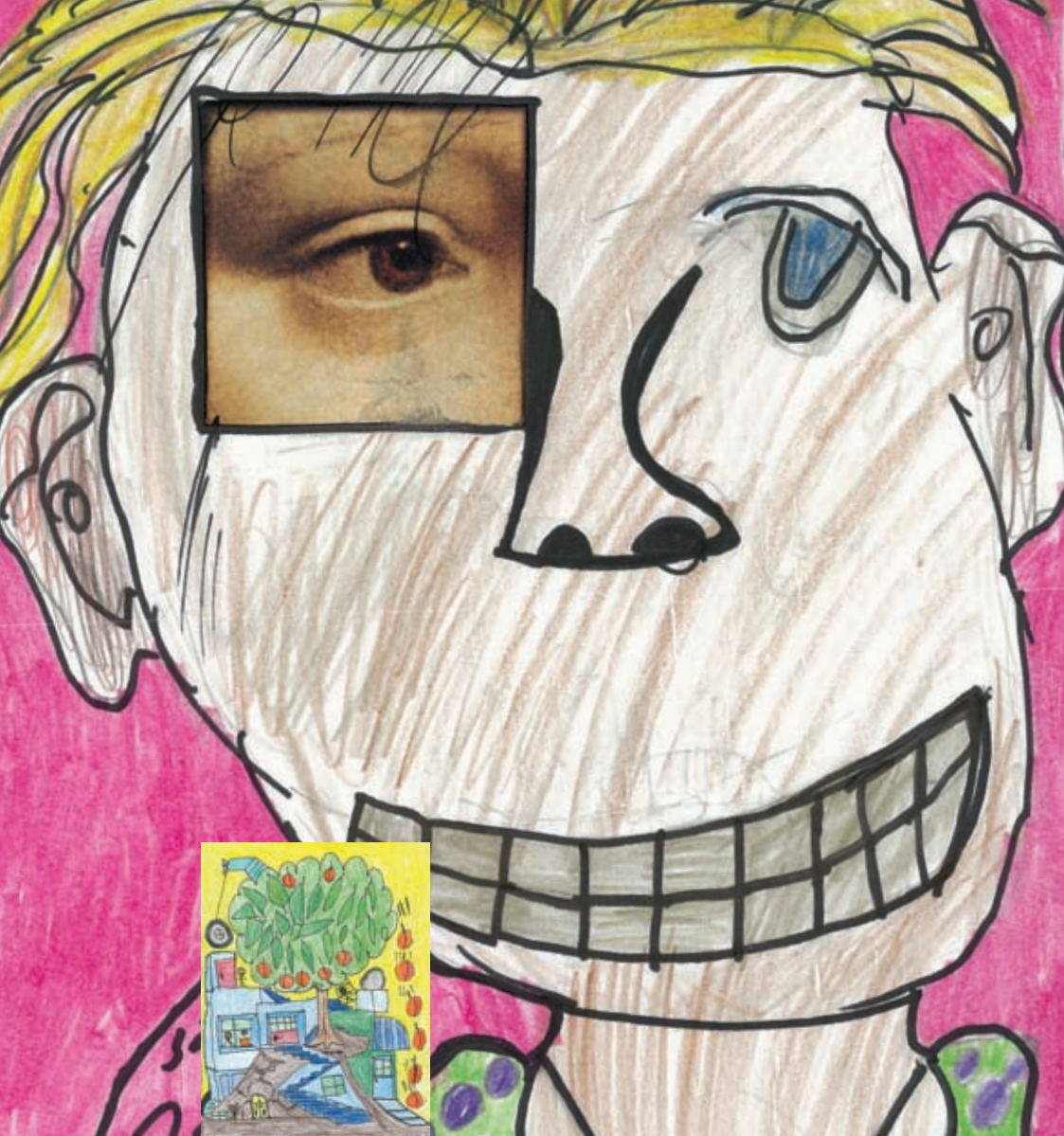


The



These paintings and drawings are part of a gallery in the Center for Autism Research, featuring art by children along the autism spectrum. Clockwise from the bottom right: "Big Heart" by Lucas Hurford, 9 years old at the time; "I Fly," Lucas Hurford; "Under the Apricot Tree," Miles Williams, 7; and "Friend," Sam Di Andrea, 12.

