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# UNDERSTANDING AUTISM

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APRIL 2007

$4.99 CAN: $6.50

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# Autism:
# It's Not Just in the Head

## The devastating derangements of autism also show up in the gut and in the immune system. That unexpected discovery is sparking new treatments that target the body in addition to the brain

**BY JILL NEIMARK**

**"There were days I considered shutting the garage** door and letting the car run until I was dead," says Colorado mom Erin Griffin, of the time nine years ago when she learned that both her boys—not just her firstborn—suffered from autism. Brendan, her angular, dark-haired older child, was diagnosed in 1996 at age 4. Kyle, her round-faced, hazel-eyed younger son, was diagnosed in 1998 at age 2½.

But Kyle and Brendan's story does not have a tragic ending. After interventions that included occupational and speech therapy, as well as dietary change and nutritional supplements, both boys improved significantly. Their tale of slow, steady recovery reflects the changing landscape of autism today. The condition, traditionally seen as genetic and originating in the brain, is starting to be viewed in a broader and very different light, as a possible immune and neuroinflammatory disorder. As a result, autism is beginning to look like a condition that can, in some and perhaps many cases, be successfully treated.

That is astonishing news about a disorder that usually makes headlines because it seems to be growing rapidly more widespread. In the United States, the diagnosis of autism spectrum disorders has increased about tenfold over the past two decades, and a 2003 report by the Centers for Disease Control suggests that as many as one in every 166 children is now on the autism spectrum, while another one in six suffers from a neurodevelopmental delay. This explosion of cases has raised countless questions: Is the increase real, is it the result of increased awareness and expanding diagnostic categories, is it due to environmental changes, or all of the above? There may be no single answer. But the public concern about autism has caught the ear of federal lawmakers. The Combating Autism Act, approved last December, authorized nearly $1 billion over the next four years for autism-related research and intervention.

Meanwhile, on the sidelines of that confusing discussion, a disparate group—immunologists, naturopaths, neuroscientists, and toxicologists--is turning up clues that are yielding novel strategies to help autistic patients. New studies are examining contributing factors ranging from vaccine reactions to atypical growth in the placenta, abnormal tissue in the gut, inflamed tissue in the brain, food allergies, and disturbed brain wave synchrony. Some clinicians are using genetic test results to recommend unconventional nutritional therapies, and others employ drugs to fight viruses and quell inflammation.

Above all, there is a new emphasis on the interaction between vulnerable genes and environmental triggers, along with a growing sense that low-dose, multiple toxic and infectious exposures may be a major contributing factor to autism and its related disorders. A vivid analogy is that genes load the gun, but environment pulls the trigger. "Like cancer, autism is a very complex disease," says Craig Newschaffer, chairman of Epidemiology and Biostatistics at the Drexel University School of Public Health, "and it's exciting to start asking questions about the interaction between genes and environment. There's really a very rich array of potential exposure variables."

In one way, the field seems like a free-for-all, staggeringly disordered because it is littered with so many possibilities. But one can distill a few revolutionary insights. First, autism may not be rigidly determined but instead may be related to common gene variants, called polymorphisms, that may be derailed by environmental triggers. Second, affected genes may disturb fundamental pathways in the body and lead to chronic inflammation across the brain, immune system, and digestive system, Third, inflammation is treatable.

"In spite of so many years of assumptions that a brain disorder like this is not treatable, we're helping

kids get better. So it can't just be genetic, prenatal, hardwired, and hopeless," says Harvard pediatric neurologist Martha Herbert, author of a 14,000-word paper in the journal *Clinical Neuropsychiatry* that reconceptualizes the universe of autism, pulling the brain down from its privileged perch as an organ isolated from the rest of the body. Herbert is well suited to this task, a synthetic thinker who wrote her dissertation on the developmental psychologist Jean Piaget and who then went to medical school late, in her early thirties.

