



A Spectrum of Disorders

The urgent search to understand the biological basis of autism

WHEN ALISON FINALLY heard her son Matthew's diagnosis, she had already spent a night on the Web, terrifying herself, as she puts it, "for the rest of my whole life." At 18 months, Matthew showed a number of the early warning signs of autism: he didn't respond to his name or point to objects of interest, he seemed to fixate on spinning things like the washing machine, and he had developed no new words since his 12-month check-up. Alison feared her son might never develop the ability to make friends, converse at the dinner table, or live on his own. The doctor who evaluated Matthew told Alison that her son met criteria for "pervasive developmental disorder not otherwise specified" (PDD NOS), a less severe condition than full-scale autism, and one that, when caught early, often responds well to intensive therapies. "This is one of the best kinds of autism to have," the doctor explained, holding a stack of treatment referrals. Alison's grief and shock gave way to a sense of

urgency: "I got started on his treatment plan like my hair was on fire."

In recent years, diagnoses of autism have soared: to as many as one for every 166 children in the United States, according to recent estimates

published by the Centers for Disease Control. Much of this increase stems from a broadening of the diagnostic category. Clinicians now recognize a "spectrum" of autistic disorders that encompasses children with mental retardation and little or no language (low-functioning autism) as well as those with high IQs and precocious vocabularies (Asperger's syndrome). The common thread linking these disparate conditions is a deficit in social relatedness that impairs a child's ability to communicate, learn, and participate in ordinary life. While some cases improve with rigorous interventions, others remain intractable. Parents like Alison face a morass of competing theories and potential cures in their struggle to increase their children's chances of recovery.

by Ashley Pettus

The growing number of families affected by autism has intensified the scientific search for answers. In the last five years, new technology and funding (much of it from family foundations) have made it possible to address the most pressing questions of causality on a large scale. Harvard researchers from a wide range of disciplines—including genetics, genomics, neurology, cognitive science, developmental medicine, and bioinformatics—have joined a collaborative effort to identify the biological roots of autistic disorders and to develop better methods of detection and treatment. Their efforts promise to yield significant findings in the very near future. But the inherent heterogeneity of autism suggests that a full accounting will likely take longer and may require investigators to look for clues in unexpected places.

“An Extreme Aloneness”

In 1943, the Austrian-born psychiatrist Leo Kanner provided a startling picture of 11 children trapped in their own worlds. The

children—all patients at Johns Hopkins Hospital in Baltimore—had previously been labeled “emotionally disturbed” or “intellectually impaired.” Kanner noticed that they shared a number of distinct behavioral and cognitive features: they all had difficulty relating to other people, delayed or unusual language, superior rote memories, and an obsession with sameness and repetition. He described their condition as an inborn disorder of social attachment, which he called “infantile autism.” “There is from the start,” he wrote, “an extreme autistic aloneness that, whenever possible, disregards, ignores, or shuts out anything that comes to the child from the outside.”

At the time of Kanner’s discovery, mainstream psychiatry was in the thrall of Freudian theory, which attributed most childhood disorders to family environment rather than biology. Autism came to be viewed as an extreme and rare condition—the result of profound emotional (and specifically, maternal) neglect. For most of the latter half of the twentieth century, clinicians used

Beyond the Genome

DURING THE PAST FEW DECADES, most scientific research into the causes of autism has been focused on the structural wiring of the brain and on the genes that control it. Evidence of chronic sickness or general physical discomfort in autistic children has largely been viewed as coincidental to the primary brain disorder or, in some instances, mistaken for the syndrome’s behavioral symptoms. But in recent years, as the number of cases has continued to rise (while the genetic pathways have remained elusive), several clinicians and researchers have begun to ask whether disturbances in children’s broader bodily systems may be influencing, or even causing, the disruption in their brains.

Associate professor of neurology and pediatric clinician Margaret Bauman has been on a crusade to ensure that children with autism-spectrum disorders receive adequate medical care. As the director of LADDERS (Learning and Developmental Disabilities Evaluation and Rehabilitation Services)—a multidisciplinary research clinic affiliated with Massachusetts General Hospital (MGH)—she spearheaded a new model for diagnosing and treating the host of physiological problems that often accompany autistic disorders. The LADDERS staff includes experts in gastroenterology, sleep disorders, and neuromuscular and metabolic disorders, as well as in psychopharmacology, neurology, and developmental pediatrics. (In 2005, Bauman cofounded the Autism Treatment Network, a national nonprofit organization of six clinical programs around the country that collaborate to promote current best practices in the diagnosis and treatment of autism-spectrum disorders.)

