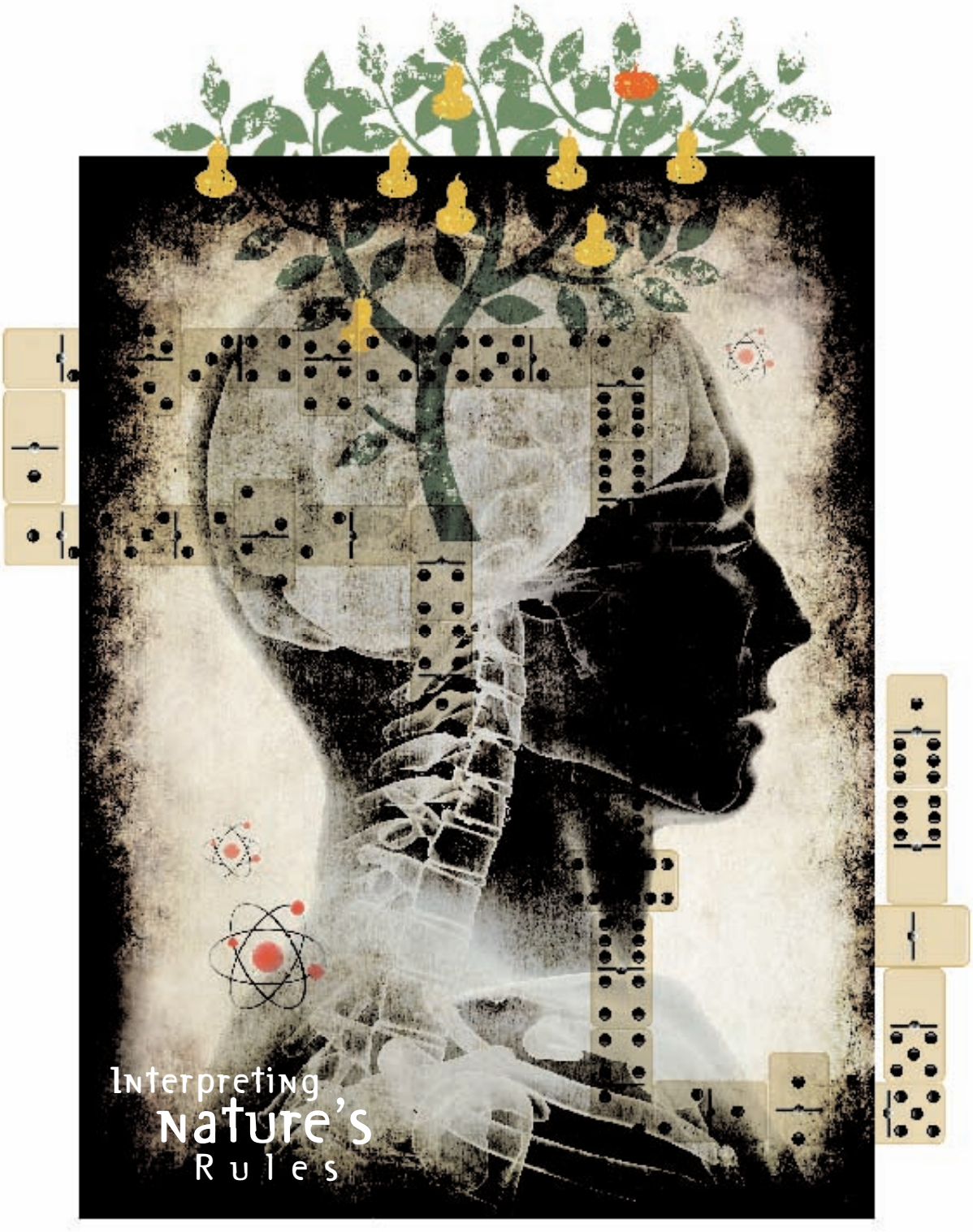
2007 Annual Review

SOUTHWESTERN MEDICINE

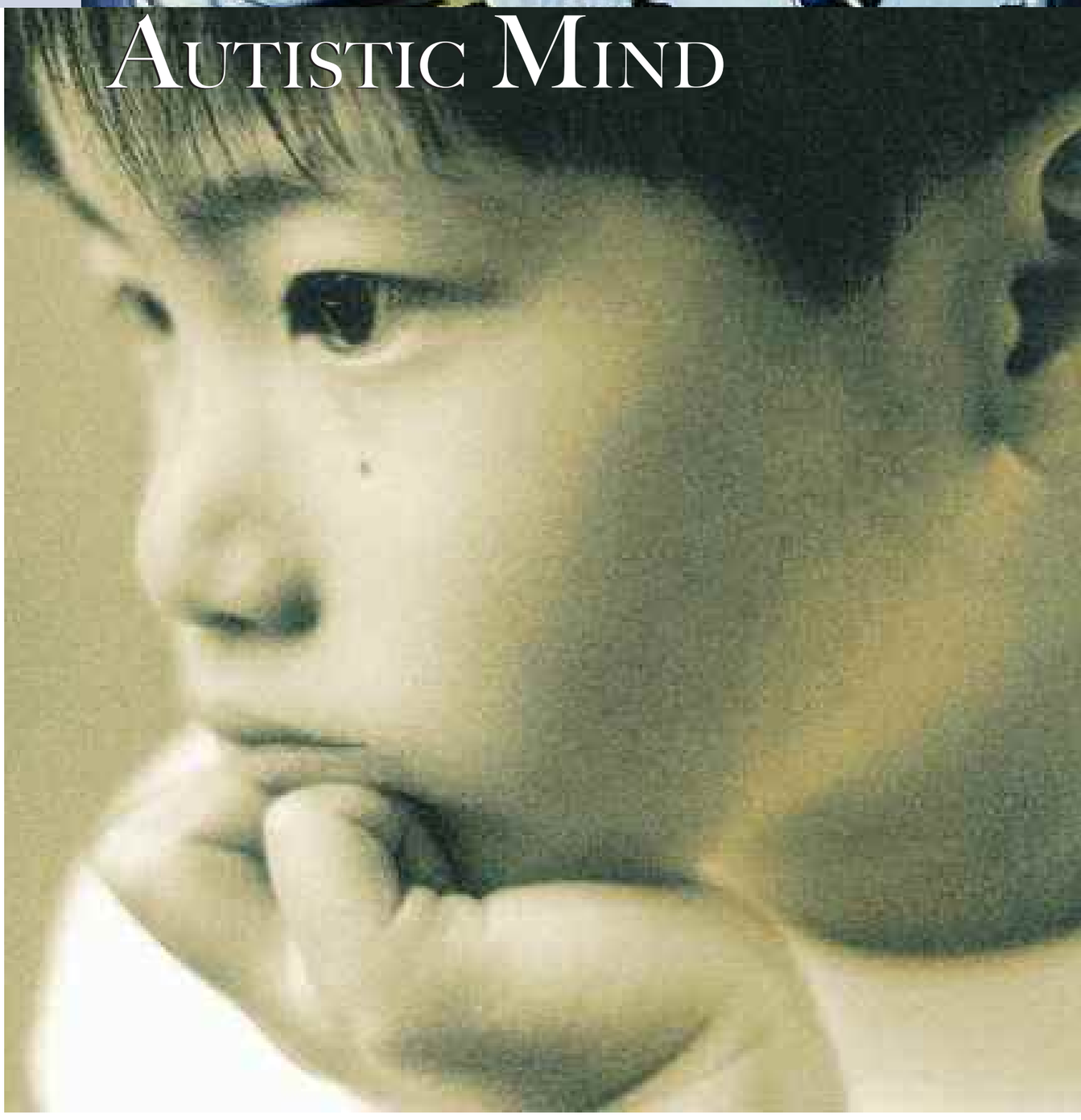


> ANGIOGENESIS > BRAIN TRAUMA > AUTISM > OBESITY

The Magazine of UT Southwestern Medical Center

C O N T E N T S

Inner Workings *of* the Autistic Mind



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

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

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

Then the progress stopped.

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

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

Jon was autistic.

