autism, so that there is no brain volume difference by adolescence, and by adulthood brains in autistic individuals are even a little smaller than those in typically developing individuals. So something is going on after birth, and though you can make up a story that it is triggered prenatally, no one has proved that or excluded the role of post-natal factors.

In my own imaging-based anatomy research I was looking at MRI scans from autistic children aged 5 or 6 to 11 years, and they had big heads. When I analyzed the data further I found that it was white matter that was big—and on yet further analysis I found that the enlargement didn't involve all the white matter, but it specifically affected the white matter right under the cortex that develops its white myelin coating the latest, well after birth, and not the deep white matter that myelinates earlier. There were more consistencies with other findings: the areas of the white matter that were bigger were the areas that were myelinating during the time that retrospective studies were identifying the brain growth spurt—and also during the time when "autistic regression"—the loss of skills like language and social interactivity and the onset of autistic behaviors like rituals and hand-flapping—tends to occur. More recently my group's finding regarding the distribution of white matter enlargement has been pursued by my colleague Carlos Pardo, a neurologist and neuropathologist at Johns Hopkins, who had already demonstrated activated microglia and activated astroglia in brain tissue from autistic individuals—these are signs of innate immune activation. After reading my paper localizing white

matter enlargement, he went back and stained tissue in the same distribution as the areas I'd measured, and he detected cellular changes consistent with immune activation in the same parts of white matter where I had detected volumetric enlargement. This suggests that this white matter enlargement may be related to immune activation, which may be driving brain enlargement and impairing brain function.

Dr Pardo's findings of brain immune activation completely change the playing field of what is relevant to how autism works. In other words, if that's going on, then you have an ongoing chronic-disease process. There may or may not be early wiring changes, but you have an ongoing chronic-disease process. And that's a totally different ball game from what we've been thinking about autism—it adds a whole extra axis to the dimensions in which we need to characterize the condition.

To flesh out the implications of these chronic changes in autism, I wrote a paper called "Autism: A Brain Disorder or a Disorder That Affects the Brain?" More recently I coauthored an article with my neurobiologist and neuropathologist colleague, Matt Anderson, about this called, "An Expanding Spectrum of Autism Models: From Fixed Developmental Defects to Reversible Functional Impairments," that will come out next spring in a volume edited by Andrew Zimmerman, a close colleague of Carlos Pardo's and an important pioneer in immune system research in autism. It's premature to say that the earlier model of fixed wiring deficits is wrong. But it is not premature to say that there are things going on later that could actively influence the level and type of functioning of the brain—all kinds of cellular changes that would affect the synapses and the blood flow and other things that can manifest as problem behaviors, either in addition to or even instead of early wiring diagram alterations.

AT: How did the TRANSCEND project come about?

Dr Herbert: I developed the TRANSCEND model because of the way a whole series of observations and study methods hung together and yet were all being pursued separately. I was doing MRI research, and I noticed that the brains I was looking at were big. Then I added diffusion tensor and spectroscopy measures in MRI because they show you something about the tissue architecture and

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the tissue chemistry of the brains, but they still don't show you anything about function. So we added EEG and MEG (magnetoencephalography), which we chose rather than functional MRI because EEG and MEG are sensitive to time intervals as small as 1/1000, whereas MRI can only discern processes as short as 1 second. Synapses function at the level of 1/1000 of a second, and you wouldn't pick up problems related to neuronal malfunction with a functional MRI, but you could pick those up with EEG or MEG. We are planning collaborative projects with several neuropathologists, electrophysiologists, and technology designers.

What TRANSCEND collaborators are trying to find out is, are the parts of the brain where we will find abnormal tissue architecture or abnormal tissue chemistry related to the parts of the brain where the timing and coordination of the connections is not typical? And if so, if we treat or modulate some parts of this, will the others change in concert? How do we best design experiments and measurement techniques to detect these changes, both experimentally and clinically? In order to do that, we have to have an interdisciplinary collaboration because no one researcher can do all of that. The next question, now going beyond the brain, is, are these individuals also, at the same time, showing signs of systemic metabolic abnormalities, immune disturbances, biochemical disturbances, and infectious disturbances? Could it be that dysregulation from immune or biochemical or other metabolic or infectious problems can have an impact across the blood-brain barrier and affect brain function? The technical word for this is *encephalopathy*. We are asking if autism is a *dynamic encephalopathy*, even a *metabolic encephalopathy*—that is, a metabolic disturbance of the way the cells can function in the brain.

"I think we need to use science flexibly and adaptively to ferret out the treatable biology in autism and other environmentally modulated illnesses."

In addition to the immune findings, we have clinical reasons for thinking that this may be a metabolic disturbance—there are times when you see children get better very briefly. There's a paper coming out in *Pediatrics* from Andy Zimmerman's group documenting that a fair number of children with autism get a lot better when they have a fever. They start making eye contact; some of them talk. I had one mother of an 18-year-old autistic boy tell me that when he would get a fever when he was younger, he would become much more communicative. And she said she welcomed those times because she would get to visit with her son, as she called it. Another time you see these children do better is when they're going to have a colonoscopy or an endoscopy, and they have to go on clear fluids and have no solid foods. Some of them will perk up and make eye contact and talk; then, when you reintroduce foods after the procedure, it all goes away.

It makes you think that the autism is not due to a broken system. It's a system that's capable of functioning, but something is suppressing the function. It's a really different model, but it fits a lot of the things that we see. So then the question is, what is suppressing the function? In some cases, it seems like the suppression is pretty easily reversed transiently, although it can't be kept reversed very easily. In other cases, it seems to take a lot of metabolic tinkering to get a child to be able to pull out of it somewhat. But even so, in order to be motivated to do the hard work needed to make those kinds of improvements endure, you need to have a model of what you're doing, one that tells you to look for and address functional disturbances and not just hard-wired disturbances.

