LENGTHS TO WHICH PARENTS OF AUTISTIC KIDS WILL GO:
Quizzing junior accountants at the NIH // Scouring scientific papers // Raising millions of dollars for research // Creating a genetic database to figure out the cause—because no one else had.

You Can Hurry Science

BY ALLAN COUKELL // PHOTOGRAPHS BY MICHAEL EDWARDS

Jon Shestack remembers shouting, throwing a lamp across the room, arguing with his health insurer and "feeling like a victim." His wife, Portia Iversen, recalls an earlier moment: walking into the kitchen of their Los Angeles home to find their one-year-old son, Dov, staring at shadows on the floor, more interested in the play of light than in the sight of his mother. "'Dov seems to be slipping into his own world,'" she remembers telling her husband. "And as I said it, I got a chill."

As Dov's second birthday approached, he became increasingly withdrawn. He stopped answering to his name and lost his few words of speech. He developed repetitive flapping and rocking movements that seemed beyond his control. The formal diagnosis—"Your son is autistic"—came by phone, Shestack recalls, on the Friday of Memorial Day weekend, 1994. "There is nothing you can do," the doctor said.

Even so, Shestack and Iversen tried behavior modification, picture exchange, gluten-free diets—nothing seemed to have much effect. By the time her son was three, Iversen says, the therapists were starting to give up on him. "I was told it was unfixable, but I was given no good reason why."

She and Shestack began looking into autism research and were surprised by what they found—or didn't find. Neither knew much about science: Shestack was a Hollywood producer then starting work on the thriller *Air Force One*; Iversen was a set designer turned writer for television sitcoms. But they spent thousands of dollars retrieving articles from the University of California at Los Angeles library and contacting the few researchers in the field.

To figure out how much the government was spending on research, Shestack would rise early to telephone junior accountants at the National Institutes of Health (NIH) in Bethesda, Md., who would help him sift through the numbers. His final calculation: $5 million a year. Shestack and Iversen hired an independent research analyst who estimated the cost of autism in the United States—for drugs, doctors' visits, institutional care and related expenses—at roughly $13 billion a year. Yet despite that human and monetary toll, the disease was being all but ignored.

"I had never thought that could happen," Iversen says. "I just expected there was a system, that every disease had government funding and somebody working to cure it." Adds Shestack: "We felt the science community had utterly failed autism."

The quest is personal for Cure Autism co-founder Jon Shestack, whose daily strugg connect with 13-year-old son Dov only strengt his resolve to quicken the pace of rese

These picture cards are worth many words to Zachary London, 18, who uses them to communicate. Parents Karen and Eric founded the National Alliance for Autism Research in 1994.

Autism was first described in 1943 by Leo Kanner, a child psychiatrist at Johns Hopkins Hospital in Baltimore. Later researchers recognized the syndrome as a brain disorder covering a spectrum of diagnoses and symptoms, ranging from severe withdrawal and mental retardation to mild impairments in children who can still attend school and sometimes college. Near the high-functioning end of the spectrum is Asperger's syndrome, in which children develop language normally but have impaired social interactions. A tiny fraction of those affected develop extraordinary math, music or other skills.

Initially the illness was blamed on parents, especially "refrigerator mothers," so named because doctors considered them distant and unloving. That notion was abandoned after studies in twins showed that autism is strongly genetic. If one identical twin is autistic, there is a 90% chance the other twin will be affected by either autism or autistic traits (males make up more than three-quarters of people with autism). Among nonidentical twins, the concordance is only 10%. That makes the genetic influence in autism more powerful than it is for any other psychiatric condition.

During the 1980s and 1990s, the number of children diagnosed with autism rose alarmingly. With Dov seeming to vanish before their eyes, Shestack and Iversen were two among thousands of confused and frightened parents. They decided to launch an organization, naming it, with more than a little bravura, Cure Autism Now (CAN).

CAN caught a wave of parents who were hungry for information and ready to get involved. The group's first public meeting was booked in a Los Angeles community center with seating for 200 people; 600 showed up. A similar scenario had played out on the East Coast in 1994 when Karen and Eric London—also parents of an autistic son, Zachary—launched the National Alliance for Autism Research (NAAR) and swiftly gained parental support. After their first annual walkathon in 2000, they were overwhelmed by the payoff. Largely as a result of its walkathons, NAAR has committed nearly $30 million to autism research, and the organization's recent announcement that it intends to combine with Autism Speaks, another well-financed, parent-led group, should mean millions more in science spending.

