AUTUMN 03

Lens

A New Way of Looking at **Science**

Understanding the tumultuous brain

How research is breaking through the mystery of mental disorders

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Lens –
A New Way of Looking
at **Science**

AUTUMN 2003

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The visions we offer our children shape the future.

– CARL SAGAN

About the cover: Advances in genetics, brain imaging and animal models are breaking through the mysteries that cloud our understanding of brain disorders. The research is providing new hope for people whose disrupted brain function impedes their ability to communicate, learn and participate fully in society.

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A professor of Pharmacology, Dr. Levitt studies the molecular and developmental basis of neuropsychiatric disorders.

Nature *and* nurture

By Pat R. Levitt, Ph.D.

Director
Vanderbilt Kennedy Center for Research on Human Development

Nothing, perhaps, in biology better illustrates the interaction between "nature" and "nurture" better than the development and functioning of the brain.

Early experiences, both in the womb and after birth, can have profound effects on the way in which genes and their protein products orchestrate the formation of circuits that control our mood, our ability to endure stress, our thought processes, our ability to learn new information, and our recall of important memories. It is the combination of these forces – genetic and environmental – that underlies the development of devastating brain disorders such as schizophrenia and autism, and functionally milder ones such as attention deficit hyperactivity disorder (ADHD).

While I have been studying some aspect of brain development since my college days, I began the process of integrating nature and nurture in 1986, after a visit to the intensive care nursery at the Medical College of Pennsylvania, where I was a young assistant professor. My colleagues wanted me to get involved in a new research project to study the effects of prenatal exposure to cocaine on brain development. I resisted; drug exposure research would only distract me from my mission of finding and describing neurodevelopment genes. Well, the images of the infants, struggling in a new world, possibly carrying the legacy of an altered wiring diagram for the rest of their lives, was more powerful than I had imagined.

I began a new scientific journey, transforming my own laboratory into one in which we became more and more engaged in multidisciplinary efforts with other scientists to investigate the interaction of genetic and environmental factors in the developing brain, how genetic susceptibility translates into disorders, and how intervention can alter the course of development to improve outcomes.

Donald Hebb, who proposed our modern view of the biological mechanism of learning and memory in the 1940s, once made the analogy that the debate about whether nature or nurture is more influential on brain development and functioning is like arguing about whether the length or the width of a rectangle is more relevant in determining its area. Like the rectangle, the trick regarding brain development is to determine how nature and nurture interact to influence the emerging properties of developing brain systems.

If genes were the sole force in brain development, it would be difficult to explain the profound difference between the mind of human beings and the nervous system of the worm, *C. elegans*, which

Pictured below: Fluorescence microscope image of neurons (nerve cells) in the cerebral cortex, or outer portion of the brain, which is involved in conscious experience, including perception, emotion, thought and language. The round center of each neuron represents the cell body, and the extensions are the dendrites that receive connections from other neurons. The neurons are colored with different dyes.

Courtesy of
Gregg Stanwood and
Pat R. Levitt,
Vanderbilt University.

serves as a model system for studies of the development of neuronal "wiring." The worm has 19,000 genes, only about 11,000 fewer than human beings, yet the 302 neurons of the worm are far outnumbered by the trillions of nerve cells in the human brain.

What, beyond the sheer number of genes, could explain the quantum leap in neurobiological complexity between a human being and a worm? One key lies in how these genes are "packaged" in human versus worm nuclei. The human genome includes long stretches of non-coding DNA that regulate gene expression cell to cell. This extra genetic material provides an organized, highly complex and flexible molecular network capable of driving the computational genius of human brain circuitry, and capable of responding to extrinsic cues (sounds, sights, touch, food, light, drugs, toxins, cruelty, abuse) perhaps in a more limitless fashion than in simpler species.

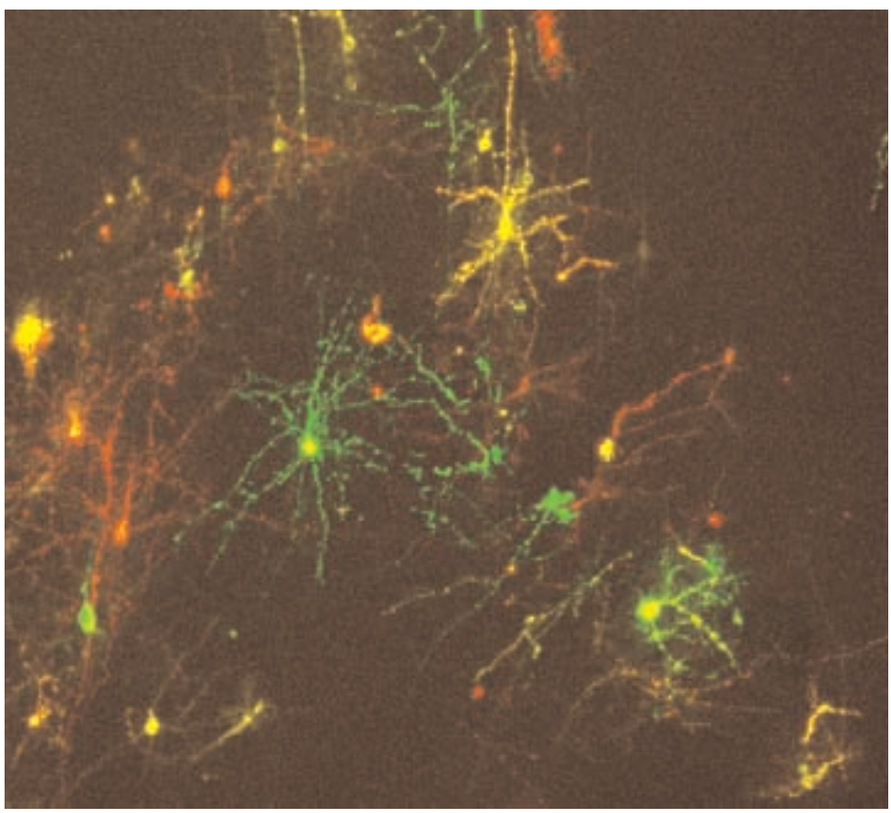
One year ago, the opportunity to build new research relationships led me from the University of Pittsburgh, where I was chair of the Department of Neurobiology, to Nashville to direct the Vanderbilt Kennedy Center for Research on Human Development. The center has a rich history of embracing interdisciplinary approaches to study brain disorders. Nicholas Hobbs, Lloyd Dunn, Susan Gray and their colleagues at the Peabody College believed that they could create assessment tools to describe better the nature of a particular brain disorder and through this improved characterization, develop cutting-edge strategies for intervention and treatment. These visionaries imagined the possibilities of doing bio-behavioral research and intervention at a time when technologies had not caught up with their imaginations.

Today, scientists here have at their disposal an armamentarium of tools capable of describing the clinical and genetic details of neurodevelopmental disorders like autism, literally peering into the brain of an individual with schizophrenia, or hunting for single base changes among billions of DNA molecules, which could correlate with increased risk of ADHD.

We at the Vanderbilt Kennedy Center are attempting to take advantage both of our history and the recent technology revolutions that have brought tools to assess our genome, or to view the brain in action, monitoring both with high temporal and spatial resolution. We're creating more opportunities for clinician-scientists, basic scientists and interventionists to co-habitate, in a sense, to interact at a level at which a common problem of great interest to each scientist serves as the basis for launching multidisciplinary research, training and educating.

Imagine the possibilities for discovery as brain imagers, geneticists, basic developmental neuroscientists and neurophysiologists sit together with developmental and clinical psychologists, psychiatrists and neurologists, special educators and interventionists. Imagine faculty in special education working with the tools of modern brain imaging or with the sophisticated molecular methods of human genetics to solve the mysteries of cognitive or behavioral disorders in children. Imagine a mouse neurobiologist attending an autism clinic to gain a better sense of the fine details of social dysfunction in an attempt to produce a better model in the laboratory.

Can we imagine that this is what Donald Hebb had in mind when he was trying to unravel the mysteries of the human learning machine? We're not debating nature versus nurture; we're embracing them both, and indeed, doing it very well at Vanderbilt. **LENS**



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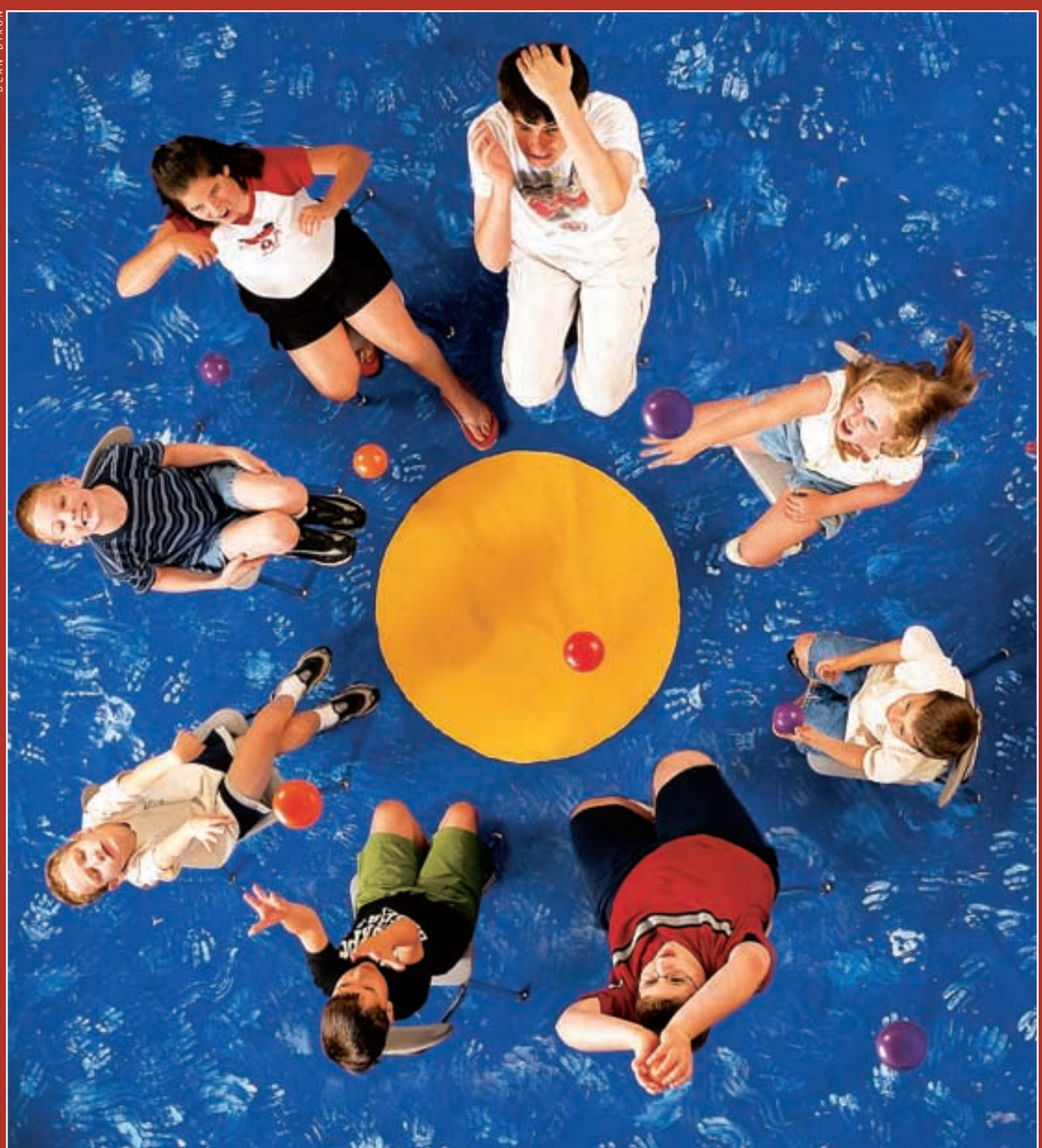

MORE THAN ONE BALL IN THE AIR

Paths to new treatments for autism

BY LEIGH MACMILLAN

Eighteen-month-old Morgan Vice scrambled up onto the table. Before her mother could get to her, she was airborne, shouting, "I can fly, I can fly." Landing in a crumpled heap, she quavered, "I cannot fly."

That was Morgan eight years ago – vivacious, engaged, talkative. Then something went wrong.

"She just stopped looking at me," her mother, Tammy Vice, recalls. "She started echoing back words instead of saying things on her own. It was like something was taking her away, and we didn't have any idea what it was."

More than a year and seven professionals later, that "something" got a name. "By then we already knew," Vice says. Morgan had autism. Her official diagnosis is Asperger disorder, one of five developmental disorders that make up the "autistic spectrum."

All children with an autism spectrum disorder share core deficits – abnormal social behavior, impaired communication, and restricted and repetitive behaviors – though the severity and constellation of symptoms vary dramatically. Intellectual function ranges from profound mental retardation to above average intelligence as measured on IQ tests. Some children, like Morgan, appear to develop typically for the first year or two and then stop, or regress. Others show signs of autism from early infancy.

This baffling variability in symptoms and their onset has added to the complexity of diagnosing, treating, and understanding autism. Today, 60 years after it was first described, autism is still a mysterious disorder. It's clear that brain development goes awry, but why and how exactly are open questions. There are currently no biological markers – genes or blood proteins – that can be used to diagnose the disorder or predict who will suffer from it, and there are no cures.

One thing is clear – autism is not a rare disorder. It affects as many as one in 250 children, four times as many boys as girls, across all racial groups. The number of children with autism spectrum disorders appears to have skyrocketed in the last 10 years, and although this finding is controversial, it has sparked a sense of urgency and an influx of federal and private research funding for autism research. The increased support is bringing renewed energy to efforts to define brain regions that are affected by autism and to identify autism susceptibility genes and environmental "triggers" for the disorder, and it is making some researchers optimistic.

"Ultimately we want a biologic cure and prevention for this disorder, and that's going to happen," says Dr. Nancy J. Minshew, director of a Collaborative

Pictured left: A group of children with autism toss balls into the air during a summer camp conducted by the Treatment and Research Institute for Autism Spectrum Disorders at Vanderbilt University. Clockwise from upper left are campers Abbey Pais, Erik Overby, Savannah Little, Stewart Chunn, Nathan Herbert, Robert Bousquet, Zachary Sutton and Brian McDonnell.

Photo illustration by Dean Dixon.

DEAN DIXON

Morgan Vice (center), shown here with her mother, Tammy Vice (left), at a summer camp for children with autism sponsored by Vanderbilt University. Morgan's 15-year-old sister Allison Vice (right) was a junior counselor at the camp, which helps children with autism learn and practice social skills.

Program of Excellence in Autism at the University of Pittsburgh. That cure may be several decades off, Minshew acknowledges, but research findings along the way are improving early diagnosis and treatment options, giving children with autism spectrum disorders the best chance for a typical life.

Exploding a myth

In 1943, pioneering child psychiatrist Dr. Leo Kanner of Johns Hopkins University published the first description of a syndrome of "autistic disturbances." He presented case studies of 11 children who shared social remoteness, obsessive and repetitive behaviors, and language disturbances. But autism remained poorly defined for decades, grouped with childhood schizophrenia in the first two editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-I, 1952 and DSM-II, 1968).

The 1950s and 60s saw the rise of theories that parents caused autism by being too "cold" and failing to psychologically bond with their children. It wasn't until the 1970s that the tide began to turn, with prominent research groups formulating diagnostic criteria for autism and speculating that it had biological underpinnings.

Then came hard proof.

Dr. Susan Folstein had just completed her residency in psychiatry when she joined Dr. Michael Rutter's group at the Institute of Psychiatry in London. She wanted research experience and took on a project to study autism in twins. Crisscrossing the English countryside, Folstein examined and interviewed as many twins as she and Rutter could find, one or both of whom had autism. They found that identical twins were much more likely to both be affected than were fraternal twins – evidence that autism had genetic roots.

The findings, published in *Nature* in 1977, "brought to a clear end the period of time when people thought of autism as something that was caused by parents," says Folstein, professor of Psychiatry at Tufts-New England Medical Center. "The study was also the impetus for many other family studies of autism."

Folstein and Rutter's initial twin study and others since then offer the most compelling evidence for the high heritability of autism. Identical twins have a greater than 50 percent chance of both being autistic. The relative risk to siblings – nine to 45 times the risk to the general population – is higher than many other complex disorders like diabetes, asthma, and schizophrenia. But the genetic factors contributing to autism have remained elusive.

Jonathan L. Haines, Ph.D., director of the Program in Human Genetics at Vanderbilt University Medical Center, began collaborating with Folstein in the mid-1990s. Compared to other diseases and disorders he was working on at the time, "it looked like the genetics of autism should be relatively easy to solve," he recalls. "Big mistake."

"The data are suggesting that there are many genes and that they are probably interacting to cause this disorder," Haines says. "It's incredibly complex." That makes sense, he adds, given the sheer variation in the expression of the disorder, in the symptoms that children have.

To search for those proverbial needles in the haystack – the small group of genes that contributes to autism out of the 30,000 or so genes that make up the human genome – investigators use a combination of two approaches. They scan randomly through the entire genome in families with at least two affected individuals, called multiplex families, looking for DNA regions with high similarity in the people with autism. And they examine "candidate genes," which because of their biological function are suspected of playing a role in the developmental changes that cause autism.

The approaches have pointed to many different chromosomal regions – areas on chromosomes 2, 3, 7, 15, and 19 that are linked to the disorder in some sets of families – and to some candidate genes. "There's a lot of disagreement about those regions, and there are no confirmed genes," Haines says. "No one's been able to say, 'this is a gene that causes or influences autism.'