"I no longer see autism as a disorder of the brain but as a disorder that affects the brain," Herbert says. "It also affects the immune system and the gut. One very striking piece of evidence many of us have noticed is that when autistic children go in for certain diagnostic tests and are told not to eat or drink anything ahead of time, parents often report their child's symptoms improve—until they start eating again after the procedure. If symptoms can improve in such a short time frame simply by avoiding exposure to foods, then we're looking at some kind of chemically driven 'software'—perhaps immune system signals—that can change fast. This means that at least some of autism probably comes from a kind of metabolic encephalopathy--a systemwide process that affects the brain, just like cirrhosis of the liver affects the brain."

In 1943 Johns Hopkins University psychiatrist Leo Kanner first described autism as a now-famous collection of symptoms: poor social engagement, limited verbal and nonverbal communication, and repetitive behaviors. Back then, autism was considered rare; Kanner first reported on just 11 patients, and Johns Hopkins still has records of about 150 patients he examined in total. Even within this small group of patients, other, less visible symptoms were evident. In his 1943 paper, "Autistic Disturbances of Affective Contact," Kanner noted immune and digestive problems but did not include them in the diagnosis. One reads with a shiver sentences lifted out of various case histories: "large and ragged tonsils . . . she was tube-fed five times daily . . . he vomited all food from birth through the third month . . . he suffered from repeated colds and otitis media...."

Herbert believes that the clues linking the obvious behavioral symptoms to more basic, but less obvious, biological dysfunction were missed early on. "What I believe is happening is that genes and environment interact, either in a fetus or young child, changing cellular function all over the body, which then affects tissue and metabolism in many vulnerable organs. And it's the interaction of this collection of troubles that leads to altered sensory processing and impaired coordination in the brain. A brain with these kinds of problems produces the abnormal behaviors that we call autism."

Herbert's full-body perspective helps make sense of the confusion surrounding the diagnosis of autism and helps justify the increasingly common use of the plural "autisms" to describe the wide variations in this disorder. As Newschaffer points out, "Children with Asperger's syndrome certainly share a lot of the behaviors of those with more severe autism. But is it the same disease, and is it caused by the same thing? A number of significant features of autism are not part of the diagnostic schema right now, but eventually, those features may end up distinguishing one causal pathway from another. How is a child sleeping? Does he or she have gastrointestinal symptoms? By looking at those things we may see risk-factor associations pop out that we've never seen before."

Herbert likens autism to a hologram: "Everything that fascinates me is in it. It's got epidemiology, toxicology, philosophy of science, biochemistry, genetics, systems theory, the collapse of the medical system, and the failure of managed care. Each child that walks through my door is a challenge to everything I ever knew, and each child forces me to think outside the box and between categories."

Each child's path to autism may be distinct, she says, but they may share common inflammatory abnormalities. She has shown through morphometric brain imaging that white matter—which carries impulses between neurons—is larger in children with autism.

"It was the most absolutely outstanding piece of information in all the brain data I looked at," Herbert recalls of the years 2001 and 2002, when she was analyzing this brain imaging data. "People were saying, don't look at the white matter, look at the cerebral cortex, but I knew we had an important finding."

Could white matter become chronically inflamed? It may well be, according to new research from Carlos Pardo, a neurologist at Johns Hopkins. In a 2005 study in the *Annals of Neurology,* he found inflammation in immune-responsive brain cells of autistic patients. "Patients with autism report lots of immunological problems. We looked for the fingerprints of those problems in the brain," says Pardo. "We had brain tissue from autistic individuals as young as 5 and as old as 45 and we found neuroglial inflammation in all of them. Neuroglia are a group of brain cells that are important in the brain's immune response. This inflammatory reaction appears to happen both early and late in the course of the disorder. If it happens early, it could dramatically influence brain development. We're very excited about this research because one potential treatment approach, then, is to downregulate the brain's immune response." To study that approach, Pardo is collaborating on a pilot study funded by the NIH to test minocycline, an anti-inflammatory antibiotic drug, on autistic children. "Minocycline is a very selective downregulator of microglial inflammation," he says. "Neurologists already use it in multiple sclerosis and Parkinson's."

