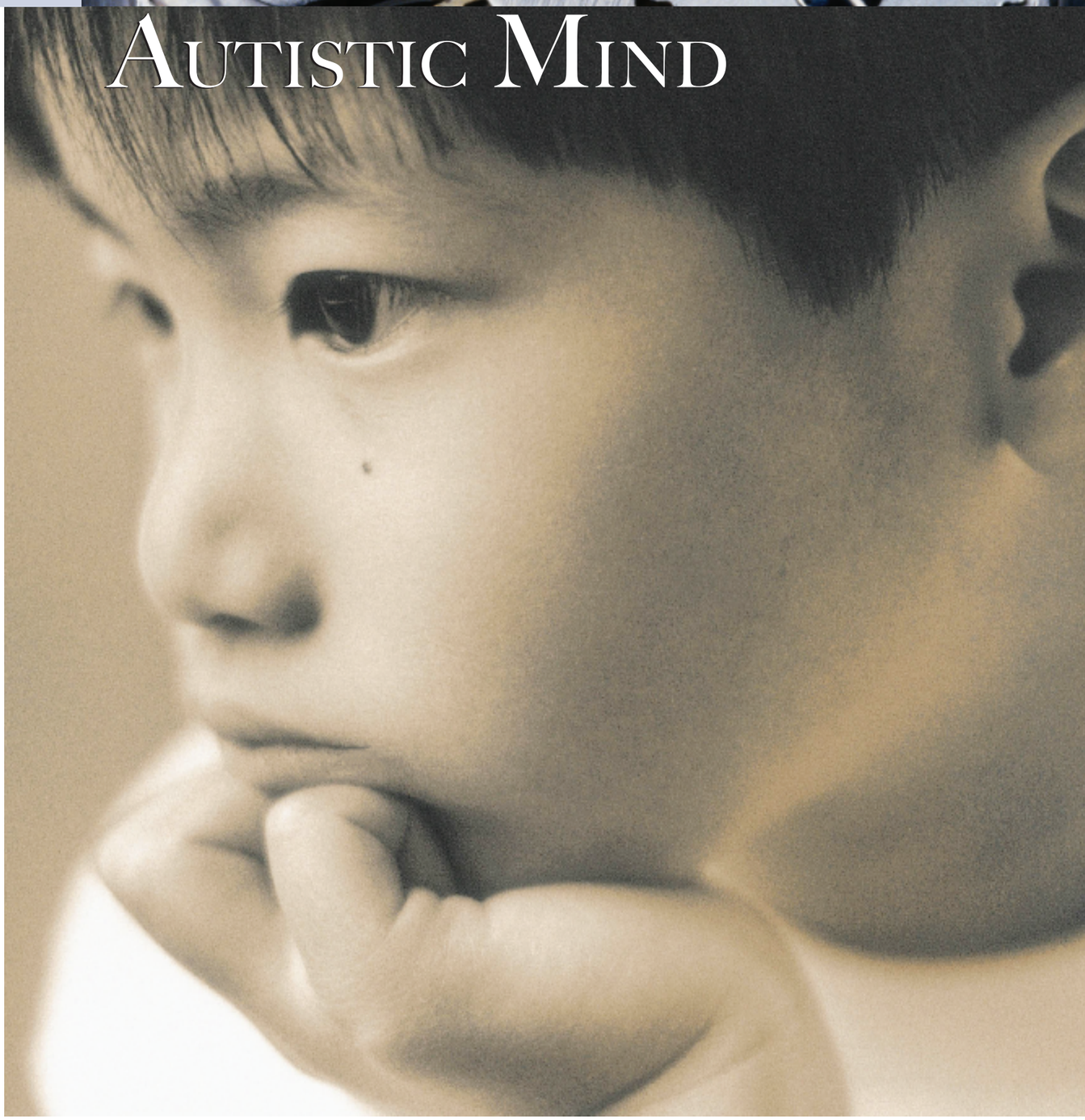
Inner Workings *of* the Autistic Mind



Researchers and clinicians at UT Southwestern are identifying which mechanisms of the brain are affected by autism and how to implement new therapies to treat the disorder.

As an infant, it seemed Jon Heighten would follow the same path as his three older sisters.