"One could argue that the field is in a great state of confusion right now," he adds. "But out of that confusion is going

to come some real progress in the next year or two."

The power of genetics

One reason for Haines' optimism: the development of the Autism Genome Project, a consortium of autism genetics researchers promoted by the National Alliance for Autism Research. If NAAR, a parent-founded advocacy group, is able to secure funding for the giant genetics initiative, up to 1,200 multiplex families will be available for study.

"With those families, we're going to do a very high density genome screen," Haines says. "That will be *the* definitive genome scan for autism, because it will include virtually all of the multiplex families in the world."

At the same time, autism genetics researchers are trying to define some of the complexity of the disorder by sub-grouping patients according to their symptoms and by characterizing autistic traits in their parents and other family members. Folstein traces this idea back to her twin studies in England, when she noticed that co-twins and other family members had subtle symptoms of autism – compulsions, language problems, or social awkwardness.

"We realized that maybe we shouldn't be looking for genes for autism, but maybe we should be looking for genes for the kinds of compulsions, for example, that you see in patients with autism and also in their parents," Folstein says.

She and Dr. Joseph Piven, professor of Psychiatry at the University of North Carolina, divided their group of multiplex families into those in which the autistic children had very poor language and those that did not, and then they considered parents "affected" if they had a history of language problems. They thought it might be possible to improve the linkage signal – the finding that affected individuals share a particular chromosomal region – and that's what happened, Folstein says. Other investigators were soon following suit.

For example, James S. Sutcliffe, Ph.D., assistant professor of Molecular Physiology & Biophysics at Vanderbilt, and his colleagues recently demonstrated that linkage to a region of chromosome 15 improved, or got stronger, in a subset of autistic patients with savant skills – extraordinary abilities in areas such as rote memorization, calculation, and mechanical achievement. Duke University investigators led by Margaret A. Pericak-Vance, Ph.D. found stronger linkage to the same chromosomal region in a subgroup of autistic patients who exhibit repetitive compulsions and extreme difficulty with changes to their daily routine.

"It seems like every time we use one aspect of the autism phenotype, one or another of the chromosomal regions that we suspect tend to make themselves better known, give better signals," Folstein says. "This strategy is allowing us to disentangle the condition into its component parts, which we hope have a connection with the component genes."

Combining this approach with the pooled resources of the Autism Genome Project may offer the best hope yet for making sense of the genetics of autism.

"The number of families we'll be looking at collectively is so large that we will finally have the statistical power to ask these kinds of questions that essentially come down to statistics," Sutcliffe says. "It will ultimately be much easier to find the

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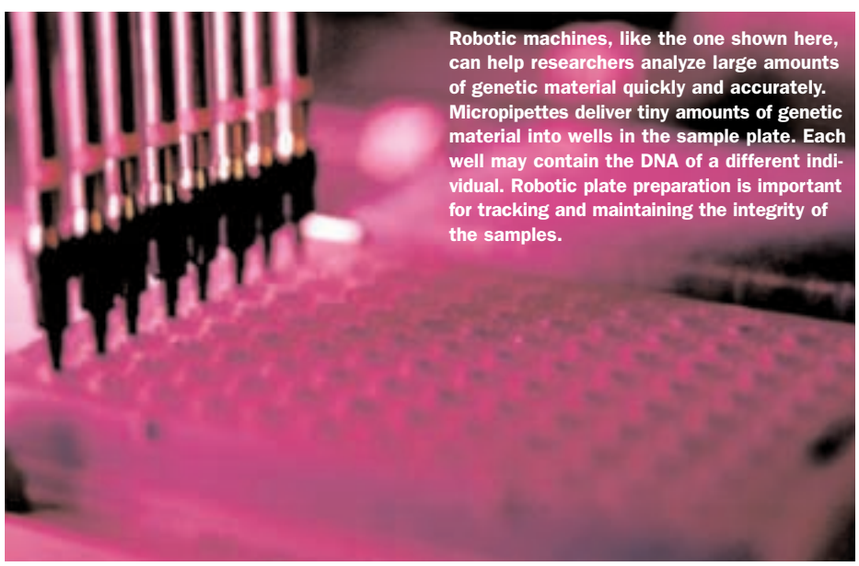


Robotic machines, like the one shown here, can help researchers analyze large amounts of genetic material quickly and accurately. Micropipettes deliver tiny amounts of genetic material into wells in the sample plate. Each well may contain the DNA of a different individual. Robotic plate preparation is important for tracking and maintaining the integrity of the samples.

An epidemic of autism?

In California, the number of individuals with autism spectrum disorders seems to be spiraling upward, from 10,000 to 20,000 cases between 1999 and 2002. California is not alone. Other states are seeing similar climbs, prompting parents and some researchers to argue that the country is experiencing an epidemic of autism.

The numbers would seem to bear that out. The few epidemiological studies conducted in the United States in the 1980s and early 1990s reported low prevalence rates, approximately four cases of autism per 10,000 children. A study published this year cited a prevalence rate of 34 cases per 10,000 – nearly 10 times higher than the earlier studies – in children in the metropolitan Atlanta area. Studies in other parts of the world are turning up rates as high as 60 per 10,000.

One explanation for an increase in cases, investigators say, is that the diagnostic criteria for autism have changed. The autistic spectrum now includes high-functioning individuals who would not have been diagnosed with autism a decade ago. But parents like Tammy Vice, whose daughter Morgan has Asperger disorder, don't buy it. "You would not have missed these kids; they're very different, very unique," she says.

"Subjectively speaking, there do seem to be more children with autism than years ago," says Wendy L. Stone, Ph.D., professor of Pediatrics and Psychology and an investigator in the Vanderbilt Kennedy Center for Research on Human Development. "I know for sure that the diagnostic criteria have changed to include the milder forms of autism and there's greater awareness, but I would not rule out the possibility that there has been an increase in the prevalence of the disorder."

Is something in the environment to blame? Although childhood vaccines have been fingered as potential culprits, there's no good evidence that vaccines are responsible for the apparent increase in the diagnosis of autism, says Jonathan L. Haines, Ph.D., director of Vanderbilt's Program in Human Genetics and a Kennedy Center investigator. "But we certainly have a lot of junk in the environment that wasn't there 30 years ago," he says. "If we could figure out what the autism trigger is and stop it, that would be fantastic."

– LEIGH MACMILLAN

genes, and I would be surprised if within the next two years, someone hasn't identified the first autism gene."

The hope, these genetics researchers agree, is that finding the genes that cause autism or increase an individual's susceptibility for the disease will improve diagnostic capabilities and pave the way for new biologically-based treatments, perhaps even preventions.

"It could be something as simple as giving folate in pregnancy to decrease the rate of spina bifida," Folstein says. "We just don't know right now."

A problem with wiring

Proceeding in lockstep with the search for autism genes have been efforts to understand the neurobiology of the disorder. Attention has focused on defining the brain regions affected by autism, with the hope that knowing which brain regions are affected and how will guide diagnosis and treatment strategies.

Autopsies and brain imaging have revealed that brains of individuals with autism are larger than normal, on average, and that there are alterations in the brainstem, cerebellum, and "limbic" structures, like the amygdala and the hippocampus, which are involved in emotional processing. But no clear picture of an "autistic" brain has emerged.

"Could you hand a CT scan to a neurologist and say 'does this child have autism based on your knowledge of structure?' The answer is no," says Stephen M. Camarata, Ph.D., deputy director of Research on Communication and Learning at the Vanderbilt Kennedy Center for Research on Human Development. "Clearly something is wrong in the brain, but we suspect it's not going to be a gross anatomical difference. More likely, it's going to involve interactions among different areas of the brain and how these areas integrate information."

Pittsburgh's Minshew calls autism a disorder of complex information processing. "People with autism can hear and remember information, but they have trouble making sense of it," she says. "It's a generalized brain phenomenon where complex circuitry and higher order cognitive abilities supported by that circuitry fail to develop." She points out that all areas of the brain – including those controlling skilled motor movements – are affected.

Minshew and colleagues first observed the disconnect between basic skills and higher order skills during behavioral testing. They have recently confirmed, using functional magnetic resonance imaging (fMRI), that basic brain circuitry, but not higher order circuitry, is intact in individuals with autism.

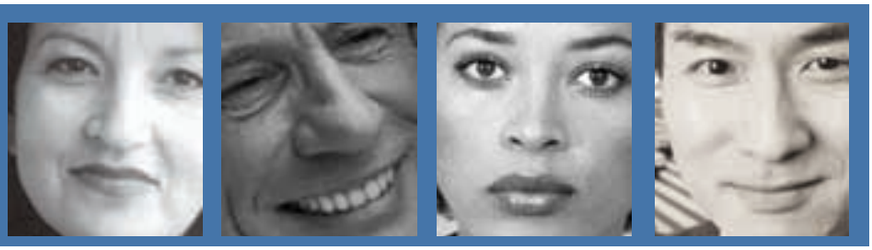
The larger than normal brain sizes of children with autism may offer clues to the miswiring that occurs during brain development. Eric Courchesne, Ph.D. and his colleagues at the University of California, San Diego reported in July that children with autism were more likely to have a reduced head size at birth and a sudden or excessive increase in head size during the first year of life. The authors suggested that this accelerated head growth could be an early warning sign for autism.

Brain development during the first two years of life sets the stage for the complex circuitry and information processing capabilities of the mature brain. An acceleration of neuronal growth during this critical period, and/or a failure of the mechanisms that normally "prune" away unnecessary neurons, could lead to disarray, Minshew says.

Using neuroanatomy and powerful new techniques like fMRI to get at the regions of brain dysfunction in autism is part of a progressive search for the cognitive and brain basis of behavior, Minshew says. "How well we understand behavior makes an enormous difference in how well we can intervene," she says. "We are most effective at changing behavior when we understand why someone's doing what they're doing."

Finding what works

Behavioral and educational interventions for children with autism have come a long way since the days when diagnosis was accompanied by a suggestion for institutionalization, but even now it is unclear



The face is key

Human beings are "face specialists" – we distinguish individuals based on their facial features, and we gather a wealth of emotional information from a muscle flex here or a twitch there. For individuals with autism, though, the human face may be little more than another object in an already confusing world.

It has long been recognized that people with autism fail to make appropriate eye contact and are inattentive or indifferent to the faces of others, says Isabel Gauthier, Ph.D., assistant professor of Psychology and an investigator in the Vanderbilt Kennedy Center. Gauthier and her colleagues, including Robert T. Schultz, Ph.D., associate professor of Clinical Psychology at Yale University, developed tasks to study face recognition using a powerful mode of brain imaging called functional magnetic resonance imaging (fMRI).

They then used the face recognition tasks to image brain activity in young adults with autism. The investigators found that instead of using the brain's face-recognition system to discriminate between faces, people with autism tended to rely on areas of the brain involved in object recognition.

The underdeveloped face-recognition system may be a result of a lifelong disinterest in people and consequent failure to develop normal expertise with faces, Gauthier says. The work also suggested that "it may be possible to design a training program that could significantly improve autistic children's ability to recognize other people by increasing their use of the facial recognition system." Efforts are underway to do just that.

– LEIGH MACMILLAN

Pictured here (from left): Jonathan L. Haines, Paul J. Yoder,James S. Sutcliffe and Wendy L. Stone represent the breadth of research at Vanderbilt University aimed at improving the diagnosis and treatment of autism.

ANNE RAYNER

which treatment will work best for a given child.

"If a parent comes to me and asks me which therapies she should use, I have no way to answer that question," says Paul J. Yoder, Ph.D., professor of Special Education and an investigator in the Vanderbilt Kennedy Center. "It would be useful to know which treatments might be counterproductive to use together, or which ones might be synergistic. And we're not just talking about educational treatments, it's pharmacological treatments too." About 50 percent of children with autism take medication to lessen anxiety or control serious behavioral disturbances like self-injury, aggression and hyperactivity.

Yoder and fellow Kennedy Center investigator Wendy L. Stone, Ph.D., professor of Pediatrics and Psychology, are collaborating on a study to compare two behavioral treatments. Complicating this kind of research, Yoder says, is the fact that children are often involved in multiple types of educational intervention in addition to the research study, making it difficult to control all the variables. "We don't have good measures of the quality of those other treatments," he says.

Despite the uncertainty about which treatments might work best, educational and behavioral interventions are effective, and the sooner they're started, the better. "The brain is more plastic at young ages," Stone says, "and I think there has been enough intervention research to suggest that young children who get intervention early have better outcomes than when the intervention is started later."

To that end, Stone and collaborators have developed and are studying the STAT, Screening Tool for Autism in Two-year-olds, and they're attempting to make it work for even younger children. The advantage of the STAT over traditional diagnostic tests, Stone says, is that it takes less time and doesn't require advanced psychological training to administer. Because it can be more available to people in the community, "it promotes an awareness of what the early signs of autism are – the early social communicative deficits that everybody should be looking for."

The STAT also offers the advantage of guiding treatment decisions by allowing the tester to directly interact with children and observe their strengths and weaknesses. "You can go right from the information on the STAT to designing appropriate educational activities for these children," Stone says.

Eventually, treatment guidance may come from genetic and neuroimaging profiles, Yoder says, but those days are a long way off. "It's exciting to me that as a nation, we're finally spending serious money on learning how to treat children with autism, how to educate them, what to do with their day-to-day moments," he says. "There are no easy solutions to this problem."

This summer, Morgan Vice spent three weeks at a camp run by TRIAD, the Treatment and Research Institute for Autism Spectrum Disorders at Vanderbilt. The camp is one type of intervention effort: when school's out, it keeps children with autism on a schedule and focuses on teaching them social skills – greetings, compliments, conversations. Now in its third year, the camp is seeing tremendous gains among its campers, says director Misty Ballew.

The slogan printed on this summer's camp T-shirts said, "I believe I can fly," and although it had no relationship to Morgan's toddlerhood experiences, the phrase seemed especially fitting. Now nine, Morgan is "coming back, bit by bit," Tammy Vice says. "When all this happened, my goals for Morgan did change," she says, "but my dreams for her are the same. I want her to be happy and successful, where she is."

Fly, Morgan, fly. **LENS**

Pictured left: *Man with flies and snake*, crayon drawing from the 1920s by Heinrich Anton Muller, an artist and inventor who spent much of his life in a Swiss psychiatric hospital under treatment for delusions and other symptoms of schizophrenia.

Courtesy of the Collection de l'Art Brut, Lausanne, Switzerland. (www.artbrut.ch/)

inside out

LOOKING AT SCHIZOPHRENIA'S INNER CHAOS

by Mary Beth Gardiner

Just one glance at a painting by a person with schizophrenia clues you in. This person, you think, is not your run-of-the-mill artist. This artist has something going on.

What's going on in the mind of a person with schizophrenia has been the subject of researchers for nearly a century. Some believe that the divergent thought processes at the heart of creativity are cousin to the delusions and hallucinations that characterize the disorder. Other, more fundamental thought processes are affected in schizophrenia, too, including some essential to navigating daily life. Surprisingly, perhaps, it is largely this cognitive impairment that prevents those with the disorder from participating in society.

Affecting around one percent of the population worldwide, schizophrenia does not discriminate by race, socioeconomic status, or intelligence. The illness typically surfaces in early adulthood, and may impact a person's ability to think clearly, manage emotions, and interact with others. Most people with the disorder suffer chronically or episodically throughout their lives, plagued by symptoms and medication side effects, as well as by stigma and the pain of lost opportunities for relationships and careers. One of every 10 people with schizophrenia eventually commits suicide.

Though its cause is still uncertain, most scientists in the field agree that schizophrenia is a problem with brain growth and development. Technological advances in neuroscience, genetics, and brain imaging are yielding convincing evidence of altered brain anatomy and chemistry. Yet the picture of when and how neurological snarls occur remains vague: Is nascent brain circuitry affected in the womb or some time later along the developmental timeline? Genes are involved, but is the initiating event biological or environmental?

Of a split mind

Our understanding of schizophrenia has come a long way since German psychiatrist Emil Kraepelin first documented the disorder in the late 1800s. The symptoms are by now well characterized, yet misconceptions still abound. The Greek-derived name translates to "split mind," but the illness has nothing to do with split or multiple personality disorders. The "split" in this case refers to the inability to separate reality from delusion and the illogical from the reasonable.

A wide-ranging array of symptoms characterizes the illness, which profoundly disrupts cognition and emotion, affecting language, thought, perception, affect, and sense of self. Diagnosis encompasses a pattern of signs and symptoms – often including psychotic symptoms, such as hearing imagined voices or espousing false yet fervent personal beliefs – in conjunction with an impaired ability to participate socially or occupationally.

Schizophrenia can occur at any age, but it tends to first become evident between adolescence and young adulthood,

somewhat earlier in men than in women but at about the same rate. Retrospective studies reveal signs of cognitive decline – a slide in grades or withdrawal from friends and family, for example – well before the first psychotic "break". The conditions necessary to produce such neurological havoc remain an enigma.

"That's why it's so difficult," says Pat R. Levitt, Ph.D., director of the Vanderbilt Kennedy Center for Research on Human Development. "It's a disorder that is complicated because it affects two major mental domains, because it is clearly multi-genic, and because it also has environmental contributors. And yet, out of all the psychiatric disorders that people work on, other than depression, it is the most prominent, affecting one in 100 people."