In TRANSCEND, we're trying to bring together different levels of research and different measures in an organized way so that we can see how they relate to each other. My colleagues who have partnered with TRANSCEND have been hungry for this kind of collaboration. The other thing we're trying to do is to develop a profile of measures that are sensitive to change, because we're looking at autism not as a fixed state, not as a trait, but as a state that can be changed. People have been treating it like it is a fixed entity, and consequently there aren't a lot of good, and particularly not a lot of validated, measures of improvement or change in autism.

When you start seeing change, you want to figure out, how do we measure that change? What domains is the change in? What parts of the brain? What sorts of functional tasks can you give a person so that their EEG will show the change? I don't know of anybody else who's doing that. I hope we get more company soon.

AT: This is fascinating on many different levels, and it brings up the question of autism—singular—vs autisms, plural.

Dr Herbert: This ties into the question of final common pathways. People have spent years meticulously defining the behavioral criteria for autism. You need to have impairment in communication, impairment in social interaction, and manifested repetitive behaviors or restricted behaviors or interests—all of that by the age of 3 in order to meet the full criteria for autistic disorder. Or you have to have pieces of it in order to be on the autism spectrum.

My feeling, and I'm not alone in this, is that these behaviors are a final common pathway, and you can get to the point that your brain will produce these behaviors by a variety of different biological pathways. So the problem is that if all you're looking for are the components named in the gene-brain-behavior model, then the links in between genes and brain and behavior become black boxes. In particular, people haven't been measuring enough of the biology that's in between the genes and the brain for us to be talking enough about what biological subgroups we may have in autism.

Our TRANSCEND model is what we call a middle-out model. The gene-brain-behavior would be bottom-up, or if you start with the behavior, it's top-down. We're saying that the intermediary biology is the middle, and then you work out from looking at the biology, the physiology of the person, and you work back to what genetic and environmental things could have led to it, and you can work out to how this would lead to behaviors. At the core, you're grounded in the biology of the person.

As an example, some people think that there could be, for instance, a calcium channel abnormality. There are a lot of different genes that can affect calcium channels, and there are a variety of toxins that can affect calcium channels. Others talk about methylation abnormalities. For each of these, there are a variety of genes and a variety of toxins that can cause such problems—making these mechanisms potential final common pathways—but the behavioral outcomes seem to wind up similar, for reasons that it would be incredibly valuable to figure out.

The point is that you can end up in a similar place even if the specific environmental trigger or the specific genetic vulnerability is different from case to case. Autism—when thought of as a singular condition (which has really gone out of fashion, and for good reasons)—is meeting the criteria for behavior and even then, there are people who have more repetitive and restrictive behavior, people who have language problems, and people who don't. So even at the level of behavior, it's heterogeneous, it's interindividually (as well as intra-individually) different. We started TRANSCEND because we have not had a research program that connects the people who are measuring the biological configurations with the people who are measuring the behavioral configurations to see whether there's a relationship between the two. It's been very fragmented. I think we need to rethink that. Our "middle-out" approach is about these different levels, and about rethinking the way we design research programs and collaborations.

AT: Does the research show that there are identifiable, different autisms—plural—or is that just emerging?

Dr Herbert: People are groping for that. I don't think that they're there yet—it depends on whom you talk to. If you talk to the behavior people, they have some subgroupings based on the categories that they're familiar with; if you talk to the biomedical people, they'll say, well, there are kids with bad gastrointestinal problems, there are immune kids with some kind of allergy problem, there are infectious kids, there are mercury kids, or there are toxic kids. For biomedical subgroups, there are some data to support this, but the people who've been thinking this way haven't had the funding to carry out these investigations in a systematic way or on a sufficient scale. At the moment, these areas have not been studied in an integrated fashion, the way they need to be.

One obstacle to identifying subgroups is the narrow and fragmented way we collect data. One cohort has imaging data, another has biochemical data, a third has EEG data. How do we know how they relate? If we ever identify subgroups, we will probably find that they are characterized by a suite of findings that cross these disciplinary boundaries.

AT: Your work has broken away from the traditional view of the condition as a genetic, brain-based disorder to look at autism as a systematic or body disorder with genetic influences that affect the brain. Yet, as you just mentioned, there are other factors, such as immune system dysfunction, chronic infection, gastrointestinal issues, and detoxification problems that, according to your research, are essential to understanding autism as a chronic disease state.

Dr Herbert: Yes. You can quote papers whose numbers range all over the place on how many children with autism have gastrointestinal dysfunction, just to start with that organ system as an example. It ranges from 9% to 95% or more, and it really depends a lot on how you ask the question. If you retrospectively review the records of psychiatrists who interview children with autism, you will get a very low rate, but then how much attention do most psychiatrists pay to taking a GI history? Unless they've done functional medicine, they're not going to do that. Other papers have figures as high as 95% or even 100%. If you prospectively look for GI problems in children with autism, deliberately seeking out signs and symptoms, you get much higher numbers. Work is starting to happen—in the Autism Treatment Network, for one—to investigate every autistic child who enters a clinic to see if they have GI problems; it will be most interesting to see what is found. These studies will have to be limited in how exhaustively they can study children who may have ambiguous or absent GI-related findings. There are ethical issues around doing invasive GI procedures in children who have no signs or symptoms. You can do a capsular endoscopy, where the child swallows a little camera that takes pictures and that's probably the least invasive thing, but really we're nowhere near being able to do that on every kid who walks in the clinic door.

I think there's an insidious and difficult to document interaction between immune dysfunctions and infection. Regarding the immune problems, an off-the-cuff estimate I got from some researchers at the MIND Institute at UC Davis is that about 70% of the autism spectrum children they characterize have immune

abnormalities. Regarding infection issues, this is tough in a clinical setting. How do you test for this? The tests available in academic labs won't clarify this issue. You can walk around with a chronic infection that doesn't meet the standard lab criteria for a fulminant, bad infection, but it can still be a chronic problem that throws the system's biochemistry and immune activity out of whack. Many people who think biomedically about autism suspect that something like this is common on the autism spectrum. But this will fly under the radar screen of standard laboratory measures.