The only son of Drs. Clay Heighten and Debra Caudy, Jon had taken his first steps and said his first words.

Then the progress stopped.

"He wasn't advancing normally," said Dr. Heighten, who specializes in internal medicine. "One day there was no 'Mommy' or 'Daddy,' and it became apparent something wasn't right. At first we thought he might be deaf because he wouldn't turn around when we called out directly behind him."

After a visit to his pediatrician, Jon was referred to a specialist who conducted a series of tests. The findings revealed a devastating diagnosis, one that took his parents' breath away.

Jon was autistic.

"Autism creates a new reality. The future you hoped your child would have is gone. It simply no longer exists," Dr. Heighten said. "As parents we had to accept and cope with the facts. Ironically, in the beginning, my wife and I knew nothing about autism, even though we'd both been to medical school."

By Erin Prather Stafford

Drs. Debra Caudy and Clay Heighten and their son, Jon

Drs. Heighten and Caudy quickly immersed themselves in literature and resources on the disease. Dr. Caudy left her successful career as an oncologist and faculty member at UT Southwestern Medical Center to focus on Jon's education and therapy.

"There are many myths and misconceptions about this disease," Dr. Caudy said. "Because there is no cure, parents are willing to explore fad treatments. As physicians, my husband and I screen out disapproved or nonscientific therapies, but as parents we understand the urgency to find new beneficial treatments to help our autistic child. Right now there are more questions than answers."

Wide Span of Conditions and Symptoms

Autism is a neurological disorder that affects development in areas of social interaction and communication skills. It typically manifests in early childhood, and four times as many males as females are affected. Recent data from the Centers for Disease Control and Prevention estimate about one in 150 U.S. children have autism.

"It is a devastating condition that develops in roughly 0.5 percent to 1 percent of the population," said Dr. Eric Nestler, chairman of psychiatry at UT Southwestern and holder of the Lou and Ellen McGinley Distinguished Chair in Psychiatric Research. "The toll it takes on individuals and their families is enormous, yet we still know relatively little about what causes autism, and treatments remain very limited."

Dr. Catherine Karni, assistant professor of psychiatry at UT Southwestern and medical director of the Center for Pediatric Psychiatry at Children's Medical Center Dallas, said even diagnosing the disorder can be difficult. Autism spectrum disorders cover a wide span of conditions and symptoms, from severe mental retardation to mild social impairment. It wasn't until 1980 that autism became an official clinical diagnosis, separate from childhood schizophrenia or retardation.

Patients often display a distinctive pattern of symptoms rather than just one. The main characteristics are impairments in social interaction, impairments in communication, restricted interests and repetitive behavior. Parents are usually the first to notice the unusual behaviors, while pediatricians initially hear their concerns.

"A pediatrician will document the developmental history while physically examining the child," Dr. Karni said. "If the parents' concerns are warranted, the pediatrician will refer the child to specialists to determine what is happening."

Dr. Karni, who also oversees the autism clinic at Children's, stresses that early intervention is crucial for the treatment of autistic children. At the clinic, patients are examined by a psychologist, psychiatrist and speech therapist before any conclusions are drawn. Following diagnosis, the family is counseled by staff on what treatment options are available. Treatment and therapy at the clinic are provided for children 2 to 5 years old.

"Autism cannot be diagnosed with a simple diagnostic test," Dr. Karni said. "Having a team of specialists conduct screening tests means there is a better chance for children to be diagnosed correctly and for the right treatments to be enacted immediately. Many parents take their child to a pediatrician because the child is not talking. But there are many possibilities for this behavior. Autism is only one."

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Peter and Joanna Townsend are acutely aware of how important it is for an autistic child to be diagnosed early and correctly. The Townsends, who have two autistic grandsons, 12-year-old Nick and 11-year-old Pete, recall how frustrating and stressful it was for their daughter, Pamela Mandt, to get an evaluation of her two sons, who were displaying developmental problems.

"It's no secret; diagnosis is difficult," Mr. Townsend said. "Nick was diagnosed at age 2 as being on the autism spectrum. Almost two years later, Pete began showing development issues, but his symptoms were different from Nick's. Pamela had to take each child from doctor to doctor before autism was diagnosed. Unfortunately, diagnosis is only the beginning. Parents and families are often left to fend for themselves in developing a treatment and therapy plan that allows an autistic child to achieve his or her potential."