> "I can't think of it as a coincidence anymore that so many autistic kids have a history of allergies, eczema, or chronic diarrhea."

"What we've got here is a far more comprehensive set of characteristics for autism," says Herbert, "one that can include behavior, cognition, sensorimotor, gut, immune, brain, and endocrine abnormalities. These are ongoing problems, and they're not confined just to the brain. I can't think of it as a coincidence anymore that so many autistic kids have a history of food and airborne allergies, or 20 or 30 ear infections, or eczema, or chronic diarrhea."

All this marks a Copernican-scale shift in our approach to the disorder. I myself was irresistibly drawn to the subject when viewing an online video of a heavily affected 11 -year-old who, after a series of chelation treatments to remove mercury, announced to his mother, "Mom, I'm back from the living dead." The statement was heartbreaking in its simple eloquence. Mercury chelation, in this particular child's case, was a near panacea.

Lisa Beck, of Oviedo, Florida, tells a similar story. Her son Joshua was diagnosed with autism in 2004 at about age 2. After 18 intensive

# THE TOXIC LINK TO AUTISM

months of treatment that involved chelation--a treatment that draws heavy metals out of the body—and dietary changes, among other therapies, Josh appears neurotypical. "We took him to Dr. Leslie Gavin, a specialist at Nemours Children's Clinic, who administers the ADOS test, a diagnostic test to see where on the spectrum a child falls," she says. "After the two-hour evaluation, Gavin said he did not meet the criteria for autism. In her words, he was 'responsive, curious, and active, able to engage in the test without a problem, able to express himself clearly.'

But, fascinating anecdotes aside, does hard evidence exist of specific vulnerability genes or how they might impair the immune system, brain, and gut—and most important, do we have any rational, reliable approaches to help repair the damage?

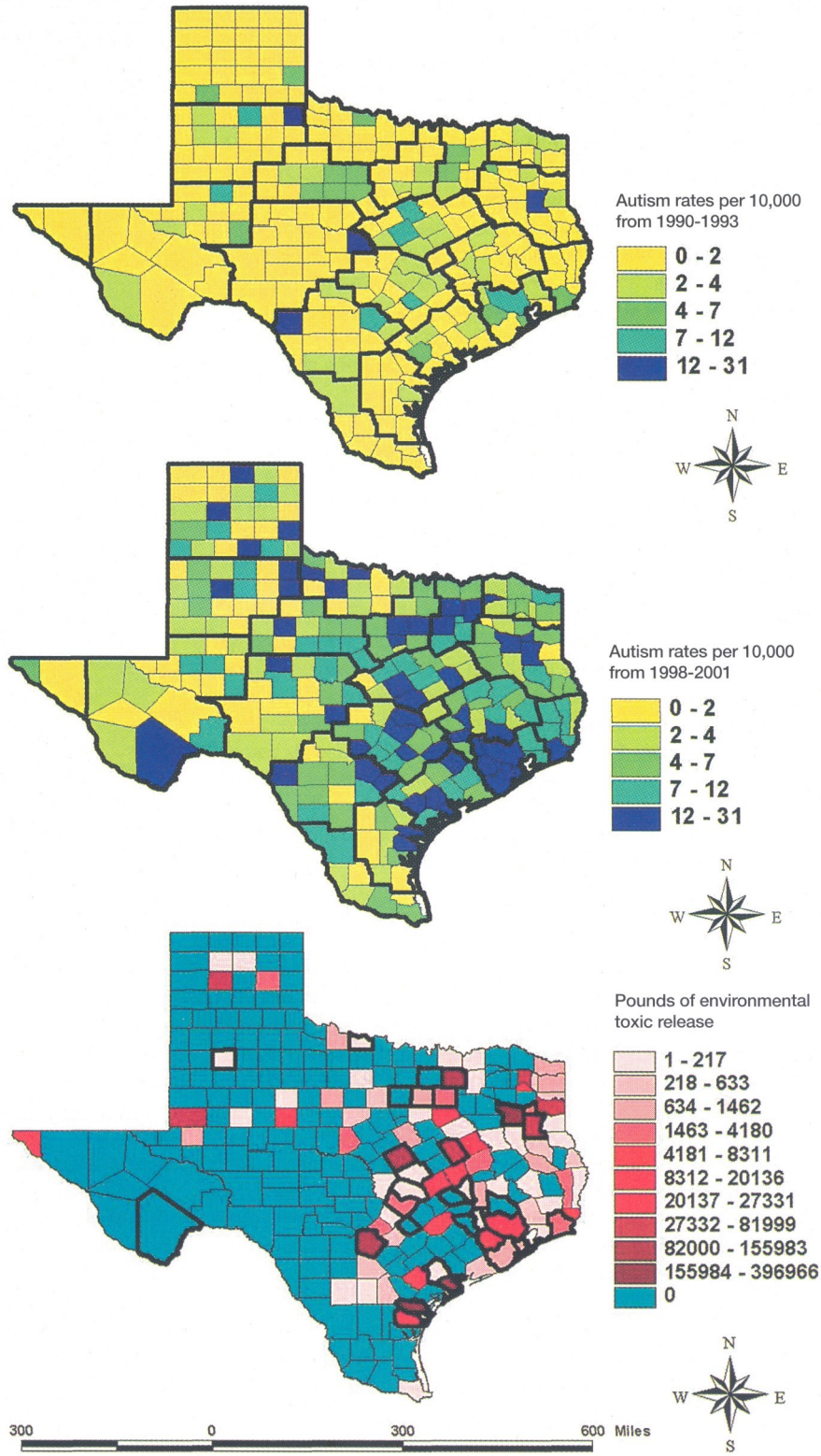
The answer is a provisional yes.

