

# Autism:

## From How it Works to How We Can Help More Effectively

**A**t present there is a vast gap between looking for what causes autism and figuring out how we can help. Lurking behind this gap are unanswered questions and unquestioned assumptions about how autism works. Emerging approaches in neuroscience and systems biology are bridging this gap, and offering us practical ways to improve the lives of people affected by autism right now.

While finding genetic causes have long been the “Holy Grail,” considering environmental factors is gaining momentum. The GUIDE framework for summarizing the set of factors that may contribute to Autism Spectrum Disorders (ASD)—**G**enetics, **U**ndiagnosed infections, immune or autoimmune disorders, **I**ncreased incidence and diagnosis, **D**iet and nutrient deficiencies, **E**nvironmental effects and epigenetics—has been ably reviewed in this issue by Anne Kelly and Kathleen Schuler.

How do such risk factors turn into autism? What happens in the brain and body to transform a child who experiences an autistic regression? How might these diverse risk factors pile up and interact to drive the emergence of autism?

Regression into autism is clearly documented by retrospective studies of videos, showing that many children had a period of virtual normalcy before becoming autistic.<sup>1,2</sup> Certainly the brain would have to change the way it performs in order for the features of autism to emerge. Remarkably we know very little about this transformation, but clues from different domains are starting to piece themselves together into a coherent picture—and one that



offers us avenues for both treatment and prevention.

My own interest in this question was sparked over the last decade by reflecting on the physiological requirements of brain activity and the emerging documentation of physiological problems in autism that might interfere with optimal brain function.<sup>3</sup>

Here are two separate sets of observations that I started to think were connected:

- The brain is the organ in the body with the highest energy demands. Synaptic firing requires a huge amount of energy. Yet mitochondrial dysfunction is common in ASD: About 5 percent of people with autism appear to have genetically based mitochondrial disease (much higher than the rate in the general population),<sup>4</sup> and a much larger proportion with no evidence of mitochondrial mutations have laboratory evidence of mitochondrial dysfunction such as

we see in other chronic diseases like obesity, cancer and diabetes.<sup>5,6</sup>

- The production of complex thinking and perceptual organization requires highly organized, finely tuned and exquisitely timed brain coordination. The behavioral domains defined as core autism—impaired communication, social interaction, recognition of emotion and flexible adaptation to change—all require complex information processing. Yet functional MRI and EEG studies are showing a strong tendency toward reduced coordination across different parts of the brain in people with ASD.<sup>7,8,9</sup>

Could it be that the behavioral manifestations we label as autism are not hardwired? Perhaps the brain was not genetically wired differently from the start—but instead lost its ability to keep up with complex, rapidly changing demands. Could this “falling behind” emerge at least in part from impaired bioenergetics metabolism? Perhaps the brain is sending less signals because it doesn’t have the energy.

As I looked at my patients and tracked the emerging research, several other seemingly separate features of autism also started to seem linked.

- **Neuroinflammation:** Neuropathology and gene expression studies are showing activation of neuroglial cells consistent with innate immune activation, and upregulation of neuro-immune gene expression rather than changes in “neurodevelopmental genes” as the most prominent alteration in gene expression in autism.<sup>10,11</sup>

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When glial cells get activated, they neglect their normal housekeeping functions. They provide less metabolic support for neurons and they fail to remove the excitatory neurotransmitter glutamate from the gap between neurons at the synapse, so it keeps stimulating the cells longer than it should. They also produce a lot of excitatory chemicals and immune substances.<sup>12</sup> As a result, the nervous system enters a state of “excitotoxicity,” producing noise, rather than signal, because the stimulation comes from chemical dysfunction inside the brain, not information relayed to the brain by the sense organs.

With the mitochondria’s weakened ability to contribute to signal, and the neuroinflammation’s abnormal production of noise, we have what in engineering is called a “reduced signal-to-noise ratio” which degrades the quality of information the brain can produce.

- Nervous system dysregulation: sleep and sensory dysfunction are nearly universal in ASDs and autonomic nervous system dysfunction and anxiety are highly prevalent as well.

Putting neuroinflammation and nervous system dysregulation problems side by side raises significant chicken-and-egg problems: which comes first? We know that sleep deprivation and stress can generate pro-inflammatory cytokines,<sup>13</sup> increase anxiety, and impairs attention and learning. All of these can be hugely vexing issues for people with ASDs. At the same time we don’t know whether the inflammation causes the nervous system dysregulation, or vice-versa, or whether both are driven by other triggers—or whether the whole thing is a vicious circle that can get ever harder to overcome over time.