“Many kids with autism have gastrointestinal problems that may affect their behavior,” Bauman explains. “But because these kids are often nonverbal or hypoverbal, they have trouble conveying their discomfort or localizing their pain.” Children with intense gastritis or colitis may bang their heads or move their bodies in strange ways in reaction to physical distress. “It turns out that when you treat the medical problem, in many cases the aggressive and self-injurious behaviors abate,” she says. Bauman has also found that a subset of children on the spectrum who do not respond to standard autism therapies have a disorder involving their

mitochondria (the cellular structures that convert nutrients into energy). These kids tend to walk late, have very little energy, and undergo periodic regressions in which they lose muscle control, attentiveness, and language. Bauman was surprised to find that a complex vitamin treatment helped improve the condition of a number of such children, enabling them to benefit from behavioral therapies.

Bauman does not suggest that such biomedical interventions will cure autism, but she believes that researchers need to pay close attention to the pattern of physiological problems that attend the autistic syndromes of a significant portion of children. “We haven’t been looking at other organ systems and how they relate to this disorder,” she says. “It’s possible that we’ve been doing genotyping on apples and oranges.”

Assistant professor of neurology Martha Herbert, a pediatric neurologist at MGH, couldn’t agree more. Herbert has been at the forefront of an effort to alter the prevailing paradigm of autism research. As a resident in neurology in the early 1990s, she spent two years studying the preserved brain samples of 93 autistic individuals, hoping to find a correlation between specific structural abnormalities and autistic behaviors. What she found instead, she explains, were “abnormally large brains with more than average white matter [the tissue through which messages pass between different areas of gray matter in the brain, where the nerve cell bodies are located]. I began to think that this is not a *localized* brain disorder but a *generalized* disorder that affects the brain. It requires a different way of thinking.”

Herbert found evidence that a subgroup of children with autism experience a sudden increase in brain size a year or so after birth. The areas that enlarge are those where the myelin sheath—the fatty electrical insulator of the brain cells—forms post- rather than prenatally. The question of whether some children are born “normal” and then “regress” into autism between the ages of one and two has been at the center of the controversy over the potential role of mercury and vaccines in causing autism. Although Herbert steers clear of this debate, her findings suggest that postnatal damage may contribute to the onset of autistic conditions in a considerable number of cases.

Herbert believes that such tissue changes in autistic brains could be signs of inflammation or oxidative stress, potentially im-

the diagnosis only in cases where no other label was possible. As Margaret Bauman, associate professor of neurology and director of the Learning and Developmental Disabilities Evaluation and Rehabilitation Services (LAD-DERS) in Wellesley, recalls: “The majority of the cases we see today would not have been labeled autistic when I was a resident in pediatrics [in the late 1960s]. The autistic kid was a kid who sat in the corner, rocking back and forth, and made no eye contact. The rest were labeled ‘mentally retarded’ or ‘childhood schizophrenia.’”

It wasn't until the early 1980s that a new understanding of autism began to emerge. The catalyst was an article published by British autism expert Lorna Wing that described a little-known syndrome called Asperger's Disorder. Hans Asperger was an Austrian-born pediatrician who studied children in a psychiatric



Wing's paper showed how the core features of autism could occur in a wide range of people, some severely mentally retarded and others highly intelligent.

hospital in Leipzig, Germany, in the late 1930s—the same time that Kanner was conducting his research in Baltimore. Asperger documented a condition in boys that he termed “autistic psychopathy,” characterized by “a lack of empathy, little ability to form friendships, one-sided conversation, intense absorption in a special interest, and clumsy movements.” His patients differed from Kanner's in that they did not exhibit developmental delays in language or cognition (Asperger in fact referred to them as “little professors”), yet they shared key impairments in social interaction, reciprocal communication, and imagination (i.e., repetitive behaviors and interests). Wing's 1981 paper brought Asperger's findings to the attention of the English-speaking world and showed how the core features of autism could occur in a wide range of people, some severely mentally retarded and others highly intelligent.