**"We're beginning to understand that** genetics is really about vulnerability," says neuroscientist Pat Levitt, director of the Vanderbilt Kennedy Center for Research on Human Development. Levitt and his colleagues recently discovered that a common variant of a gene called *MET* doubles the risk of autism. The finding was widely regarded as a breakthrough because *MET* modulates the nervous system, gut, and immune system—just the kind of finding that matches up with the emerging new view of autism.

"Everyone was focusing on genes expressed in the brain," says Levitt, "but this gene is important for repair of the intestine and immune function. And that's really intriguing because a subset of autistic children have digestive and immune problems." Equally interesting is that the gene variant occurs in 47 percent of the population — in other words, it is just one contributing factor, and it probably works in concert with other vulnerability genes. And finally, in a twist that intrigues other researchers, the activity of the gene is affected by what is known as oxidative stress—the kind of damage one sees with excessive exposure to toxins. "As we identify other vulnerability genes like this," says Levitt, who hopes to engineer a mouse model of this gene variant for study, "we may be able to develop effective interventions for children."

In other provocative research, Jill James, director of the Autism Metabolic Genomics Laboratory at the Arkansas Children's Hos-

The first two maps compare rates of autism in Texas counties in the early 1990s (top) and in the late 1990s (center). The blue map (bottom) shows pounds of toxins released in each county in 2001. The darkest patches in the blue map represent counties where increases in autism rates over the past 10 years have been in the top 20 percent. The correlation between toxins and autism is suggestive, though not definitive.



pital Research Institute (and professor of pediatrics at the University of Arkansas for Medical Sciences) has found that many children with autism do not make as much of a compound called glutathione as neurotypical children do. Glutathione is the cell's most abundant antioxidant, and it is crucial for removing toxins. If cells lack sufficient antioxidants, they experience oxidative stress, which is often found with chronic inflammation.