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

By Erin Prather Stafford

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

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

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

Wide Span of Conditions and Symptoms

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

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

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

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

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

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

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

"Having a team of specialists conduct screening tests means there is a better chance for children to be diagnosed correctly and for the right treatments to be enacted immediately."
—Dr. Catherine Karni

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

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

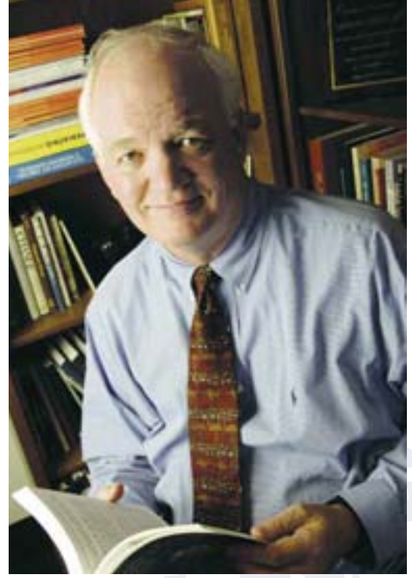
Dr. Graham Emslie, professor of psychiatry and head of child and adolescent psychiatry at UT Southwestern, said his department hopes to expand autism services.

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

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

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

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



Clues to the Mystery

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

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

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

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

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

"We want the program to be a recognized place where families come to obtain an accurate diagnosis and assistance in finding the appropriate treatments for their child."
—Dr. Graham Emslie

DR. LUIS PARADA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Hope for a Better Future

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

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

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

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

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

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

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

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

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

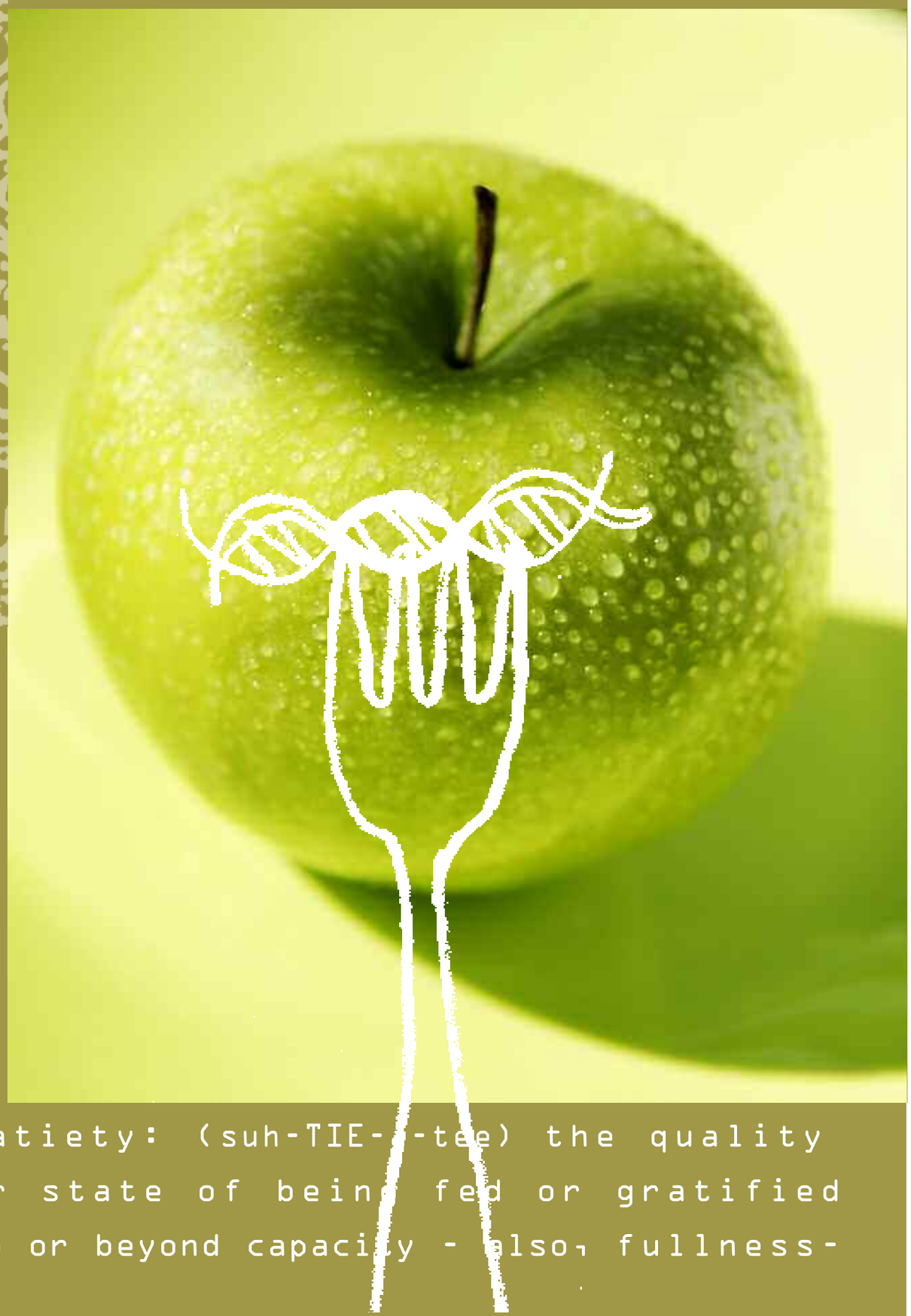
Dr. Caudy acknowledges that many parents have asked why she and Dr. Heighten chose to invest in finding the root of autism instead of improving how to treat it.

