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The incidence of autism is growing at an alarming rate. Experts are struggling to discover why.

Slowly, a strange and complex picture is coming together.

It suggests that autism's mysterious mechanisms could ultimately reveal health truths relevant to us all.

ILLUSTRATIONS: STUART BRIERS

BY PAMELA WEINTRAUB

Ashley Morgan's story would strike terror in the heart of any parent. Morgan's son, Leo (not their real names), seemed normal at birth in 1998 and appeared to hit his milestones — sitting, walking, laughing — for his first 12 months. But then he plateaued. He didn't gesture or demonstrate even the rudiments of pre-language. He didn't make much eye contact. And he was constantly stressed out. "When he was 15 months old, he started turning over trucks and spinning their wheels for hours," says Morgan. "That's when I knew for sure that something was wrong."

Since Morgan lived in Connecticut, her quest for help took her to the famed Child Study Team at Yale University. Experts there diagnosed Leo, then 2 years old, with a pervasive developmental disorder (PDD-NOS), a mild form of autism spectrum disorder (ASD). "He can have a nice life, but he'll always live with you," a Yale doctor told Morgan at the time.

From Asperger's to PDD to autism itself, ASD is a series of overlapping disorders marked by impaired social interaction and reduced ability to communicate. Once detected in just dozens of children a year, autism today afflicts nearly 1 percent of children, wreaking havoc in families, setting the stage for years of intense and costly therapies and a host of confounding physical ills.

The statistics of the last few years are staggering enough, but a recent study in the *American Journal of Psychiatry* says these estimates may be low. Surveying a district in South Korea, the researchers found autism in 2.64 percent of children between ages 7 and 12, or more than two and a half times the reported U.S. rate. Rather than suggest a bizarre new cluster in the district, study authors think we have woefully underestimated autism on our home turf. That conclusion is being

debated, but either way, there's ample cause for concern. What is at the root of this rapidly expanding epidemic? What in the world has changed?

One thing is perception. First described in the 1940s, autism was reportedly caused by cold, rejecting "refrigerator mothers." By the 1980s, with more cases emerging, scientists had moved on, redefining autism as a disorder caused by damage to the brain that has many genetic risks. But as prevalence has skyrocketed over the last decade and research has progressed, experts have reconceptualized autism yet again. In the new view of the disease, autism is not a single affliction of the brain but a series of brain- and body-based physical diseases — inflammatory, gastrointestinal, mitochondrial and immune.

While genetics are involved and some specific genes have been implicated in the disease, scientists now contend that there is no single autism gene. Instead, many genes appear to represent risk factors that require environmental or infectious triggers to tip a child into troubled territory. And a disease once considered a genetic brain disorder is now seen by many as a systemic body disorder that affects the brain as well. All forms of autism involve a failure to communicate and socialize, but from case to case, different metabolic and immune problems may be afflicting different organs of the body and circuits in the brain.

It was pediatric neurologist Martha Herbert, MD, PhD, of Harvard, who came out with the seminal paper describing the new view of autism as a complex, multisystemic condition in *Clinical Neuropsychiatry* in 2005. Autism had long been associated with physical ills — especially gastrointestinal discomfort — but Herbert pointed to an association with immune issues and multiple other problems whose biological underpinnings had yet to be learned.

As far as she was concerned, the "heterogeneous biologies" underlying autism might converge through a variety of →

mechanisms, in the brain. By the next year Herbert had refined her hypothesis: She said that vulnerable genes triggered by environmental insults might be perturbing metabolic pathways and damaging the brain.

This was a whole new way of looking at autism. But there was an even bigger implied bombshell: By unlocking autism's complex code, scientists might have new hope for treating other chronic disorders, from asthma and allergies to obesity.

"Autism is a hologram for chronic disease. In it is reflected all the causes and cures for chronic disease," explains Mark Hyman, MD, an expert in functional medicine and author of *The UltraMind Solution* (Scribner, 2008). "Remove the diag-

nostic labels from a patient with autism and a patient with Alzheimer's, and you will discover the same biological forces at work" — inflammation, oxidative stress, impaired protein synthesis and detoxification, mitochondrial dysfunction, and damaged DNA."