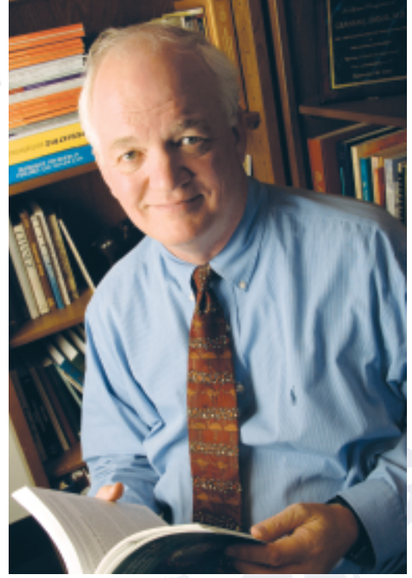
Dr. Graham Emslie, professor of psychiatry and head of child and adolescent psychiatry at UT Southwestern, said his department hopes to expand autism services.

"We currently have a specialized autism program that provides multidisciplinary diagnostic services to preschool children. We also offer psychological assessments and psychiatric services to children with autism spectrum disorders in all groups. In collaboration with UT Dallas' Callier Center and Center for Brain Health, as well as with Children's Medical Center, we are working toward developing comprehensive integrated services that will allow for coordinated care for children with autism from age 12 months to 18 years," said Dr. Emslie, holder of the Charles E. and Sarah M. Seay Chair in Child Psychiatry. "We want the program to be a recognized place where families come to obtain an accurate diagnosis and assistance in finding the appropriate treatments for their child. We also want it to serve as a link between the extensive research occurring at UT Southwestern and autistic patients who might benefit from cutting-edge studies."

Existing medications can improve a patient's attention and reduce agitation and aggression, while special schooling can optimize the patient's functioning. Still, improvements in most individuals are modest.

"Finding out why this disease occurs has to happen. There is no reason medicine cannot have the same success with autism that it's had with childhood cancer," Dr. Heighten said.

Dr. Nestler said, "Our goal at UT Southwestern is to expand clinical and research efforts in autism at the medical center, which will span multiple departments and range from the autism clinic to clinical research in autism to fundamental research into the neurobiological and genetic causes of this illness."



Clues to the Mystery

Researchers at UT Southwestern hope that breakthroughs in genetics and neurobiology will one day lead to dramatic improvements in the diagnosis and treatment of autism. Many scientists are working to identify the genes linked to autism, while others are exploring how autistic brains differ from those unaffected by this condition.

In 2006 Dr. Luis Parada, chairman of developmental biology and director of the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration, discovered that deleting the gene *Pten* in certain parts of the brain created mice that displayed deficits in social interactions similar to humans with autism disorders. *Pten* genes control the size and functioning of nerve cells. Previous research had found that some people with autism also had mutated *Pten* genes, but it was unclear if this caused symptoms of the disease.

To test that hypothesis, Dr. Parada and his research team deleted the gene in the front of the mice's brains and in areas of the hippocampus, a structure involved in memory and other functions.

"The exciting thing about this mouse is it helps us zero in on at least one anatomic location of abnormality, because we targeted the gene to very circumscribed regions of the brain," he said. "In diseases where virtually nothing is known, any inroad that gets into at least the right cell or the right biochemical pathway is very important."

Dr. Parada, who holds the Diana K. and Richard C. Strauss Distinguished Chair in Developmental Biology and the Southwestern Ball Distinguished Chair in Nerve Regeneration Research, said mice are social animals and good models for autism research. The altered mice's brains were noticeably different in the areas where the gene was deleted. The nerve cells were thicker than normal and had a higher-than-normal number of connections to other nerve cells. Dr. Parada suspects this may explain the sensory overload people with autism are believed to experience.