New Arsenal

By Martha Ledger

Photographs by Tommy Leonardi

The Center for Autism Research integrates a variety of investigative and clinical specialties to better understand and treat a complex neurological disorder. Despite much media attention in recent years, scientists acknowledge that, at present, there is no cure for autism or even a significant understanding of its causes.



Robert T. Schultz, Ph.D., is founding director of the Center for Autism Research.

You meet the children before you meet the specialists. Not in person, but through 50 or so paintings — all nicely framed, each labeled with a child's name, age, and interests. They fill the walls of a long narrow gallery that opens into the Center for Autism Research. Each work of art is a channel of communication with a kid who finds it hard or even impossible to make verbal conversation. Some talk is cheery; some somber. In one painting, the message is a whirr of color; in another, the child speaks through meticulously executed imaginary creatures. Each statement is distinctly individual.

Autism itself, more precisely called autism spectrum disorder (ASD), takes hugely varied forms. Two-thirds of autistic people have some level of mental retardation, and “some people with autism have IQs of 160 and are going to Yale,” says Robert T. Schultz, Ph.D., professor of pediatrics at Penn Medicine. Two years ago, he left Yale to become the founding director of the center, located on Market Street near the Penn campus.

What autistic children have in common, explains Schultz, are “domains of impairment,” and an autistic child can have symptoms in some or all domains. The defining symptom, perhaps, is an inability for normal social interaction. “An extreme aloneness from practically the beginning of life” is how Leo Kanner, a Johns Hopkins University psychiatrist, first characterized the disorder, in 1943. Deficits in language and communication often bolster this isolation. Autistic children may also have unnaturally restricted interests — like memorizing train schedules or calculating what day of the week any date falls on. They often exhibit repetitive behaviors — like hand-flapping or head-banging.

Kanner's scholarly publication didn't cause much stir. Nor did a paper by Hans Asperger, who in Austria in 1944 described the high-functioning form of autism that now bears his name. It wasn't until the 1970s, when Josh Greenfeld began a trilogy of books about his son Noah and the family was interviewed

on *60 Minutes*, that autism really entered public consciousness.

Nowadays, everyone has heard of it. Karl Taro Greenfeld, Josh's son and the author of the 2009 memoir *Boy Alone*, a book about being Noah's sibling, described autism as “among the most financially successful and mediagenic diseases ever.”

The buzz is partly fueled by what appears to be an increase in the prevalence of ASD. Statistics from the Centers for Disease Control and Prevention illustrate a dramatic rise across the nation. The Centers estimate an average of one in every 91 children aged 3 to 17 is being diagnosed with ASD, up from one in every 150. (Pennsylvania recently issued the final report of its autism census project, which anticipates a sharp growth in the number of residents living with ASD. That growth will make necessary increased funding and policy changes. One of the authors of the report is Penn Medicine's David S. Mandell, Sc.D., whom we will meet later.)

Unfortunately, the lion's share of attention has had little to do with evidence-



Edward S. Brodtkin, M.D., uses mouse models to study social behavior and also works with people who have social learning disorders. Here he confers with Ashley Guthrie, in the Biological Basis of Behavior program.

based medicine. Some parents whose children developed normally at first but then regressed have claimed that vaccines or their mercury preservatives caused the disorder. Properly conducted studies — and many have been done — have shown no link between vaccines or mercury and autism. Quite the contrary, after mercury was removed from vaccines, the rates of autism in carefully monitored test areas actually increased. In a series of cases known as the Omnibus Autism Proceedings, judges appointed by the U.S. Court of Federal Claims reviewed a vast amount of published scientific material, heard testimony by experts in all relevant fields, and in February 2009 rejected the claim that vaccines or mercury had caused the plaintiffs' autism.