It has long been accepted that schizophrenia has a genetic component. The risk for inheriting the disorder is 10 percent in those who have one immediate, or first-degree, family member affected, and about 40 percent if both parents or an identical twin have the illness.

It's important to note, however, that the majority of people with schizophrenia have no close relatives who are affected, an indication that there are other factors at play. Epidemiological evidence suggests certain external circumstances, such as viral infection during pregnancy, insufficient prenatal nutrition, or a child's being born during the winter months or being born in an urban setting, may increase risk.

"This is not to say that you have a higher risk being born in a city hospital rather than in the country," says Levitt. "It's probably related to some increased incidence of something a mother is exposed to – infection or peri-natal stress, for example – if pregnancy occurs in these different environments."

Stilling the tempest

Sorting out which behaviors in schizophrenia are linked to genetic changes in the brain, and how those changes impact neurological chemistry and circuitry, has proved challenging. One of the first clues about altered brain chemistry in schizophrenia came in the early 1950s with the introduction of the antipsychotic drug chlorpromazine (trade name Thorazine). Originally used as an antihistamine during surgical procedures, the drug's sedative properties inspired a psychiatrist to try it on agitated institutionalized mental patients.

To everyone's surprise, the drug not only sedated, it also diminished delusions and hallucinations. As doctors pushed the dose, however, patients developed Parkinson's-like conditions: rigidity, loss of movement, drooling. The story led Swedish scientist Arvid Carlsson, who would later win a Nobel Prize for his work, to discover dopamine and its role as a neurotransmitter in communicating instructions between the brain's nerve cells.

Studies showed that many antipsychotic agents block dopamine receptors, suggesting that an excess of dopamine in the brain may be part of schizophrenia's pathophysiology. Dopamine's role in schizophrenia dominated the field for some time, and though other neurotransmitters – glutamate, GABA, acetylcholine, and serotonin, for example – have since been implicated in the disease etiology, the "dopamine hypothesis" continues to be a central focus.

"The evidence is that multiple brain chemical systems all come to bear on the synthesis, release, and inactivation of dopamine in various areas of the brain – too much in some, too little in others" says Dr. Herbert Y. Meltzer, Bixler/Johnson/Mays Professor of Psychiatry and director of the Division of Psychopharmacology at Vanderbilt.

The delusions and hallucinations appear to be the result of excessive dopamine, while the cognitive impairment is due, in part, to too little dopamine, according to Meltzer.

"It's like the six degrees of separation concept," he says. "You might start over here with glutamate or GABA, but sooner or later it's going to link up with dopamine as a key element in the final common pathway of the disordered brain function."

Meltzer has a history of contributions to the field of schizophrenia drug development, beginning with his efforts showing that clozapine – the first of the second-generation "atypical" antipsychotic drugs – effectively treats psychosis without producing Parkinsonism. The results were compelling enough to justify its use despite the risk in one percent of those taking the drug to develop a disease of the white blood cells. Late last year, the FDA named clozapine the drug of choice to reduce suicidal behavior in schizophrenia, an endorsement due in large part to an international clinical trial led by Meltzer.

During the course of his studies with clozapine, Meltzer and his colleagues found that the drug improved some elements of cognitive function in schizophrenia patients. Confirmation of this first evidence that an antipsychotic drug could improve cognitive impairment changed the focus of the search

Creativity and madness: are they linked?

Biologists with an evolutionary bent observe that schizophrenia must be adaptive in some way or it would have been eliminated by now. Some theorists suggest that there is a creative element associated with schizophrenia that ensures the disorder stays in our genome.

Schizophrenia has affected a number of well-known artists or their relatives, including Russian dancer and choreographer Vaslov Njinsky; painter, writer, and dancer Zelda Fitzgerald; artist and dancer, Lucia Joyce, daughter of writer James Joyce; and author and pediatrician, Mark Vonnegut, son of writer Kurt Vonnegut.

"I'm really interested in looking at this link between creativity and madness that people have alluded to for thousands of years," says Sohee Park, Ph.D., associate professor of Psychology at Vanderbilt. "Studying relatives of those with schizophrenia and other schizotypal people – those who have elevated symptoms but who will probably never be ill – we've been finding that the schizotypal subjects are much more creative than normal individuals."

In interviewing schizotypal individuals, predoctoral student Brad Folley has collected striking examples of creative thinking. When asked what a person would do with a bowl, cup, napkin, and fork, one individual answered, "You could use the fork to shred the napkin to use as confetti in a parade." Another, when presented with a needle and thread, said, "If you were romantic but poor, you could write 'I love you' in the sand with the needle, make a ring out of the thread, and propose to your girlfriend."

Folley has developed a three-factor model for defining creativity, encompassing divergent thinking, creative problem solving, and practical creativity (an example might be cooking a meal without recipe or measurement).

"Using that estimate of creativity as our dependent variable, we think we can compare individuals in terms of brain function and structure," says Folley.

With Adam Anderson, Ph.D., in the Vanderbilt Institute of Imaging Science, Folley is using an advanced imaging technique called Diffusion Tensor Imaging to study connectivity in the brain. "Because creative people make more connections between ideas," he says, "we think we'll find more connections in the brain, too."

– MARY BETH GARDINER

DEAN DIXON

Dr. Herbert Y. Meltzer, who has helped pioneer the development of "atypical" antipsychotic drugs at Vanderbilt, is using positron emission tomography (pictured here) to study the effect of these medications on cognitive function in patients with schizophrenia.

for better drugs for schizophrenia, making cognition a primary and separate target.

Meltzer's current research is designed to identify new treatments to further improve cognitive impairment in schizophrenia. Success, he believes, may lead to drugs to treat many forms of cognitive loss, including those due to aging and Alzheimer's disease.

A shift in focus

A look inside the brains of schizophrenia patients shows that the structure is not dramatically changed by the illness. One subtle change is the decreased size of the frontal lobe in schizophrenia patients compared to normal individuals. Since the frontal lobe is the seat of many of the brain's higher cognitive functions, it's been a logical destination for schizophrenia researchers including Sohee Park, Ph.D., associate professor of Psychology at Vanderbilt.

When Park was working on her doctorate, Yale researcher Patricia Goldman-Rakic reported that monkeys with lesions in the frontal lobe were bad at tasks that required spatial working memory – the ability to remember the location of an object after a brief delay. Park adapted Goldman-Rakic's work in the primate model, designing a spatial working memory test for humans.

Park used the test to study performance of schizophrenia patients versus normal individuals and patients with bipolar disorder, and found that only those with schizophrenia had problems with the task. She expanded her studies to people with schizotypal personality disorder, or schizotypy, a milder version of schizophrenia often seen in first-degree relatives.

"As might be predicted," Park says, "the performance of people with schizotypy falls in-between that of normal controls and people with the full-blown disorder."

Monitoring the brains of those performing the task using a special scanning technique called functional magnetic resonance imaging, or fMRI, Park found that normal individuals have increased activity in a specific region of the frontal lobe – the convex shaped area on either side of the head, just above the temple, known as the dorso-lateral prefrontal cortex.

Results in schizophrenia patients are very different. "In those with schizophrenia, you don't see increased activity in this part of the brain and you see a higher error rate," says Park. "But they don't get all the answers wrong, so it's not that the area isn't functioning at all."

In some studies, even when patients

"That's the gap we can fill – to take cutting-edge biological discoveries and translate them into useful information and useful tools that companies can develop into drugs."

– P. Jeffrey Conn, Ph.D., Vanderbilt University

got the right answer, this part of the brain wasn't activated. This suggests that they don't seem to need that area to perform the task correctly, she adds.

"So the fMRI literature is in some sense murky right now, because we don't know what the activation really means in normal individuals versus schizophrenia patients," says Park. "Overall, it gives the idea that something is wrong with the way they use the brain, though we don't know yet exactly how."

Working with Park, predoctoral student Junghee Lee has developed a paradigm for further defining how the processes of working memory play out in the brain – which areas are responsible for encoding information, maintaining it in memory, and manipulating it. She is now collecting and analyzing imaging data.

Park is collaborating with Meltzer, using fMRI to look at how working memory is affected in schizophrenia patients treated with both an atypical antipsychotic and the drug buspirone, which specifically targets the brain's serotonin system. In addition, she is exploring the use of other brain imaging technologies with the help of John C. Gore, Ph.D., director of Vanderbilt's Institute of Imaging Science, and his colleagues.

Park expects that one method, near infrared optical imaging, may prove particularly helpful, since it provides the same kind of information that fMRI does, but has the advantage of allowing the patient to sit up and move more freely while being tested. Her lab is currently studying verbal fluency and verbal working memory in schizophrenia using this technology.

Another method that Gore is pioneering is called Diffusion Tensor Imaging, or DTI, which specifically images the "white matter" of the brain – the axons that connect neuron to neuron. The tool should be a powerful aid for researchers looking at how such circuitry is disrupted in schizophrenia.

Neural circuitry and its genetics

Dr. David A. Lewis has spent years studying neural circuitry in the brain, specifically the prefrontal cortex and related brain regions, and how it is altered in schizophrenia. It was at the University of Pittsburgh where he is director of the Center for the Neuroscience of Mental Disorders, and where Levitt was chairman of the department of Neurobiology at the time, that the two first began their collaborative research into the genetic underpinnings of those alterations.

"David and I partnered with Karoly Mirnics, who was an M.D. neurophysiologist in my lab, and who was also fantastic with computers and data analysis," Levitt recalls. "We were the first group to use gene microarrays applied to a major brain disorder, and we focused on the dorsolateral prefrontal cortex, the area that mediates working memory, which is disturbed in schizophrenia."

Gene microarray studies allow for simultaneous screening of thousands of genes to look for patterns of gene expression. The Pittsburgh group has published a series of papers demonstrating that expression of a certain class of genes – those encoding proteins that control synapse function – is deficient in schizophrenia. Some of these proteins have other roles in the body, but in the brain they play a critical role in the modulation of how neurons communicate with one another.

"We found that in one of those genes, *rgs4*, there are some polymorphisms – differences in gene sequences – that are found more prominently in people with schizophrenia than those without," says Levitt. "What we're trying to do now is to figure out whether the changes we see in our microarray studies are primary to the disorder or whether they actually reflect an adaptive state – an attempt by neurons to compensate for the principal defect."

"What's been striking to us is that the components of the prefrontal cortex that we knew were likely to be important for working memory activity appear to be those that are preferentially disturbed," adds Lewis. "And other components, which seem to be playing different roles in the prefrontal cortex, are relatively preserved."

Studies of brain tissue from schizophrenia patients show fewer neurons extending into the prefrontal cortex from the thalamus, a brain region that serves as a processing center for sensory impulses. In addition, communication among neurons is impaired, due to reduced synaptic connections and a lower density of dendritic spines, the nubs on neuronal cell bodies whose job it is to receive thalamic input.

Lewis' lab has discovered further surprising detail about the prefrontal cortex neurons: A subset that connects with a distinct population of inhibitory neurons has an altered receptor for GABA, the major inhibitory neurotransmitter in the brain. Lewis is designing a clinical trial to evaluate a new drug targeted at this altered receptor.

"To me, what is exciting is to start with very basic science – how the prefrontal cortex normally mediates working memory – then to go to the illness and ask what's wrong with that circuitry, and in the context of that find an alteration that might be druggable," he says. "We'll see in the initial clinical trial whether there's any evidence of cognitive improvement."

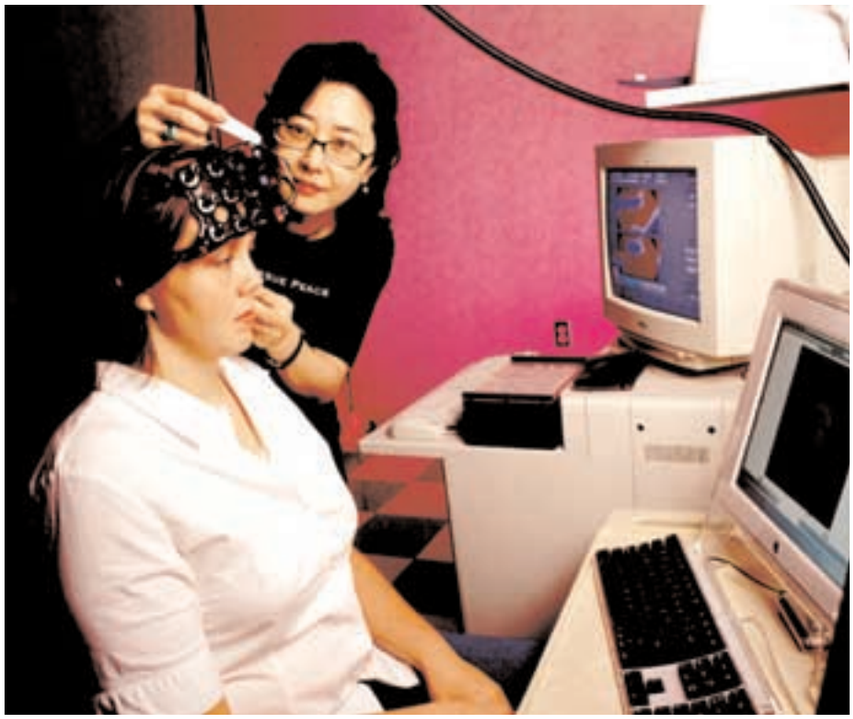
Translational research

This kind of systematic application of scientific method to the goal of drug discovery is an important aspect of what is called translational research, and it's the bailiwick of P. Jeffrey Conn, Ph.D., professor of Pharmacology and director of the Program in Translational Neuropharmacology at Vanderbilt. Conn, who earned his doctorate in Pharmacology at Vanderbilt and went on to join the faculty at Emory University, was recruited earlier this year from Merck & Co., Inc., where he headed the company's schizophrenia drug development efforts.

Having seen both sides of the coin, Conn believes that academic research centers can play a critical role in drug discovery.

"Drug companies have the ability to make drugs, but they are not, in all honesty, that well-equipped to decide in what direction to go, biologically speaking," he says. "Basic scientists, on the other hand, love the biology, but they're not terribly serious about taking the next step. That's the gap we can fill – to take cutting-edge biological discoveries and translate them into useful information and useful tools that companies can develop into drugs."

Conn has been investigating the role of the neurotransmitter glutamate in schizophrenia. Glutamate is the "major workhorse in the brain, affecting virtually every circuit involved in any brain function," he says. Unfortunately, it's that broad functioning that makes the neurotransmitter such a difficult drug target – effects of a drug would be seen throughout the central nervous system. So when a new class of glutamate receptors, called the metabotropic glutamate (mGlu) receptors, was discovered, a door to more specific control opened.



ANNE RAYNER

Sohee Park, Ph.D., adjusts a device used in a new non-invasive technique called near infrared optical imaging that she uses in her studies of cognitive function. As research subject Mikisha Doop takes a computerized working memory test, her brain activity will be monitored through the cap-like device and recorded by a second computer.

"The evidence suggested that they could fine-tune activity in glutamate circuits," Conn explains. "So instead of hitting the circuit with a sledgehammer, it's a subtle modulation of activity in that circuit."

Because mGlu receptors are located on both sides of the synapse, they are involved in both sending and receiving messages. That renders them capable of serving as a sort of "dimmer switch," says Conn, dampening or enhancing transmission in specific brain circuits.

Conn and others are looking at compounds that target mGlu receptors as potential antipsychotic therapeutics. "The goal is to screen tens or hundreds of thousands of small molecules to find compounds that have these actions, to develop them to the point where we can show very specific effects on these glutamate circuits, and then test those compounds to see if they have the effect we predicted," he says.

Conn also is investigating the role of another neurotransmitter, acetylcholine, in schizophrenia. Some compounds that target specific cholinergic receptors, including a drug under development by Eli Lilly and Co. to treat Alzheimer's disease, have been found to have both cognitive and antipsychotic effects.

"This is, I think, one of the most promising new directions in antipsychotic research," says Conn, "and it's probably one you haven't heard a lot about. But this psychosis-cognition interface is why those compounds may stand out in terms of potential antipsychotic efficacy."

Conn, Meltzer and their colleagues, Dr. Junji Ichikawa and Zhu Li, Ph.D., in the Psychiatry Department are investigating whether the improvement of cognition by atypical antipsychotics may be related to their ability to trigger acetylcholine release. If so, the connection could lead to the next generation of "cognitive enhancers," says Meltzer.

Tracking inherited traits

The best chance at cracking schizophrenia's mysteries may lie not with the people who have it but with their relatives. A significant percentage of first-degree relatives display schizotypal behavior, exhibiting some number of traits common to the disorder – for example, verbal memory or difficulty tracking objects moving through space – but not the more disabling symptoms.

Rather than look for single genes, some researchers are bundling these traits, which they call endophenotypes, and are tracing their occurrence in families affected by the disorder. The hope is that whatever genes are controlling these endophenotypic markers may lie in close proximity to a gene, or genes, that directly contributes to schizophrenia's pathophysiology. A similar strategy proved successful in colon cancer, where it was found that the disease is not inherited, but its endophenotype – the tendency to form polyps – is.

Three large genetic studies of schizophrenia are already in the works. Two of the studies were launched in 2002 by researchers at the University of Pennsylvania and the University of Pittsburgh. One plans to enroll 150 families, each of which has at least two affected members. The other – the Project Among African Americans to Explore Risks for Schizophrenia – will be a larger study of families in which two siblings have the disorder. The studies will test for attention, working memory, and executive functions, such as organization, problem solving, and decision-making.

