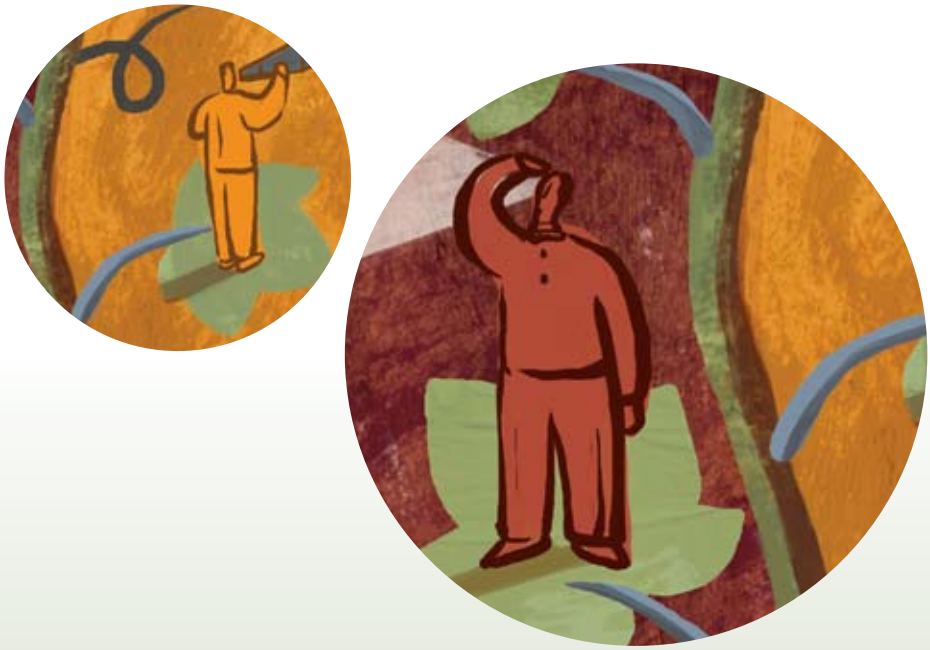

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Treatment–Guided Research

Helping People Now with Humility, Respect and Boldness

With the high prevalence of autism, millions of individuals and their families are dealing daily with chronic hardship and great costs. We need both to help those who need it now, and to learn more about providing the most effective help. Ideally, this should mean a marriage of research with treatment, with research improving treatments and treatment responses informing the direction of research.

Since its identification by Kanner in 1942, however, autism has been thought of as a life sentence that has no cure, relegated along with other complex conditions to that day when future science will unlock secrets that will give us a cure or at least an effective treatment. Meanwhile, the declaration of "incurability" has made treatment seem palliative and futile, at best a stepchild of science. Thus, we have a separation between treatment and research, so that at present they do not for the most part feed and inform each other.

Another reason treatment and research are in separate silos is that treatment research and basic research have been asking different questions. Treatment research generally takes the form of clinical trials, where the question being asked is whether a treatment works. Basic research looks for mechanisms relating to how a condition or disease works. We will argue that new understandings of autism open the exciting possibility of more strongly linking treatment research with basic research and, ultimately, transforming research and treatment across many chronic conditions today.

Toward Integrating Research and Treatment

There are five levels of understanding of autism that point us toward an integration of basic and practical research. Four levels have to do with autism itself: *1) Chronicity*— autism now appears to be not simply a result of something broken before a child is born, but instead a result of processes that are ongoing and active; *2) Plasticity*—we are gaining a greater appreciation of dynamic, changeable features of autism and the possibility of sustained improvement; *3) Complexity*—growing bodies of knowledge are illuminating the many levels of autism within each individual—neurological, medical, metabolic, molecular and genetic—that exist alongside communication and behavior; and *4) Heterogeneity*—we have a groundswell of understanding that there is no "one autism" but rather *many autisms*, a heterogeneous set of ways of having autism.

A fifth level concerns how autism relates to other conditions: *5) Non-specificity* of components of autism—while autism spectrum disorder is specifically defined, there are substantial overlaps between components of autism and other conditions.