In her most recent study, published in the *American Journal of Medical Genetics* in 2006, James found that common gene variants that support the glutathione pathway may be associated with autism risk. Intriguingly, this pathway is linked metabolically to the methylation pathway. Methylation is a fundamental biochemical process that helps regulate which genes are expressed; abnormal methylation can cause disease. Because the pathway provides the precursors to glutathione, impairments in methylation can also lead to oxidative stress. "It's very provocative," James says. "It suggests that some autistic behaviors are a neurologic manifestation of a genetically based systemic, metabolic derangement." Some of the abnormalities James saw in this study have already been associated with gastrointestinal and immunologic dysfunction.

The good news is that oxidative stress in some autistic children may be treatable with targeted nutritional intervention. James and her colleagues have tracked eight autistic children who were taking supplements of key nutrients in the methylation pathway—folinic acid, trimethylglycine, and methyl-$B_{12}$—and found a significant increase in important markers of methylation and glutathione synthesis. The next step is to see if the symptoms improve as well.

James and her colleagues just received a $2.4 million grant from the NIH, part of which will be devoted to sorting out the relationship between metabolism, genes, and behavior. "What would be incredible is if we could correlate individual differences in behavior with specific abnormal metabolites," James says. They will then look at children between 18 to 24 months old, which is usually before autism is diagnosed. That could help identify the causes of the disease, as well as permit earlier intervention.

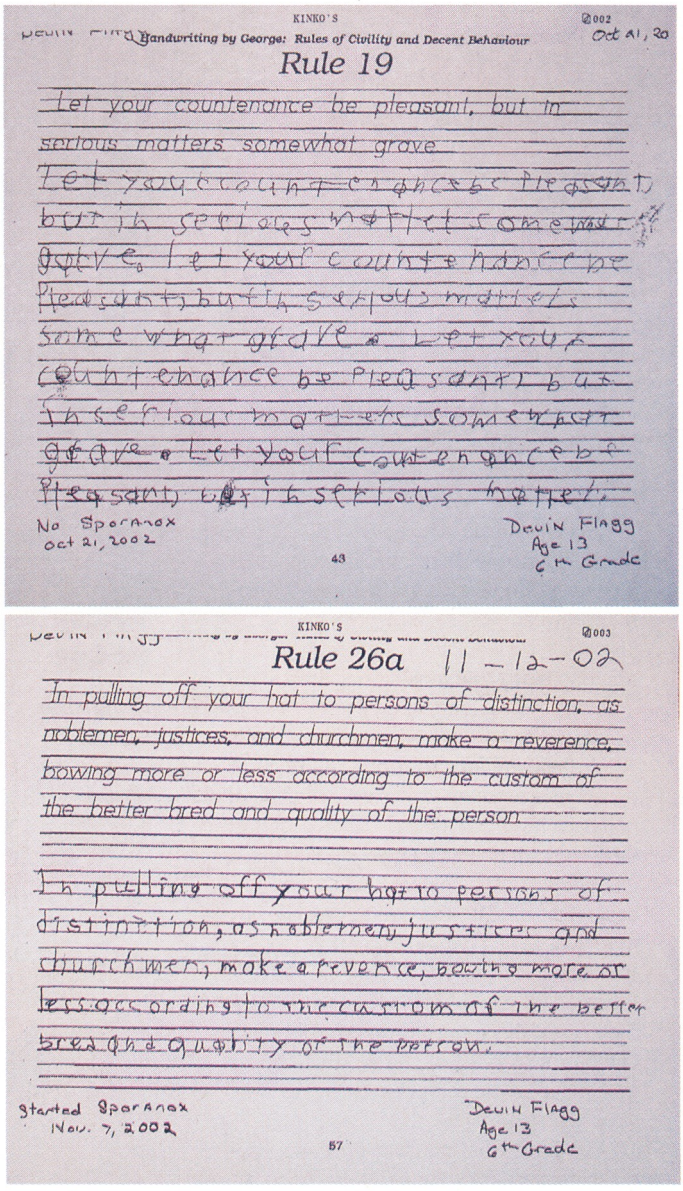
"We also plan to look at mitochondrial dysfunction," she says. "Since mitochondria are the energy powerhouses of the cell, they're also the place where the most free radicals (which play a role in oxidative stress) are produced. If the electron transport chain in the mitochondria is faulty and you're not efficiently making ATP, you'll produce more free radicals and deplete your glutathione. If this hypothesis turns out to be correct, we can give nutrients like coenzyme Q10, magnesium, and acetyl-L-carnitine to help stabilize the mitochondria. Now, this is just a hypothesis, but that's the risk you take with science. You make your best guess and you carry out your study and you see."