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

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

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

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



Satiety: (suh-TIE-a-tee) the quality or state of being fed or gratified to or beyond capacity - also, fullness-

A is for appetite:

UT Southwestern scientists are discovering the most elemental triggers for hunger and satiety.

You lean back in your chair, stretch out your arms and legs, and utter a simple phrase as you stare back at the empty plate that only minutes ago housed a savory steak, freshly buttered baked potato, piping hot garlic bread and a crisp salad:

"I'm stuffed."

What first got your appetite going, or spurred your tummy to rumble? How much steak and potato did you have to eat, and how long did it take to get full, a feeling known as satiety (pronounced "suh-TIE-a-tee")? Why did you overeat to the point of *stuffed?*

The answers to these questions vary from person to person.

Unlocking the mysteries of appetite and satiety are what some call the "Holy Grail" in the fight against surging obesity and its associated health risks.

UT Southwestern Medical Center scientists, clinicians and nutrition experts are working together on many fronts to understand how appetite and satiety work. They are examining the brain's chemicals and molecular pathways, tracking hormones that tell the body to start or stop eating, and evaluating the eating behavior of humans, mice and even worms. They hope to find new ways to curb overeating, enhance the feeling of fullness and, ultimately, make people healthier.

"Obesity is the most pressing medical problem facing us this century," said Dr. Jay Horton, professor of internal medicine and molecular genetics and holder of the Dr. Robert C. and Veronica Atkins Chair in Obesity & Diabetes Research at UT Southwestern. "Along with a general reduction in physical activity, the affordability and availability of high-calorie foods has contributed significantly to this problem, so it is imperative that we develop a detailed understanding of how appetite and satiety are regulated.

"Such an understanding may permit the development of targeted approaches to reduce food intake that can ultimately be used to curb the explosion of obesity in Western societies."

By Cliff Despres

Leading the Way in Obesity Research

Dr. Horton, one of the nation's top researchers investigating the myriad aspects of obesity, is the coordinating investigator for a $22 million grant from the National Institutes of Health devoted to obesity research. The money, awarded in September 2007 and to be given over five years, strengthens UT Southwestern's Taskforce for Obesity Research, a team of 29 scientists and clinicians from genetics, endocrinology, nutrition, neurology, lipid metabolism, psychiatry and epidemiology. The multidisciplinary approach is aimed at a better understanding of the processes that lead to obesity and associated metabolic disorders.

"These findings increase our understanding of the molecular circuitry that controls appetite initiation and suppression."

— *Dr. Joel Elmquist*

"This grant extends and strengthens our task force's ability to conduct studies to gain much-needed insight into key molecular pathways that govern energy metabolism and translate that into the development of new approaches to prevent obesity and treat associated metabolic complications, such as heart disease and diabetes," Dr. Horton said.

A still greater boost in support of UT Southwestern's programs in this crucial area of medicine came from the 2007 Texas legislative session. The Legislature and the governor, with active support from the state comptroller, approved a $9 million per year "special item" to fund the institution's new Center for Obesity, Diabetes and Metabolism Research. This pivotal state funding ensures that UT Southwestern will be a worldwide leader in obesity and diabetes research for decades to come.

History of Hunger

Eat all you can. You don't know where your next meal is coming from.