In the ensuing years, the predominant view of autism as a discrete psychoemotional condition gave way to the idea of a continuum of biologically based autistic syndromes, requiring greater diagnostic specificity. By 1994, the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* listed detailed criteria for five “pervasive developmental disorders” (PDDs), including Asperger's, that comprised the “autism spectrum.”*

The increased awareness of autism's related conditions and their symptoms corresponded to a steep rise in diagnoses in the early 1990s. Many parents became convinced that the escalating numbers of cases stemmed from exposure to thimerosal, a mercury-based preservative used in childhood vaccines. Another theory linked the measles/mumps/rubella (MMR) vaccine, in particular, to the onset of autistic symptoms. Numerous epidemiological studies have failed to substantiate these claims, and in 2004 the Institute of Medicine of the National Academies found no causal relationship between either mercury or MMR vaccine and autism.

But even though it is not possible to get an accurate count of real cases prior to the early 1990s, there is a growing sense among researchers and clinicians that the real incidence of autism is on the rise and that environmental triggers likely play a role. The potential factors range from chemicals in food and cosmetics to

*The pervasive developmental disorders (PDDs) comprising the autism spectrum share core deficits in social interaction, language, and range of interests or behaviors. They differ in degree of severity, number of areas of impairment, pattern of onset, and rate of prevalence. *Autistic disorder* (the most common) is four times more common among males than females and generally involves mental retardation. *Rett's disorder*, a rare condition that occurs only in females, usually involves severe mental retardation. *Childhood disintegrative disorder* (CDD), involving a precipitous loss of abilities after at least two years of normal development, appears rarely, and more often among males. *Asperger's disorder*, diagnosed five times more frequently in males than females, involves pronounced social deficits but no significant cognitive or language acquisition impediments. *Pervasive developmental disorder not otherwise specified* (PDD NOS), a “subthreshold category,” applies to cases in which some criteria for autistic disorder are present and the onset of symptoms doesn't fit other PDD diagnoses. For details, visit www.nimh.nih.gov/health/topics/autism-spectrum-disorders-pervasive-developmental-disorders/index.shtml, posted by the National Institute of Mental Health.

plicating environmental factors. (Oxidative stress refers to an imbalance between the rate of oxidative damage to cells and the rate of cell repair.) “Perhaps the brain is caught ‘in the crossfire’ of whole-body changes related to environmental stress,” she says. She has not proposed any particular toxin exposure as a cause of autism; rather she underscores the need to expand the investigative lens beyond the genes-brain-behavior model in order to look for broader problems in physiological functioning. “We need more study of environmentally responsive metabolic and signaling pathways,” she explains, “since these will guide us both to where to look for relevant genes and also where to look for treatment targets.”

Herbert's ideas are not universally accepted by neurogeneticists; but among many in the mainstream of autism research there is growing support for a more biological approach to diagnosis. Susan Santangelo, associate professor of psychiatry at Harvard Medical School and an associate professor in epidemiology at Harvard School of Public Health, who also serves as director of statistical genetics and genetic epidemiology in the psychiatric and neurodevelopmental genetics unit at MGH, argues that researchers need to begin to look for more precise measures to identify and sort individuals with autism disorders.

Santangelo, an executive committee member of the Boston Autism Consortium (which links more than 50 local researchers who tackle different aspects of the disease cycle and share results), suggests that tests such as an EEG (electroencephalogram, which measures electrical activity in the brain), an ERP (event-related potential, which records brain activity during specific tasks), or a measure of blood plasma levels for certain metabolites could provide investigators with markers that they could correlate to a given set of behavioral traits, thus helping to distinguish patients' functions on a variety of levels. “If we can start to map the genes for something more biological,” Santangelo explains, “something closer to the genetic action, then maybe we'll have more success than [we've had] trying to map the genes for a very heterogeneous psychiatric classification that may bear absolutely no relation to underlying pathophysiology. We need to cast a wide net and then tunnel deep into some of these measures.”

parental age, stress, and reproductive technologies—offering no clear indication of where epidemiological studies might begin. Before scientists can isolate possible external causes, they need a clearer understanding of the biological pathways that lead to the combinations of traits and deficits along the autism spectrum.