The third study, which began this year, is the effort of the seven-center Consortium on the Genetics of Schizophrenia (COGS), led by the University of California, San Diego. The five-year study will use both cognitive and neurophysiological tests to track six characteristic traits in over 2,000 individuals, all schizophrenia patients or first-degree relatives.

> The best chance at cracking schizophrenia's mysteries may lie not with the people who have it but with their relatives.

Knowing the genes at the root of schizophrenia will be useful for designing targeted therapeutics, and may allow for early pharmacological intervention. It may even point the way to future gene therapy. Yet when heading down such a path, we may want to tread lightly, suggests Park, whose lab is also exploring creative thought as an adaptive reason that the disorder is still in our midst.

"Once we identify a gene or genes, who's to say they might not also be responsible for divergent thinking and creativity," she says. "If we turn these genes off, are we going to remove those traits from the human race?" **LENS**

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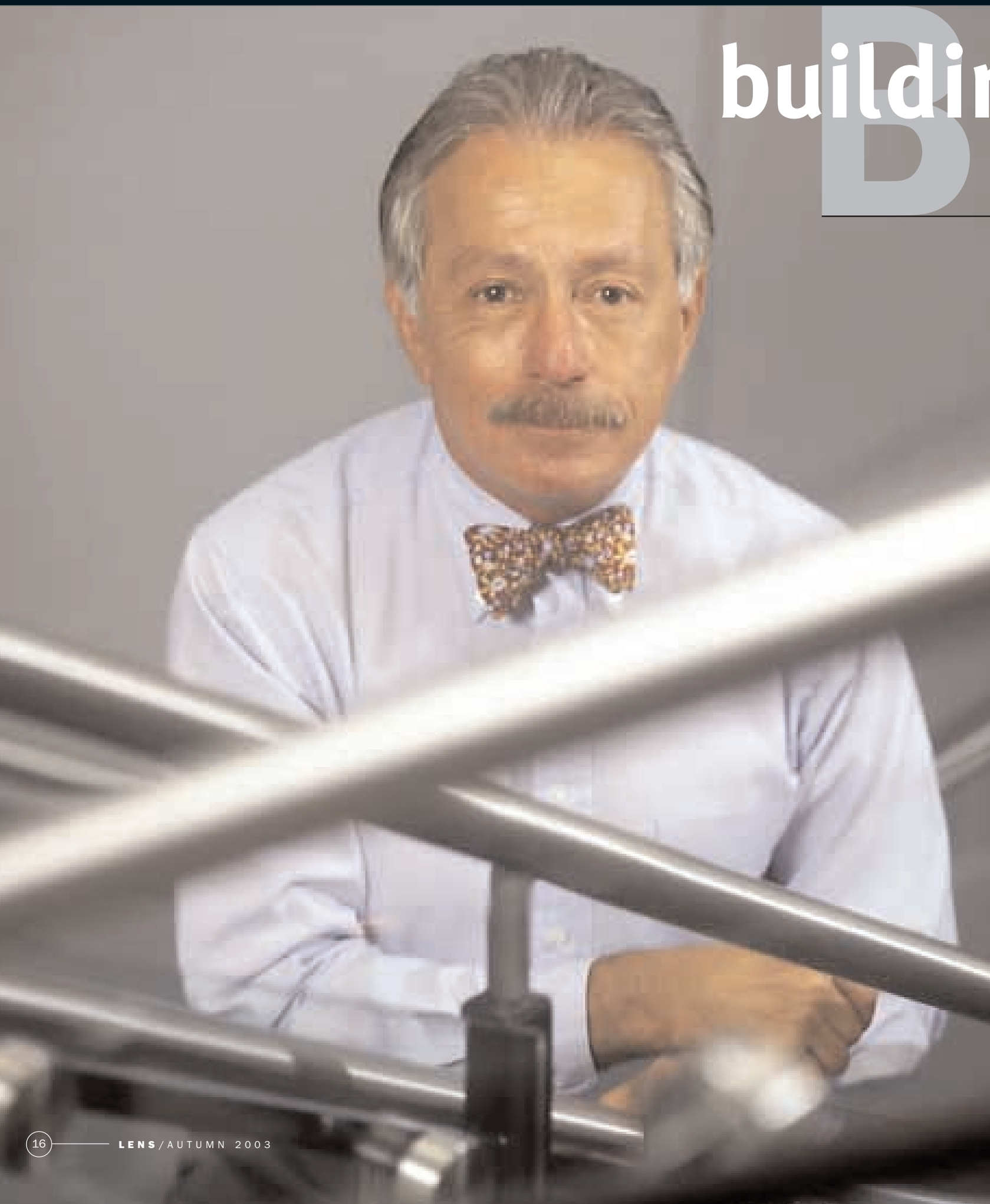
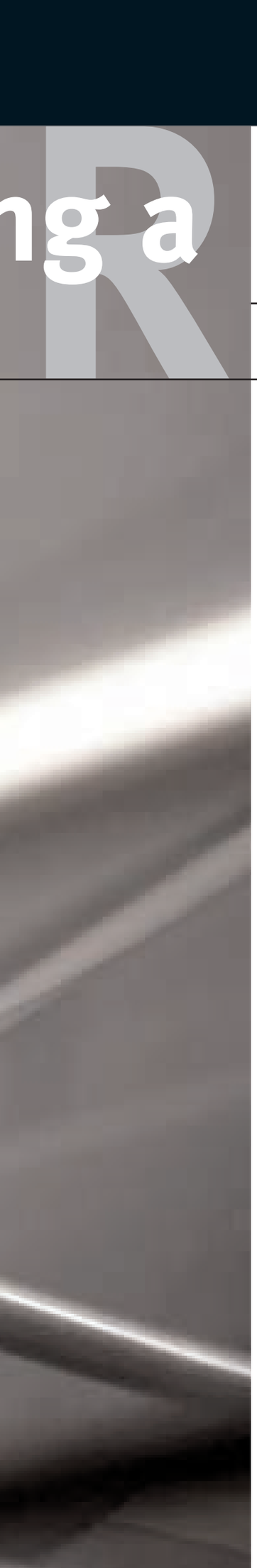




FRANK ROGOZIENSKI

ng a BRIDGE to the future

Floyd Bloom and the transformation of brain research

BY LISA A. DUBOIS

In the late 1960s, Dr. Floyd Bloom was so frustrated by his administrative and teaching responsibilities at Yale University Medical Center that he asked if he could resign his position as assistant professor and become a postdoctoral research fellow again. Such a request was unheard of in the venerable halls of the Ivy League.

But Bloom was serious. Over his chairman's objections, he left Yale and returned to his familiar training grounds at the National Institute of Mental Health (NIMH) in Bethesda, Md. There in a laboratory in St. Elizabeth's Hospital, surrounded by patients with profound mental illness, many of whom had spent 20, 30, or 40 years hospitalized with schizophrenia, depression or debilitating psychoses, he resumed his true passion – trying to decipher the biochemical reactions that lead to both normal and abnormal brain function.

Bloom is ardently devoted to basic science, a man willing to jump disciplines in order to test a theory or reach a solution, a firm believer in the integration of ideas. As a physician, he is equally dedicated to moving discoveries rapidly from the laboratory "bench" to the "bedsides" of patients.

"Floyd has this huge 'super' vision," says Lee Limbird, Ph.D., professor of Pharmacology and associate vice-chancellor for research at Vanderbilt University Medical Center. "He conceptualizes problems at a 30,000-foot level, but then he drops down to the ground to make those problems tractable to human experiments."

Over the course of his career, Bloom has identified new neurotransmitters and neuromodulators that led to the mapping out of the brain's chemical pathways; he has spearheaded breakthroughs in the neurophysiology of drug addiction, alcoholism, degenerative diseases, and AIDS-related dementia; and he has ascended to a leadership role as an activist, calling for a national policy review that would jumpstart a complete restructuring of the American health care system.

"To me, he's the Carl Sagan of neurobiology," Limbird adds. "One of the things that Carl Sagan did was to help laypeople put words not only to the science, but to the excitement and the importance of what was discovered. Floyd has that same contagious enthusiasm. Yet even though he has one of the most extraordinary and gifted minds, he's totally unpretentious. There's no feigned humility. He's just a passionate human being."

Floyd Bloom is a small man, fit and tanned, in his mid-60s, a long-time runner until he suffered a recent knee injury. Married since 1980 to Dr. Jody Corey-Bloom, a professor of Neuroscience at the University of California, San Diego, he is the father of two and the grandfather of four. Sitting in his office at the biotech neuroinformatics company, Neurome, which he co-founded three years ago, he speaks with energy and he smiles often. And, most strikingly, he listens. Intently.

Pictured here: At right, this page, Bloom (second from left in the first row) with his colleagues in the Laboratory of Neuropharmacology at St. Elizabeth's Hospital in Washington, D.C., in 1974.

From left to right, page 19, Bloom demonstrates stereotaxic injection techniques for studying brain function to postdoctoral fellows (left to right) Leonard Koda, James Nathanson and David Taylor at St. Elizabeth's Hospital in 1974; measures how long it takes the drug naloxone to reverse the effect of opioids in an experimental rat model at the Salk Institute in 1977; and at the electron microscope at the The Scripps Research Institute in 1987.

Courtesy of Floyd Bloom.

Born in 1936 in Minneapolis, Bloom has vivid early memories of sitting by the family radio listening to reports about World War II. His father Jack, who was a pharmacist, had dreamed of going to medical school, but had been turned down because of the pervasive quota system that thwarted many Jewish applicants. His son would not have to suffer the same indignity. Following a younger sibling who told him, "Jewish boys can get a break in Texas," Jack Bloom sold his Midwestern pharmacies and, in 1945, moved his family to Dallas.

Bloom graduated from high school in Texas, attended Southern Methodist University, where he majored in German literature, and, at his father's directive, applied to medical school at Washington University Medical School in St. Louis. He had been a brilliant student in a variety of subjects – except for calculus. Calculus proved to be his nemesis in medical school as well, when he needed it to understand physiology.

Despite his less-than-stellar performance in that subject, his physiology professor, Gordon Schoepfle, was sure that Bloom had the capacity to master the course if he could study it in context. Schoepfle invited the medical student to spend a summer in his lab on a student fellowship at the National Institutes of Health, where he could learn physiology through bench research.

Doctors were still being drafted in the early 1960s in response to Cold War tensions, and Bloom decided to meet his service requirements by working at the NIH. After traveling to Bethesda for the interviews, however, he was told his research position had fallen through at the last minute. A jobless medical resident, he was suddenly a prime target for the draft and pictured himself being shipped off to Germany or serving on a Coast Guard cutter off the coast of Alaska.

Thrill of discovery

Frantically, he called the director of the research associates program, Dr. Robert Berliner (whom he would later know as the dean of Yale Medical School), and begged him to find him another spot in their program. At Berliner's suggestion, Bloom interviewed at one of the oldest government-run psychiatric hospitals in the country, St. Elizabeth's Hospital in southeast Washington, D.C. He was accepted into the lab of Dr. Giancarlo Salmoiraghi, but he had no idea what he was being hired to do.

"That was a brain laboratory, not a peripheral nerve lab," he says. "I'd done all my biophysical work on the sciatic nerve of a frog. And now I was working with the brains of cats. It was neurosurgery, physiology, and pharmacology all in one. It was terribly exciting – one of the neatest times of my life. We were doing things that no one had ever been able to do before. We were discovering stuff that had just been lying there waiting to be discovered." Hooked, Bloom never returned to St. Louis to complete his residency.

Using multi-barreled microelectrodes, the NIMH investigators would supply very small amounts of chemicals to various parts of the animal's brain and record the activity of nerve cells, trying to examine the action of the neurotransmitters.

One of Salmoiraghi's colleagues, Dr. Erminio Costa, helped mentor the young physician-scientist. "In those days there were only one or two known neurotransmitters, and the NIMH labs assisted in the discovery of 20 or more additional ones. There was an explosion in known neurotransmitters," says Costa, now 80 and scientific director of the Psychiatric Institute at the University of Illinois at Chicago. "At the time nobody believed a chemical substance would be important for brain function. Everything in the brain would be electrical and neurotransmitters would be like part of a machine. During that period we began to discover that electrical impulses were stimulated by chemical substances."

Bloom realized that in order to study a cat or rabbit's brain, scientists had to anesthetize the animal. He stepped back and asked a question: "Is the response I'm seeing in the anesthetized animal predictive of what the response would have been if the anesthesia wasn't there?" To answer that question, he and his colleagues developed methods for surgically isolating the brain.

"We found that some neurotransmitters totally changed the quality of what they did in the absence of anesthesia from what we would have predicted. Whereas others were absolutely consistent," he says. "I think this was the first time that kind of insight had been obtained – that the actual act of studying the brain was confused by the use of the anesthetic."

Propelled by this new paradigm, in 1964 Bloom accepted another postdoctoral fellowship at Yale, so he could learn histochemistry, using tissue sections to understand the chemical basis of brain function and define where neurotransmitters and their receptors are located. Bloom and others were sowing some revolutionary seeds: If certain brain diseases arise from chemical imbalances, perhaps those imbalances could be corrected with new medications that avoided the serious side effects of the older psychotropic drugs, and without having to use electroconvulsive shock therapy.

Although Bloom was gaining prestige for his research, over time he began to feel too squeezed by the demands of his job to pursue it as effectively as he wanted. He asked his Yale superiors to demote him back to the position of postdoc. Instead, they promoted him to associate professor.

Throwing up his hands, he returned to the NIMH where he could spend more time in the lab. Within a year he was named chief of the laboratory of neuropharmacology at St. Elizabeth's Hospital.

George Siggins, Ph.D., professor of Neuropharmacology at The Scripps Research Institute, was one of Bloom's first post-doctoral fellows at the NIMH and the two have continued their collaboration for 35 years. "St. Elizabeth's Hospital was where the federal government put all the worst psychiatric cases that they did not know what to do with," Siggins recalls. "It was kind of grim in an 'Addams Family' kind of way.

"The setting thus added to the plight of the patients, who ran the gamut of serious psychiatric problems … We got to know them and their afflictions pretty well. But the daily encounters greatly reinforced our sense of duty, that we had a mission to improve their lives and conquer these disorders by our research."

Pedals of the piano

Bloom was particularly intrigued by norepinephrine, a neurotransmitter related to adrenaline that causes blood vessels to constrict and the heart to beat more forcefully and rapidly, and he began what he calls a career-long "obsession" with that neurotransmitter. Initially focusing on the cerebral cortex, the center of higher mental functions in the brain, Bloom and his associates mapped out the pathway of norepinephrine-associated nerve fibers, and discovered that the origin of the fibers came from an area of the brainstem called the locus coeruleus. The researchers found that while other neurotransmitters directly affected the "excitability" of this small group of cells, norepinephrine worked by modulating other signals.

"It was a completely novel action, not predictable by anything that was previously known," Bloom says. "Along with others, we were then able to extend that action to the hippocampus and other areas of the brain. (The finding) told us that norepinephrine does not convey specific information, but is more like the foot pedals on a piano. It changes the harmonics of the other information that's going on. People like to call it a modulator instead of a transmitter. It is transmitting modulatory information. It's enhancing, or in its absence, diminishing, the effectiveness of other inputs."

> It is very exciting to return to norepinephrine. It speaks to the point that science, like a good wine, can age with time …"
>
> George Koob, Ph.D., The Scripps Research Institute

With a better grasp of these novel chemical pathways, investigators began relating synaptic information to behavioral responses, such as depression, and then biochemically lacing those responses with epinephrine, dopamine and serotonin. Those experiments, in turn, ultimately led to the development of such antidepressant drugs as Prozac. Citing other seminal work that he and Bloom completed together, Siggins says they were the first to dissect the neurophysiological effects of prostaglandins in the brain, the first to describe the actions of beta-endorphin in the brain, and the first to report a novel mechanism of action of brain endorphin and other opiate peptides, termed "disinhibition," that could cause epilepsy-like effects.

Building on discoveries in the "norepinephrine days," Bloom's lab members were open to the notion that the brain has adapted many unusual ways of sending messages, which inspired them to search for other possible novel ways neurons communicate. "It put us in the right frame of mind to study brain peptides, for example," Siggins says. "What we ultimately found with opiate peptides and virtually every other peptide we studied much later is that they all had their own unusual signature or fingerprint of action very different from the fast, rapidly-conducting classical pathways. And Floyd had this intuition early on that the peptides were the wave of the future."

Bloom was so energized by the concept of neuropeptides that while he was being recruited to join the Salk Institute in La Jolla, Calif., he persuaded the Salk researchers to share their compounds. His coat pockets loaded with little vials of endorphin, enkephalin and other opioids, Bloom flew back to his lab in Washington, D.C., to test their action on brain neurons.

George Koob, Ph.D., a behavioral neuroscientist, joined Bloom's lab in the mid-1970s, when Bloom moved his group to the Salk Institute. The two men still collaborate. "I think we both always believed that the brain was the key to behavior – in fact, that behavior was the ultimate expression of the brain's function," Koob says. They began to explore the relationship between the action of certain neuropeptides and observable physical behavior. The focus on neuropeptides was Bloom's idea. Recalls Koob, "He said his mustache whiskers were twitching, so he knew we were on to something.

"Another corner we turned," Koob continues, "was our work on alcohol where Floyd insisted – and he was right – that alcohol MUST act on neurons to (create) its intoxicating- and dependence-inducing

Pictured below:
George Siggins (left) and George Koob (right) share memories of their long-time collaboration with Floyd Bloom at The Scripps Research Institute.

effects. That work has been confirmed, and our Alcohol Research Center (which Floyd started and directed for almost 20 years) is well on the way to determining what changes in the brain lead to alcohol dependence, alcoholism."