Upon learning that Shestack and Iversen planned to start an organization, the Londons invited them to join NAAR's board. But Shestack was impatient with what he considered NAAR's overly cautious commitment to working within the scientific establishment. During lunch one day, Shestack recalls, London told him, "You can't hurry science."

"I work in the movie business," Shestack says. "I know you can hurry anything. You put more guys on the job, you spend more money. You just can't do it for free."

In its first year, CAN raised $400,000 and spent almost all of it on research grants, advocacy, education and outreach. CAN and NAAR now have annual science budgets of more than $6 million and $7 million, respectively. NAAR's early goal was to establish an autism brain bank; CAN focused on genetics. "We couldn't even define autism in those days," recalls London.

NAAR's autism tissue program began the postmortem collection of brains from autism patients and their family

members—about 100 have been amassed—so scientists can search for chemical, cellular and anatomical clues about the underlying disease. In contrast, genetics researchers work from blood samples, comparing the genes and chromosomes of patients with those of unaffected siblings and parents.

Despite the strong evidence that autism has a genetic cause, finding the genes involved has proven exceedingly difficult. Studies implicate at least 15 genes and possibly many more, though any individual patient is likely to have just a few of them. To tease apart the intricate clinical picture—a complicated genetic disease possibly triggered by environmental factors—scientists need genetic information from a large number of autistic children, their siblings and their parents. Yet during the mid-1990s, most research groups were working with relatively small amounts of data, and each group jealously guarded its findings. Shestack and Iversen set out to change that.

Their brainchild, the Autism Genetic Resource Exchange (AGRE), would find the families, have blood samples taken and arrange for clinical assessments. But the scientific community was skeptical. The initial reaction was "quite negative," says Daniel Geschwind, a neurologist CAN brought in as an adviser. The chief concern, he says, was whether a parents' organization could carry out the work with the necessary scientific rigor.

Shestack thinks the real objection was the requirement that data be freely shared. AGRE would open its files only to qualified researchers who promised to share the raw data from their analyses, rather than just the summary statistics that usually appear in scientific publications. He tells the story of a meeting at the NIH at which several established autism researchers threatened to withdraw from the field if AGRE went ahead. In response, Shestack says, he reached into his wallet for a photo of Dov. "There are 500,000 of these people," he said, passing the photo around, "and six of you. Which side do you think I should err on?"

Though it's difficult to confirm Shestack's version of the story, the confrontational approach would not be out of character. Says Clara Lajonchere, director of the AGRE program: "He will put people on the spot and might raise his voice to get the point across, but it gets people moving."

While wrangling with scientists, Shestack also lobbied on Capitol Hill for funding, and he proved adept at finding sympathetic legislators. Congress established an autism committee

Akin to Autism

A YOUNG CHILD HAS PROBLEMS SOCIALIZING, CONCENTRATING AND UNDERSTANDING LANGUAGE—IS SHE AUTISTIC? PERHAPS. BUT SHE COULD ALSO BE SUFFERING FROM ONE OF THE OTHER PERVASIVE DEVELOPMENTAL DISORDERS.

DISORDER	WHOM IT AFFECTS	HOW IT'S DEFINED	WHY IT'S NOT AUTISM
RETT'S DISORDER	While it was first believed to occur only in girls, recent studies have suggested Rett's in boys; complications begin at five months, after a period of normal growth.	Head growth slows; previously acquired hand skills diminish; or movements resembling hand-wringing and hand washing occur.	Decelerated head growth and loss of hand skills are not associated with autism.
CHILDHOOD DISINTEGRATIVE DISORDER	Studies suggest prevalence in boys; unusual behavior begins between ages three and four.	At least two of the following skill sets are lost: language, bowel and bladder control, social skills, desire to play.	Symptoms develop after two years; in autism, abnormalities are usually observed within the child's first year.
ASPERGER'S SYNDROME	Although signs are present from birth, parents generally notice them when children begin to interact with same-age children around the age of three.	Restricted, repetitive patterns of behavior focus on one topic or interest; lack of desire to establish friendships; display of higher talents, such as "adult" vocabulary.	Asperger's patients tend to amass information on narrow topics such as TV listings; early cognitive and language skills are not significantly delayed in the first few years.
ATYPICAL AUTISM	Research suggests prevalence in males, often in the profoundly retarded; symptoms manifest only after age three.	Characteristics can include impairment in social interaction, problems with communication, repetitive behavior—the three major criteria for autistic disorder.	Symptoms come close to those for clinical diagnosis of autism but arise often in severely retarded individuals; characteristics emerge later in life or individuals do not meet all three criteria.

to coordinate research efforts between various branches of the NIH. During a seven-year period, autism spending at the National Institute of Mental Health (NIMH) quadrupled.