These levels of understanding necessitate a fundamental change in how we view treatment. It is not enough to ask simply, "Does this treatment work?" We need to ask, "How does this treatment work in the people for whom it works, and what is different between the people for whom it works and the people for whom it does not?" This shift from a simple *whether* question to a more nuanced *how* and *for whom* question is the essence of treatment-guided research.

The disconnect between research and treatment transcends autism, and it is coming into central focus in planning for future medical research, especially for chronic diseases and conditions. In the broader scientific community, the idea that research and treatment should help each other has been dubbed "translational research," and it aims to "translate new knowledge from lab bench to bedside, and then back again" (NIH 2003). Translational research is a major theme at the National Institutes of Health (NIH), which aims to develop a new discipline of clinical and translational science and is giving dozens of Clinical and Translational Science Awards (CTSA) to academic centers around the country. These centers will be well equipped with the best-available laboratory and information analysis tools to produce the molecular treatments of the future.

Learning from Treatment Now

While the CTSA Centers focus on developing detailed understandings in the laboratory and embarking on complicated processes to translate these understandings into treatments sometime in the future, we can gain knowledge from the treatments already being applied and available to patients now. Of these presently available treatments, investigators have only asked *whether* they work, not *how* or *for whom*. When treatment works only for a subgroup of patients, this effect can be averaged away in the larger group analysis, and the treatment is then discounted as having no utility for autism. When this happens, we are ignoring the complexity of the disease, missing potentially effective interventions and losing a chance to help the subgroup that could benefit.

Conducting and publishing more research on effective treatments carries with it a double impact: It builds a body of evidence to aid professionals and families, and it creates a moral imperative to offer each child optimal treatments and services. For example, we know that early intervention is the best way to maximize the options of people on the autism spectrum. Referring newly diagnosed children to programs that help them learn language and social skills, communicate their needs, relate to people around them and behave appropriately—this is a standard of care, not to mention affording them their basic human rights. Treating the medical problems that so often come along with autism should also be a standard of care, as reducing pain often improves attention and compliance with treatment regimens, sleep and therefore learning, well-being and sometimes even the core symptoms of ASD.

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Confronting the Challenges

It is imperative that the best treatments be available to children as early as possible and as abundantly as necessary. How can we do this better? Which are the best treatments, and for whom? How can we expand options? Science must address these critical practical challenges right now. For science to help the most, researchers will need to confront the challenges posed by the new levels of understanding of autism:

1) CHRONICITY—ongoing and active processes, not just "inborn wiring problems" We are learning that autism has physical features that have ongoing effects that sustain themselves over time and affect well-being. It now appears that autism is not simply the result of a genetically caused change in brain systems, but that the brain may be impacted by processes that continue to be active for a long time into the life course.

What we are appreciating is that changeable features, and significant improvements and recoveries, suggest that autism may be a "state" (something that can change) and not necessarily a "trait" (something that is fixed) (Herbert & Anderson, in press). People with autism certainly change during development, but change can also be something else—a less age-dependent reconfiguration of medical and/or neural systems functioning.

While various changes in the brain have been identified that appear to suggest that autism is based on hard-wired brain changes that begin prenatally (a "trait"), there is also brain research identifying changes that could begin or worsen after a child is born (a chronic "state") (Anderson, Hooker, & Herbert 2008). It is important to remember that none of these studies have been done on more than a handful of individuals, and we have no way of knowing whether they are found in all individuals with autism or only various subsets. We also do not know either the long-term trajectory or the underlying cause of many of these changes. And there is hardly any study of their responses to treatment. This body of knowledge is therefore merely suggestive; it is nowhere near solid enough to justify closing the door on treatments and interventions that could improve the future of children with autism. Meanwhile, research on brain plasticity—the capacity to improve and recover—is advancing on many fronts and for many previously "hopeless" conditions (Doidge 2007), much of which may be relevant to autism.

Autism's features and symptoms span every level of biology and behavior, with many levels being affected at the same time...

2) PLASTICITY—variable "state" versus fixed "trait"
Accumulating evidence and experience are showing capacities for change, improvement and recovery in autism that render the assumption of hopelessness outdated.

