LEARNING FROM THE AUTISM CATASTROPHE: KEY LEVERAGE POINTS

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Autism sits at the intersection of the contradictions and gridlocks of multiple systems. This is true of the systems of the body, the systems of the brain, the systems of science, medicine, and society, and the systems of the planet. Reductionism and piecemeal approaches are not working very well. Autism is associated with dysfunction at all of these levels, and as such it is a profound example of both systems failure and the need for systems solutions. It is not so much a tragedy as it is a catastrophe.

Autism entered the medical landscape with a psychiatric definition based on dysfunction in behavioral domains. But there was already the presence of medical compromise in almost all of even the very first 11 cases.[1] While established science and medicine are finally acknowledging these medical problems, they still formulate this dysfunction as a genetic and prenatally determined brain disorder with accompanying incidental somatic comorbidities. The idea that this may be a systems "disorder that affects the brain" in parallel with or downstream from the body[2] has not yet been assimilated. Consequently the standard medical treatments are symptom-oriented, and the treatments of underlying mechanisms (such as inflammation and oxidative stress) are not present even in the newly revised standard practice parameters.[3]

Brain research for a long time took a piecemeal approach to autism, looking for "broken brain parts"—specific regions whose malfunction or malformation might explain the specific behavioral deficits. But now there are dozens of papers documenting network disturbances using measures of connectivity (functional MRI) and coherence (EEG and MEG).[4,5] In addition, there appear to be underlying metabolic disturbances in brain tissue (innate immune activation, oxidative stress).[6] Although most autism brain researchers do not connect the metabolic with the neurocognitive findings, some are beginning to note that the excitotoxicity associated with these brain tissue changes could alter the pathways and coordination of information processing.[7,8]

The scientific approach to autism has been scattered and fragmented. Just as cognition in autism has been described as characterized by "weak central coherence" (seeing parts but not wholes or gestalts),[9] autism research itself can be described as characterized by weak central coherence.[10] This is a function not of a specific failure regarding autism but of much more pervasive problems. The policies encouraging hyperspecialized investigator-initiated research, dating back to Vannevar Bush's 1945 report to President Truman entitled *The Endless Frontier,* are not only failing to produce a coordinated response to the multisystem complexity of autism but in fact are by no means clearly targeting many other areas where citizens need scientific analysis.[11]

The medical establishment has until recently been "allergic" to autistic patients. This is partly because of a sense that this is a hopeless and incurable brain condition, partly because the patients can be difficult and disruptive, and partly (presumably) because of a visceral aversion to facing brain and developmental disability. It is also a fiscal aversion: given the psychiatric classification of autism, reimbursements are terrible, and an autism diagnosis can even cause rejection of insurance claims for comorbidities!

But as autism has become "hot" and big money has been given to support autism research and treatment, is established medicine prepared? Do its diagnostic tests and treatments represent the optimal ways to help? A systems perspective highlights some critical gaps. At the core are weaknesses in looking beneath disease categories to underlying function and physiology and facing the ways environment can degrade optimality at these levels.[12] With these weaknesses, how could it occur to established medicine to look for physiological (and potentially treatable) mechanisms associated with the rising numbers?

At present, standard practice parameters do not include several things that would seem critical if we are facing any increases associated with environmental factors. Medical leaders call for rigorous standards of evidence for medical treatments, but where is their outcry about the majority of chemicals on the market that are grandfathered and therefore never tested for health effects?[13-15] With the apparent but unproven assumption that our environment is basically safe, standard medical measures of environmental exposures are very limited. More comprehensive measures are not clinically available in hospitals. And the notion that environmental exposures might have physiological, metabolic consequences is essentially absent—although there is a specialty oriented to inborn errors of metabolism, environmental disturbances of metabolism are not categorized, taught, or worked up.

From a public health standpoint, the prudent approach to the debate and uncertainty about the existence or extent of an autism "epidemic" would seem to be to assume there is a real (and potentially preventable) problem until rigorously proven otherwise—not the other way around. Can you explain away a 10-fold to 17-fold increase in diagnoses with assumptions?[16] Even if a large proportion of these numbers are due to greater awareness, any remaining substantial increase is a public health crisis—there is no other way to describe such a significant increase in the incidence of a serious neurobiological and systemic childhood disorder. Yet for various reasons, including a deep-seated belief that autism is strongly genetically determined (which is not yet supported by actual genetic evidence but only by inference from heritability data, which could also be interpreted differently), as well as a fear of giving support to vaccine critics, there has not been a "call to arms" about this problem which, if real, is very serious.