Translation? Autism might just be our wake-up call. Some experts now posit that individuals with autism are early indicators — canaries in a coal mine of pervasive health threats that are affecting increasing numbers of us. If we can unravel the immune, metabolic and genetic problems at play, we may have a head start in treating not just autism but a great many other chronic and environmentally triggered forms of disease.



Bodywide Vulnerability

For years, the new view of autism as a systemic body-based disorder triggered by environmental insults was met with resistance, largely because it was associated with the antivaccine movement to argue that the trigger was often childhood vaccines, a theory not supported by most published epidemiological studies.

Yet, some doctors were able to look past the stigma to see that a variety of biomedical malfunctions appeared in large numbers of children with autism, and that, often, associated clinical symptoms could be relieved.

Lawrence Rosen, MD, was part of a large pediatric practice in New Jersey in 2000 when he noticed an explosion of developmental disorders, including the upsurge in autism and associated physical ills. Of the autistic children he surveyed, 68 percent suffered gastrointestinal symptoms, including diarrhea, constipation, abdominal pain, vomiting and gastroesophageal reflux; 66 percent suffered neurologi-

cal problems, including seizure disorders, apart from the autism; 62 percent reported allergies; and an estimated 30 to 40 percent were afflicted with mitochondrial disorders or dysfunction. These patients also had strange rashes, had more ear infections and coughs than non-autistic patients, and were frequently anxious and fatigued.

While Rosen didn't know the cause, he found that thoughtfully treating the problems, one by one, could dramatically increase his patients' comfort *and* would often lessen the behavioral symptoms of autism as well.

For instance, when lab tests pointed to sluggish mitochondria (the cellular energy factories), he treated patients with the supplements carnitine or coenzyme Q10. (For more on CoQ10, search for "CoQ10: The Miracle Molecule" at experiencelife.com.)

In the face of gastrointestinal problems or allergies, he examined food choices systematically. On gluten-free, casein-free diets, a subset of children dramatically improved.

Another subgroup with abdominal pain and diarrhea or constipation, often associated with yeast and bacterial overgrowth, were treated with probiotics.

When treated for three months with omega-3 fatty acids, one nonverbal 3-year-old abruptly began speaking. While evidence already shows omega-3 fatty acids are effective for bipolar disorder and depression, Rosen says they can often help autism as well.

Rosen's colleague, family physician Patrick Hanaway, MD, was running a local practice in Asheville, N.C., when he, too, witnessed the autism explosion from the late 1990s on. Hanaway also began taking a functional medicine approach, eventually working with a lab to diagnose and restore disrupted metabolism one biochemical pathway at a time.

One vulnerable pathway was methylation, the interconnected cascade of biochemical reactions that control protein and DNA synthesis throughout the body. By supplementing with nutrients known to support methylation — antioxidants, B6, B12 and folate — Hanaway has seen some patients improve.



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But there is no magic bullet. For the genetically vulnerable, suspects Hanaway, "there are multiple small hits from the environment." Thus, multiple nutrients or cofactors may be needed to help any given patient heal.

That was certainly true for Ashley Morgan's son, Leo. From the moment

doctors told Morgan her son's case was hopeless, she "was on the warpath," relentlessly seeking treatments and even a cure. High on the list of helpful therapies was a gentle form of ABA (applied behavior analysis) to help Leo understand others' thoughts, intentions, motives and desires — the chief psychiatric deficit among those on the spectrum.

But Leo was also dogged by physical illnesses. His bowel movements were soft. He had a toxic, pasty look. He lacked energy. He had asthma. And he had hypotonia — weak muscles that lacked tone.

Because Leo seemed so physically sick, Morgan sought to ease his pain, one symptom at a time. Just eliminating gluten, she reports, resulted in significant improvement. After doctors found nine other food allergies and 11 tree allergies, they treated him for these. Adding the B vitamin biotin further enhanced his energy.