- **Variability within individuals:** Many behavioral, nervous system and health features fluctuate for many affected individuals, often over a great range.
- **Outcomes:** Many children sustain improvements and a fair number are mainstreamed in school.
- **Core features can change:** Improvement in core features of autism in some children in association with fever (Curran & Newschaffer 2007) suggests that these core features may not be entirely hardwired and may respond directly to medical interventions.
- **Autism responds to treatment at many levels:** Improvement has been observed from interventions at many levels, from behavior to communication, from psychopharmacological to antiepileptic medications, and from metabolism to diet and nutrition.

3) COMPLEXITY—Autism's features and symptoms span every level of biology and behavior, with many levels being affected at the same time and affecting each other in complex ways.

Autism is defined behaviorally because these features are prominent and have the most easily perceived impact on others, but its other features are equally real. These features require research and treatment partnerships across a range of disciplines.

- **Neurological features:** Symptomatically, autism can involve disordered sleep, sensory challenges, seizures and epilepsy, coordination issues, low motor tone and more. At the level of brain imaging research, there are changes in brain volume and weight, brain cells and cellular organization, brain tissue, and brain functional activation and coordination. There are also measured abnormalities in the autonomic nervous system related to arousal and stress.
- **Medical features:** Documented clinical experience reveals various kinds of gastrointestinal problems, food malabsorption issues, allergies, autoimmune disorders, hormonal problems and more.
- **Metabolic features:** Clinical experience and documentation of a range of metabolic problems include mitochondrial cellular energy problems, immune abnormalities, inflammation, oxidative stress, methylation and trans-sulfuration biochemical pathway abnormalities, and nutritional deficiencies and insufficiencies. There are also various metabolic conditions that are often accompanied by autism (e.g., Smith-Lemli-Opitz syndrome, a cholesterol-metabolism disorder), as well as "shadow syndrome" versions of such problems—that is, individuals with ASD who have similar metabolic abnormalities (e.g., very low cholesterol) but without the full metabolic syndrome.
- **Genetic features:** A range of common and uncommon genetic mutations have been identified that are linked to various molecular pathways, cellular functions and vulnerabilities to environmental stressors conferring risk for autism.

Since behaviors are a product of the brain, and the brain is connected to the body, we cannot assume that these other levels are "secondary." They may be secondary to a behavioral definition, but at least some may be central to the underlying biology of autism (Herbert 2005). Even if some features manifest themselves before others, once they are all present, they all need to be addressed.

4) HETEROGENEITY—There may be many autisms. At every level of autism experience and research, we are finding differences among individuals, each of whom meets the behavioral-level criteria for autism. There are differences in the palette of behaviors, but also differences at all of the other levels listed above. These differences reflect that a range of different genetic combinations, gene-environment interactions, cell biological mechanisms and even neural system alterations may underlie what we categorize at the behavioral level as autism.

But the differences raise an important question: What is it about brain biology that may allow many different underlying biological mechanisms to produce a set of behaviors that look so similar? Addressing this question is very important for both research and treatment.

5) NON-SPECIFICITY of components of autism—Autism overlaps with other conditions. Each level listed above contains features of autism that are found in other conditions. While much research has focused on overlaps with other neurobehavioral conditions, such as attention deficit disorder or obsessive-compulsive disorder, there are overlaps at other levels: with neurocognitive conditions such as language impairment; with neurological conditions such as epileptic syndromes; with medical conditions such as digestive, allergic and immune disorders; with various metabolic conditions; with impacts of various toxicants and infectious agents; and with a range of genetic syndromes that

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frequently include features associated with autism.

We can learn three lessons from this:

1) While autism may be defined by a specific combination of features, and while there are probably important reasons why these features are so often found together, they can also be teased apart.
2) Components of autism that are also found in other conditions may lead to autism because of the specific timing in development or combinations in which they appear, rather than because they uniquely cause autism. A feature that is not specific to autism may still be important.
3) Moreover, we may gain insight into autism by studying other conditions that share features with autism.

What do these five levels of new understanding imply?

1) CHRONICITY: We need to see how treating some of the chronic and persistent processes in autism might lower the burden of suffering and increase options.