"It's interesting to see metabolic abnormalities addressed this way," says Isaac Pessah, chairman of Molecular Biosciences and director of the Center for Children's Environmental Health and Disease Prevention at the University of California at Davis. "I think glutathione balance in the kids is potentially very important in terms of toxic environmental exposures."

There is a growing sense, Pessah adds, that our heavily industrialized, chemical-soaked environment—and the way it acts on vulnerable genes in some individuals—may be a major culprit. In December 2006, Harvard researchers boldly announced in *The Lancet* that industrial chemicals may be impairing the brain development of children around the entire world. And at a November 2006 conference at the University of California at Davis's M.I.N.D. Institute, Pessah gathered experts to discuss the clinical implications of environmental toxicology in autism. Says Herbert, "We discussed the enormous number of chemicals in our environment and how little we know about chronic, low-dose, multiple exposures and their effect on diseases like autism. Maybe the many autism cases we are now seeing are a new illness of the current generation."

Several large-scale, federally funded epidemiological studies are under way to pinpoint possible environmental triggers, as well as early biomarkers of autism. "We have to build a large enough study to be able to look at both genes and environment together," says Newschaffer, who is a principal investigator on a study by the Centers for Disease Control that will look at 2,700 children over the next five years.

In another ambitious study, called the Autism Birth Cohort, Columbia University and the Norwegian Institute of Public Health will


KINKO'S 002
Oct 21, 20
Handwriting by George: Rules of Civility and Decent Behaviour
Rule 19
Let your countenance be pleasant, but in serious matters somewhat grave
Let your countenance be pleasant but in serious matters somewhat grave. Let your countenance be pleasant but in serious matters somewhat grave. Let your countenance be pleasant but in serious matters somewhat grave. Let your countenance be pleasant but in serious matters
No Sporanox
Oct 21, 2002
Devin Flagg
Age 13
6th Grade
43
KINKO'S 003
Rule 26a 11-12-02
In pulling off your hat to persons of distinction, as noblemen, justices, and churchmen, make a reverence, bowing more or less according to the custom of the better bred and quality of the person
In pulling off your hat to persons of distinction, as noblemen, justices and churchmen, make a reverence, bowing more or less according to the custom of the better bred and quality of the person.
Started Sporanox
Nov. 7, 2002
Devin Flagg
Age 13
6th Grade
57

Penmanship samples by Devin Flagg, a homeschooled boy with autism, show improved coordination after he received antifungal medication. The maxims come from an etiquette book that belonged to George Washington.

COURTESY OF DEVIN FLAGG, DEBORAH GEE-TRITSCHLER, AND S. G. KAHLER, M.D.

follow 100,000 pregnant women for 72 months, studying their health and genetics and testing everything from blood to urine samples. The hope is to discover environmental factors that contribute to autism risk, from diet or infection to toxins like heavy metals, pesticides, and the countless synthetic molecules in products today.

Other large NIH- and EPA-funded studies are teasing out immune abnormalities that may contribute to autism. In research on more than 700 families with an autistic as well as a neurotypical child, Pessah and his colleagues have found in the autistic child a significant reduction in immunoglobulins and an abnormal profile of cytokines, which are critical to immune response. "The immune system is involved in important aspects of neurodevelopment," says Pessah. "We've found the presence of immune antibodies that we think may influence brain proteins. In the next five years, as the study continues, we hope to reach about 1,600 families total. We need that many to get real statistical power. We hope to find out what type of skewed immune response the typical autistic child has and to isolate toxic exposures, such as proximity to highways or toxic waste dumps."