Leo was also diagnosed with Lyme disease following his years in Connecticut and treated with antibiotics. And cleansing his blood (as is often done for children exposed to strep) eased his symptoms as well.

With each new treatment, Leo's health and ability to communicate improved.

"It took four years to bring him back," says Morgan. Leo's treatment team deemed him recovered in 2004, and Yale officially withdrew its autism diagnosis in 2008.

The various symptoms and the trial-and-error treatments could help to solve the autism puzzle by offering insight into the biological systems that have gone awry, says Rosen, who is currently director of the Whole Child Center in Oradell, N.J. "If we can elucidate the genomic, proteomic [proteins expressed by specific genes] and metabolic differences associated with subtypes of ASD, then we can develop therapies targeted at correcting these imbalances. The ultimate goal is not just treating visible symptoms but actually rebalancing biochemistry — in fact, altering genetic expression — to prevent autism from developing at all," says Rosen.



Immune Confusion

The most striking news from the research front could be the role of run-away inflammation — the process by which white blood cells release chemicals to protect the body from outside attack. In a healthy person, inflammation rids the body of the invader and subsides. In the sick person, inflammation goes on and on.

Shortly after his wife was diagnosed with chronic fatigue syndrome (CFS) in the 1980s, Los Angeles pediatrician Michael J. Goldberg, MD, began following the neuro-inflammation trail. His observations seem prescient today. Along with the emerging epidemic of CFS in adults, he noticed that patients in his practice were developing a new type of attention disorder, different from the ADHD (attention deficit hyperactivity disorder) he'd known in the past. The original group had been frisky but otherwise healthy and alert. Not so with the new crew. Spacey and tired, they seemed sick and "couldn't think straight," Goldberg says.

And that wasn't all. The parents of these children were complaining about other problems: asthma, migraines, rheumatoid symptoms, skin conditions like eczema and even CFS. Many of these children had increased levels of antinuclear antibodies, which serve as a marker for autoimmune disease (in which the body basically attacks itself). Just one thing could tie all this together, Goldberg thought back then: an immune system under attack.

In the early 1990s, brain scans allowed Goldberg to track blood flow to see if his theory was right. He started

by comparing scans of classic-ADHD kids with the new ADD (attention deficit disorder) group, which was now the majority of those with attention disorders. Although Goldberg found that the ADHD kids, who had represented 5 to 10 percent of the total, had more blood flow to the frontal lobes, the rest of the brain was normal. The ADD group, in addition to having more blood flow to the frontal lobes, also had decreased blood flow in the temporal lobes — brain regions crucial for language, communication and social skills — indicating a far more widespread problem and suggesting neuro-immune dysfunction and inflammation of the brain. Later scans showed his CFS patients had lowered blood flow in the temporal lobes as well.

Goldberg says the situation really gelled for him between 1995 and 2000 with the jolting upsurge in autism. "Representing nothing I was ever taught about in medical school, internship or residency, there was now a newly emerging family constellation of a mother or father with CFS or some other immune-related disorder, an older child or two with ADD, and a younger child or two with autism," Goldberg says. What's more, he found, family members often shared allergic problems, recurrent ear infections, frequent sore throats and flulike illness. It was almost as if the same insult was manifesting in different ways depending upon the age of the person when it hit.

Because this "shocking pattern" was like no genetic disorder Goldberg had ever seen, he felt it had to be the result of some combination of neuro-immune insults, infections, or both. As the rising tide of autism attracted national attention, Goldberg felt many doctors were getting an essential part of the story wrong. While the buzz from Goldberg's colleagues was all about an exploding autistic disorder with immune abnormalities, Goldberg was instead seeing a widespread immune disorder with autistic (or ADHD, CFS, etc.) symptoms.

