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Autism Biology and the Environment

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Autism is a severe disorder of communication and emotional attachment, once thought rare, that is now recognized as a significant cause of chronic illness in childhood. Autistic children are caught in the middle of an intense debate about whether or not their numbers are increasing—whether or not there is an autism epidemic. Hanging in the balance are the nature of the treatments and services available to them, the funding levels for providing these, and the urgency with which their problems are addressed. And for these children, time is a pressing concern, as everyone agrees that interventions work far better for autistic children when they are begun early and pursued intensively.

Parallel and intertwined with the debate about the autism epidemic are a series of other areas where we can see also substantially different points of view. These include different framings of the way genes influence autism, the way the brain produces autistic behaviors, the relationship of physical symptoms to the core defining behaviors in the autism syndrome (impaired language, social reciprocity and behavior), and the levels at which treatment targets should be sought. In addition, because autism appears to be markedly heterogeneous, the question arises of what it is that "autisms" of different etiologies have in common to produce a common behavioral syndrome.

It is not surprising that autism should engage discussion at all of these levels, because while autism is defined behaviorally, it is clearly a biologically based disorder. The difficulty at this time is that the biological basis for the autism syndrome has not been established. This uncertainty about both cause and disease mechanisms also has great significance for autistic children, because while we are waiting for clearer science, we are operating on the basis of provisional models that shape how we choose and prioritize care regimens for these children.

The positions in the parallel sets of debates tend to cluster into two provisional models, each of which links clinical and research data into a different gestalt.[6] One model sees autism as a strongly genetic brain-based disorder, with a constant prevalence but a recent increase in awareness that has led to the appearance—but not the reality—of an epidemic. The other model sees autism as a genetically influenced but environmentally modulated condition involving multiple systems of the body, with increased numbers being real and related to changes in environmental factors.

The model of autism as strongly genetic and brain based is associated with a set of hypotheses about the relationships between genes, brains and behavior. Autism is defined by a cluster of three specific behaviors, though there is a lot of heterogeneity in how these behaviors manifest. The specificity of behaviors is assumed to rest on alterations of specific brain regions or discrete neural systems that are genetically based.[3] These behaviors and brain changes are often construed to be due to a set of independent genes and brain alterations that aggregate to yield autism.

This model has led to a research program seeking to identify autism genes, and to choose candidate genes from regions in the genome on the basis of their relevance to brain or behavior. It has also led to investigations of brain regions associated with the behavioral domains altered in autism. However the yield of this program has been more modest than had been hoped. Genetic investigations have been inconclusive, and regional brain findings in the brain have been intriguing but variable.

On the other hand a series of unexpected findings have emerged that challenge the expectations of the strongly genetic, brain-based model. These include:

- A tendency toward large brains, the most strongly replicated brain finding in autism. Brains of children (though not adults) in autism are upwardly shifted in their size distribution—about 20% of autistic individuals have head circumferences over the 97th percentile, while most have head circumferences that are above average, while volumes measured by MRI in adults are not increased over controls. This finding needs further specification but it does not fit into localization-oriented models of brain-behavior correlation.[5]
- Widespread reductions in "functional connectivity"—the tightness of signaling coordination across the brain—that are also not strictly localized. Impaired connectivity could preferentially impact functions requiring the highest degrees of brain networking—such as autism's defining three behavioral domains.[9]
- Evidence of inflammation and oxidative stress in autistic brain tissue from individuals ranging from childhood to middle age,[11] as well as in peripheral blood and urine samples.[8] These changes are signs not of inborn alterations of brain architecture in otherwise healthy tissue, but rather of chronic and ongoing disease processes in the same class as those found in conditions such as Alzheimer's Disease, Parkinson's Disease or HIV.
- Common patterns of non-nervous system somatic illness, particularly involving the gastrointestinal and immune systems. These organ systems are both on the front lines of encounters with the environment.[1]
- Mitochondrial abnormalities milder than would be expected from clear genetic etiology. Environmental toxins are known to inhibit mitochondrial metabolism.[4]
- A higher relative risk associated with combinations of gene polymorphisms in pathways associated with metabolic biotransformation of environmental chemicals. These involve environmentally responsive rather than brain- or behavior-associated genes.[7]
- Evidence of an increased "excitation-inhibition ratio" in the autistic brain. This could be a consequence of multiple genetic factors (e.g. GABA or glutamate related mutations) as well as multiple toxins (e.g. PCBs, heavy metals), which could interact to synergistically increase overall risk.[10] It could also be related to metabolic changes that are not restricted to the brain but are systemic, including inflammation and oxidative stress. Indeed, the degree of environmental exposures may affect both whether genetic vulnerability turns into disease and how severe this disease becomes.

It can be argued that these are just the types of findings that one would predict from a gene-enviroment interaction model, where the environmental exposures are sub-toxic, persistent and multiple. These levels of exposures alter the body's signaling mechanisms without killing cells.

In the brain, impacts may include subtle but pervasive changes in brain volume detectable only through volumetric measurement, as well as modest but systemic degradation of connectivity—just what we see in autism. And in the body, modest shifts may lead to a bias toward different disease patterns—e.g. autistic children appear to have reduced ability to fight infections but greater vulnerability to immune and auto-immune problems.

These findings raise a further question. Could common underlying mechanisms underlie both brain and body symptoms in autism? This question would probably not be asked from the "strongly genetic, brain-based" disease model vantage point, but it is central within a "systemic, gene-environment interaction" approach. If there are indeed such common mechanisms, it has enormous implications for autism treatment targets. It would mean that instead of treating autism symptomatically (one set of treatments for behaviors, another for seizures, further medications for gastrointestinal disease and still others for the commonly seen allergies and recurrent ear infections) there might instead be a few underlying but strategic treatment targets that would address the basic causes driving inflammation, oxidative stress and the increased excitatory chemistry that may underlie both the defining behaviors and many other "comorbid" features. This argument is supported by the Fragile X mouse model, which has a glutamate receptor deficit: these animals show a spectrum of features ranging from repetitive behaviors and poor socialization to anxiety, sleep disorders and even gut dismotility, all frequent in autism.[2] Moreover, we may be able to target certain final common pathways as treatment targets even though they are downstream of heterogeneous causal mechanisms.

We thus come around full circle, back to the children. How can we best help them? It appears that the "systemic, gene-environment" model for autism not only has support from research findings, but also opens a range of new avenues toward potential treatment targets that may give us fresh ways to improve quality of life and even level of functioning. While the idea of an autism epidemic is certainly disturbing, no one has definitively explained it away. Now we need to forthrightly look at the mechanisms such a phenomenon would imply, because they may contain keys not only to understanding autism but also to treating it.

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