Genetic Complexity

A 1977 STUDY OF TWINS provided the first evidence of a genetic basis for autism. If one twin had the disorder, the other was far more likely to have it if he or she was identical rather than fraternal. (Because identical twins share their entire DNA, while fraternal twins share only half on average, a disease that tends to co-occur in identical pairs indicates genetic influence.) The discovery helped undermine the prevailing psychoanalytic theories that blamed autism on bad parenting and, in particular, on cold, unaffectionate, “refrigerator” mothers.

Yet the task of identifying the culprit genes has proved daunting. Although the concordance rate for autism in identical twins is high—with recent estimates ranging from 60 percent for the same diagnosis and 90 percent for related disorders—it is not



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100 percent. The fact that identical twins do not always share the disorder indicates that environmental influences are also at play. Furthermore, the variability in the traits and deficits associated with conditions along the spectrum (and often between individuals in a single family) suggests that multiple genes are involved; higher-functioning autism, for instance, may arise through separate genetic mechanisms than lower-functioning autism.

These complexities have made cooperation among research teams and among institutions essential. “Autism is a problem that no one person or discipline can figure out alone,” explains James Gusella, Bullard professor of neurogenetics and director of the Center for Human Genetic Research at Massachusetts General Hospital (MGH). Gusella chairs the executive committee of the Boston Autism Consortium, a largely privately funded initiative that began in 2005 to take advantage of the wealth of expertise, technological resources, and patient databases concentrated in the area. The consortium brings together more than 50 researchers from Harvard, MIT, the Broad Institute, MGH, Children’s Hospital, Boston University, Beth Israel Deaconess Medical Center, and Tufts University to tackle different aspects of the disease cycle and to share results. Gene discovery is a top priority. “We’re not saying that it’s all genes,” Gusella is careful to point out, “but the genes will accelerate the search for other factors. They provide the crucial starting point.”

The pursuit of autism’s molecular roots has led Christopher Walsh, Bullard professor of neurology and chief of the division of genetics at Children’s Hospital Boston, on a cross-cultural journey. Walsh, who also directs the division of neurogenetics at Beth Israel Deaconess Medical Center, travels regularly to Dubai, Kuwait, and Saudi Arabia to study the genomes of large Middle

Eastern families. Because Arab cultures have a strong tradition of first-cousin marriage, the children in these societies have a higher likelihood than other populations of inheriting genetic mutations that can cause a developmental disorder. If both parents carry a recessive gene associated with autism, each child in the family has a 25 percent chance of getting the disease. With an average birth rate of six children per couple, a family in which both parents are carriers may well have more than one child with an autism-spectrum disorder.

Walsh uses a technique called homozygosity mapping to look for causative recessive mutations. He checks all the sets of chromosomes in each family member, searching for spots where the affected children have two identical chunks of DNA and unaffected children have something different. Walsh and his team have identified four chromosomal locations in three separate families, and they have begun sequencing the genes in these spots to look for a disabling mutation. “Once we find it,” Walsh explains, “we can sequence any kid anywhere to see if he or she is subject to the same condition.”

Inherited mutations hold the promise of explaining some, but not all, of the genetic paths to autism. Walsh points out that many genetic mutations that affect the brain—particularly those involving severe cognitive impairment—are spontaneous. “Mental retardation is frequently *not* inherited within families because it is so crippling,” he explains. “People with this condition are not likely to have children, so the mutations that cause the disorder are sporadic, rather than inherited.” (Down Syndrome, which arises from the presence of an extra chromosome, is an example of this type of nonhereditary genetic disorder.) Walsh estimates that about 15 to 20 percent of autism cases may fall into this category.

In order to identify spontaneous genetic changes that are causally significant, researchers need to look for gains or losses of DNA that are present in children but not in their parents. If they find a change in the child that they can associate with a set of symptoms that is absent in the parents, they can then conclude that the mutation caused the disorder. In the case of autism, however, the isolation of disease-causing mutations has proven particularly difficult because the genetic changes and the clusters of disease traits (phenotypes) do not present a clear one-to-one relationship. “We’ve found that sometimes some of the sub-microscopic changes in the kid’s DNA are also present in one of the parents,” Walsh notes. “And these parents may be either asymptomatic or mildly symptomatic: in some cases, some of the parent’s cells don’t show the mutation, while other cells do, which suggests that the change may have happened part-way through the development of the parent.” The first step, Walsh says, is to determine which of these sub-microscopic changes are meaningful and which aren’t.