One of the things I've gotten into sociologically and philosophically, as well as scientifically and clinically, is thinking about how our assumptions shape even something as ostensibly "objective" as laboratory measures. I started to think about, number one, how do you decide what is a normal range for a laboratory measure? And number two, what sorts of things do you measure? I got into this because like many clinicians, I have sent organic and amino acids to academic labs for metabolic workups of autistic patients, and they come back with lots of individual values being high or low, but with the whole study being interpreted as normal. This frustrates even colleagues who know nothing about functional medicine. You start to be able to think about it when you add environment to your equation. If you have a metabolic pathway that is being inhibited by the environment, or an immune system that just isn't working up to par, a much lower level of noxious stimulus can get you into trouble and yet if you send a sample to a lab, they'll call it normal because it won't fit the patterns of genetic diseases that they are looking to diagnose. I think that the whole domain of environmental illness of which autism, in my view, is one example, raises these kinds of problems.

We come from a paradigm where diseases are serious and life-threatening and somebody's in a hospital bed and they can't get around—or, it's due to a specific identifiable gene or microbe; with that as a standard of disease, if you don't meet the criteria for being a train wreck or for having a highly specified and fully manifested disease pattern, then you're considered normal. If your laboratory uses train-wreck reference ranges or only looks for specific and narrowly defined disease patterns, its interpretations of its measurements simply won't be sensitive to the kind of chronic, insidious perturbations that could be going on. But if a person has a whole set of chronic, insidious perturbations, this situation can drag the system down in interactive ways. This is pertinent metabolically; it's also relevant in the central nervous system. If you have an exquisitely regulated brain, where the timing has to be just right and the coordination and the synaptic thresholds and the levels of firing, the amplitude of the signals, the gating of the sensations, all of that has to be exquisitely regulated, and if you start having altered enzymes and altered cellular function, the exquisite coordination is going to start breaking down and you will only be able to produce approximations, not finely tuned synchronizations. A brain in this condition will not be able to pull off doing complex, integrated things. But the problem is that a brain in this condition can still look "normal" on standard brain measurement instruments. And the wall between standard and non-standard is high.

As I thought about this more, I started seeing parallels between the resistance of conventionally trained physicians to integrative metabolic measures on the one hand and to computational EEG measures on the other. In both cases the measures are characterizing dysfunction as continuous variables, not as discrete categories. Autistic patients bear the brunt of resistance on both these fronts. They are metabolically sick, but not in ways that standard laboratory measures capture very well. And their brains malfunction, but most don't have grossly abnormal brain anatomy, and while a third have seizures, the other two thirds have brain problems as well, but not in ways that standard MRI scans or standard EEGs detect so well either. With computational EEG assessments you often get abnormal power spectra, EEG coherence, and evoked potentials, but right now that does not link in standard practice parameters to any meaningful treatments.

Parents of patients have complained to me that their pediatricians have ragefully thrown their notebooks of integrative metabolic, body burden, and stool measures across the room. My neurology colleagues complain that quantitative EEG "always finds something wrong, and what good is that?" and yet will be satisfied calling someone's problem "psychiatric" if they cannot identify explicit seizures on an EEG study. In both cases I'm watching what looks like my colleagues viscerally rejecting measures that not only are strange to them but also don't work with their categories. How you respond to the proposition that you could measure metabolic dysfunction before it turns into a disease category, or brain dysfunction before it turns into seizures, locates you in relation to a pretty profound epistemological and world-view divide. For the moment at least, a lot of my writing and thinking and talking has been oriented to explaining things to my colleagues on the other side of this divide.

Then there is the question of what you measure. A lot of the things that some of the functional medicine and integrative and environmental medicine doctors measure, you can't get in a standard hospital. What is that about? Part of my educational background before I got into this was in sociology of knowledge, and I just find this completely fascinating. You have these parallel universes of laboratory measurements going on. It's absolutely fascinating. The question of what it takes for a measure to be validated enough to be used academically is rich to explore. If your criterion is that a biomarker needs to be sensitive and specific for a specific disease entity—and this is an FDA criterion—then many of the functional medicine lab measures, which address metabolic compromise such as inflammation and oxidative stress that are common across many conditions, may never make it over this hurdle.

I have a biomarker project going on right now. It's partly in self-interest—what metabolic correlates do I want to use in MRI and EEG/MEG studies? It's partly pedagogical—a big part of my agenda is to convey the importance of looking at autism biologically, pathophysiologically, to people who think autism is just about behavior and brain. And it's partly sociological—why are there these two different worlds? I hooked up with somebody similarly obsessed with doing bibliometrics, bio-informatics, searching the literature for an overview of what has been measured biologically in autism. The first thing we're doing is just to survey what has

been studied already. Even doing this project we run up against the ways the categorization systems you use for computational analysis of literature data are set up. They are not really tailored for some of our questions. This throws us right back into needing to make a case that there's something socially constructed about what we measure as well as the laboratory reference ranges we use to think about it. It's a very delicate argument. You don't want to call the whole laboratory endeavor socially constructed; it's really about the interpretation of what you measure. I think it's a huge issue.

On a more limited scale we are also collecting on a wiki some of the rationales for what is being measured and used clinically in functional and integrative practices. We would like to have this as a resource both for ourselves and for those parents whose pediatricians angrily throw their lab notebooks across the room. Interestingly, it's hard for me to convey what I'm doing to some of my clinical and laboratory-based friends. Some of them are so absorbed in their specific measures that they do not get that there is some use to identifying the patterns in what is going on. I'm persisting at the pattern-seeking level because I'm not sure we'll conquer this by validating one lab measure after another, piecemeal. That will help, but it won't do the whole job. I think the problem is more systematic and needs to be addressed at the paradigm level.