There is evidence, for example, that norephinephrine may play a role in the motivational aspects of opiate and alcohol dependence. "It is very exciting to return to norepinephrine," Koob says. "It speaks to the point that science, like a good wine, can age with time, and observations that made little sense 20 years ago can then fit into the puzzle later on to clarify the picture."

Cinnamon stick

In the early fall of 1979, Bloom was running a meeting of scientists at Woods Hole, Mass. He was a widower and had two teenaged children. A second-year postdoctoral fellow, Jody Corey, was working in a lab at Woods Hole, and she sneaked downstairs to listen to some of the lectures.

She noticed that he would jump up and comment after every talk, drawing parallels and contrasts to previous talks, explaining their relevance to each other. "It was pretty fascinating to listen to him synthesize what we just heard and to tell the audience why what we had just heard was so interesting and important," she says. "I was very taken by his ability to do that, actually. It was a very attractive feature of him, I thought."

Bloom recalls his future wife introducing herself to him after the session when she offered him "a cup of coffee she had made with a cinnamon stick." A year later they married. With a Ph.D. in anatomy in hand, she then went on to medical school at the University of California, San Diego, graduating in 1986, and is now a professor of Neuroscience at UCSD, specializing in the clinical care of patients with cognitive and degenerative problems like Alzheimer's and Huntington's diseases.

Bloom moved his labs to The Scripps Research Institute in 1983, and is now the chairman of the Department of Neuropharmacology. He is a member of the National Academy of Sciences, the Institute of Medicine and a foreign member of the Royal Swedish Academy of Sciences. He served on the Science Advisory Board of the MacArthur Foundation and has received an abundance of awards, including the Janssen Award in the Basic Sciences and the Pasarow Award in Neuropsychiatry.

"Floyd has an ability to bridge different disciplines in neuroscience," Corey-Bloom says, citing as an example the large center grant he was awarded to attack the problem of AIDS-associated dementia. "Only someone like my husband could have brought it all together, because he saw the pathology, the pharmacology, the chemistry and the neurochemistry. There are few sub-fields in neuroscience that he hasn't touched in some way."


FRANK ROGOZIENSKI

The mapping of the human genome has led to some of the most exciting possibilities for neuroscience, Bloom says. The next great challenge is to understand how modest mutations in several different genes can make a person vulnerable – but not necessarily certain – to develop a psychiatric disease.

"It's an inheritability to vulnerability," he explains. "You can have two identical twins with exactly the same genomes, experiencing the same life. One of them gets schizophrenia and one of them doesn't. One of them gets depression and one of them doesn't. One of them becomes an alcoholic and one of them doesn't.

"Whatever the history of your life is, you have the same genes you start with, but you're following slightly different trajectories. So, where is it that the brain fails to adapt to those demands of the environment? And what is it about the twin who didn't get the disease that I can draw from?"

In the 1990s, Bloom began assuming editorial positions at some of the most esteemed scientific journals, most notably, as editor-in-chief of *Science* from 1995-2000. During that period he made some radical changes, such as moving *Science* – which is published by the American Association for the Advancement of Science – onto the Internet, greatly expanding its reach.

Fixing health care

After he retired as editor, and while he was president of AAAS (he is now chairman), he stood before his constituency at its annual meeting and delivered a clarion call about the wretched state of the American system of health care. His cry, repeated in an essay in the June 13, 2003, issue of *Science*, called for a complete

overhaul of the way American medicine is taught, delivered and financed.

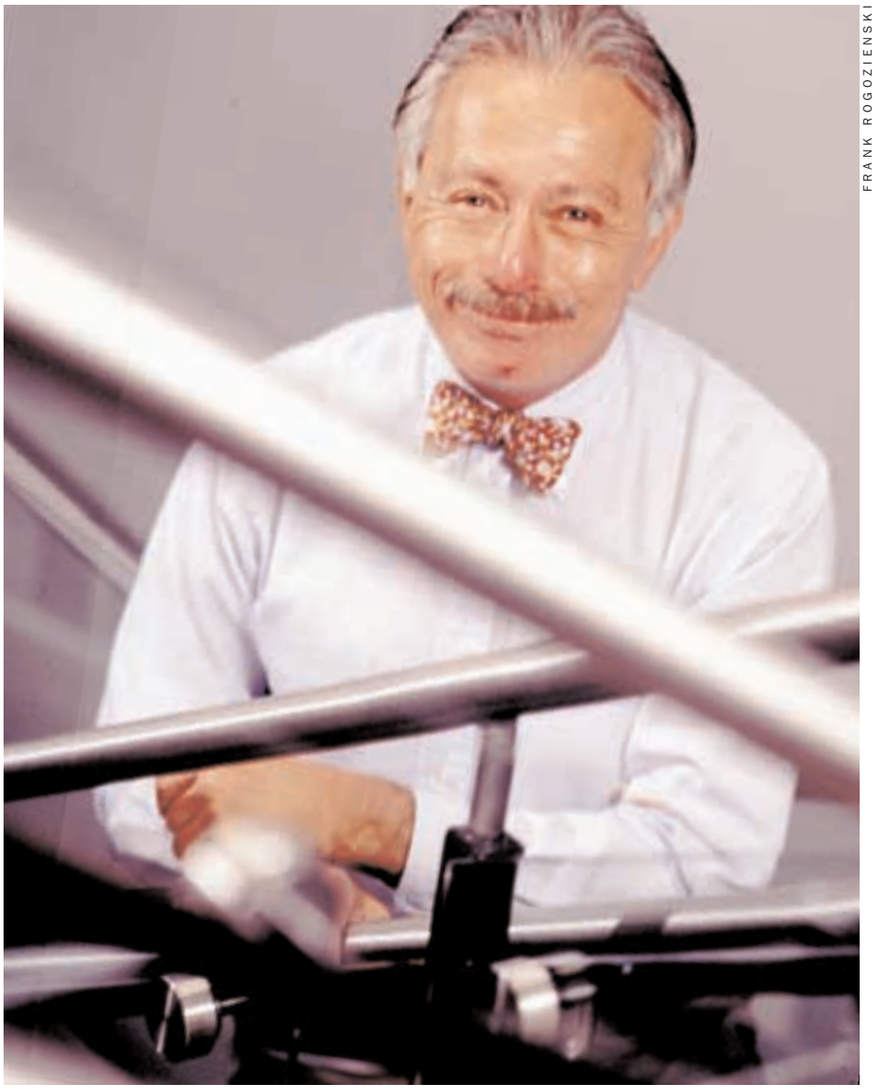
The speech shook the venerable scientific community to its core. AAAS is an esteemed organization dominated by basic scientists, who have made tremendous contributions to the body of medical knowledge. Suddenly a physician who hadn't been involved in clinical care in 40 years was putting it all on the line – the American medical system is failing not scientists, but patients, he claimed, because the fruits of science are not being applied to the needs of the public.

"I think what he said is tremendously important," says Alan Leshner, Ph.D., executive publisher of *Science* and CEO of AAAS. "It brings to bear a new pressure in understanding that health care won't be able to take advantage of advances that are coming and it adds urgency to our need for fixing the health care system."

Bloom used the AAAS as his bully pulpit because he had continued to listen. He observed his wife battling with HMOs and insurance agencies over treatment for her patients with dementia and severe degenerative diseases. He knew that layers of bureaucracy were being added, almost daily, layers that waylaid the delivery of new discoveries and the delivery of appropriate care.

"Floyd knows that it's becoming increasingly frustrating because we are no longer in control of what our patients can and cannot have – even when new discoveries become available," says Corey-Bloom. "What he's seeing now, at the time that you'd expect fruition in the setting of the Human Genome Project, is that many of the decisions about treatment and patient care are being taken out of the hands of people who were trained to make those decisions. And he's aghast at it."

Three years ago, when Bloom was at an age when many academic physicians begin winding down their careers and settling into emeritus status, he joined with colleagues John Morrison, Ph.D., and Warren Young, Ph.D., to form the biotech firm, Neurome, Inc.



FRANK ROGOZIENSKI

"Floyd has this ability to bridge different disciplines in neuroscience. Only someone like my husband could have brought it all together."

Dr. Jody Corey-Bloom

The company is developing standardized, quantitative databases that can integrate gene expression patterns within the brain and correlate that data with the rapidly growing store of information on brain structure and function. The goal, says Bloom, is to aid the discovery and development of new ways to diagnose, treat and prevent brain disorders such as Alzheimer's disease.

"Do you treat the disease when it's so bad that nothing your body does will bring it back into health? Or do you try to detect the first point at which you veered off the normal healthy track and get a medication that will keep you healthy?" he asks. "The right time to treat Alzheimer's patients might be when they're 30 years of age."

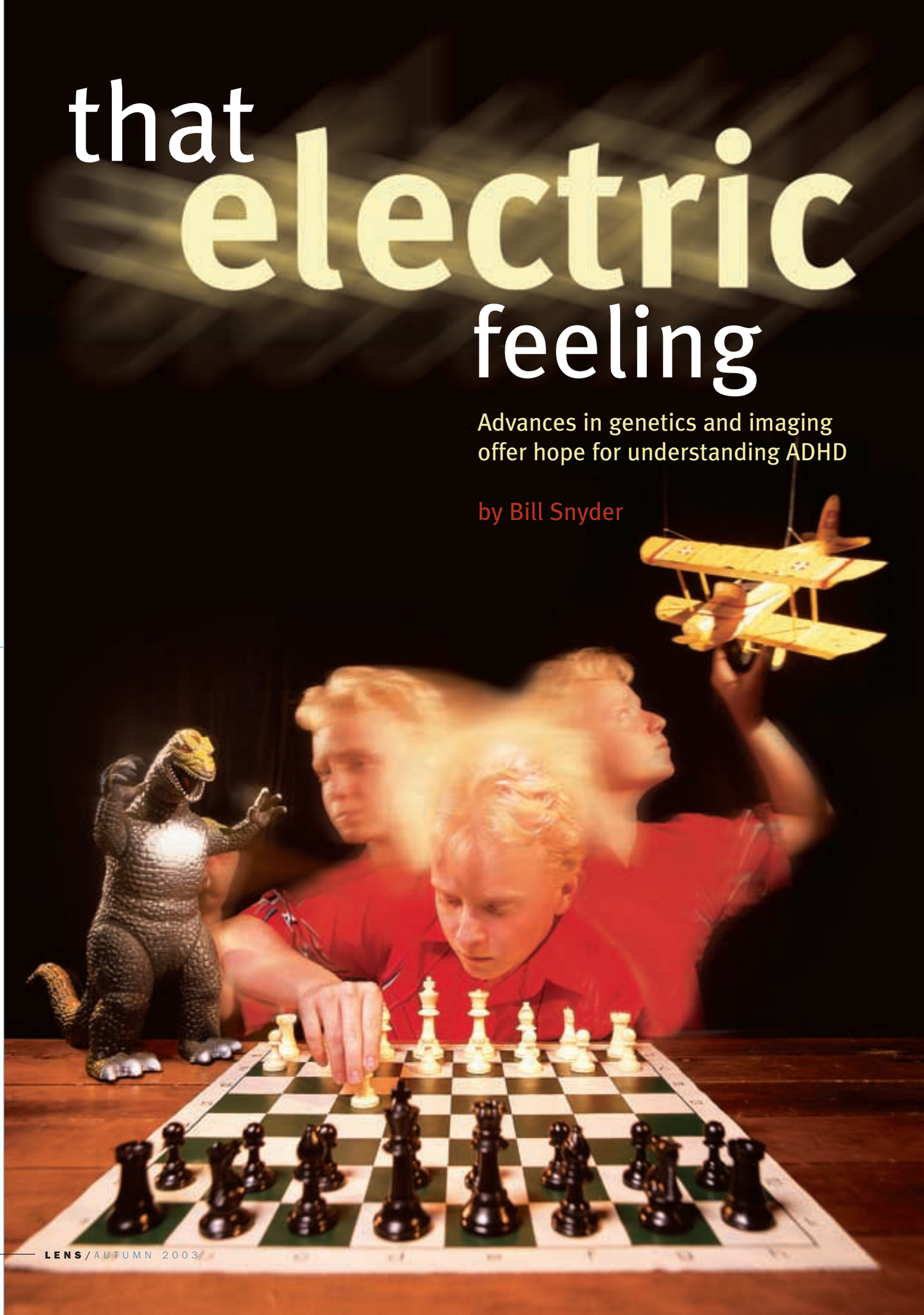
Therein lies the root of the problem with American health care: There is no room for what Bloom calls "medical engineers," scientists and physicians who could design and implement earlier treatments or even ways of preventing the most debilitating diseases. "We have chemical engineers, we have civil engineers," he says. "They take the rules of physics and bend them to the needs of society. We need somebody who can make the transistors that can make medicine."

Bloom raises his arms for emphasis. "I want to be able to be in this big, bubbling vat of new information, and this clamoring throng of patients in need," he says, "and make soup that will feed the hungry." **LENS**

that electric feeling

Advances in genetics and imaging offer hope for understanding ADHD

by Bill Snyder



Before he started taking Ritalin four years ago, J.T. King just couldn't sit still. "I feel like I have electricity running through me," he told his parents when he was in the second grade. "I feel like if I stuck my hands out, ... lightning bolts would come out of my fingers."

J.T. is still bothered sometimes by that electric feeling. But today, thanks to the medication, his parents' perseverance and his own determination, the gregarious seventh grader is succeeding in school, competing in chess tournaments and mastering every video game he tries. "He's awesome," marvels his mother, Jere King.

This 14-year-old computer whiz from Franklin, Tenn., has attention deficit hyperactivity disorder (ADHD), the most commonly diagnosed behavioral problem in children. There is recurring debate about whether ADHD is over-diagnosed, or whether some hyperactive youngsters aren't getting the treatment they need.

What confounds any discussion about the diagnosis and treatment of ADHD is its complexity. ADHD is actually a constellation of symptoms – the hallmarks of which are a persistent pattern of hyperactivity, impulsive behavior and difficulty paying attention. No single cause for these symptoms has yet been found and, to complicate matters even further, ADHD is often diagnosed in conjunction with learning disabilities and other behavior problems.

These mysteries are rapidly being unraveled, thanks to recent advances in genetics, brain imaging and the ability to manipulate the genetic make-up of laboratory mice. "Advancements in technology have changed the whole field completely," asserts Dr. Richard Shelton, professor of Psychiatry and Pharmacology at Vanderbilt University Medical Center, and an expert on the treatment of depression, bipolar disorder and ADHD. "I'm asking questions now that I couldn't possibly have asked even five years ago."

To understand ADHD, as well as other disorders of brain functioning, we must first journey deep into the nervous system – down to the cellular level. There we'll find the molecules that make it possible for electrical signals to jump the gaps between individual nerve cells, called synapses, and transmit information at lightning speed throughout the body.

The first molecules we'll meet are the neurotransmitters, which actually jump the gap. They include dopamine, norepinephrine and serotonin. After leaving their nerve cell, they attach to and activate receptors on the next cell in line, much like a key fits into a lock. Millions of locks must be opened in this way to send messages down their "signaling pathways." The ultimate goal may be to bend an arm or trigger the recollection of a childhood memory.

When these signals go awry, the body cannot function properly. Depression has been linked to a lack of serotonin. A loss of dopamine-producing cells in the brain causes Parkinson's disease, the inability to control voluntary muscle movement. Altered levels of norepinephrine can trigger heart disorders, depression and attention deficits.

These three neurotransmitters have been implicated in a wide range of other brain disorders, from ADHD to schizophrenia, and they represent just a fraction of the molecules known to carry or modify messages along the convoluted avenues of nerves between our ears.

But it gets even more complicated. Dopamine has five known receptors (some of which also can be activated by norepinephrine), while serotonin has at least a dozen. On top of that, one of the dopamine receptors, D4, exists in several genetically distinct forms, or variants. Your dopamine messaging system may function differently, and you may respond differently to drugs that affect it, depending on which genetic variant you inherit.

A clean sweep

The next molecule we'll meet on our journey is the transporter, an important regulator of neurotransmitter function. The transporter acts like a molecular vacuum cleaner, sweeping neurotransmitter back into the nerve cell after the message has jumped the gap, so it will be ready for the next signal.

When the transporter is blocked, neurotransmitter builds up in the synapse. This can be a good thing, if you're trying to treat depression. By blocking the serotonin transporter, drugs like Prozac increase the supply of serotonin at the synapse, and help elevate mood.

Psychostimulants like cocaine, amphetamines and methylphenidate (Ritalin, etc.) are thought to act primarily

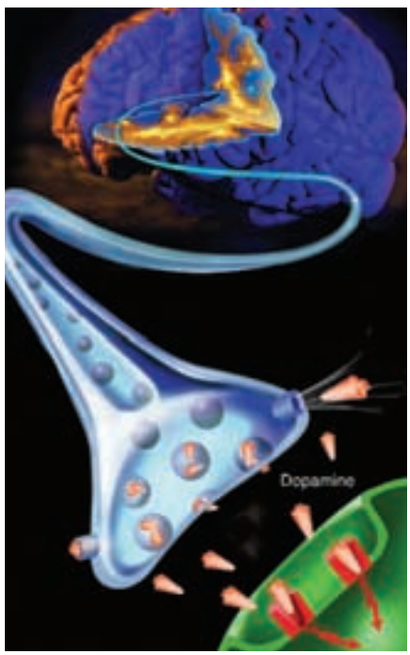
Pictured left: ADHD hasn't stopped 14-year-old J.T. King from succeeding in school or competing in chess tournaments. He says the medication he takes – a long-acting form of methylphenidate – helps him stay calm and "think harder."