Stalking Likely Suspects

TODAY’S RESEARCHERS DO HAVE some possible signposts to help them navigate the maze of potential routes to autism. There are 10 spots, called chromosomal “linkage peaks,” along the genome, where deletions or insertions of bits of DNA have been



statistically correlated with the presence of autistic traits. But hundreds of genes are associated with a single “linkage peak.” Teasing out the causal genes presents a formidable task.

Louis Kunkel, professor of pediatrics and genetics and director of the genomics program at Children’s Hospital, is pursuing an unconventional approach to this puzzle. He has joined forces with Isaac Kohane, Henderson associate professor of pediatrics and health sciences and technology, who directs the hospital’s informatics program, to look for irregular patterns in the way genes are expressed in the white blood cells of autistic children. “We’re asking: if gene expression is off-track in the brain, is it also off-track in whole blood?” Kunkel explains. “And can we categorize kids with autism based on gene-expression profiling in blood?” (Gene expression refers to which genes are “on”—giving instructions for how the cell should work—in a given cell.)

Tiny microarrays or “gene chips” now enable lab technicians to examine the activity of 30,000 genes at once. Kunkel and Kohane plan to draw on hundreds of thousands of samples to compare patterns of gene expression in children with and without autism-spectrum disorders. “I think we’re looking for a lot of different variants in a dozen or so genes that in combination with other genes may cause autism,” Kunkel says.

The researchers are paying particular attention to networks of genetic activity that affect 12 genes already known to play a role in autism. These are genes that regulate the brain’s response to environmental stimuli, affecting learning and memory by regulating the plasticity of connections between neurons. Here, the work of Michael Greenberg, professor of neurology and neuroscience and

director of neurobiology at Children’s Hospital, has been critical. Greenberg looks at animals to examine how experience shapes the formation and refinement of synapses during brain development. He believes that autism-spectrum disorders may result from flaws in synapse development that affect the brain’s ability to process incoming signals. During the first years of postnatal development, trillions of synapses form in the brain as a child interacts with his or her surroundings; many synapses that aren’t needed naturally fall away, while others are strengthened. One possibility, Greenberg suggests, is that this pruning process doesn’t happen effectively in people with autism. Another theory holds that autism may involve a defect in the balance between excitatory and inhibitory synapses. A deficit in inhibitory synapses causes seizures, a common problem in more severe forms of autism.

Greenberg is involved in identifying the genetic program that controls these synaptic processes: “It turns out,” he explains, “that as synapses are forming in the first years of life there are about 300 genes that get activated. We study how they get activated, how the signal goes from a synapse to the nucleus where genes get turned on, what the genes are, what they do, and how they control the program.” (One gene, *MECP2*, that has been linked to Rett syndrome—a rare autism-spectrum disorder primarily affecting girls—has already been implicated in this chain of synaptic events.) He continues, “The expectation is that, as we figure out this network of signaling, when the geneticists identify the causative genes for autistic disorders, we will be able to tell them: ‘This is why they’re important, and this is what they do.’”

The coordinated efforts of Walsh, Kun- (please turn to page 89)

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kel, Kohane, and Greenberg, along with others in the consortium, will lead, they hope, to better parsing of the various subtypes of autism. “I would like every kid on the spectrum to have *not* ‘autism,’ but a more specific disorder,” Walsh says. By isolating the genes involved and understanding their functions, researchers can begin to develop particular treatments aimed at particular disorders. So far Rett syndrome and Fragile X (the most common inherited cause of mental retardation, which accounts for 2 to 6 percent of autism cases) have been distinguished from other variants of autism by genetic



Problems with processing faces and emotion and with acquiring language are core symptoms of the disorder.

markers, and advances in treatment for those two types are already under way.

But DNA tests are still far from detecting the majority of cases of autism. In the meantime, scientists need to look for other indicators that can help ascertain the presence of an autism-spectrum disorder at the earliest possible time, in order to enhance the chances for effective intervention.