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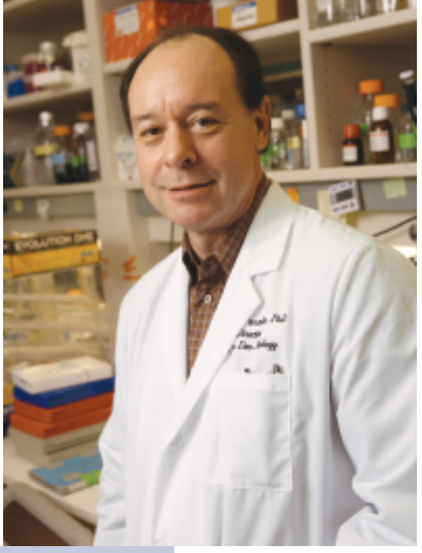

DR. LUIS PARADA

"It would be really exciting if it turned out that we've zeroed in on the anatomical regions where things go wrong in autistic patients, regardless of how the autism occurs," he said, adding that the next step will be to treat the mice with drugs to see whether it's possible to reverse the condition.

Dr. Lisa Monteggia, assistant professor of psychiatry, is studying how a gene called *MeCP2* mediates autistic-like behavior in mice. Mutations in *MeCP2*, which result in loss of function of the gene, occur in a developmental disorder called Rett syndrome, a human disease that shares many clinical features with autism. Mutations in *MeCP2* genes also have been identified in people with autism.

In a recent study, Dr. Monteggia found that mice lacking the *MeCP2* gene in specific brain regions exhibit deficits in social interaction, increased anxiety-like behavior, and alterations in certain forms of learning and memory, recapitulating aspects of Rett syndrome and autism. These studies have started to provide a framework of the neural circuitry that is involved in mediating aspects of the disorder and set the stage for future research.

Through collaboration with Dr. Ege Kavalali, associate professor of neuroscience and physiology, Dr. Monteggia also has found that neural activity in the mouse brain is limited by an imbalance between excitatory and inhibitory neural connectivity in neurons lacking *MeCP2*. Scientists have hypothesized that such an imbalance in nerve transmission is a feature of human autistic disorders. Drs. Monteggia and Kavalali's research was some of the first to demonstrate this imbalance, and they are working to elucidate the reasons behind it.

Separate research by Dr. Kavalali in collaboration with Dr. Thomas Südhof, chairman of neuroscience and director of the Gill Center for Research on Brain Cell Communication and the C. Vincent Prothro Center for Research in Basic Neuroscience, further exposed the role of an imbalance of excitatory and inhibitory nerve connections as a potential basis of autism spectrum disorders. Two proteins, called NL-1 and NL-2, control the strength and balance of nerve-cell connections. One protein increases the excitability of nerve cells, while the other inhibits cell activity. The proteins were discovered by Dr. Südhof and colleagues at UT Southwestern a decade ago, but their function had been unclear.

"Mutations in these proteins have recently been linked to certain varieties of autism," Dr. Kavalali said. "This work provides clear insight into how the proteins function. We can never design a therapeutic strategy without knowing what these mutations do."

Dr. Südhof recently discovered that mice containing a mutated human gene implicated in autism exhibit poor social skills but increased intelligence akin to the title character's traits in the movie "Rain Man."

Dr. Südhof, a Howard Hughes Medical Institute investigator at UT Southwestern, and his research team used genetic engineering techniques to introduce a mutated human form of the neuroligin-3 molecule into the mice. They then tested the animals' social interactions by exposing them to an unfamiliar mouse in a cage. The genetically engineered mice spent less time near the strange mouse than their normal littermates and preferred to spend time with inanimate objects.

The altered mice were significantly better than normal, though, at learning a water maze, in which they had to find and learn the location of an underwater platform. They also were better at relearning a new position of the platform after it was moved.

"When you manipulate a brain, you usually don't improve it," Dr. Südhof said. "The fact that we got an improvement is very good. It shows we're changing something specific; we're affecting how the brain processes information."

Other tests of coordination, anxiety and motor ability showed normal results, indicating that the changes in brain activity were specific, Dr. Südhof said.

The researchers also studied the patterns of electrical activity in the brain. Nerve cells from the genetically engineered mice showed a significantly greater inhibitory action than their normal littermates, even though only about 10 percent of the normal amount of neuroligin-3 was present. The results indicate that focusing on inhibitory action might be a way to treat autistic behaviors, said Dr. Südhof, holder of the Gill Distinguished Chair in Neuroscience Research and the Loyd B. Sands Distinguished Chair in Neuroscience.