For autism, I think that the core of the paradigm shift will occur as we show concretely that metabolism relates to brain function. I think this is plausible based on the kinds of psychological and brain functional issues we see. If you look at the psychological domains that are characteristics of autism, you have breakdowns in the areas that involve complex integrative information processing, a formulation Dr Nancy Minshew has done much to develop. With language, for example, you have to get so many things together at one time for proper functioning: motor production, breathing, meaning, associations, nuance. You can have a very bright autistic person who's articulate, and you can have a substantive conversation, but when you try and tell them a joke or make a sarcastic remark, often they don't get it—they can't take that extra step. They have a hard time adapting to change. This is the "repetitive and restricted behaviors and interests" part of the definition of autism. They have a hard time reading the emotion conveyed in facial expression. These are all things that require complex information processing.

One of the things that comes up here is, does this help explain the relationship between a severe condition such as autism and some of the milder conditions like specific language impairment or attention deficit disorder or other things? You see various brain features that are common between autism and developmental language disorder—same as specific language impairment—where there are language problems but where the behavioral and communication problems are absent or more subtle. You see similar problems processing sensory stimuli that come in rapid sequences. In my work, as I mentioned, we also measured larger brain and white matter volume in both conditions. Yet autism has overt challenges in more domains than the milder conditions. Is it that there's a kind of a threshold effect, a tipping point, where these disruptions that mess up the exquisite regulation of brain function start out being modest and when they cross a certain point, they start challenging and taking out more domains? Do the disruptions make it harder for you to do the things that come naturally to other people because they don't face an overwhelming physiological struggle to make the cellular machinery of integrative connections work?

In my mind, these problems have become linked to the metabolic things we are learning about autism. If you look at the brain as a functioning system, and if you have abnormal cytokines floating around your body, if you have abnormal metabolites, if you have malabsorption and you're not absorbing your zinc or a whole variety of other neurologically important substances, you're not going to be able to do brain business as usual. You just won't. It also links to environmental things. Maybe the increased numbers of reported cases of autism relate to more people getting hit hard enough by environmental overload to cross the tipping point into more complex involvement, into having their brains struggling so hard that even more domains cannot be coordinated.

And conversely, if you recognize all of this and you start fixing some of those systemic conditions, then the basic materials that will allow the brain to function will be provided again, and various of the cellular maladaptations can be corrected (either quickly or over time) and you can potentially achieve a more optimal, functioning state. Then the brain can start optimizing its system and coordinating functions. That's where you go from a systemic model to a model of treatment and potential reversibility.

It may be that the most strategic research intervention is to demonstrate in published peer-reviewed literature that these levels are yoked to each other. If brain measures that fascinate the cognitive neuroscience people can be shown to co-vary with metabolic measures that fascinate the physiologically oriented researchers, it might open the gates and increase the motivation to tackle a lot of the other issues that need to be straightened out in order to pursue these intrinsic relationships. Opening these gates is a core part of TRANSCEND's mission.

AT: Will improvements in these areas result in improvements in function for the patient?

Dr Herbert: There's a whole movement right now on autism recovery. There are people who insist that their children have recovered. There are claims that there is recovery through biomedical intervention, but also through behavioral intervention. I became fascinated with this concept when I met children who had substantially improved—I didn't know them before recovery, but I saw videos from when they were severely affected so either they all had unaffected identical twins or clones or they had substantially improved. I think that in the last 3 or 4 years since I first became acquainted with the notion of autism recovery I've seen a lot more receptivity to this idea. There's a lot of documentation on the Internet and increasingly in the media. But there are almost no academic papers—we are just beginning to see academic literature on recovery. Deborah Fein at the University of Connecticut is working on this; she is studying what predicts children who later lose

their diagnosis and what problems are left over. For example, some kids wind up no longer autistic but are still language impaired.

The whole premise of treating autism, particularly biomedically, is that improvement and recovery are possible. The implausibility of these treatments to mainstream practitioners is linked to the generally framing of autism as genetically hard-wired and hopeless. Recovery may be happening, but until it appears in the peer-reviewed scientific literature, it won't be considered real. So we need to collect data and write it up. Some of my colleagues and I have organized something called the Autism Recovery Documentation Project, and we are intently, intensively working on collecting documentation of recovery and tabulating and analyzing it. How severe were they when they were affected? How far have they recovered? I expect we will have something drafted in the next several months.

This concept of recovery or even loss of diagnosis with milder residual has huge implications for both research and treatment. Take research. Two years ago, I was at an autism think tank of academic environmental researchers, and everybody was completely convinced that autism was totally hopeless and irreversible and therefore we had the next 30 years to leisurely research it because there was nothing you could do in the short run anyway. Jill James and I talked about improvement and recovery but it went over like a lead balloon. But now, you just can't say, "assume hopelessness" in quite the same way because more people have heard something a little different. I think this has enormous implications for the research agenda. I am biased to wanting to favor hope rather than no hope. If we think autism recovery phenomena are real, then we need to validate and publish them. And we really need to be orienting research toward documenting and facilitating constructive change, and especially we need to prioritize offering and optimizing treatment now because if some kids can make it all the way or even a fair amount of the way to optimal outcome, then all children should be given the treatment that might help them to improve their functioning.

All too often when parents take their child in for diagnosis, they will hear, "Oh, it's autism. It's hopeless. There's nothing you can do; you'll eventually have to institutionalize the child." Or, "Just get some basic services and go home and don't have any expectations." There are huge implications if those statements are shown to be incorrect. It means we need a major change in practice parameters. For this change to happen, the public pressure that comes from putting up websites and doing videos and films and so forth will help a lot in changing the atmosphere. But the sociology of this is that a precondition for changing practice parameters in autism to reflect the possibility of major improvement and recovery is documenting these phenomena in the peer-reviewed scientific literature.