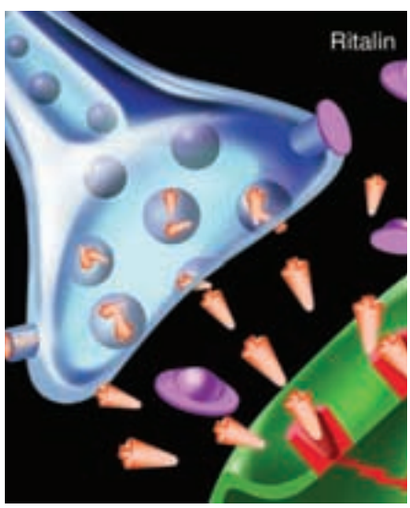
Photo illustration by Dean Dixon

Sweeping the synapse

ILLUSTRATIONS BY DOMINIC DOYLE

The dopamine transporter, pictured here as a vacuum-like tube, sweeps dopamine back into the nerve cell after its job is done (top panel). Drugs like Ritalin are thought to block the dopamine transporter, thereby increasing the supply of dopamine in the synapse (bottom panel).





on the dopamine transporter to increase the supply of dopamine in the synapse. In the average person, however, the results are less desirable: hyperactivity, impaired cognitive function and, potentially, addiction.

Children with ADHD have a paradoxical response to methylphenidate – they become less hyperactive, not more. They are better able to pay attention and are less impulsive, and they don't become addicted to the drug. This suggests that there's something different about their dopamine transporter, or about the complex interplay of molecules that carry dopamine messages through their brains.

And this is where the new science comes in.

ADHD appears to be highly heritable – meaning that it tends to run in families, especially when the disorder persists into adolescence and adulthood. Scientists believe that genetic mutations or variations may be involved, at least in some "subtypes" of ADHD.

The search for ADHD genes began with the observation that the drugs used to the treat the disorder act primarily on the dopamine system. To date, the strongest candidates are the genes for the D4 dopamine receptor and the dopamine transporter, for which variations, also called polymorphisms, have been found in studies of children with ADHD and their families.

The role of these genes in ADHD also is supported by studies of "knockout" mice, in which the genes have been altered so the proteins they encode do not function properly. Pioneering studies by Marc Caron, Ph.D., and his colleagues at Duke University, for example, have shown that disruption of the gene for the dopamine transporter in mice results in hyperactivity when they're put in a novel environment.

The mice also "have a lot of problems in learning and memory tests," says Caron, James B. Duke Professor of Cell Biology. When put in an eight-arm radial maze with a sweet breakfast cereal at the end of some of the arms, the knockout mice have a harder time finding the treat, compared to normal mice. "They keep going back to the same arm they've just been in," he said. "They don't learn."

What was most surprising, however, was that when the knockout mice were given methylphenidate, they became less hyperactive and their cognitive skills improved. This finding challenged the conventional wisdom that the drug acts through the dopamine transporter to increase the brain's supply of dopamine. Knockout mice didn't have a functional transporter, and methylphenidate didn't boost their dopamine levels. Yet the drug still calmed them.

The Prozac clue

Caron believes serotonin may be involved. In a 1999 study, he and his colleagues reported that the antidepressant Prozac, which blocks the serotonin transporter, reduced hyperactivity in mice with the "knocked out" dopamine transporter. So did L-tryptophan, the amino acid from which serotonin is synthesized. Both agents boost serotonin levels.

Mice are not humans, Caron cautions. In human studies, for example, Prozac has not been found to be effective in relieving symptoms of ADHD. But the mouse model suggests that ADHD is more than a dysfunction of the dopamine system. "My guess is that it's probably 20, 30 or 50 genes that are involved in modulating pathways in the brain that could give you symptoms of ADHD," he says. "It's probably an imbalance between neurotransmitter systems."

Randy Blakely, Ph.D., director of the Center for Molecular Neuroscience and Allan D. Bass Professor of Pharmacology at Vanderbilt, agrees that a lack of dopamine by itself cannot explain ADHD. There is evidence that norepinephrine is involved, he says.

For one thing, a new ADHD drug, Strattera, blocks the norepinephrine transporter, and seems to be particularly good at improving attention. Another clue, discovered recently at Vanderbilt, is the link between a mutation in the norepinephrine transporter and attentional problems in children and adults.

In the early 1990s, Blakely and his colleagues at Yale and Emory were the first to clone the genes that encode the norepinephrine and serotonin transporters. The identification of these genetic sequences, coupled with automated, high throughput screening techniques for evaluating them, has speeded the search for new drugs that may affect the function of the transporter proteins. These methods also are aiding the search for mutations in transporter genes, or variations in those genes that might be associated with a greater risk for disease.

Soon after coming to Vanderbilt in 1995, Blakely began collaborating with Dr. David Robertson, professor of Medicine, Pharmacology and Neurology, and an internationally known expert on heart rate and blood pressure regulation. They suspected that a mutation in the norepinephrine transporter might be responsible for orthostatic intolerance experienced by one of Robertson's patients and her identical twin sister. The syndrome is characterized

"We're dealing with a syndrome with many, many complexities and variable presentations. We need to be able to categorize subjects better. And one way to do that would be if we could link their genetics with the risk for this disorder, and link more than their genetics, link specific biochemical pathways."

Randy Blakely, Ph.D., director of the Center for Molecular Neuroscience and Allan D. Bass Professor of Pharmacology at Vanderbilt

DEAN DIXON

by a racing heart, nausea and dizziness when a person stands up.

Upon testing the women and their family, the researchers found a genetic mutation that effectively disabled the transporter in five family members, including the twins and their mother. All five had high blood levels of norepinephrine, and their heart rates jumped when they stood up, although only the twins had the full-blown syndrome.

While the mutation does not explain all cases of orthostatic intolerance, the finding, reported in 2000 in *The New England Journal of Medicine*, remains the only known neurotransmitter transporter mutation that has been associated with specific symptoms of a disease, Blakely says.

The norepinephrine transporter in the heart comes from the same gene that makes the norepinephrine transporter in the brain. Since the mutation also would be expected to affect brain norepinephrine, the researchers recently evaluated members of the same family for attentional problems.

"The folks we were able to interview who have this particular (genetic) alteration had a consistent complaint that they had a hard time maintaining focused attention and concentration," says Shelton, who has not yet published his findings in a scientific journal. "That certainly sounds very much like attention deficit disorder, and in fact if you go down through the symptoms, what they had was an alteration in attention without apparent hyperactivity."

More than genetics

In another study, Blakely and Dr. Steve Couch, assistant professor of Pediatrics, are looking for genetic mutations that may affect the function of dopamine and norepinephrine transporters in children with ADHD and their family members.

"We're dealing with a syndrome with many, many complexities and variable presentations," Blakely explains. "We need to be able to categorize subjects better. And one way to do that would be if we could link their genetics with the risk for this disorder, and link more than their genetics, link specific biochemical pathways."

Just as dopamine alone cannot explain ADHD, neither can genetics. Environment must play a role.

Exposure to nicotine, cocaine and environmental pollutants in the womb has been implicated in the later development of ADHD, as have thyroid problems. Stress has been linked to various behavioral and attentional problems, and chronic sleep deprivation paradoxically produces hyperactivity in children.

In the late 1990s, Michael McDonald, Ph.D., and his colleagues at the National Institutes of Health became interested in a rare genetic condition called resistance to thyroid hormone (RTH) syndrome, which can cause mental retardation, short stature, deafness – and ADHD.

Most children with ADHD have normal thyroid function. But when the mutated version of the human gene that causes RTH is inserted into mice, the resulting "transgenic" animals exhibit the hallmark characteristics of ADHD – hyperactivity, impulsivity and difficulty paying attention.

"The hyperactivity dissipates when they get into adulthood, but the attentional deficits and impulsive behavior persist," says McDonald, who has continued to study these "transgenic" mice since moving his lab to Vanderbilt in 1999. Males are more likely than females to exhibit these symptoms. In addition, methylphenidate dampens their hyperactivity, whereas the drug spurs more activity in normal control mice.

Tracing the circuitry of the brain

Another way to study ADHD is by taking "pictures" of the brain. Using a technique called functional magnetic resonance imaging, or fMRI, scientists can determine which parts of the brain are "activated" when performing a task that measures attention or learning.

The MRI scanner consists of a large, doughnut-shaped magnet that can generate magnetic fields several thousand times stronger than the Earth's field. Functional MRI measures changes in the magnetic properties of blood as it transports oxygen to brain tissue in response to increased neuronal activity.

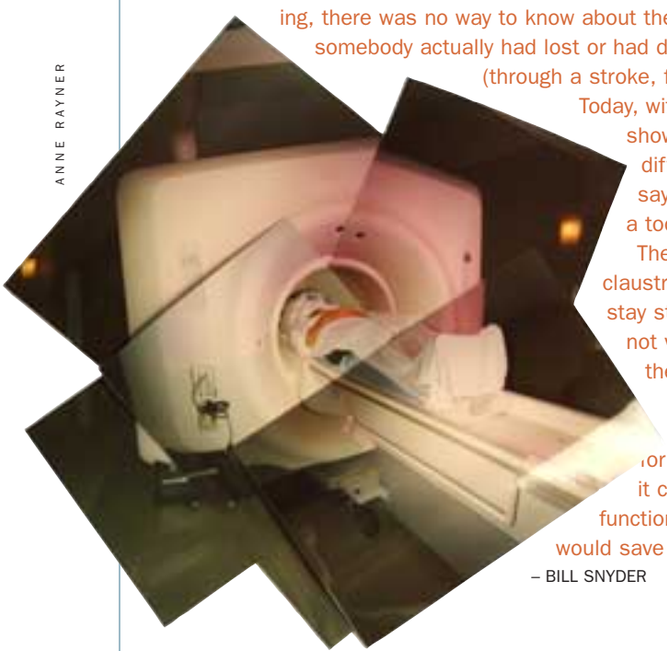
"Neuronal activation requires energy," says John Gore, Ph.D., director of the Institute of Imaging Science at Vanderbilt University Medical Center. "To get the energy, the blood flow increases, bringing oxygen and glucose. The net effect is you wash out deoxygenated hemoglobin (hemoglobin that has given up its oxygen) from tissue, and the MRI signal increases."

After climbing into the magnet and staying very still, the subject is asked to look at a picture, or listen to sounds, or perform a physical function, such as tapping his or her finger during the study. The signal can then be used to pinpoint the area of the brain involved in the cognitive function. Because it is non-invasive and does not involve the use of radiation, fMRI is a preferred technique for scanning the brains of children.

Before he moved last year to Vanderbilt, Gore helped pioneer the application of fMRI to reading disabilities at Yale University. He and his colleagues, who included Dr. Sally Shaywitz, reported this summer that the neural circuitry for reading is present in even the most persistently poor readers, but it has not been properly activated. The study supports the value of early interventions aimed at stimulating the ability to sound out words and understand word meanings.

Gore, who is Chancellor's University Professor of Radiology & Radiological Sciences and of Biomedical Engineering, is continuing to push the frontiers of fMRI. He and his colleagues at the Vanderbilt Kennedy Center for Research on Human Development are studying brain activation in children who have trouble with math, and they're planning to study children with ADHD who were exposed to cocaine in the womb, to see if they respond differently to methylphenidate.

"The main issue at the moment is to even know which circuits are involved because different drugs do target different parts of the brain," Gore says. "Until we had imaging, there was no way to know about the circuits in the brain, other than if somebody actually had lost or had damage to a particular part of the brain (through a stroke, for example)."



ANNE RAYNER

Today, with techniques such as fMRI, "we've shown that you can detect the effects of different types of interventions," he says. "You can now begin to use this as a tool to actually monitor treatments."

There are limitations: Some children feel claustrophobic in the "doughnut," or can't stay still for very long. The technique also is not very good at determining which part of the brain activates before another.

The technique also is expensive – currently running about $500 to $800 for an hour-long exam, Gore says. But if it can help identify problems with brain function and achieve better outcomes, fMRI would save money in the long run, he says.

– BILL SNYDER

This mouse model, which displays many characteristics of the human condition, may be useful in testing new drugs to treat the disorder. It also may help explain how environmental factors – including exposure to hormones – can contribute to the development of ADHD, says McDonald, who is assistant professor of Pharmacology and director of the Murine Neurobehavioral Laboratory.

As pups, the transgenic mice have a mild "thyroid resistance phenotype," characterized by high levels of thyroid stimulating hormone and high thyroid hormones, which also are seen in the human condition (RTH). This lasts for only three or four weeks, however. By the time the mice exhibit ADHD-like behaviors, their hormone levels are completely normal. "We think it's the elevated thyroid hormones (during development) that are causing the long-term brain and behavioral abnormalities," he says.

The tender brain

"The thyroid hormone is critically important for brain development, and regulates hundreds of genes," McDonald continues. "What these mice show us is that it's possible to have a transient thyroid abnormality during development, and later on to have many of the symptoms associated with ADHD."

In McDonald's studies, normal pups born to transgenic mothers have transient hyperactivity, suggesting that exposure to excess maternal thyroid hormones in the womb also can contribute to ADHD. "My suspicion is that transient thyroid abnormalities during development contribute to a lot more cases of ADHD than we're currently aware of," he says.

McDonald and his colleagues are using gene microarrays, plates containing thousands of different pieces of genetic sequences, to search for the expression of genes during different periods of development in the mouse that may be associated with the RTH mutation. Not long ago, it might have taken years to determine the impact of a single gene. Today, the Vanderbilt researchers can screen 23,000 genetic sequences simultaneously.

The thyroid connection to ADHD also raises questions about the role of pollutants. In particular, exposure to PCBs through breast milk or in the womb has been linked to problems with learning, memory and attention.

"A lot of these environmental chemicals like dioxins and PCBs impinge on the thyroid system," McDonald explains. "These are ubiquitous toxins found in many

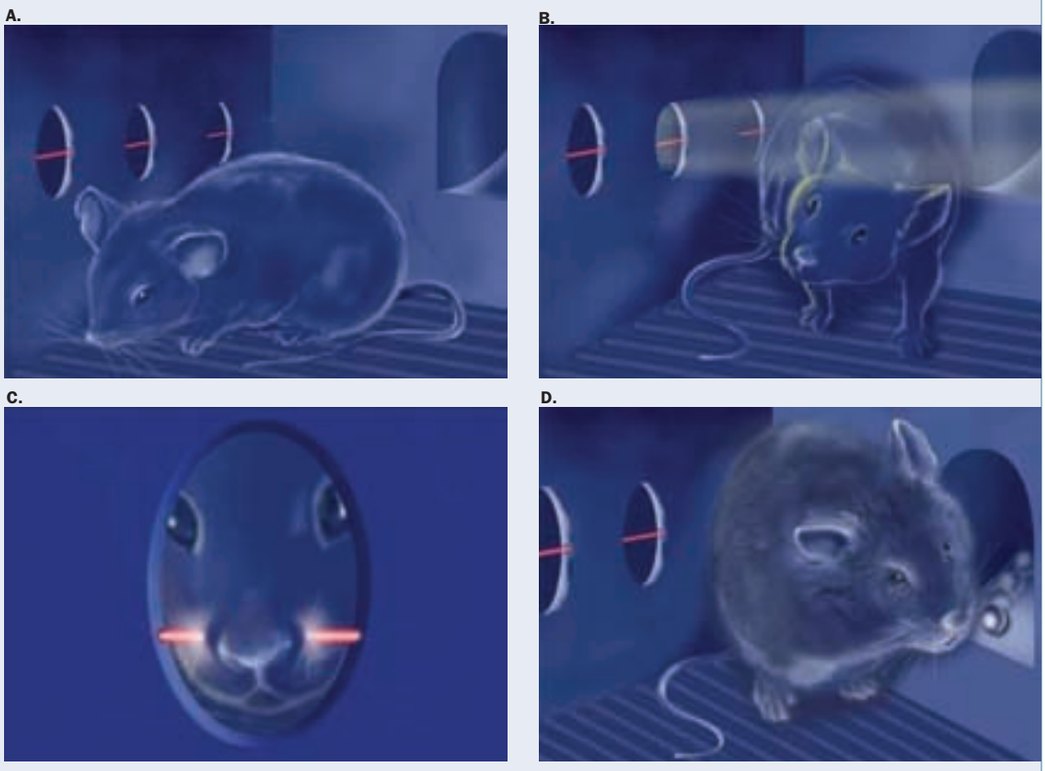
Paying attention

ILLUSTRATIONS BY DOMINIC DOYLE

To test the reaction time of a genetically engineered mouse that displays ADHD-like behaviors, Michael McDonald, Ph.D., and his colleagues at Vanderbilt University Medical Center shine brief flashes of light through one of three holes in the mouse's cage (B).

By sticking his nose into the lighted hole, the mouse breaks an invisible infrared beam (C), triggering the release of a food pellet into the tray behind him (D).

Because the genetically engineered mice have difficulty paying attention compared to normal control mice, they have slower reaction times, fewer correct responses and, as a result, they are rewarded less often.



of our foods. Children are very sensitive to that, much more than adults."

Understanding ADHD will require "converging evidence" from a wide range of disciplines, including molecular genetics, behavioral neuroscience and clinical research, McDonald says.