Dr. Greg Allen, assistant professor of psychiatry, is delving into a different area. His investigation explores the cerebellum and how dysfunction of this brain structure could relate to autism. Located at the base of the brain, the cerebellum had long been thought to be involved only in motor coordination.

"The traditional view of the cerebellum is that it is a structure that helps a person coordinate movement," Dr. Allen said. "Because motor skills are not part of the conventional autism diagnosis, early findings of cerebellar abnormalities in autism were not widely accepted as being relevant to the disorder. My previous work using magnetic resonance imaging showed that the cerebellum actually functions differently in individuals with autism, and we now know that the functional role of the cerebellum extends well beyond motor coordination to include language and aspects of social interaction. Thus, understanding the role of the cerebellum in autism is now thought to be a crucial aspect of understanding the brain basis of this disorder."

Advances in brain imaging make it possible to examine regions of the brain that function abnormally in autism. Dr. Allen is currently developing studies to look at how changes in the cerebellum might affect the way brain regions connect during development and how the occurrence of abnormal cerebellar connections might impact autistic behavior and symptoms. He believes such investigations will lay a foundation for larger studies examining the cerebellum's role in the disorder.

"MRI anatomic studies have shown that the cerebellum is the most consistent site of brain abnormality in autism. It's not only important, but essential, that we increase our understanding of this particular brain structure," he said.

Hope for a Better Future

The research at UT Southwestern gives hope to families like the Townsends and Drs. Caudy and Heighten. Although autism emerges in childhood, it's not simply a childhood disorder. Autistic children often have a normal life span, and families cope with the costly disability for decades.

"Autism has an enormous impact on society," Dr. Heighten said. "Jon is unlucky to be autistic, but he is fortunate to be part of a family with the resources to care for him. There are thousands of families worldwide who struggle both emotionally and financially to care for their autistic child."

In their quest to help, Drs. Caudy and Heighten have created a nonprofit organization, designated "BRAINS," with the mission to raise funds for autism research specifically at UT Southwestern. "BRAINS" is an acronym for "Benefiting Research for Autism Investigators Now at UT Southwestern."

"We feel UT Southwestern has the talents and capability of making a meaningful contribution to understanding autism," Dr. Caudy said. "This type of research is essential if autistic children hope to have a better future than what they currently face."

In 2006 Drs. Caudy and Heighten pledged $750,000 to UT Southwestern to initiate the Endowed Scholars Program in Autism Spectrum Disorders. In 2007 the Townsends also pledged $750,000 for the program, which is designed to provide start-up research support for four years to bright young researchers investigating the causes, diagnosis and treatment of the neurological disorder.

Additional gifts are being sought from other donors to create a $6 million endowment for the program, which is the first step in the creation of a Comprehensive Clinical and Research Center in Autism Spectrum Disorders at the medical center.

"One of the most important reasons we decided to invest in autism research at UT Southwestern is the long-standing tradition the school has of integrating different disciplines," Mr. Townsend said. "Only by bringing together the knowledge of these different disciplines will we get a better understanding of autism and its possible cures."

Both couples are optimistic that collaborations between top researchers focused on autism, combined with the clinical expertise available at UT Southwestern, will lead to an understanding of the causes of the disorder and result in better treatments and prevention.

"Our hope is that UT Southwestern will become one of the great leaders in the field of autism research," Mr. Townsend said.

Dr. Caudy acknowledges that many parents have asked why she and Dr. Heighten chose to invest in finding the root of autism instead of improving how to treat it.

"We looked at making donations to existing organizations, but felt a lot of the money was being used on projects that didn't have merit," she said. "Clay and I wanted to invest in science and get down to the basics of this disorder. UT Southwestern is a good investment. The researchers supported by the Scholars Program may not find the penicillin growing in the mold, but they might be the ones to discover clues leading to a breakthrough discovery.

"It's our dream that by the time Jon reaches adulthood, autism will no longer be this grave mystery."

For more information on autism treatment, please call 214-456-5900, or visit www.utsouthwestern.org/patientcare/medicalservices/pediatrics.html.

"Our hope is that UT Southwestern will become one of the great leaders in the field of autism research." —Peter Townsend, with Joanna Townsend, his daughter Pamela Mandt (rear), and grandsons Nick (right) and Pete Mandt