AT: Your work has proposed a direct link between environmental toxins and their impact on common pathways as manifested in autism. But it's not a simple equation, is it, when you consider the criteria used to determine the level of baseline impairments from these toxins as well as the impact of multiple toxin exposures?

Dr Herbert: There are 85000 or God knows how many new-to-nature chemicals in the environment, not to speak of other stressor, such as infectious and electromagnetic agents. We don't have an intrinsic or new physiological pathway for every single chemical that is invented. They basically come into your body, and your body has certain ways to respond. Any one substance can stress out a range of pathways—and you can have problems way before you hit what has been called "toxic." Combinations of such substances synergize, so that you can get a cumulative effect that's noxious, toxic, impairing, and hurtful even if no one substance crosses the so-called line that somebody decided was safe or not safe. Which gets back to the question of, says who? And with what level of technology and sensitivity? With emerging knowledge of epigenetics and endocrine disruption and more, we are seeing an unprecedented ability to measure and mechanistically understand much more subtle changes that can happen in gene expression and in metabolism. In this setting the old idea of a threshold between what's safe and not safe is becoming meaningless.

So what if it doesn't kill half the laboratory animals? That's not the level at which the problems we're talking about are occurring. We're babes in the woods with regard to how the regulatory apparatus can cope with what our advances in science are allowing us to understand about what we really might be doing with our "advanced" way of life. The idea that you study one thing at a time and each input is separate seemed so logical and systematic, but it isn't really good for understanding what's going on with our health.

This gets to an existential question. This is something I wrote about last December in an article called "Time to Get a Grip" in the *Autism Advocate.* In a special issue on environmental health and autism, I wrote that we've set up a situation right now where we really didn't think things through, producing all these chemicals because "we"—that is, the people who decide what is important and who need to have it be "scientific" or else it doesn't exist—didn't know that we were making a mess because we didn't know how to measure it. Now the measurements are revealing embarrassing information. And interestingly, the Bush administration is closing down the Environmental Protection Agency libraries and not letting people even look at data. They're closing libraries and packing up the information. You would think that at this point in time, when we really need to see the information because we're in trouble, it would be even more available, but instead it is being put away. Closing these libraries is a crisis for democracy in a scientific world. I think that the closing of libraries reflects that the information is becoming damning.

The complexity and huge diversity we are starting to be able to measure is outstripping our simple models in many domains. I love to listen to Jeff Bland, when he talks about the incredible explosion of knowledge, for example, of the thousands of phytonutrients and the things we are learning that they do. There's incredible diversity. I read the interview with the ethnobotanist Jim Duke in the March/April issue of *Alternative Therapies* that addresses the same thing. With this incredible diversity of natural substances, combined with genetic individuality and individual variations in state, it seems to me that it's becoming meaningless to talk about

standard dosing recommendations for nutrients or safety limits for toxins.

Basically, we are not equipped to get final certitude on the level of complexity that we're coming to appreciate is in play. Autism is so complicated—and so is other environmental illness and so is the planetary situation right now—that we're going to have to use some kind of good judgment way before we can have scientific certitude and comprehensive precision about these things—which indeed we won't ever get, realistically. We're going to have to transition how we make our decisions from a model of precise science as the arbiter of what is permissible to think and what is not, to the use of science as a kind of tool to check our judgment. Our standards will need to come from a more healthful approach as a fundamental basis as opposed to assuming things are safe and then requiring precision science to prove otherwise for one exposure at a time.

The final common pathway argument takes you here because you realize that we've created a production system that hits us with a huge number of exposures, with which we're basically trashing supportive body pathways and body systems, even if we don't know specifically what's doing the metabolic damage. And if you have any kind of genetic vulnerability in any of those pathways, you're going to be a sitting duck to suffer. In this regard, one of the models going around now in autism is that these kids just have more genetic vulnerability, and they'll need fewer environmental hits than their less genetically vulnerable neighbors to overtly suffer from exposures. There are other people in the autism debates who think maybe you don't even need that genetic vulnerability if the exposures are sufficiently strong. So no one has resolved this discussion at this point because we've just started to ask those questions, and there's almost no data because the research programs in place so far have not been designed to answer those kinds of questions.

AT: It sounds like we won't be at a point of resolution anytime soon.

Dr Herbert: No, and meanwhile, we have to handle the situation now: this one and many others. We're going to have to handle these situations on the basis of something other than the results of the next 40-year perspective study. We can't sit around doing nothing while we wait for these data to come in.

AT: And yet that premise, as you mentioned, flies directly in the face of using the science and the research as the traditional arbiter of the decision-making and regulatory processes.

Dr Herbert: That's exactly right. But this is a colossal epistemological crisis on top of the environmental crisis. Even some of my closest friends and allies want to base decision making on what we call "sound science." The problem here is that the term "sound science" can be defined in different ways that carry different motivational and ideological loads. It's very important to seek the best scientific understanding that we can have, but at the same time, we want to use science as a guide, a tool, but not as a censor, as a bully.

Who makes the call about what is "sound" has a big impact, including on treatments that may help in autism. There's a lot of criticism that complementary and alternative treatments in autism have no scientific evidence, that there are no studies. For many of these treatments, if you zoom out from autism to the class of conditions in which autism fits (at least when formulated as an environmentally modulated syndrome) there's a lot in the literature beyond autism that supports the *plausibility* of the interventions for various classes of metabolic problems some doctors measure in autism. But often these haven't been measured in "autism." To make it harder, the measurements, even when done, don't come out identical for everyone on the autism spectrum. And yet we don't know how to distinguish between subgroups, since what works for some won't work for others and some presume that this relates to distinct biological mechanisms. One of my colleagues says that maybe we won't have subgroups; we'll just have a "mess with final common pathways." Maybe it's not going to break down into distinct subgroups. There are differences, but maybe they don't cluster out into neat little groups. If we try to produce "sound science" by using standard clinical trial methodologies where everyone who meets behavioral criteria for autism is lumped together, the noise will drown out the signal and it will look like the whole biological dimension has no pertinence.