“The Brain Doesn’t Lie”

PROFESSOR OF PEDIATRICS Charles Nelson, who directs the cognitive neuroscience laboratory in the Developmental Medicine Center at Children’s Hospital, has had a longstanding interest in how the human brain processes faces. His research has shown that the architecture in the brain that enables children to recognize faces becomes increasingly specialized through early experience. While a six-month-old can distinguish between monkey faces as well as between human faces, a nine-month-old can distinguish only between human faces. A similar perceptual narrowing occurs in the ability to recognize speech sounds: at six months, babies can distinguish sounds in virtually any language, but by one year they begin to discriminate only sounds in their native language. Subsequent studies revealed

that a significant degree of plasticity exists in this specializing process; babies who were exposed to monkey faces between six and nine months of age could still distinguish between monkey faces at nine months, while babies who did not receive this training could not do so.

Nelson believes these findings provide a window onto the cognitive deficits involved in autism, because problems with processing faces and emotion and with acquiring language are core symptoms of the disorder. He wants to know whether there is a corruption in the architecture of autistic brains from the beginning that prevents these children from benefiting from experience in the typical way, or whether the circuits begin by functioning properly

but, for other reasons, do not develop normally, thus preventing these children from benefiting from experience the way they should. He

also wonders how early in development signs of an underlying neurological cause can be identified.

To get at these questions, Nelson has been conducting a study with Helen Tager-Flusberg of Boston University to compare the brain activity in siblings of autistic children with that of non-autistic language-impaired children and with controls. Because of autism’s strong hereditary component, a child with a (non-identical) autistic sibling has up to a 20 percent chance of developing an autism-spectrum disorder. (The relative risk is substantially higher for male than female siblings, because boys outnumber girls on the spectrum by a ratio of 4 to 1).

These numbers motivated the Phillips family to put their younger child, Kaia—a six-month-old—in the study. Kaia’s older brother, Torin, 3, has a diagnosis of PDD NOS. “We understand that early detection is critical,” explains their father, Tom Phillips. “We also want to do anything we can to help families in the future.” Kaia will undergo a battery of tests aimed at detecting potential abnormalities in brain function that are not yet apparent in her outward behavior. “Because a child’s behavioral repertoire is limited in the first years of life, it can be difficult to tell whether an apparent language delay is

developmental or something more significant, like autism,” Nelson explains. “But I like to say, ‘The brain doesn’t lie.’”

The first test examines how Kaia’s eyes track alternating images of her mother and a stranger. Does she scan one face longer than the other? What part of the face does she focus on? (Children at risk for autism, Nelson points out, will tend to spend less time on the eyes.) An electrode cap is then placed on her head to measure continuous brain activity as she views the images. Normal babies will take more time to process the picture of the stranger than the picture of the mother. A third test measures her ability to distinguish three highly similar sounds. At three to six months of age, babies should hear three distinct sounds, but by 12 months they should be able to distinguish only two. Nelson and his team hypothesize that a language-delayed or impaired child may not show this perceptual narrowing, or may lack the ability to distinguish the sounds from the start. The final component of the study gauges patterns of interaction with an adult—such as response to facial emotion, eye contact, general social babbling, social interest, shared affect, engagement of attention, and orientation to name. If the researchers pick up any significant irregularities in Kaia’s measures, they will alert her parents to begin appropriate early therapies.

In a related piece of the investigation, Nelson’s team is looking at the brain activity of older children who have already been diagnosed with autism, in the hope of finding clues that can inform early intervention strategies. “We want to know what the neural circuits are that underlie the primary deficits in face processing,” he says. “If we can get kids to process faces normally before that system is derailed, then perhaps we can avoid the further problems in social communication.”

Early Action

THE INSIGHTS OF Nelson and other developmental neuroscientists into early brain plasticity have already begun to inform the predominant approaches to autism therapy. Currently, the most widely recommended research-based intervention—known as Applied Behavioral Analysis (ABA)—aims to “wire in” missing or impaired connections in a child’s brain through an intensive trial and reward system. Children work one-

Looking For Love?

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on-one with a trained therapist to learn the basic components of communication. They begin with general compliance (how to sit in a chair, look at the clinician, and imitate nonverbal behavior in response to verbal commands) and then move on to verbal imitation and receptive language (how to follow one-step commands, and discriminate body parts, objects, and personal names). The approach relies on repetition and reinforcement; each correct behavior or response earns the child a consistent prize, such as a favorite food, access to a toy, or praise.