Herbert argues that "we can address the disturbed pathways now, before the gene hunters have definitive information. Genes, after all, don't specify behaviors. They make regulatory factors that interact in highly complex ways. And as far as the impact of chemicals on neurodevelopment, only about 20 to 30 of the 85,000 chemicals made have been studied. We can, at the very least, try to modulate autism by treating the tissue inflammation."

"As far as the impact of chemicals on neurodevelopment, only about 20 to 30 of the 85,000 chemicals have been studied."

**In other words, treat now, before the gavel of science strikes** a final judgment, which might be decades away. That's what Erin and her husband, Michael, did for Brendan and Kyle: They blended mainstream treatments like speech and occupational therapy with the best biomedical approaches available. "I was told to take my boys home and love them," recalls Erin. "The neurologist said don't waste your time on alternative treatments, nothing about them is proven. My boys could have ended up institutionalized, or my husband and I would have had to take care of them their whole adult lives. When your child gets a diagnosis of autism, you lose the child you were dreaming about, the one who will go to college, get married, become a parent. That just wasn't an option."

The boys first saw an alternative Colorado practitioner who had been trained by a group called Defeat Autism Now! (DAN!). DAN! was cofounded in 1995 by the psychologist Bernard Rimland, whose own son was autistic. DAN! treatments focus on intestinal issues, detoxification, nutrition, and neuroinflammation. Recommendations include dietary restriction, usually eliminating gluten (present in wheat and other grains) and dairy.

"For weeks after Kyle stopped drinking milk, he had welts all over his body," Erin recalls, "as if he were going through a detoxification reaction. At the same time, he had his first formed, regular bowel movements. His sleep improved."

Other DAN!-recommended treatments include detoxification to remove heavy metals and other suspected pollutants, nutritional supplementation, and sometimes off-label use of anti-inflammatories, antivirals, and allergy medications. These so-called biomedical treatments range from relatively inexpensive dietary changes costing a few hundred dollars a month to doses of antifungal drugs that can cost several hundreds of dollars. Many DAN! supplements play critical roles in the pathways studied by scientists like Jill James. DAN! practitioners are, of course, leaping into the deep end of the pool before science has truly proved these treatments effective, but there are many anecdotal cases of improvement.

Not surprisingly, there has been criticism of the biomedical approach, especially when doctors promise too much or parents hope too desperately for recovery. As James notes, one mother killed herself after seeking every possible treatment for her autistic daughter to no avail, causing a furor among parents with autistic children.

Some children just do not get better, no matter what the intervention. Elizabeth Mumper is CEO of a group called Advocates for Children and former director of pediatric education at the Lynchburg Family Practice Program affiliated with the University of Virginia. Of the 2,000 children in her practice, about 400 have autism spectrum disorders. She describes one boy whom "I have not helped despite my best efforts. He is 17 and still nonverbal and has horrible, erosive esophagitis in spite of the fact that he works very closely with a gastroenterologist. He has to sleep standing up and leaning over his dresser because of the pain, and he has very idiosyncratic reactions to medications. And even though he is nonverbal, he can type anything to me. He's alpha-smart. The horror is that he's trapped in a body that doesn't work."

"I hate the term 'full recovery,'" James adds, "because of this false hope. Some children do lose the diagnosis, but that's rare. I don't think that should be out there as a goal. We need to accept [the kids] and love them for who they are—because they are lovable. They're quirky."