Meanwhile, individuals with autism and their families are left to a large extent to their own devices. Treatments are not reimbursed, care is not coordinated, very few treatments have been systematically studied, medical problems are ignored or written off as "the autism," and innovative attempts by parents to do whatever they can for their children are derided as desperate foolishness. Were this neglect to be overcome, it would be necessary to face the gigantic cost of caring for all these people along with the phenomenal hurdles of providing comprehensive and ongoing care.

This autism epidemic (and I will be surprised if my choice of that word is truly proven inappropriate) is way too much to be handled just by professionals. Although some professionals still believe that parents are not capable of delivering therapies to their children, studies are emerging showing that for at least some methods, there is no detectable difference in efficacy when the therapy is administered by a parent vs a professional.[17] For this public health crisis, we really need all hands on deck, and we need to impart to people as many skills as they can learn.

The help we need to generate is not just in providing services, but in figuring out what is going on, figuring out how to help better, and figuring out how to stop the damage. And not just "figuring out" is needed—we need to do something about all of this.

In the last couple of years, 4 momentous papers pertinent to autism were published. The first, "Neuroglial activation and neuroinflammation in the brain of patients with autism," demonstrated the presence of innate immune activation in brain tissue from individuals with autism.[18] At the time of publication, this had been shown in tissue from 11 individuals; the lab has now examined at least 20 brains and has found this in every person's brain, including someone with the "milder" Asperger's syndrome. This shifted the condition from a prenatal brain wiring problem to a chronic medical condition.

The other 3 papers were mouse models of developmental disorders—Fragile X syndrome,[19] Rett Syndrome,[20] and tuberous sclerosis,[21] all considered genetic and incurable—in which symptoms were reversed by molecular intervention, including in older animals. This is momentous because it forever undermines the basis for taking for granted that neurodevelopmental disorders are incurable or have only a narrow critical window after which intervention is pointless. Another paper, showing transient improvement in core symptoms of autism in the setting of fever in the vast majority studied,[22] further supports the shifting of research and treatment assumptions to understanding and supporting plasticity.

Medicine has occasionally "lucked out" and found a way to precisely target a therapy to the molecular underpinnings of a disease—the use of imatinib mesylate (Gleevec) to treat chronic myelogenous leukemia, for example. However, most drugs do not fit a target so specifically. For the vast majority of present chronic illnesses, treatment needs to go after other processes in the complex interplay of problems. This is where a functional medicine approach comes in, as is discussed in more detail by others in this issue.

What can we do to shift the model and link treatment with research? In terms of leverage, I would recommend 2 critical actions:

1. *Document that measurable brain changes result from metabolic interventions that lead to improvement or recovery in autism.*[23,24] In the last few years, the notion of "autism recovery" has migrated from the fringe to something that is generating research papers and even possibly grant funding opportunities at the National Institutes of Health. In autism, the notion of a pristine and incurable brain disorder might be weakened by documentation of improvement in some individuals, but it would be more seriously undermined if clear documentation of brain changes could be produced, particularly if they resulted from biomedical interventions. To liberate resources for helping people, this evidence is critical. This would show that (a) environment influences brain, (b) brain is very connected to body, (c) there are mechanisms for plasticity, and (d) autism is a dynamic and not a static encephalopathy.

2. *Make available to the public a prospective clinical data repository for tracking clinical experience, treatments, and lab measures.* A real partnership between all the players needed to help people with autism requires a smart way of sharing and mining data. In this approach, the patients are not merely resources for researchers; they are partners. This deeply granular data collection will allow us to learn about (a) how the different dimensions (medical, behavioral, educational) relate to each other, (b) what the dimensions are of the profound heterogeneity in autism,[25] (c) which treatments produce which effects in patients with which characteristics. We need to model new ways of dealing with complex, chronic, heterogeneous environmentally modulated illnesses, and granular data collection is a basic prerequisite. We also need lots of other kinds of research and infrastructure, but in terms of making our whole endeavor plausible, these are key.

Dealing with the catastrophe of autism requires facing that it is a catastrophe and establishing a model that demonstrates the plausibility of plasticity and treatment-created improvements. As this is accomplished, we can move faster and in a more

concerted fashion to produce resources for dealing not only with autism but also with many other health, social, and ecological crises. We need to learn while we are doing, not before. We know enough now that we don't need to delay. We need to perform "treatment-guided research"[26]—to use the database we build and our collaboration to learn from what we do, so we can do it better. Optimal outcomes are possible and important to strive for and achieve, and systems changes are possible at all levels.

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