What's needed, adds Shelton, is a "molecular dissection" of ADHD – a way of matching an essential characteristic, such as hyperactivity, with a specific pathway, in this case, the dopamine system. This approach aims to rewrite the current classification system for ADHD, spur discovery of more specific and effective treatments, and resolve the debate over the over-diagnosis or under-diagnosis of the condition, he says.

J.T. King's parents hope the answers come soon. He currently takes Metadate, an extended-release form of methylphenidate that can be given once a day. Concerned that the long-term effects are not well understood, they take J.T. off the medication on weekends, holidays and during the summer, and depend on patience and a healthy sense of humor to get them through the rough spots.

"I could pull my hair out sometimes with my son," says J.T.'s mother, Jere King. "Then you have to stop and think, 'OK. He didn't mean it. It's not intentional. Get a grip.' "

Constant reinforcement is essential. "You just have to always raise them up on the areas that they're strong, praise them a lot to get their self confidence up, and in the areas that they're not, you just have to be supportive and tell them they can do it," she says.

Like most parents of children with a challenging condition, King often has wondered: "Why did this happen?" That question may not be answerable, although perhaps some day she'll know how it happened. In the meantime, she's determined to prevent ADHD from becoming for her son a disability – or an excuse.

"That's not a crutch you can take through life with you," she tells J.T. "That's something you have to recognize, accept and surmount." **LENS**

Questioning the tide of ADHD

An estimated 3 percent to 6 percent of school-aged children in the United States are diagnosed with attention deficit hyperactivity disorder. Little information is available about racial and ethnic differences in the incidence of ADHD, but some experts worry that the disorder may be over-diagnosed in certain groups.

At historically black Meharry Medical College in Nashville, Dr. Susanne Tropez-Sims and her colleagues noticed that a number of African-American children who were being referred by their physicians to the pediatric clinic with a diagnosis of ADHD actually did not have the disorder.

Some of the children had other psychological problems that were related to the stress of being exposed to violence in their neighborhoods. "Those issues have to be addressed before you can get a change in behavior," says Tropez-Sims, W.K. Kellogg Professor and chairperson of the Department of Pediatrics.

Tropez-Sims doesn't know how often children are misdiagnosed, but she wants to find out. She and her colleagues are planning to conduct a needs assessment for establishing a center for ADHD services and research at Meharry.

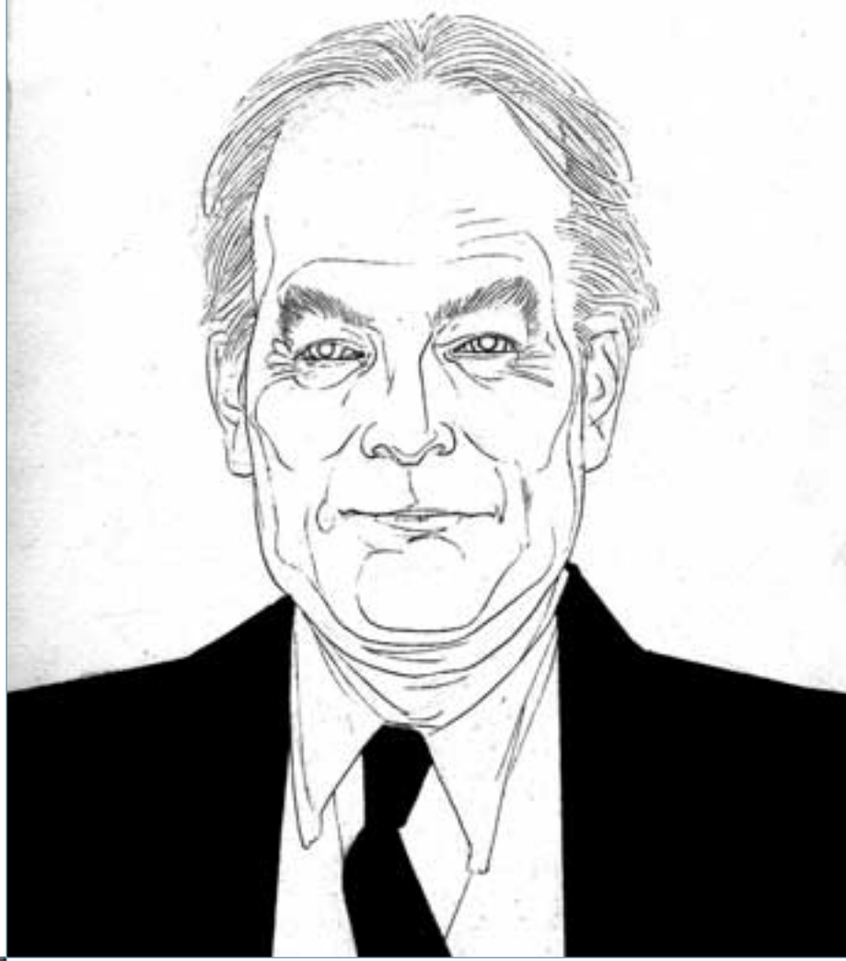
Treating behavior problems in children is important, but so is a correct diagnosis. "We just need to make sure that if we place children on stimulants they really need it, and that it does help," she says.

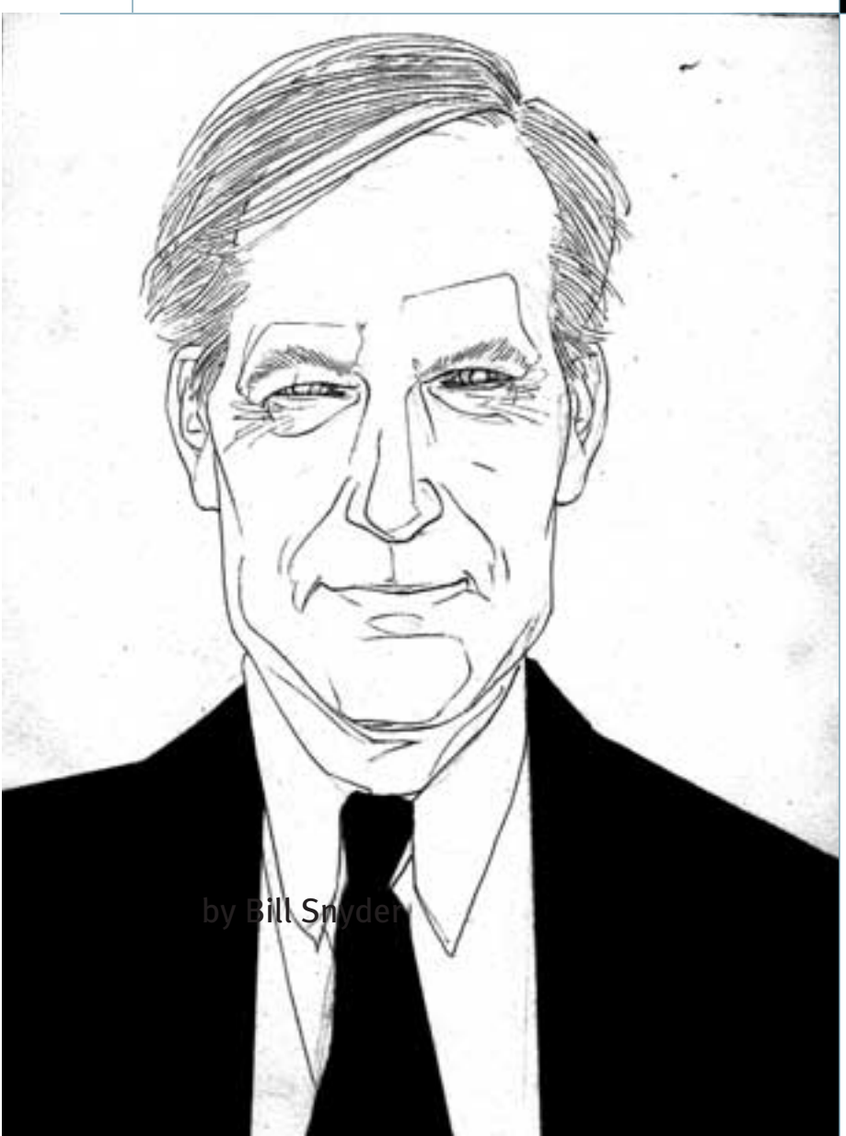
– BILL SNYDER

Cracking the brain's genetic code

A conversation with Drs. Joseph T. Coyle and Edward M. Scolnick

ILLUSTRATIONS BY DAVID JOHNSON





by Bill Snyder

Two of the nation's leading experts in neuropsychopharmacology discuss the opportunities and challenges facing scientists as they search for better ways to treat disorders of brain function. The discovery of "risk genes," advances in brain imaging and animal models are providing powerful tools for "teasing apart the pathological pathway." But are there enough clinician-scientists to follow up these leads?

Pictured lower left: Dr. Edward M. Scolnick is President Emeritus of Merck Research Laboratories and is continuing his research at the company's West Point, Pa., facilities.

Pictured upper left: Dr. Joseph T. Coyle is Eben S. Draper Professor of Psychiatry and Neuroscience, and former chair of Psychiatry at the Harvard Medical School.

What are some of the challenges in developing new drugs for psychiatric disorders?

Coyle: The major challenge that we face for psychiatric disorders is that there is no obvious brain pathology that leaps out at you, unlike neurological disorders where there's some very clear pathology and clear targets. And so the approach has historically relied on serendipity – that is developing novel compounds and looking for behavioral effects. That's really a very inefficient way to attack these problems. Even the development of SSRIs (serotonin-specific reuptake inhibitors, a new class of antidepressants that includes Prozac and Paxil) was not linked to a detailed understanding of the pathophysiology of depression.

I think what has taken place over the last 15 years is the development of more powerful strategies to help us out. One strategy is brain imaging, both structural and functional brain imaging, which has allowed us to identify areas of the brain and circuits that do not appear to be working properly. These approaches give us a bit of a functional pathologic signature. The second strategy is genetics and the contributions of the Human Genome Project.

How useful are animal models for developing drugs for cognitive disorders?

Scolnick: They have been useful in many fields of medicine. Finding the genetic predispositions or the causative genes for any number of human diseases has allowed scientists over the last 10 or 20 years to model those diseases in genetically altered mice and rats. It's been done in the atherosclerosis field, the cancer field; it's been done somewhat in the field of inflammation, the obesity field. It's quite remarkable how well and how much information has come from it, even though in some cases, like the lipid field, many years ago people didn't think this was a worthwhile thing to do at all.

Finding risk genes for cognitive disorders will allow scientists over the next decade to put these genes in animals or alter these genes, and then ask, "What can you learn from the behavior of a mouse or rat with a mutated or altered human risk gene that's been associated with one of these illnesses? Will that become a useful way to test for more drugs?"

It's probably impossible, given the difference in the brains of a rodent and a human to model it perfectly, but I think useful information will come. It will be one of the ways the field progresses.

Coyle: I think in our field, the best example has been the work in Alzheimer's disease. Mice don't develop the pathology of Alzheimer's disease because the gene that encodes for the protein that creates amyloid deposits in human beings has a different amino acid sequence in the mouse, and so amyloid deposits are not formed naturally in rodents. Scientists have created an animal model for Alzheimer's disease by inserting into the mouse genome the mutation in the human gene that has been linked to the inherited form of Alzheimer's disease. A similar approach has been used with another gene, the mutant human presenilin gene, which increases the risk for Alzheimer's disease and acts on the amyloid protein.

And so we now have mice that develop the pathology of Alzheimer's disease. Major drug companies are developing drugs that will interfere with the generation of the amyloid or enhance its clearance. So, while these mice may not be behaviorally perfect models of Alzheimer's disease, they certainly are powerful tools for teasing apart the pathologic pathway and providing drug targets.

One point I'd like to emphasize is that many of these risk genes ultimately may exert their effects by disturbing the development of the brain. And the abnormal behavior that is seen in the animal, the mouse, when it's mature, may not simply reflect abnormal neuronal function, but the disruption of developmental processes that ultimately caused this behavioral manifestation. Several of the risk genes that have been identified or implicated in schizophrenia are genes that encode for proteins that play a very important role in brain development.

How do you think our increased understanding of genetics of brain disorders will ultimately improve therapeutic development?

Scolnick: Through the emerging risk genes. But we're only really starting to identify them because they required the human genome sequence being there in order to really make progress in the field. So it's much too early for that to pay off with practical new therapeutics.

Coyle: I would agree. It's a lot more complicated than disorders that follow classical Mendelian genetics. Autism, schizophrenia, the mood disorders involve, or likely involve, what is known as complex genetics in which there will be multiple genes of small effects that in combination result in the observed disease, and so that presents real challenges.

It turns out that because of the complex genetics, it's quite possible that in different populations we'll see certain risk genes that we don't see in other populations. So it's going to take a while, but I have to say that I'm much more optimistic than I was 10 years ago.

Why are you more optimistic?

Coyle: Because we have the human genome pretty much mapped, our ability to find these risk genes has been very powerfully enhanced. Right now is going to be kind of the grunt work of identifying them. If we can use the Alzheimer's story as sort of a template, I think that once one or two are identified in a specific disorder, we'll get a handle on a pathway that could be quite revealing.

Scolnick: I think finding these risk genes was a literally impossible problem before the human genome was mapped. I think it was just too hard. The technology wasn't

there and the information to do the studies wasn't there. I don't think anyone ever would have found them.

What are some of the ethical issues that impede hypothesis-testing in the psychiatric clinic?

Scolnick: I don't think they're special to this field. Clinical research studies require clear informed consent forms, and protocols need to be evaluated in advance by institutional review boards. The special problem in studying brain or behavioral diseases is whether the patient is competent to understand the form and sign it or whether someone else representing the patient needs to do it. I think that's the more unique part of this field.

Coyle: I would agree with that. I think a very special challenge would be autism, where the symptom onset is typically in the second year of life. There's growing evidence from behavioral and educational intervention research that the earlier the intervention is brought to bear, the better the outcome. If we're going to think about potential pharmacological interventions to treat autism, we're going to be presented with special challenges about how do you do this in very young children.

The final thing I would say is that I don't see these disorders as being easily parsed into disorders that simply respond to drugs and not to psychological interventions. I think what we're finding more and more is that the combination of an appropriate psychological or psycho-educational intervention with the appropriate drug can result in much more robust responses.

Scolnick (to Coyle): Do you think that the system for conducting clinical trials in younger patients in the U.S. is optimally set up from an operational and training perspective, or do you think more attention or more training programs are needed?

Coyle: The National Institute of Mental Health funds a consortium of child and adolescent psychiatry clinical trial units, so that's the good news. The bad news is that the clinician-scientist is an endangered species, and especially in the area of child and adolescent psychiatry, the number of individuals who are involved in research and have the knowledge and skill sets to do this research is really quite small. At the leading residency training programs, a significant portion of the M.D./Ph.D.s – about 20 percent – go into psychiatry. But that is not enough to carry the load. This is an area that really needs, I think, a sustained investment from NIH.

On the other hand, the proposed merger of the National Institute of Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism is a positive sign. Genetic studies are revealing risk genes common to different types of substance abuse, and including problems with gambling. Furthermore, serious mental illnesses such as schizophrenia and bipolar disorder have a high prevalence of co-occurring substance abuse that adversely affects outcome. Anything we can do to increase the cross talk among these three institutes, the NIDA, NIAAA and NIMH, should be beneficial for developing more effective treatments.

Is it more difficult to develop drugs for children and adolescents?

Scolnick: Developing drugs for use in children is harder. Significantly more safety data are required. Characteristically any trials with a new medicine are started in children only after almost all of the animal safety is done, including carcinogenicity studies, and after significant information is available in adults on efficacy and safety. And then you have to start again to find the right dose (in children and adolescents), because the dose that you find in adults may or may not be the right dose based on the size of the younger people plus their metabolic state. It's significantly more work to do that.

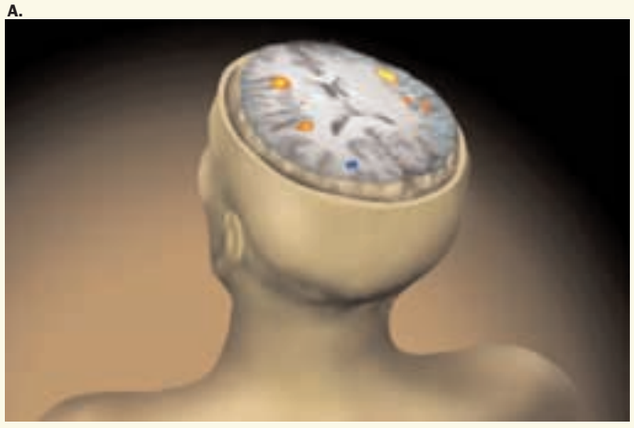
Are there concerns in treating children with these kinds of drugs, considering that their brains are still developing?

Coyle: Yes, and it cuts two ways. Up until about 15 years ago, because of the dominance of psychoanalytic thinking in the

Imaging the brain

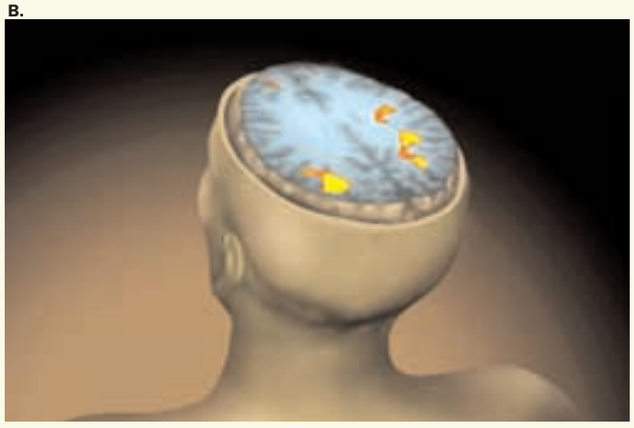
ILLUSTRATIONS BY DOMINIC DOYLE

A.