2) PLASTICITY: We need to learn to measure change. We can learn much about how autism works by seeing what can change from interventions, and when and how it changes. For the sake of helping people, we need to learn which changes are constructive and how to bring these about most effectively.

3) COMPLEXITY: We need to understand all of the levels of autism, how they relate to each other, and which features can most easily and usefully be treated.

4) HETEROGENEITY: We need to understand where the differences lie, and to see whether some subgroups have different treatable features than others.

5) NON-SPECIFICITY of components of autism: When more research on various components of autism has been done for other conditions that share features with autism, we can explore applying these lessons to autism. If treatments exist for these other conditions, we should explore them to see if they can help at least some people with autism. This applies at both the biological and behavioral levels.

Most important, we need to incorporate autism's changeability into our understanding of what autism IS. At present, people talk about curing autism, recovering from autism and living with autism. Our definitions of each of these are unclear. Learning about what changes with treatment can help us gain clarity.

Autism and More

The chronicity, plasticity, complexity, heterogeneity and non-specificity issues that we are coming to appreciate in the autism spectrum are also found in many other illnesses and conditions, particularly chronic and highly prevalent conditions. These include other childhood conditions such as asthma and allergies, as well as obesity, heart disease, cancer, arthritis and much more—many of which also have increasing prevalence. Emerging research is telling us that our disease categories may not be the best way to organize our research on cause and treatment. Within any one disease category there may be different genes or alleles in different people, a range of various environmental exposures, and a range of treatment response and non-response. Studies are also finding great overlap at each of these levels among many disease conditions.

This complexity is emerging in basic research as well. In genetics, a single gene can have hundreds or thousands of different mutations, with a range of different effects. Scientists are now studying genes not only individually, but increasingly also in networks. A network approach is also being taken in the study of proteins and metabolites. Genomics is being linked to other considerations, like proteomics and metabolomics. Genes are coming to be seen as acting virtually always in relation to other genes, to metabolism, to their environment and particularly to chronic conditions. Science is pushing us far beyond looking for single genes that cause single disorders.

In neuroscience, our understanding of brain cells and "wiring"

is becoming much more complex. Whereas it used to be thought that neurons were either firing or not, now we know that there are many states in between. There are many more types of receptors and interneurons than we suspected, with a great range of different effects. Even more, the "glial cells" (which appear to show immune activation in brain tissue in individuals with autism) (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo 2005), previously thought to "support" the neurons, actually play their own roles in signaling. They also respond to various kinds of stress (such as degeneration, infection or toxic stress) in ways that affect brain functioning. Even the most sophisticated present models barely touch at this complexity.

In environmental science, we used to ask: "Is it toxic?" But now studies are also showing real impacts of toxins on cellular function at doses far lower than what were previously considered safety thresholds. Moreover, research is showing that substances act differently together than they do by themselves, making it necessary to study things in combination. Virtually all of us have low-level body burdens of hundreds of chemicals (Grandjean & Landrigan 2006; CDC 2005), which can no longer be assumed harmless. This introduces huge complexity because the many thousands of substances on the market that have never been screened now have to be investigated at much lower doses and in many combinations (Grandjean & Landrigan 2006). This doesn't take into account the timing of exposures and the genetic individuality that affects the impacts of an exposure on a particular person. This complexity is so huge that it will in principle never be comprehensively modeled.

In nutrition, complexity is emerging as well. Nutrigenomics is identifying great differences among individuals regarding their nutritional needs. The RDA, or recommended daily allowance, may be enough to prevent the most serious nutritional deficiency diseases in most people, but it does not address the genetically influenced higher needs that some people may have, particularly when they are stressed. We are also learning that in addition to the forty essential vitamins, minerals, amino acids and fatty acids, there are thousands of "phytonutrients"—such as the substances that impart distinctive tastes and colors to different foods—that carry information to our bodies to the point of affecting gene expression. We are learning that much more matters than the nutrients listed on our food packages.

At the same time as this complexity about our biological world is emerging, there are also great advances in informatics—our ability to process large amounts of complex information. But these methods yield probabilities, not certainties.