During its first year, AGRE enrolled 100 families—a remarkably fast start. In 2002 the NIMH announced $6 million in additional funding to expand the AGRE program, and the database now stands at more than 600 families. Then, in 2003, NAAR launched the Autism Genome Project to bring together large autism gene banks from around the world, including AGREs. The initiative combines data from 1,500 families, and the sharing of raw data has become standard in the field. Yet, despite all that, a complete picture of the genetics of autism has been slow to emerge.

// Can Parents Push Too Hard?

Assiduous behind-the-scenes lobbying convinced Congress to pass the Children's Health Act of 2000, which made autism research a federal priority. How effective are patient-advocacy groups that influence legislation and research funding—and is there a downside to such lobbying?

Mary Woolley, president of the health-research advocacy group Research!America, calls patient- and parent-led groups "the most important piece of leverage" for mobilizing federal spending. But is disease advocacy a zero-sum game? When disease-specific interest groups win added resources for one condition, does another suffer? In 1993 the National Cancer Institute boosted funding for breast cancer research by $53 million and also approved increases for cervical, ovarian and prostate cancer research. To balance the budget, research for leukemia, lymphoma and several other cancers took corresponding cuts.

Jerome Kassirer, a former editor-in-chief of the *New England Journal of Medicine* and author of *On the Take: How Medicine's Complicity With Big Business Can Endanger Your Health*, says that "the squeaky wheel gets the oil...sometimes for better, sometimes for worse." He is concerned about financial links between family advocacy groups for some diseases and the companies that produce drugs to treat them. For their part, autism advocates say they will be glad of the day when the pharmaceutical industry begins to pay attention to the potential market for a treatment for the disorder.

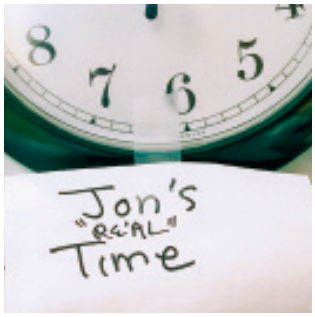
Many scientists doubt that genetic research, by itself, will ever solve the puzzle of autism. "The work so far has mainly been done on autism vs. no autism," says Gerard Schellenberg, a geneticist at the University of Washington. He thinks further progress will depend on more carefully differentiating the disorder's symptoms. Like many researchers in the field, Schellenberg suspects that autism may not be a single, narrowly defined illness but a collection of overlapping symptoms and syndromes. In that case, jumbling together the genes of 1,000 patients with "autism" might actually camouflage important genetic pathways.

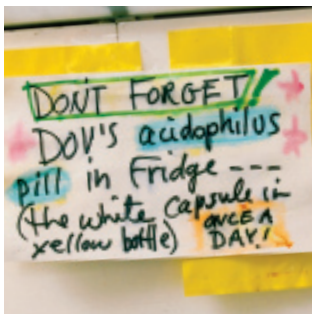
Understanding the genes, Schellenberg thinks, may depend on scientists becoming better at defining and measuring the symptoms. "So out of seven or eight genes, maybe two impact language the most. We need a better description of those language problems," Schellenberg says. Iversen agrees, and the AGRE gene bank, along with other groups, is now developing a project to more accurately define and classify the symptoms of the people whose genetic material has been collected.

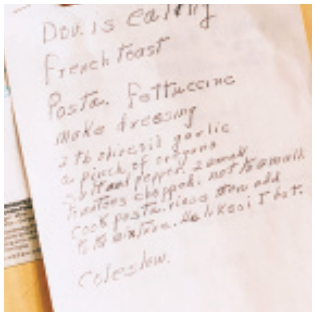
As the science of autism has grown, so has Iversen's grasp of it. In the beginning, she struggled to understand the complex technical papers she was reading. But she persevered—peppering her psychiatrist sister-in-law with questions, hiring a tutor, spending a week working in a lab, focusing on one discipline after another for months on end. Scientists have come to expect—and welcome—her calls.