Although ABA strikes some parents as an unnatural and excessively regimented treatment, many researchers now agree that, for the most severely affected children, it is necessary to apply the most intensive strategy at the youngest possible age. As pediatric psychologist Janice Ware, the associate director of the Developmental Medicine Center at Children's Hospital, explains: "If a child is identified on the spectrum early, they're so disorganized and dysregulated in their communication system that you need to teach them to learn and listen and make eye

teraction problems, which will increase his chances of receiving an autism diagnosis. But speech and motor delays can have various etiologies, and the child may turn out to have a learning disability or a psychiatric disorder. Whether the early intervention remediated away the autism, we'll never know." Many clinicians acknowledge that they have an incentive to apply an autism label to children who may meet some but not all criteria, because under the Individuals with Disabilities Education Act (IDEA), an autism-spectrum diagnosis ensures children both early-intervention services from birth to 3 years and an appropriate educational program once they reach school age. Most psychiatric diagnoses do not carry this guarantee.

The exposure of a young child who may not be autistic to intensive behavioral, speech, and language therapies will certainly not harm the child's development. But it is important to recognize the burden that an early-intervention regimen exacts from parents. When Alison received Matthew's diagnosis, she was told that he needed a minimum of 25 hours of intensive therapy a week—the standard recommendation for PDD NOS. For the mother of an



She reoriented her life around an exhausting regimen of therapy and more therapy.

contact, and look at faces. Kids learn how to say words by watching faces." Once the most basic communication skills are in place, she says, more interactive "child-centered" techniques may enable children to acquire the higher order social and emotional skills that are lacking in autism, such as shared affect and reciprocity.

The push for early intervention has undoubtedly contributed to some degree of over-diagnosis of autism, but current thinking holds that it is better to act early than risk missing a crucial window of plasticity in the developing brain. As Ware points out, "There are a lot of kids who are getting the label now who are not going to end up on the spectrum. This doesn't mean they won't have anything. If a very young child's speech and motor skills are off, he is likely to have social in-

18-month-old child, this is a daunting prescription that requires a certain leap of faith. As *Educating Children with Autism*, a publication put out by the

National Academy of Sciences, states clearly, "There is not a simple, direct relationship between any particular current intervention and 'recovery' from autism." Alison, like many parents, chose to pursue a combination of strategies in order to optimize the odds of success. Driven by the idea that "every moment counts," she reoriented her life around an exhausting regimen of therapy and more therapy. "You become incredibly invested in the treatment," she explains. "I know moms who even put headphones on their children while they're asleep."

The race to "recover" a child from autism can put an enormous strain on a family's emotional and financial well-being. Siblings often suffer as home life begins to revolve around the affected child. Marriages fray. Two-salary households may find their incomes halved as one parent stays home to manage the

child's extensive care. Families with the resources may spend tens of thousands of dollars on private specialists, often moving to a new city or state to have access to a premier program. But the cost of failing to intervene may be even greater. A recent article in the *Archives of Pediatric Adolescent Medicine* estimates the "lifetime per capita incremental societal cost of autism" at \$3.2 million. Lost productivity and adult care constitute the largest portion of the expense.

SOLVING THE PUZZLE OF AUTISM will require close collaboration between those in the laboratory and those on the front lines of patient care. Neurogeneticists will not be able to isolate the genes involved in disorders along the spectrum without well-identified subject populations. By recognizing the often subtle combinations of symptoms within families and by recording the differential responses of patients to various treatments, clinicians can help to inform the search for distinct pathways to autistic syndromes. As genomic and brain-imaging studies begin to provide identifying markers, doctors and therapists can better tailor interventions to individual conditions, providing families with real hope based on scientifically grounded prognoses. Janice Ware refers to this evolving relationship as "an arranged marriage with great potential" and notes optimistically that "today Ph.D. and M.D. candidates are learning about autism from both perspectives right from the start."

A quarter-century ago, a diagnosis of leukemia meant a child had less than a 50 percent chance of survival. Since then researchers have identified many types of leukemia and have developed a battery of specialized treatments, leading to a cure rate of nearly 90 percent. Many in the field of autism research are hoping their work will follow a similar path, yielding an understanding of many distinct disorders with clear remedies. Huge challenges lie ahead—from teasing out combinations of genes to determining the developmental mechanisms and the role of the environment—but the necessary teams of investigators are finally in place to begin to make the connections.

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