Resources and press have also been squandered on unproven treatments whose "successes" cannot be replicated. Among

these are chelation (the chemical removal of heavy metals from the body), special diets (adding megavitamins or eliminating wheat, barley, rye, and dairy products), and assisted communication (a technique in which a helper supports the autistic child's hand over an alphabet so that the child can spell out his or her thoughts).

At present, there is no cure for autism or even a significant understanding of its causes. Genetics are known to play a role, and scientists expect that multiple genes (most of which have not yet been identified) are involved. They also think environmental factors figure into the picture, and these, too, remain unidentified.

Schultz expects that the Center for Autism Research (CAR), a merger of multi-disciplinary investigative talent from the Children's Hospital of Philadelphia (CHOP) and Penn Medicine, will be a breakthrough enterprise. It certainly

won't fail for lack of his energy. When a staff meeting and then a run across campus to advocate for a researcher's promotion cuts into our interview time, he stays after work to talk, which he does at breakneck speed. His kid calls. His wife calls. He juggles all of us handily.

Schultz organized CAR quickly. Arriving in October 2007, he had the center formally inaugurated by April of 2008. "There were tremendous strengths here," Schultz says, naming experts in neurobiology, genetics and magnetoencephalography. "What was missing was a center of gravity for those strengths," he continues, and a means of integrating research and clinical resources.

An amalgam of 15 already well-funded researchers, plus post-docs, clinicians, and staff of 34, the center now has more than \$10 million in grants on its own. According to Schultz, who, as a former president of the International Society for Autism Research, is familiar with all the strong autism programs worldwide, "We're in the top three. We've got it all going on here."

An autism specialist at Yale agrees. The center "has emerged as one of the very best interdisciplinary programs in the country," says Matthew W. State, M.D., Ph.D., associate professor of genetics and co-director of the Program on Neurogenetics at Yale University School of Medicine. "I think it sets the bar now for interdisciplinary studies of children with autism." State, a former colleague of Schultz, adds, "We were absolutely devastated to lose Bob Schultz from Yale."

The center's newly funded proposals integrate everyone's studies, and Schultz has put in place yet another vital piece of the research puzzle. "Autism is so heterogeneous that to understand its causes, you have to have big samples," he says. He wants data on 2,000 children with the disorder, and the CAR model is designed around this research need. The

center will diagnose children for free, and the diagnostic data will feed into its research protocols.

"The real power," Schultz says, "is in having the same kids you do neuropsychological testing on have the MRI, diffusion tensor imaging, magnetoencephalography, the genetic screen, and the behavioral interventions. Then you can ask, across these different kinds of measurements, what are the [points] of integration, how can we deepen our understanding of the causes and the course of autism, and how can we change that course?"

"CAR is the best possible place regionally for parents to get rigorous, state-of-the-art diagnoses for their children," he asserts. Evaluations include IQ testing, language testing, various kinds of neuroimaging, and DNA screening. Parents are matched with specially trained psychologists or social workers who explain diagnoses and go out into the schools — where most treatment for children with autism takes place — to advocate for each child's individual educational plan. Elsewhere, parents typically pay \$5,000 for a diagnosis that is much less complete and lacks the out-of-office services.

Diagnostic evaluations began in 2008, and Schultz hopes to get the center's numbers up quickly. Meanwhile, for DNA samples, geneticists at CAR have used other data banks, specifically the Center for Applied Genomics at the Children's Hospital, where CAR researcher Hakon Hakonarson, M.D., Ph.D., is director, and the Autism Genetic Resource Exchange (administered by Autism Speaks, the nation's largest autism advocacy organization), where another CAR researcher, Maja Bucan, Ph.D., professor of genetics at Penn Medicine, is chair of the steering committee.

Last year saw the publication of three significant papers in autism genetics under the joint auspices of Hakonarson and geneticist Gerard D. Schellenberg, Ph.D.,

professor of pathology and laboratory medicine at Penn Medicine. The research behind these papers was selected by *Time* Magazine as one of the Top 10 medical breakthroughs of 2009.