I think we need to use science flexibly and adaptively to ferret out the treatable biology in autism and other environmentally modulated illnesses. How do you test treatments when people are so different from each other? Once you acknowledge that, you have to be humble about the results of treatment trials. It's really complicated because of course you don't want to introduce interventions that hurt people, and you don't want to do things that waste people's time and money. At the same time, how do you make judgment? I think we're going to have to take on a systematic reevaluation of the judgments and gate keeping involved here.

AT: Why are we seeing such a rise in autism? Is this real or simply an artifact due to broader definitions and better reporting?

Dr Herbert: Certainly, there's more awareness and more reporting. The more affected people you have, the more you're going to see it and the more you'll report it. And it's on the news all the time. There were children I saw during my residency whom we would now call autistic, but we didn't then. In these cases, the problem back then was awareness. Regarding broader definitions, I don't think the diagnostic criteria have changed a lot in the past 15 years—certainly not enough to explain the 10-fold increase in the numbers. Some people say, "Oh, they haven't changed lately, but it takes people time to learn what the new ones are." Then other people say, "Well, people get called autistic because that's how they get services, even if they aren't really autistic."

I think all of this is true, to one degree or another, but it begs the question, do all of those lines of arguments exhaustively explain how the numbers shot up from 3 to 4 in 10 thousand in the mid 1980s to current figures of 1 in 150 or even more? A recent UK

report said 1 in 86 children are on the autism spectrum. You'd have to be pretty confident that all those inferences explaining these numbers away, such as "It's just better diagnosis" and so forth, were absolutely, solidly, the only possible explanation for such striking increases. And if you are not absolutely clear about the reasons why, then you had better treat this as a public health emergency until proven otherwise.

I think there's an emotional issue going on here, too, that people are conservative, and they don't want to say something alarmist if it's wrong. There is also cognitive dissonance—how could a genetic disease truly increase? People don't realize how tenuous the evidence is for this truly being "genetic" so they treat the genetic *model* of this condition as fact. Many of my colleagues who will not consider the possibility of an epidemic have no vested interest in anything that would bias their judgments except that this is what they believe and it's very hard for them to entertain anything else. To consider that we may have an epidemic of autism and childhood neurodevelopmental disorders is emotionally painful because it raises profound questions about our environment, our progress, our way of life, and what we deeply trust. To avoid asking those painful questions, people try to maintain the assumption that nothing significant is changing.

But if you look at graphs of the number of new-to-nature molecules that the chemical industry has produced, you get an astonishing, exponential increase in substances on the planet that we've never seen before. That's just the physical substances, the chemicals. The next thing that happens, when you start thinking about this, is that it becomes so overwhelming that you go back to genetics because it feels like at least we can study that in an organized fashion, whereas looking at environmental factors would be total chaos. This argument is one of the standard talking points of some of my genetics researcher colleagues.

Advanced scientists should start to realize that the only way they can maintain this point of view is to advocate advanced techniques to study genetics and old-fashioned insensitive techniques to study environment. They need to partition their intellects to do this. As I've already said, we're learning so many more sensitive ways of measuring things, including the impacts of these new environmental inputs, and this is so new that we have hardly had time to think of how to apply these things. One of the expressions around this that I like is, "Absence of evidence is not the same as evidence of absence." The intellectually honest thing to say is not that there is no evidence, but that we have hardly started to look. Then, when you get interested in looking, you see that there isn't a lot of support for such investigations, and there is a fair amount of resistance. This becomes a political and economic question as well as a scientific question. Who's going to fund it, and who's going to get paid by which vested interest to shoot down whatever you say, who's going to sue you if you uncover anything that sheds a bad light or creates potential liability, and all the other related considerations? Given all these potential challenges, it's ever so important to think carefully and strategically about how to proceed.

My personal opinion is that while it may take years to sort out exposures and which ones may have strong impacts, there is a lot we can do right now with the knowledge we already have about the physiology of vulnerability to environmental impacts. My interest is in helping to figure out the points of intervention that can help people do better now, and in helping others to understand that this is a critical area of work. That's where I want to focus my energy. It's important to point out that there are destructive connections between chemicals and our health, and it's important to substantiate these connections, but we really need to understand the mechanisms of how health is impacted in order to be able to help people who are already affected right now. I would like to work on this area, which has been a black box in my field, and make it not a black box anymore but an area that's richly differentiated with carefully made observations.

To do this, we need to move ahead sooner rather than later not just with preclinical studies but even more with observations that come from treating people with basic protocols that we know aren't dangerous or at worst are low risk. For example, if you study interventions using diet and nutritional support and you study the differences in the treatment responses, you can learn a lot more about subgroups than if you don't treat people. In the Autism Society of America, we started the Treatment-Guided Research Initiative (TGRI) to do this work. TGRI is looking at what kind of infrastructure we can build to support learning from the actual treatments that are going on right now—and you need to understand that in autism there is a massive, basically underground, clinical rebellion going on with people saying, "My doctor is telling me there's no hope. I don't believe this. My child has a short developmental window of opportunity, so I don't have time to wait around, and I'm taking matters into my own hands." In many ways, highly motivated parents are leading the charge, and many are being their own medical case managers. Rather than dismissing these parents as gullible and crazy, as so many mainstream doctors do, we think it would be more constructive to ask how we can turn this huge body of experience into data that can feed back into the process and help it work better. What kind of database can we build to capture the information? What do we measure and how do we best document improvement and recovery? We need a whole new way of collecting our data and following it.