With these considerations in mind I started to look at my patients and the research to see how much these problems were intrinsic, irretrievably built-in and fixed, and how many things we could find in their lives that could be modified to reduce the severity of these problems. Various individuals with autism have:

- Genetic vulnerabilities—not just in “brain genes” but also increased presence of physiology that is vulnerable

(either because of genetic reasons or prior environmental hits) to disturbance or degradation—this includes presence of multiple single nucleotide polymorphisms (SNPs) in one-carbon metabolism pathways, oxidative stress, impaired methylation, certain genetic biases toward immune dysfunction, SNPs increasing vulnerability to harm from toxicants such as lead and PCBs, and mutations increasing vulnerability to the above mentioned mitochondrial dysfunction.<sup>14-18</sup>

- Environmental exposures: Several studies, including a recent large one,<sup>19</sup> report an association between exposure to air pollution and vulnerability to autism. Interestingly air pollution is associated with the development of brain inflammation.<sup>20</sup> Exposure to pesticides also increases risk for autism and can interfere with various biochemical pathways.<sup>21</sup>
- Self-restricted diets, nutrient malabsorption and low levels of nutrients important for biochemical metabolism and nervous system function: Many children with autism restrict their diets to beige colored foods like milk and cheese, to certain textures, and/or to sugary foods, giving them poor intake of vitamins and minerals; and the impact of this on nutrient status can be worsened by chronic diarrhea, fat malabsorption and other digestive system disturbances.<sup>22,23</sup> This poor nutritional status can increase physiological and brain vulnerability.<sup>24,25</sup>
- Lack of exercise, dysregulated bowel regimens and poor sleep hygiene. All of these problems can exacerbate inflammation and poor health and feed health-degrading vicious cycles.
- Abnormal intestinal microbiome, with missing varieties of healthy organisms and presence of potentially harmful organisms.<sup>26-29</sup> This can be further worsened by a diet high in sugar or other high glycemic index starches, failure to include probiotics or fermented foods in the diet and repeated courses of antibiotics for recurrent ear or strep infections common in the medical history of

infants prior to regression into autism, which can deplete important species in the microbiome. Research into the impact of gut microbiome on brain function is rapidly emerging.

- Exposure to high glycemic index, low nutrient density junk food as reinforcers in behavioral therapy, leading to satiation of the child on these substances and reducing their appetite for healthier higher nutrient density whole foods.
- Side effects from potent medications such as atypical antipsychotics utilized for severe behavioral dyscontrol that can promote weight gain and hormonal dysregulation and make it harder for a child to exercise.

It thus appears that while there may be certain built in biases toward dysfunction, there are many additional contributors where modifications could be made to reduce risk and improve health and resilience.

Finally, both published evidence and clinical observation has been accumulating to undermine the idea that ASDs are intrinsically irreversible.

- A growing number of papers are showing reversal of autism-like features in mouse models of genetic syndromes like Fragile X, Rett syndrome and tuberous sclerosis commonly associated with autism.<sup>30-33</sup>
- Studies are documenting loss of diagnosis in a significant minority of children previously rigorously diagnosed with autism.<sup>34</sup>
- Published evidence that significant numbers of children show transient amelioration of core features of autism in the setting of fever (a phenomenon also being investigated in other neuropsychiatric disorders such as schizophrenia).<sup>35,36</sup>
- Published reports of transient amelioration of autism symptoms during antibiotic treatment, as well as many anecdotal reports of transient improvements in communication, social interaction and calmness during clear fluids only diet in preparation for procedures, during steroid therapy, and after anesthesia.<sup>37</sup>

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Put together, all of these pieces seem to suggest that the “autism” may be more like a state than a fixed trait—more like a chronic dynamic encephalopathy than a fixed static encephalopathy. This combination of factors starts to suggest that autism spectrum disorders may not emerge simply from a genetically “broken” brain wiring diagram, but may in fact emerge from and/or be worsened by struggling physiology.<sup>38,39</sup>

If struggling physiology can make things worse, improving physiology may improve the brain’s signal-to-noise ratio, by improving the ability of the brain to have the energy to coordinate information more effectively, and reducing the endogenous noise generated by neuroinflammation.

Given the alarming and expensive rise in the number of reported cases of autism, this approach of using lifestyle modifications to improve the signal-to-noise ratio in the brain in autism offers approaches worth investigating that are practical and inexpensive, and could potentially help large numbers of people.

We need to look at lifestyle modifications and how they may impact the severity

of autism. Given the severity of physiological and developmental disruption, more aggressive lifestyle modification is likely to be more successful. This would include high nutrient density diet, avoidance of toxins in household and personal products, removal of allergens and immune triggers from the diet, aggressive sleep hygiene, vigorous exercise and stress reduction.<sup>40</sup> I am currently part of a team of researchers developing a research program to document this approach in the largest residential facility in the state of New York, the Center for Discovery, which is based on a biodynamic organic farm and sees dramatic reductions in adverse behaviors and increases in function when this program to reduce allostatic load is applied in a consistent and coordinated fashion.

Lifestyle modification is surprisingly difficult to implement in today’s health economic milieu. But just as we know that a large portion of the \$750 billion a year we spend on type II diabetes is preventable,<sup>41</sup> the same may be true of autism spectrum disorders. Moreover, alongside the rises in reported cases of autism are rises in ADHD, asthma, obesity, diabetes, and neuropsychiatric and learning

disabilities where similar considerations apply.

In conclusion, since a plausible argument can be made for taking lifestyle considerations more seriously in autism spectrum disorders, physicians should look at poor lifestyle choices and low-grade chronic medical problems as things that could be improved and ramified through the person’s whole system rather than as things that would not impact the autism. ♦

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