Functional magnetic resonance imaging (fMRI) enables scientists to "see" how the brains of different people respond differently to specific mental tasks, such as reading or doing math problems. The image on the left shows a section of the brain of a person with schizophrenia performing a spatial working memory task; for example, remembering the location of an object after a brief delay.

B.



The image on the right shows the brain of a person without schizophrenia performing the same task. Areas shaded in red indicated increased brain activity; areas colored blue indicate decreased activity. These pictures of differing brain function may provide clues to the cognitive impairment experienced by many people with schizophrenia. See pages 13 and 27 for more information about the technique.

Brain scans courtesy of Sohee Park, Vanderbilt University

field, it was believed that children could not have depression. Unfortunately, children not only can have depression, they can commit suicide, suicide being the third most common cause of death in adolescents. Studies done characterizing depression in children have shown that at any point in time about 1 percent to 2 percent of children under the age of puberty would satisfy the diagnosis of major depressive disorder.

When depressed children were followed longitudinally, it turned out that they would spend somewhere around 70 percent of their time in a state of depression or minor depression, so when you think about the impact of being psychologically depressed, feeling bad about yourself, feeling pessimistic, perhaps feeling suicidal, from say the age of 8 until the age of 15, that's half one's life. So there's clear evidence that not treating can markedly distort the developmental trajectory.

So, as I say, it cuts two ways. Yes, there is a very real concern that these drugs, which affect how neurons communicate with each other in the brain, could have some adverse effects on brain development. That is currently a topic of investigation and research supported by the National Institute of Mental Health. On the other hand, not intervening can result in a child with a condition being persistently symptomatic and having a very skewed developmental trajectory.

By studying genes that affect drug metabolism, scientists are beginning to understand better why certain individuals respond differently to medications. Will this field of study, called pharmacogenomics, contribute to a new era of "individualized medicine," the tailoring of medical treatment to individuals with psychiatric disorders?

Scolnick: Again, I think it's a long way off because we're just starting to find the genes and then there are the genes that affect the metabolism of the drug, and those will be different in different people, so it's a long way before we can do that. Ultimately, that's what will happen in most of medicine over the next, I don't know, 10 years, 50 years. It's really hard to tell, but ultimately that's the way it's going to be.

Coyle: I agree that pharmacogenomics will have a substantial impact on psychiatric treatment. I think we'll look back at this time with our DSM-IV (fourth edition of the *Diagnostic and Statistical Manual*), and see it as an incredibly naïve way of categorizing these disorders.

The manual is a catalog of mental disorders based on diagnostic characteristics that have been developed through epidemiological studies. For example, we've worked really hard to try to separate schizophrenia from bipolar disorder, both of which are characterized by psychosis. Now with these genetic studies, it looks like there may be risk genes unique to each disorder; some may be shared by both. Once we understand the genetics better, we'll have a very different take on how to parse these disorders out, and therefore how to treat them.

How will that pharmacogenomics affect the economics of drug development? If there are no more "blockbuster drugs," will it become economically difficult to develop new medications for niche markets?

Scolnick: No, no, that's just not going to happen. Pharmacogenomics is going to improve the ability to find drugs, make better drugs, make safer drugs, do the clinical trials better. Trials are going to be cheaper and easier to do, and so if the big companies don't do it, the littler companies will do it. It's not going to impede anything. **LENS**

Hunting for genes that "conspire" with environmental triggers to cause disease

Now that the sequence of the 30,000 or so human genes has been mapped, one of the biggest challenges facing researchers is identifying groups of genes that collectively conspire to make some people susceptible to common yet complex diseases, from cancer and heart disease to disorders of brain function.

One place to start is to study candidate genes that already have been implicated in disease. For example, drugs used to treat attention deficit hyperactivity disorder (ADHD) primarily affect regulation of the neurotransmitter dopamine, which transmits messages between nerve cells. Thus, it is reasonable to look at genes involved in dopamine regulation and, in particular, for polymorphisms, or variations in the DNA sequences of these genes that are found in the population.

Genetic polymorphisms that occur more frequently in families of children with ADHD than in unaffected families suggest that, while each variation alone may not be sufficient to increase risk, the combination of polymorphisms may be important in the development of the disorder.

Another way to search for disease-related genes is to use markers to scan all of the 23 pairs of chromosomes contained by normal human cells, looking for regions that are inherited more frequently by people who have a certain disease than would be expected to occur by chance, or to cull through the millions of single nucleotide polymorphisms, or changes in a single letter of the DNA code, that are estimated to occur throughout the entire human genome.

This "needle in a haystack" approach is made possible by today's powerful supercomputing capacity, which can rapidly determine complex, statistically significant associations between dozens of genetic variations.

Using these statistical techniques, researchers also can look for interactions between genes and the environment. "Association analyses" are often used to determine whether a combination of genetic polymorphisms and environmental factors are more common in people who are diagnosed with a particular disease than in a "control group" of people who aren't.

For example, a study published this summer in the journal *Science* found that people born with a variant of a gene important in the regulation of the neurotransmitter serotonin are significantly more likely to become depressed after experiencing four or more stressful life events, than are people who don't have the polymorphism. This finding suggests that the presence of genetic variations alone may not be sufficient to cause some complex diseases – they require an environmental "trigger."

"Essentially, genetics deals the cards, and environment plays the hand," says Jonathan L. Haines, Ph.D., director of the Program in Human Genetics at Vanderbilt University Medical Center. – BILL SNYDER

Randy Blakely's parents, Glenn and Elizabeth, in happier times – in a park near their home in Columbus, GA.

Courtesy of Randy Blakely

An explosion in the family

Motivated by the discovery of his father's suicide, a Vanderbilt researcher seeks clues to depression

By Bill Snyder

More than 40 years after his father committed suicide, and 25 years after he found out about it, Randy Blakely is still trying to understand why it happened.

Blakely, director of the Vanderbilt Center for Molecular Neuroscience, was only 22 months old when, in December 1960, his father ended his life. "It was like a bomb went off," he says. "The debris that scattered through the lives of my siblings and my mother didn't allow a lot of penetration into this issue for a long time."

As soon as they could, his three older brothers and older sister drifted away from the family home in Columbus and nearby Fort Benning, Ga., where their father, Glenn Blakely, a career Army officer and veteran of World War II and Korea, had directed the ROTC program.

One sibling would flee to the jungles of Vietnam. Three other siblings and Blakely's mother would later be treated for depression. But because he was not told what had happened – "I thought he had a heart attack," Blakely says – he was sheltered from the shock, the sadness and the anger that continued to reverberate for years through the rest of his family.

It was not until he was a college junior, and already planning a career in science, that his mother told him the story: How his father had become severely depressed the previous autumn. How she sought help from their minister, and how her husband angrily rejected it. How desperate he became and how, that December morning, "The children found him."

In shock, Blakely scoured his father's medical and military records. Glenn Blakely had been diagnosed with hepatitis, inflammation of the liver that could have left him fatigued, depressed and perhaps convinced that he was going to die anyway. But there is no evidence of a family history of depression, no biological clue to explain why he ended his life at the age of 47.

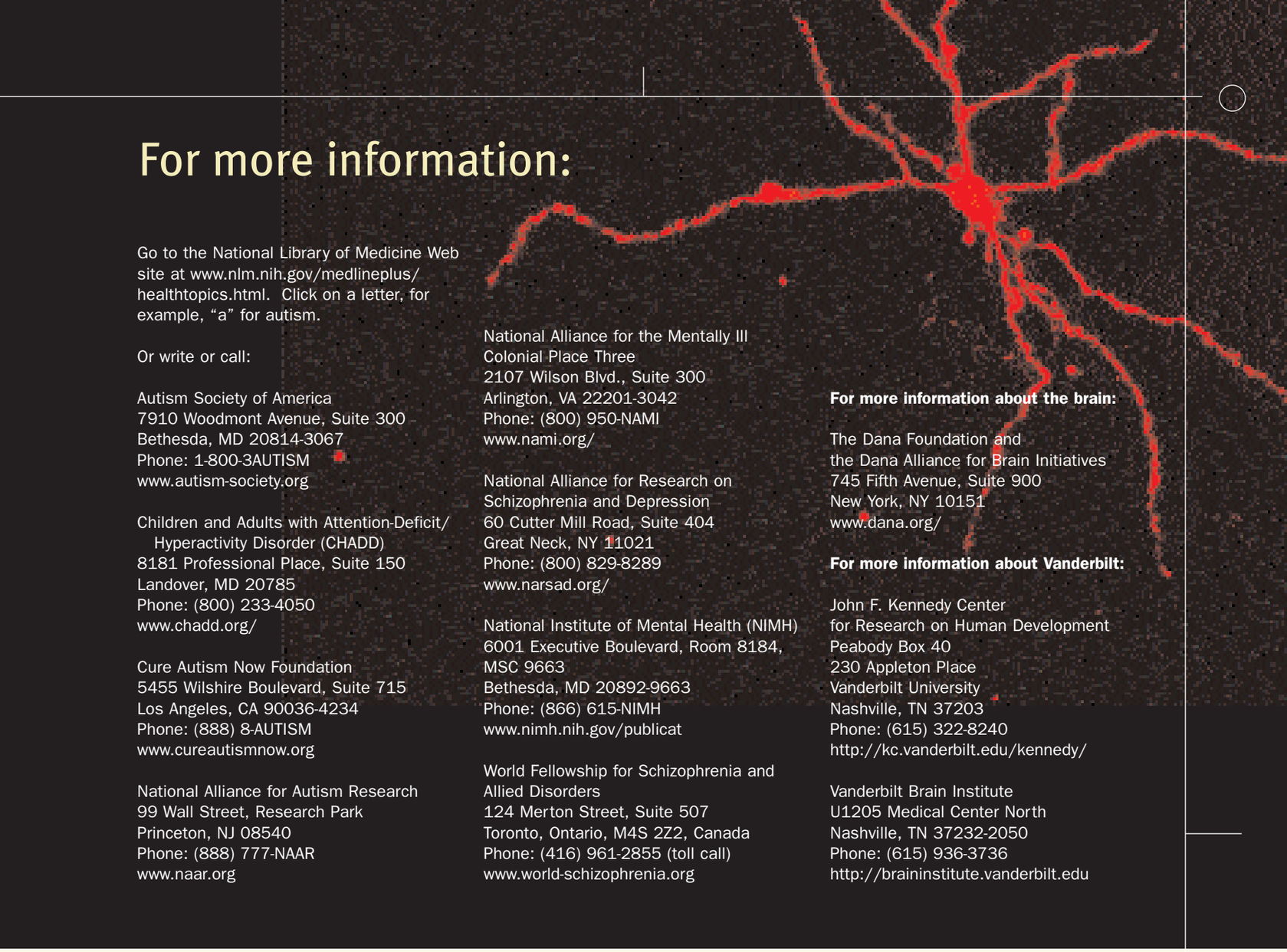
Meanwhile, Blakely pursued his career, earning his Ph.D. in Neuroscience from Johns Hopkins University in 1987, and teaching and doing research at Emory University before joining the Vanderbilt faculty in 1995. His research involves neurotransmitter transporters, proteins involved in transmitting electrical signals through the brain. "It is a very odd turn of events that my research would end up identifying genes that are the targets in the brain for antidepressants," he says.

"In a very personal way, (the suicide) has remained a motivation for me staying in the hunt for clues to mental illness," Blakely says. "I certainly developed my own interest in science and brain independent of this … But I know my awakening to the horrors of brain disease in my own family reinforced that trajectory, and made me much more aware of what other families have to go through, and particularly children who have traumatic events happen to them."

In collaboration with his Vanderbilt colleagues, including Dr. Richard Shelton and Elaine Sanders-Bush, Ph.D., Blakely has found some genetic clues to depression. But it's not as simple as genes determining behavior. "All the really complex disorders (especially those involving brain function) are a very rich mix of genes and environment, and the interaction of early childhood events," Blakely says.

"The more we learn about how the brain works, the way the environment and the brain interact, hopefully … the events that happened to my family would be less likely to happen again," he says.

"Tragically, I know that they happen every day, still … (But) it's getting better." **LENS**



For more information:

Go to the National Library of Medicine Web site at www.nlm.nih.gov/medlineplus/healthtopics.html. Click on a letter, for example, "a" for autism.

Or write or call:

Autism Society of America
7910 Woodmont Avenue, Suite 300
Bethesda, MD 20814-3067
Phone: 1-800-3AUTISM
www.autism-society.org

Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD)
8181 Professional Place, Suite 150
Landover, MD 20785
Phone: (800) 233-4050
www.chadd.org/

Cure Autism Now Foundation
5455 Wilshire Boulevard, Suite 715
Los Angeles, CA 90036-4234
Phone: (888) 8-AUTISM
www.cureautismnow.org

National Alliance for Autism Research
99 Wall Street, Research Park
Princeton, NJ 08540
Phone: (888) 777-NAAR
www.naar.org

National Alliance for the Mentally Ill
Colonial Place Three
2107 Wilson Blvd., Suite 300
Arlington, VA 22201-3042
Phone: (800) 950-NAMI
www.nami.org/

National Alliance for Research on Schizophrenia and Depression
60 Cutter Mill Road, Suite 404
Great Neck, NY 11021
Phone: (800) 829-8289
www.narsad.org/

National Institute of Mental Health (NIMH)
6001 Executive Boulevard, Room 8184, MSC 9663
Bethesda, MD 20892-9663
Phone: (866) 615-NIMH
www.nimh.nih.gov/publicat

World Fellowship for Schizophrenia and Allied Disorders
124 Merton Street, Suite 507
Toronto, Ontario, M4S 2Z2, Canada
Phone: (416) 961-2855 (toll call)
www.world-schizophrenia.org

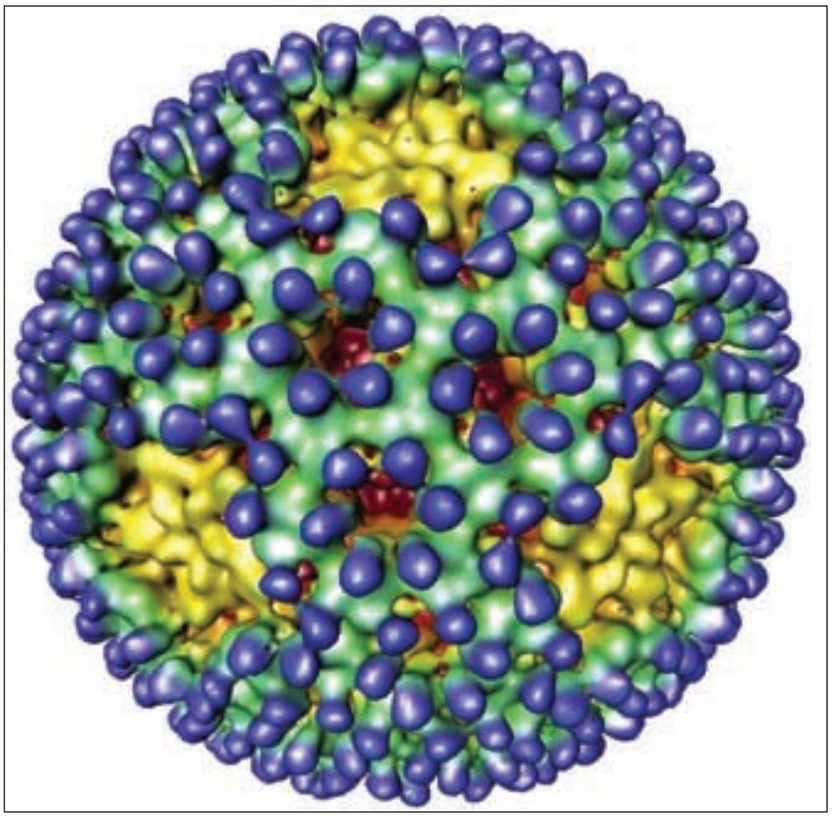
For more information about the brain:

The Dana Foundation and the Dana Alliance for Brain Initiatives
745 Fifth Avenue, Suite 900
New York, NY 10151
www.dana.org/

For more information about Vanderbilt:

John F. Kennedy Center for Research on Human Development
Peabody Box 40
230 Appleton Place
Vanderbilt University
Nashville, TN 37203
Phone: (615) 322-8240
http://kc.vanderbilt.edu/kennedy/

Vanderbilt Brain Institute
U1205 Medical Center North
Nashville, TN 37232-2050
Phone: (615) 936-3736
http://braininstitute.vanderbilt.edu



Three-dimensional image of a reovirus particle, a common pathogen used as a model for studying viral infections. This image, a computer reconstruction of cryo-electron micrographs of several reovirus particles, shows outer capsid protein (blue) used to infect cells, and core protein (yellow) important in replication.

Image prepared by Emma Nason and B. V. Prasad (Baylor College of Medicine) and Denise Wetzel and Terence Dermody (Vanderbilt University School of Medicine).

IN THE NEXT ISSUE:

Plagues and parasites
Research is providing new answers to an old question: Why do some viruses become deadly – and most don't?

The promise of vaccines
Understanding how viruses invade cells and how the immune system responds is key to preventing infection.

Early warning system
Thanks to the Internet and advanced genetic testing, scientists can stop new epidemics before they start.

Lens

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