Two of the three were published in *Nature* online (April 28, 2009). One

Recent findings related to synapses reinforce a commonly held theory that autism is a disorder of connectivity in the brain. Brain scans show "an absence of synchronized activity across systems that should be synchronized."

identified a commonly occurring genetic variant — the first to be discovered — that confers a risk of autism. The other described 13 genetic duplications or deletions, known as copy number

variations (CNVs), that occurred more frequently in autistic people than in a healthy control group. The common variant is located on chromosome 5, between two genes that encode cell-adhesion molecules important for synapse formation and maintenance. Some of the newly found CNVs target genes that encode ubiquitins, a class of enzymes that degrade proteins in the synapse and help eliminate connections.

According to Schultz, the findings related to synapses reinforce a commonly held theory that autism is a disorder of connectivity in the brain. "If you look at fMRIs," Schultz says, "over and over again, you find an absence of synchronized activity across systems that should be synchronized." (Although dysfunctional synapses may be involved in some forms of autism, scientists also expect to find aberrations in other pathways.)

Bucan (pronounced BOOCH-n) is the first author of the third paper, which appeared in the June 2009 issue of *PLoS Genetics*. It identified 27 genomic areas in autistic people that contain rare variations not found in the general population. These are CNVs that specifically af-

According to Maja Bucan, professor of genetics, "Genetic analysis now depends on huge amounts of data" — and collaboration.



fect protein-coding parts of the genome.

Scientists originally thought they would find more common variants than rare ones. “We’re now thinking that rare variants might cause a bigger portion of autism and probably confer a lot of risk,” says Schultz. “In some cases, a rare duplication or mutation might actually be the cause of the disorder.”

CAR is now in the midst of a four-year, highly integrated study funded with \$4.7 million through the Pennsylvania Department of Health’s tobacco settlement money. With the grant, Hakonarson continues to search for common variants, Bucan for rare ones. The children being diagnosed at CAR enlarge both geneticists’ samples. The center’s children will also supply a more diverse cohort, an advantage because the recently published findings had subjects and controls of European ancestry only.

Schultz and David Mandell, an epidemiologist who serves as associate director of CAR and assistant professor in psychiatry at Penn Medicine, have already gone to work on Hakonarson’s common variant. They checked its presence against scores given to 545 autistic children for their ability to communicate, tendency toward repetitive behaviors, and social skills. According to preliminary findings, having the variant showed some relation to social dysfunction. At the same time, there was no correlation with other traits.

More precise measurements of social-information processing are needed to make this correlation useful, says Schultz. Social awareness develops as a sequence of stages, he explains. “First you have to attend to social things and be rewarded by them. Then you have to perceive the social event. You have to be able to judge non-verbal behaviors. You have to read faces and facial expressions. This allows you to build an understanding of what another person is thinking and feeling.” Schultz wants to determine if there’s a specific part of this flow that

is more correlated than others with the newly found risk factor.

Through the Department of Health grant, Mandell is characterizing the various stages of social processing by tracking the eye movements of autistic children as they watch social interactions in videos and through other studies. He’s also developing more refined measures for repetitive behaviors and language processing. If scientists can reliably match dysfunctional behaviors to genetic variants, children can be screened early on and get the behavioral interventions they need most.

“Parents of autistic children were desperate for their kids to get intensive, behavioral interventions.” Such training breaks down complex actions into small parts and rewards the children when they master each part.

Mandell entered autism research about eight years ago when the City of Philadelphia requested a review of its mental health expenditures. Officials wanted to know why some children were costing hundreds of thousands of dollars a year. Half of the most expensive 100 children, he discovered, had diagnoses of autism.

“I did what I’d never yet done during my research career,” Mandell recalls. “I got out from behind my computer and talked to families.” He found them qualitatively different from families who are dealing with other psychiatric disorders. “Parents of autistic children were desper-

ate for their kids to get intensive, behavioral interventions,” he says. This training, which breaks down complex actions into small parts and rewards mastery of each part, is the current standard of care for autistic children.