In recent years, studies have traced immune abnormalities to brain inflammation and a significant autism subgroup, supporting Goldberg's point of view. In 2008, for instance, University of California at Davis scientists tested →

maternal blood and found that in mothers of autistic children, 12 percent produced autoantibodies against the fetal brain.

Other studies, most of them very recent and some still in progress, show that a substantial number of autistic patients tend to produce antibodies against various brain proteins. Some of these are associated with one class of neurons that maintain a balance of excitability in the brain. For patients in the large-scale Autism Phenome Project at the UC Davis MIND Institute, the greater the number of antibodies against the brain and the more pronounced the inflammation, the more behavior problems a child has.



Triggered by Infection

Experts are still investigating the origins of the inflammation from which autistic individuals tend to suffer. Emerging science supports the observation that infectious or environmental agents may trigger risky genes in the vulnerable, broadly explaining part of the surge in autism diagnoses as well as the physical ills.

“Autism science has identified up to 100 involved genes so far, but each one appears in no more than 1 to 2 percent of patients,” says David Amaral, director of research at the MIND Institute. “The genes are important, but most of the time, to get autism you need another hit.”

This was certainly the case for brother and sister Ryan Blanco, 30, and Stacy Blanco, 22. Twenty years into their autism diagnoses, they were finally diagnosed with Lyme disease and a host of other tick-borne and opportunistic infections, including

Babesia duncani, *Bartonella henselae*, *Mycoplasma fermentans*, herpes, and Epstein-Barr virus. Their stool indicated past exposure to toxoplasmosis, streptococci and corynebacteria.

The working hypothesis put forth by psychiatrist Robert Bransfield, MD, of Redbank, N.J., is that the infections, the immune reactions they provoked, or some combination of the two are driving a rising tide of medical problems, including grand mal seizures, mitochondrial disorder and the autism itself.

SPECT scans performed on the Blancos indicate atrophy of the brain and a hyperperfusion (excess blood flow) pattern indicative of inflammation through the frontal lobes (the seat of cognition), the temporal lobes (explaining their seizures), the cerebellum (accounting for all their balance problems) and even the basal ganglia (associated with anxiety).

Can autism really be triggered or worsened by chronic infections, including the ones the Blancos have been diagnosed with? Bransfield points out that strong evidence already supports the model for brain damage in rubella, malaria and syphilis, and says we should be on the lookout for two modes of action with other pathogens: (1) “hit-and-run” infections that do most of the damage through immune reactions; and (2) chronic infections that may persist after treatment or simply fly under the radar, still damaging but undiagnosed. “We are living in a global community with increasing exposure to toxins and infections,” Bransfield warns.

Some with ASD may have such a powerful genetic defect that it is sufficient on its own to cause the disease, notes neurologist Ian Lipkin, MD, John Snow Professor of Epidemiology at the Mailman School of Public Health and director of the Center for Infection and Immunity at Columbia University, who is directing a large-scale autism study. Lipkin suspects that a second group is genetically predisposed but must encounter some factor or factors, perhaps in combination, for development or aggravation of ASD. “And by factors, I include everything from heavy metals to toxins to infectious agents,” Lipkin says. “You can be genetically predisposed but not manifest autism until the trigger is present.”



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Infection can cause disease directly by damaging brain cells or circuits, or by inducing antibodies that impair brain function.

Although some critics have questioned the ability of antibodies to pass the blood-brain barrier, Lipkin points out that a range of conditions, from fever to infection to stress, can open it temporarily, letting antibodies through. If the antibodies gravitate to one part of the brain at one moment in time, they could result in one type of disease, he says. If they go to another part of the brain at another moment in time, another disease may result.

“These nuances highlight the importance of understanding gene-environment-timing interactions,” Lipkin adds. And the impact may be widespread. Autoantibodies going to the brain not only cause neurological disease but they can travel to the heart, the digestive tract, or other body systems as well.