The Way Forward: Humility, Respect and Boldness

Twentieth century science and medicine sought certainty and precision. Twenty-first century science and medicine need to confront an enormous flowering of complexity. Our old methods make things too simple and uniform. We need new methods to handle all this complexity and interaction, and yet such new methods are in their early infancy. Autism cannot be solved by simple methods; however, scientific tools are behind our growing awareness of its complexity.

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A constructive approach is to see the enormous complexity as a gift. We can use this complexity to move toward humility about the limits to precise scientific knowledge. Humility will help us perform better clinical research. The inherent "messiness" and individuality of treatment is something that current research methods try to eliminate. This places an enormous roadblock to gaining useful and practical knowledge and to marshalling sophisticated scientific tools to accomplish this task. The "perfect" becomes the enemy of the "good." Instead, humility can allow us to seek the "good enough," which is much more practical than grasping for unachievable perfection.

We also need a renewed respect for clinical judgment. Current clinical research studies treatments, usually one treatment at a time. Caregivers on the front lines treat real human beings, who

have multiple problems and often receive many treatments. The clinician's brain integrates a huge range of information to figure out the right treatment for a particular individual. No group study can do that. A well-trained clinical mind is richly resourceful and deserves great respect.

Finally, we need boldness. A child with autism needs help right away. There are more and more such children every day. And people with autism need help through the lifespan. We need to help now. We need to overcome the disconnect between treatment and science, and learn from our present treatments so we can have better treatments in the future.

Treatment-guided research does just this—turning treatment experience into science, without waiting for science to eventually result in treatments. Learning from the different ways that people respond to treatments is not just a way of helping now; it is also a nearly untapped resource to gain immensely valuable insights into how autism works.[1] That is, treatment-guided research can potentially lead to important insights, scientific as well as practical, that could not be achieved in other ways.

Effective response to crisis is a challenge we face in autism, and in our planetary existence as well. Our health and planetary problems will not wait for the perfection of our knowledge base—we need to act now (Herbert 2006). The way forward is challenging, but it is exciting and the rewards are great.

References

Anderson, M., Hooker, B., & Herbert, M. (2008). Bridging from cells to cognition in autism pathophysiology: Biological pathways to defective brain function and plasticity. *American Journal of Biochemistry and Biotechnology, 4*(2):167-176. Available at: http://www.scipub.org/fulltext/ajbb/ajbb42167-176.pdf.

Centers for Disease Control and Prevention. (2005). *Third national report on human exposure to environmental chemicals.* Available at: http://www.cdc.gov/exposurereport/.

Curran, L.K., & Newschaffer, et al.(2007). Behaviors associated with fever in children with autism spectrum disorders. *Pediatrics, 120*(6):386-92.

Doidge, N. (2007). *The brain that changes itself.* New York: Viking Press.

Grandjean, P., & Landrigan, P.J. (2006). Developmental neurotoxicity of industrial chemicals. *Lancet, 368*(9553):2167-78.

Herbert, M.R. (2005). Autism: A brain disorder or a disorder that affects the brain? *Clinical Neuropsychiatry, 2,* 354-379. Available at: www.marthaherbert.com.

Herbert, M.R. (2006). Time to get a grip. *Autism Advocate, 45,* 5. Available at: http://www.autism-society.org/site/DocServer/eh_get_a_grip.pdf?docID=4821.

Herbert, M.R., & Anderson, M.P. (In press, 2008). An expanding spectrum of autism models: From fixed developmental defects to reversible functional impairments. In Zimmerman, A. (Ed.), *Autism: Current Theories and Evidence.* Totowa, NJ: Humana Press.

National Institutes of Health. (2003). NIH Roadmap for Medical Research. Available at: http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp.

Vargas, D.L., Nascimbene, C., Krishnan, C., Zimmerman, A.W., & Pardo, C.A. (2005). Neuroglial activation and neuroinflammation in the brain of patients with autism. *Annals of Neurology,* 57, 67-81.

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[1]One research program with this approach is TRANSCEND: www.transcendresearch.org or www.massgeneral.org/neurology/childneurology/TRANSCEND/index.html.