So a portion of my energy is going into helping to frame that effort so that we can learn from what we're doing, what's actually going on, as opposed to having some sort of ideal of what a perfect study is like, a false homogenization of everything into a standard clinical patient receiving a standard intervention. You can never reach that "ideal," and you never find out what's going on because the situation at baseline is not homogeneous like that. In this effort we are finding allies in a lot of other venues.

AT: The environment clearly has effects on brain development and it also has a number of other effects, and it would make sense that these environmental factors accumulate through the course of life. How does that impact the mechanisms that might underlie what we refer to as autism?

Dr Herbert: I talked a little bit about that earlier when I was talk-

ing about the cellular metabolism functioning poorly. New-to-nature chemicals set you up so that you don't handle infections right; they set you up for all kinds of systems not really working in top form. And then you can get into this vicious-circle cascade of the more you're compromised, the easier it is to become further compromised. The ways in which these compromises impair the brain—that bridge needs to be made, even for those of us who already think that this a whole-body disorder. There is a historical trajectory in the definition of autism, first as a behavioral disorder and then as a brain disorder. It started as behavioral and it moved more to brain. Now we need to move it clearly and irrefutably to whole-body.

We need to make that link. We need to study the ways that environmental factors affect more than the way the brain hooks itself up in utero. We need to look at the way that these factors mess up all kinds of biochemical systems and immune systems in the body. It's helpful to think about the old serenity prayer: accept the things you cannot change, identify the things you can, and be granted the wisdom to know the difference. If we focus on irretrievably faulty brain wiring, we are looking at something we probably can't change. We're saying, let's look for things that we can change. If you have toxins that have accumulated and moreover, if there are ways of either improving your body's resiliency to handle them if you can't get rid of them or detoxing if you can, that's something that can be done. If you have disorganized responses to sensory overload and an intervention helps you manage this overload so it doesn't spiral out of control and get even more overwhelming, that is something that can be done. And I think that when we do those things we need better measures of how the interventions are affecting the central nervous system—and I mean brain measures like EEG, not just behavior-oriented questionnaires.

That's what both the TRANSCEND Research Program and the TGRI are about: developing measures that can track treatment impacts (TRANSCEND) and developing infrastructures so the treatments can be used and the data can be collected (TGRI). This means helping to develop ways in which people can track what they are doing and learning from this, and this means helping people on the ground, not just in lofty universities, to do that in their practices and with their kids so they can judge whether they are achieving effect with what they're doing.

Pursuing this program is based on the model that autism involves functional problems, not just fixed genetically determined brain problems, and that these functional problems can potentially be reversed. I think that one of the reasons people haven't thought of autism as a functional problem is that it just never occurred to them. This is paralleled by the heavy emphasis in neurotoxicology on fixed brain developmental impacts of toxic exposures as contrasted with the very limited literature to date on chronic ongoing functional impacts. In the article I mentioned before that my colleague Matt Anderson and I are publishing called "An Expanding Spectrum of Autism Models: From Fixed Developmental Defects to Reversible Functional Impairments," we—Matt Anderson in particular—reviewed a lot of neurobiological changes in brain cellular functions that could be consistent with what we call autism. These mechanisms simply haven't been studied because so far as I can tell it hasn't occurred to anybody to bark up this set of trees.

I was looking in the literature to find electrophysiological studies of low-dose toxic exposures in animals to find out whether researchers could document by EEG the electrical changes from exposures, and I couldn't find anything. First, I thought I wasn't finding this literature in Medline because I wasn't using the right search terms. Then I found a symposium review in the journal *Neurotoxicology* saying that even though we're living in a kind of low-level toxic soup and have chronic, low-dose exposures of multiple kinds, the impact of these exposures to date has not been studied in an animal model at the level of electrophysiology—at all. I was stunned. I have been coming to appreciate the incredible bias toward studying big doses and studying what horrible permanent things they do to development and the accompanying belief researchers and others tend to have that it's all over after that. This has led the environmental health advocacy community to focus on prevention but not to address treatment. But I think that the idea that "it's all over after the exposure" and there is nothing you can do for the people affected now is simply not true. It's not all over after that. Let's look at functional measures and study what makes them worse and what makes them better. I confess to still sometimes feeling perplexed about why this line of thinking and work is not obvious to other people and wondering whether I'm missing some hidden mother lode in the literature—after all people use such models in studying drugs—but as time goes on I have had a number of my colleagues look into this question and they haven't found a whole lot of literature on this either. There's a whole universe of careers out there if people want to go out and fill these gaps. This is important because if we understood this better, we might be able to identify more mechanisms that could help us develop ways of helping people who are suffering from chronic environmental diminution of function.

AT: As it relates to the development of autism, the environmental inputs you're discussing are occurring within a very short time frame within a very young, developing body, literally from before birth to 2 or 3 years of age, so it sounds like there is a multitude of impact.

Dr Herbert: That's right, that's what it looks like. Plus, these are occurring during transitions in brain and immune and other development where there probably isn't a lot of room to buffer a challenge, so that if you're hit with a challenge when you're going through one of those transitions, it's not going to take you much to kick you off track. We see that in other conditions. For example, children have febrile seizures between 6 months and 6 years, and they are not so vulnerable after that. That's not an autism thing, although about 30% of people with autism do develop seizures and epilepsy. This is just one example suggesting that there are periods of time where it takes less to get you in trouble.

And if you fall down that rabbit hole, even if it has to do with metabolic responses such as screwed up methylation, inflammatory cytokines wandering around, nutritional deficiencies, a lot of

oxidative stress—a lot of that can be reversed, but it isn't going to reverse very easily unless you work really hard on it. The parents who say they've recovered their kids through biomedical interventions in general have worked really hard. It's a full time job to get your kid back. I can understand why my colleagues would think that this is inconceivable because they wouldn't know how to do that, either in terms of knowing what to do clinically or how to get paid for it under managed care. Even more, they wouldn't approve of the ways that people are doing this. Up until this point, their mistrust of the methods used has overwhelmed any receptivity to looking seriously at positive outcomes.