**Erin's boys benefited from their DAN! doctor, she says, but it** was in 2003, when she switched to a highly unconventional molecular biologist and naturopath based in Maine, Amy Yasko, that she began to see more striking changes. Yasko blends the new findings on methylation with a scientist's background in the finer steps of fundamental detoxification pathways in the body. However, she largely favors herbs, dietary change, and nutritional supplements over prescription medications. She monitors biomarkers of detoxification in the urine as often as every week or two and tweaks supplements accordingly. Her program is intensive and steeped in molecular biology; her twice-yearly conferences are extremely dense, scientific, and intended to help parents become at least semiproficient in the biology and chemistry themselves. It is a far cry from the old doctor-patient model—Yasko works primarily on the Internet now,

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with phone consultations, to interpret test results. She decided to do this when her waiting list for individuals stretched to five years, and, she says, she felt she was not helping enough children. Erin e-mailed me about 40 charts of metal "dumps" for both of her boys—urinalyses Yasko had ordered and charted on a graph to show the excretion of everything from arsenic to aluminum, mercury, and lead over time. "All these little things started clicking after we started with her," says Erin.

"I call this approach biomolecular nutrigenomics, after Bruce Ames, a professor of biochemistry and molecular biology at the University of California at Berkeley," says Yasko. "He said that someday it would become routine to screen individuals for polymorphisms and that nutritional interventions to improve health were likely be a major benefit of the genomics area." Yasko tests for common polymorphisms in the methylation pathway, even though these findings are still preliminary. This has made her controversial among her peers. Yet several doctors and scientists with autistic children admitted privately to using Yasko's services while being unwilling to go on the record to support her.

Yasko, who says she moved her Husband and three daughters from Connecticut to a rural area of Maine to "hear the snowflakes fall on the snow and get to that quiet place inside where I can think," seems immune to the controversy. "I was in a research environment for a long time, where you had to publish. Then I was in biotech for a long time, where you had to keep everything quiet. When I began to focus on autistic children, I made a decision that instead of publishing in peer review journals, I was going to go directly to the moms and help them. I knew in making that decision I was going to get flak. That's OK. It was like I was on those cliffs you see in the movies, and you're going to jump. You don't know if there's water below, or enough momentum to get to the other side, but you just jump."

Today Erin's boys participate in individualized programs at school and are being monitored in two national studies of families with more than one autistic child—one at the Duke Center for Human Genetics, another at the University of Washington. Kyle has, in addition, been tested three times at the University of Colorado Health Sciences Center's toddler development program. Both are still on the autism spectrum—but the incessant tantrums, digestive problems, and infections have vanished. Brendan no longer chews on his shirt, flaps his arms, and grinds his teeth. In fact, he made honor roll in his classes last year. Kelly Swift, the boys' schoolteacher since the autumn of 1996, describes them as "sociable and on the whole very happy, with a great sense of humor. Kyle is probably the most changed of any autistic child I've ever worked with."

**Can we cajole a mysteriously shuttered brain and body back toward normal? And if so, will autism give us new insight into other disorders?**

Kyle, who stopped speaking entirely at age 2, is now a font of creative language. I know this because Erin and the boys spent a weekend at my house. At lunch, Kyle poured a Vesuvius of ketchup onto his plate and began transforming his french fries into boats that sailed across the ketchup before they were disposed of in his mouth; he then began to entertain us by pretending he was an announcer at a regatta, where he, of course, was winning the race. What had once been autism had erupted into a geyser of quirky creativity.

The boys' blossoming, according to their mom, is one not easily measured on tests. "It's the length of their sentences, their empathy and sense of humor. Last night we went by a house that was all lit up for the holidays and Kyle joked, 'Does that guy want to be seen from space?' When we used to take Kyle to the dentist, he would scream bloody murder and we'd try to papoose him —put him on a board and wrap him in sheets, but even that didn't work, so they put him to sleep just to clean his teeth. Last year we went to the dentist, and he heard a little boy crying, walked over to him, rubbed his back, told him it wouldn't hurt, and not to worry. My heart was melting."

Can we cajole a mysteriously shuttered brain and body back toward normal? And if so, will autism give us new insight into other disorders? Martha Herbert thinks so: "A lot of these metabolic pathways are pretty fundamental to life. If we can crack the puzzle of autism and be clear about how we did it, that may have huge implications for other chronic environmentally triggered systemic illnesses. Autism could be a much-needed wake-up call to us all." ■