Assembling Answers

Autism is still a giant jigsaw puzzle, way too complicated for scientists to piece together in full right now. Until we can separate autism into categories that reflect genetic risks and environmental

assaults, we're unlikely to make a serious dent in the rate of diagnosis, which David Amaral says may still be on the rise. Until we subject the wide range of biomedical treatments to controlled clinical trials, we're unlikely to grasp, in the deep way required, which treatments work best, and for whom.

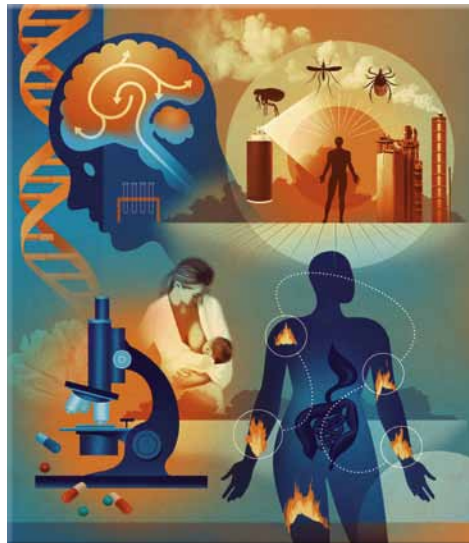
While the experts seek answers, parents pray for miracles. Hope is better than hopelessness, and patients like Leo Morgan, who has shed the diagnosis, keep hope alive.

According to Harvard's Martha Herbert, the evidence suggests that between 3 and 25 percent of children "reportedly lose their ASD diagnosis and enter the normal range of cognitive, adaptive and social skills." Those most likely to recover start with normal to high intelligence and score better on measures of receptive language, verbal and motor imitation, and motor development.

Early diagnosis and treatment counts, too. Today, the techniques supported by solid evidence are still behavioral: encouraging outward attention, enriching the environment, reinforcing social interaction, intensive practice of weak skills, reducing stress and stabilizing arousal. Each biomedical treatment, on the other hand, seems to help just a subset of patients — sometimes a small subset — making proof of efficacy more difficult. And yet, one of the key points of autism is that there is no one disease called autism, but a series of unique, individual conditions.

Doctors like Rosen remain acutely aware of the need for more studies and refuse to oversell their results. "We don't see many miracles," he says, "though improvement is common." Yet what the biomedical approach does emphasize, says Rosen, is that we — each of us — have a biochemical individuality. In order to address any condition, autism included, we must remember that "at the heart of medicine lies the individual and each individual patient's unique story." It is only by respecting that individuality that we can truly treat complex chronic illness. Although nowhere near as simple a theory as the refrigerator mothers, it holds more promise in the end. 🌀

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Reasonable Recommendations

Without knowing the exact cause of any given form of autism, the idea of preventing it is a stretch. Yet Lawrence Rosen, MD, observes that healthy families following his preventive medicine program from birth have far lower rates of ASD: one in 100 diagnosed for the state of New Jersey, but just an estimated one in 1,000 for Rosen's Whole Child Center in the town of Oradell. Rates of allergy and asthma are low among children born into his practice as well. "It could be in part due to a referral bias," Rosen concedes, since his practice attracts families already tuned into the dangers of pesticides and other chemicals and devoted to exercise and whole foods. Still, the preventives Rosen recommends are worth a note:

- Supplements of vitamin D and omega-3 fatty acids for most children, and prenatal vitamins for expectant mothers and women trying to become pregnant.

- Breast feeding at least until a baby reaches the age of 12 months (or for as long as one can personally do it).
- Conservative use of pharmaceutical medicine, including avoidance of antibiotics for common viral coughs and colds.
- Reliance on organic and whole foods when feasible.
- Avoidance of toxic cleaning products and pesticides.
- A family-centered, individualized approach to vaccinations. "There's no proof that vaccines have caused the autism epidemic," says Rosen, "and we support the public-health concept of immunization. But, we are willing to be flexible in scheduling vaccinations separately, and in helping families understand the risks and benefits of their decisions. This way, parents have increased trust in us and in the healthcare system, and we find they are more likely to make the most informed decisions for their children."