AT: At this point in time, is it possible to speak of curing autism?

Dr Herbert: You have to define your terms. There's a movement within autism called the Neurodiversity Movement, and their point of view is that autism is a way of life and a way of perceiving. It's not a disease. They equate the idea of curing autism with genocide. I think that premise needs to be picked apart. People with autism can make incredibly fantastic, unique contributions to society. They have unique perceptions, unique perceptual capabilities. This is outstanding. Some of us wonder whether there is certain a kind of biochemical feature—this is pure speculation—that works for having those wonderful capabilities, but then if the person with this capability gets environmentally challenged, that person is more vulnerable to becoming metabolically and medically overwhelmed.

My feeling about treatment and autism is that we want somebody to function optimally. It's not that we want the brilliance to go away; it's that we want the suffering to go away. We want the painful gastrointestinal inflammation, the sleep disturbances, the self-injurious behaviors—the things that cause the individuals themselves to suffer—to go away. We're not trying to change the way someone thinks; we're trying to allow the person's capabilities to come to full flower because they're not being tripped up all the time by suffering and medical illness.

AT: It appears that there is an intellectual or creative capacity that people who have autism exhibit that is beyond what we would consider normal or baseline.

Dr Herbert: It's completely fascinating. I think it's fantastic, and I have friends who are either autistic, have been autistic, or are sort of broad autistic spectrum, which means that they have some features that are autism-like but that these features aren't prominent enough for them to be classifiable as "on the autism spectrum"—kind of like an autism "shadow syndrome"—and I learn remarkable things from them. It's a real treasure for me. It's a treasure for the world. This again poses the question of what is the delicate relationship between those capabilities and when it goes awry.

The people that I'm talking about have pretty full and independent lives: they can hold jobs, they can talk, they can write, they're toilet trained. I include that last item because it gets pretty primitive—a lot of people with autism are not toilet trained. That's a problem. It really cuts your options not to be toilet trained. It cuts your options not to be able to talk, particularly if you want to talk. Some people in the Neurodiversity Movement say that not being able to talk is not a problem, but not everyone with autism feels the same way. And it cuts your options to be distracted by pain.

What is the cellular foundation for the brilliance, and does it have any overlap with the cellular foundation for vulnerability to the physical suffering? That's an open question. I don't know the answer. Some people speculate that autistic people have more glutamate in their brains and you don't need that much more to get into trouble, but at this point that's just a theory, although I think it's a promising and interesting one.

AT: What area of all of the research around autism are you most excited about?

Dr Herbert: Well, aside from documenting recovery, which would just open doors into understanding the mechanisms that make it possible, the other part is getting at the intersection between the immune and metabolic perturbations and the basic brain processing, the sensory processing problems, which may underlie a lot of what we see in autism to make that link. This is just what my group is doing. Getting the people who do this work at these different levels to realize that the heart of autism is probably in that intersection. I think we're kind of circling in upon it now.

AT: Do you anticipate a time frame in which we can expect to see some major breakthroughs?

Dr Herbert: You will of course get so-called "major breakthroughs" every time a lab has a good public relations department and they announce new results. In terms of really major breakthroughs, I think in the next 5 years the existing researchers as well as the new people who are getting drawn in will come up with some important findings. It depends on funding. The funding situation from the National Institutes of Health now is abysmal beyond all description. The funding pay lines are horrible. It's very hard for people to get funded to do research, so that will slow things down. But on the other hand, autism is hot, so more people are getting into it and there's more private money. So hopefully, with the proper resources, I would say 5 years. I could be wrong, but I think that this time frame is reasonable, given the proper support, because there's so much that's hanging together right now.

AT: How has the mainstream medical community reacted to the new thinking about autism, and what is the future of funding for the research needed to create new paradigms in dealing with it?

Dr Herbert: I have said some things about the popular cultural understanding of autism. I think that both the popular and professional understanding of autism is shifting. One of the things I and others have been noticing is that if you talked about gene-environment interactions a few years ago, you'd be marginalized, whereas now you can hardly submit a paper on causes of autism if you don't say it involves gene-environment interaction.

Also, as I said, people are starting to think about treatment and recovery. It's not everywhere, but it's enough places, and there is interest from enough reporters and enough researchers that I think we're hitting a tipping point. In the last number of months there has been a much more steady flow of press coverage friendly to one or more dimensions of the inclusive whole-body model—treatment, environment, recovery. Some people have been saying online that the paradigm shift has occurred—that we need to do more work, but that we have crossed the line and are on an upsurge.

In the last year I've seen very well-placed people starting to entertain models featuring gut metabolomics and other complex and intrinsically environmentally modulated models. People who a few years ago would never talk about these things are now getting that this is really important. We are on the verge of having the weight be more with this model. It will take a lot of work to flesh it out, but at least this is going to be a legitimate model, and it's going to be an area of genuine concentration. You won't have to scrape together your pennies and do it in your garage.

There is still a lot to do in advancing the new model. Seeing autism as a whole-body condition, looking at all of the biological levels—and not just the behavioral "outputs"—as part of the "autism" is a way of perceiving that can be learned and that can change research and clinical practice. As the plausibility of the approach is more widely accepted, the work will become more full-bodied and expansive. People who previously might have shunned it will increasingly work to find common ground. I am certainly experiencing this in my relations with a growing number of conservative colleagues. I hope that this work interpenetrates with the approaches of others so all become richer. And most of all, I hope this approach helps us efficiently and rapidly find more ways to help individuals affected by complications of autism—and others, as well—more effectively.