Here’s how it works. An intervention that helps develop a response to language might consist of a trainer placing four pictures of different animals on the table and asking the child to pick out the elephant. “The child doesn’t care about the picture,” Mandell explains, “but he does care about the bag of M&Ms that the trainer is holding. The trainer first gets the child to sit in a chair and rewards this behavior with an M&M. Next the child will be rewarded for paying attention to the activity. There’s another M&M for picking out the picture of the elephant, and another for handing it over. The reward might be praise or high fives or being tickled. Part of the challenge for the trainer is finding the right reinforcement for each child.” Interventions for a multitude of deficits can involve 25 to 30 hours a week of one-on-one work.

Mandell, whose CAR office overlooks a slice of Philadelphia and whose shelves are cheerfully decorated with *Where the Wild Things Are* sculptures, a Miss Piggy diorama, and a pyramid of Play Doh containers, is now studying how behavioral interventions are delivered in the special-education classrooms of Philadelphia’s public schools. Called the Autism Instructional Methods Survey (AIMS), it is the largest randomized study of behavioral interventions ever done. Two curricula are being tested in 52 classrooms, kindergarten through second grade. But beyond that, Mandell is tracking what kinds of support teachers need to use these specialized curricula productively.

“Traditionally,” he explains, “we develop and test curricula in university settings with state-of-the-art clinicians – and, not surprisingly, they work.” They

tend to work less well or not at all in real classrooms, he adds. Mandell hopes to change this pattern through system-wide teacher training, continuing support for teachers, and the development of a core of trainers within the public school system who will keep the program going after the research project is completed.

Mandell plans to have 100 children from AIMS also participate in some of CAR's research protocols. They would join children who are diagnosed at the center in getting DNA screening and brain imaging. "Typically, only 50 percent of autistic children improve their ability to communicate and interact socially as a result of behavioral interventions," he says. DNA screening could help pinpoint which risk variants the children are more likely to overcome. Imaging could provide answers to some basic science questions about the workings of the brain.

Imaging is Schultz's area of expertise. Through structural MRIs, researchers have found that the autistic brain is about 5 percent larger than a typically developing brain and that the increase begins at 12 month of age – exactly when symptoms of autism first appear. Using functional MRIs, Schultz has found another significant difference. During fMRIs, as typically developing children identify faces or facial expressions, their brains show activation in the amygdala and fusiform gyrus. Face identification produces little or no activation in these areas in autistic children, although they show normal activation in tests requiring the identification of objects.

Schultz's working model is that autistic children probably have a deficit in the amygdala-fusiform gyrus network. The amygdala alerts you that something is socially or emotionally important and that you should pay attention to it. It tells the fusiform gyrus through feedback-feedforward connections to process what you're seeing at some deeper level. "It's what lets



David Mandell, Sc.D., is studying how behavioral interventions are delivered in the special-education classrooms of Philadelphia's public schools.

typically developing kids become experts in people," he says, "whereas kids with autism might become experts in train schedules or calendar calculations."

Schultz posits an important role, as well, for the frontal lobes that plan, organize, and inhibit impulses, because this part of the brain has a lot of connections to the areas that are underactive in autistic people. If training in face identification and facial expression makes the amygdala and fusiform gyrus more active, he thinks it might be because the frontal lobes are managing them better. As he puts it, "If it were just underperforming areas getting better, it begs the question of why they were underperforming in the first place." Schultz anticipates that imaging AIMS children before and after a year of behavioral interventions will give him an exceptional window into compensatory cerebral processes.

Other insights into autism will come from animal models. CAR researcher Edward S. Brodtkin, M.D., assistant professor of psychiatry, has been studying social behaviors in an inbred mouse strain (BALB/cJ) that is characteristically not very social. "It's not an autistic mouse," Brodtkin explains in a sleek laboratory building on the new eastern front of Penn's campus, his office window filled by a colorful mu-

ral on a nearby building. "It just exhibits a natural variation in social behavior. Whatever is causing its lack of sociability," he says, "could have nothing to do with any ASD, or it could have something to do with a small subset of it."