Edwin Cook, a longtime autism researcher now at the University of Illinois at Chicago, recalls Iversen asking about a connection between an old finding of his and a newer one published by another group. "She's reading my papers that I've forgotten about," Cook says. Martha Herbert of the Massachusetts General Hospital (MGH) and Harvard Medical School calls Iversen a "creative out-of-the-box scientific thinker who excels at pulling together her own observations of Dov and other children with findings from across scientific disciplines."

During the 1990s, CAN was among the first to fund Herbert's studies. Using MRI scans, Herbert built on an earlier finding by Eric Courchesne at the University of California at San Diego: In 2001, Courchesne found that the brains of autism patients had an excess of white matter (nerve fibers sheathed in a kind of insulating material called myelin). The white-matter enlargement suggested for the first time where to begin looking for the missing connections afflicting children with autism; and in 2004, Herbert found that the enlargement is greatest in the outer regions of the brain. That work builds on an earlier finding by Courchesne that children who develop autism are born with slightly smaller than average heads (and hence, brains),







Reminders and instructions paper the walls of the Shestack/Iversen home. From top: the one clock in the house that isn't 15 minutes fast; a nudge for Dov's many caretakers about a dietary supplement; and a list of what Dov can and will eat.

which then grow much more quickly than normal during the first year of life.

Meanwhile, a team in Pennsylvania was taking a different approach to demonstrating connectivity problems in the brain. Nancy Minshew of the University of Pittsburgh and Marcel Just of Carnegie Mellon University compared brain scans of young "high functioning" autistic adults with those of healthy individuals with similar IQs. Examining language processing in the brain, the researchers found that people with autism had much greater activation of a region known as Wernicke's area, which is involved in understanding individual words. In contrast, Broca's area—a region involved in sentence processing—was less active. The autistic subjects were also much less able to synchronize the activity of the two regions. In experiments with other, nonlanguage tasks, the researchers saw a similar degree of impaired connections between different areas.

These findings, along with the work by Herbert, Courchesne and autism researchers in London, have led to the "underconnectivity theory," which suggests that autism could be a result of a reduced ability to coordinate long-distance processing across different regions of the brain. Intuitively, the theory helps explain the behavior of children who are obsessed with details yet unable to integrate those details into a larger whole.

The cause of the abnormalities that Herbert and Courchesne noted isn't known, but new work suggests one possibility. At Johns Hopkins Hospital, neurologist Carlos Pardo and his colleagues, scanning autopsy slides made from the brains of autism patients, noticed an inflammation in the frontal lobe and cerebellum. That could partly explain Courchesne's observation that overgrowth of the brain is not inborn but develops over time. Though the relationship is unproven, Courchesne and others speculate that brain overgrowth is a response to environmental factors that trigger an inflammatory reaction in genetically predisposed children. That inflammatory process might also offer a target for drugs aimed at slowing down or reversing the disease.

In 2004 the confluence of these distinct strands of research caught the attention of Iversen, who decided again to push the science. She called Herbert at MGH and asked her to co-chair a kind of "white-matter summit." In February 2005, 25 scientists flew to California to spend a weekend reviewing progress and working out the important questions that need to be tackled. Herbert says the process made her "feel like we are acting as a collective scientific enterprise, like we are supposed to," adding, "And the parent groups are crucial."

Shestack and Iversen didn't set out to become part of the scientific establishment, but that is where they've ended up. "We've gone from being yippies to yuppies in 10 years," says Shestack, who still questions whether they'd be more effective on the outside "chained to the balustrade."

Dov is now 13 years old. After more than a decade in which he seemed to make little progress, he has been receiving some new therapy involving rapid prompting and constant stimulation that has helped him begin to communicate through writing. Still, Shestack says, "he has a long road ahead." ■

DOSSIER

1. "Molecular Genetics of Autism Spectrum Disorder," by Jeremy Veenstra-VanderWeele and Edwin Cook, *Molecular Psychiatry*, Sept. 2004. A well-referenced overview of the search for autism genes.
2. "Why the Frontal Cortex in Autism Might Be Talking Only to Itself: Local Over-Connectivity but Long-Distance Disconnection," by Eric Courchesne and Karen Pierce, *Current Opinion in Neurobiology*, March 2005. A highly readable review that weaves together the strands of research on brain size, structure, function and pathology in autism.
3. www.cureautismnow.org/researchresources This resource page on Cure Autism Now's site provides a rundown of recent autism research and further details on the Autism Genetic Resource Exchange.