Brodtkin, whose speech is simultaneously keen and calm, thinks of all social interaction as a double-edged sword — sometimes rewarding, sometimes anxiety-provoking — and suggests that perhaps the balance in autism spectrum disorder is tilted away from reward and more toward aversion. "If we break things down this way," he says, "we can start to model some of it in mice and get a better understanding of the neurobiological circuitry involved."

Under the Department of Health grant, Brodtkin and Ted Abel, Ph.D., professor of biology and CAR researcher, are studying brain and behavior development in mice with mutations in the area of the newly found common variant.

Unlike Alzheimer's disease, where many brain banks can supply tissue samples, there is very little human tissue available for neuropathological studies of autism. The disorder is diagnosed in childhood, and the children grow up and live out a normal life span. Animal



Robert Schultz demonstrates a mock MRI that helps children on the autistic spectrum become used to such scanning devices. With him is Janelle Letzen, a research assistant.

models offer a unique opportunity to study related brain tissue at a molecular and cellular level, allowing scientists, for example, to actually look at the structure of a malfunctioning synapse.

Brodtkin's work with Penn Medicine's Adult Social Learning Disorders program keeps him people-oriented. It also makes him a special advocate for those with Asperger's syndrome whom the program serves, and who, he points out, don't think of themselves as needing to be cured. "We're not just trying to find the gene and fix them," he says. "We want to be able to help them with the things they want to be helped with. And if we can get to the root of the problem, we'll be in a better position to help."

CAR is coming at "the problem" in a collaborative way, because there is no other meaningful way. Schultz: "Science is more complicated than it ever was. The questions that we're asking now are deeper questions. And I think we're all recognizing the value of multidisciplinary research, because it's wholly impossible for any one person to be a geneticist, a neuroimager, an expert clinician, and an epidemiologist."

As a geneticist, Bucan has long considered collaborations a necessity in her own work, which she explains to me on a "not normal day" in the south part of campus that is home to most of Penn's biomedical research. She works with mice models as well as the human genome and had been called that morning to the animal facility to do an emergency cleanup. "No one else knew how," she says. A very professional-looking black suit hangs on a peg in her office, but she's in work clothes, a tad flushed from rushing back to meet me. This same morning, a station in her lab had sprung a leak, and two burly maintenance workers have now sealed it and are vacuuming the area.

"Genetic analysis now depends on huge amounts of data," she explains, wholly focused on the interview, "and this requires new methods, which the statistical geneticists and computational biologists have developed for us, and huge data bases, which the computer science department across the street helps us with."

That there could be even deeper collaboration was just a wish of hers in 2006, when she, Brodtkin, Abel, Timothy P.

Roberts, Ph.D. (professor of radiology at Penn Medicine and vice chair of research in radiology at CHOP), and Anthony Rostain, M.D., M.A. (professor of psychiatry) organized a retreat on autism for the PENN/CHOP community. According to the program, their goal was "to assess the standing of our institutions [and] our potential for organizing new collaborative initiatives." Mandell was among several PENN/CHOP presenters. Schultz was one of the invited speakers.

The Allerton Foundation had just funded a chair at CHOP dedicated to autism research, and it was suddenly possible to recruit a basic scientist and develop a center. "By getting together, it was easier to recruit Bob Schultz," Bucan says. "My sense was it's better to come to the place where colleagues are already willing to collaborate."

She had great intuition, but there's also something resolute about Maja Bucan that helps make things happen.

On another "not normal day" just three weeks earlier, she was on a train to New York. She'd just submitted a grant proposal for which, she tells me, "I read every article ever written on autism." The man sitting next to her — "incredibly" — began reading an article about autism on his laptop, and Bucan immediately realized that she had never seen this article before. When she asked if he could send it to her, he said he had written it and she would find it in *Time* magazine in just two days.

The man was Karl Taro Greenfeld, Noah's sibling, who was traveling to various cities on a book tour for *Boy Alone*. They talked, and long before they reached New York, Greenfeld perceived how passionate Bucan is about her work. He inscribed a gift copy of his book for her, writing, "To Maja, Keep Faith."

It's a good bet that she will — that they all will. ♥