This has been man's philosophy throughout much of history, as food was always scarce. Whether it was in Europe during the Middle Ages or the farmlands of 1800s America, few had the wealth needed to eat as they pleased, let alone overeat. Most people had to eat when they could, fight hunger and struggle to keep their weight up.

After World War II, all that changed.

Processed foods became a big part of the U.S. food supply, and food production left home kitchens for large factories. Inexpensive food became abundant.

A propensity to eat as much as possible mixed with easy access to food, and, in the last 50 years, a threefold increase in portion sizes of common foods has led to nearly two out of every three Americans being overweight or obese.

Some speculate that ingredients in food itself may be part of the problem.

For instance, why can't lovers of chocolate or snack foods stay away from them? Maybe because such foods often contain a pleasing mixture of fats and sugars, sparking the brain's pleasure centers or training the body to eat more to get more energy to burn – only to inevitably store the excess calories, said Dr. Elizabeth Parks, associate professor of clinical nutrition and internal medicine and a nutrition scholar in the Center for Human Nutrition at UT Southwestern.

"It is the signal the brain is receiving that keeps us eating long after we're full," said Dr. Parks, who is conducting studies on whether there is a taste bud for fatty foods on the tongue, as well as the link between dietary-fat intake and fatty-liver disease.

Still, no one has definitively identified what it is about food that predisposes certain people to overeat and become obese, said Dr. Roger Unger, professor of internal medicine at UT Southwestern.

"This makes it absolutely critical for scientists to find out the genetics and molecular biology behind appetite, satiety and metabolism," said Dr. Unger, who holds the Touchstone/West Distinguished Chair in Diabetes Research.

Brain Food

A small, mysterious region of the brain called the hypothalamus is the primary focus of one of the task force's top investigators.

Considered the "center" of the brain, the hypothalamus is a gateway for appetite and satiety. It's central not because of its location in the brain, said Dr. Joel Elmquist, professor of internal medicine and pharmacology and head of hypothalamic research at UT Southwestern, but because it regulates all basic life functions, including the release of hormones like insulin, the regulation of body temperature and heart rate, and complex behaviors like sleeping.

It also is the key brain site regulating the balance of appetite and satiety and body weight.

"We know the hypothalamus controls how much food you eat, how much energy you burn, and how you maintain your body weight and glucose state, but the molecular identity and brain sites targeted by these key nerve cells haven't been clearly defined," he said.

Over the past decade or so, scientists have created a basic map of the hypothalamus, including nerve cells clustered at its base.

The interactions of these nerve pathways and signals from the body drive the mechanisms behind feeding, Dr. Elmquist said. In basic terms, the hypothalamus receives and processes many signals – smell, taste, stretching of the stomach, different hormones relevant to energy balance – to orchestrate the starting and stopping of feeding behavior.

Dr. Elmquist, who holds the Maclin Family Professorship in Medical Science in Honor of Dr. Roy A. Brinkley, is trying to define the anatomy and molecular mechanisms regulating body weight and blood glucose levels.

One area of his focus is a group of nerve cells called the arcuate nucleus of the hypothalamus. Dr. Elmquist and his colleagues have found that the arcuate nucleus is a major target for the hormone leptin. Leptin is a key signal released by fat cells. Mice and humans lacking leptin are morbidly obese, eat ravenously and are diabetic.

The researchers also have found that serotonin – a brain neurotransmitter – interacts with the same set of neurons in the arcuate nucleus that leptin does. This is potentially important because increasing serotonin action in the brain is the mechanism by which the now-banned weight-loss drug fenfluramine-phentermine (fen-phen) worked to reduce feeding and body weight in humans. Dr. Elmquist and his team have shown that leptin and serotonin both activate brain cells called pro-opiomelanocortin neurons in the arcuate nucleus. These neurons in turn release a chemical that acts on proteins called melanocortin-4 receptors, or MC4Rs.

MC4Rs are main access points for the hormones and chemicals that signal for appetite and satiety. The normal activity of MC4Rs is vital for these functions.

Dr. Elmquist also has shown that serotonin simultaneously blocks other neurons from being able to inhibit activity of MC4Rs. The end result: serotonin prevents an increase in appetite.

"These findings increase our understanding of the molecular circuitry that controls appetite initiation and suppression," Dr. Elmquist said.

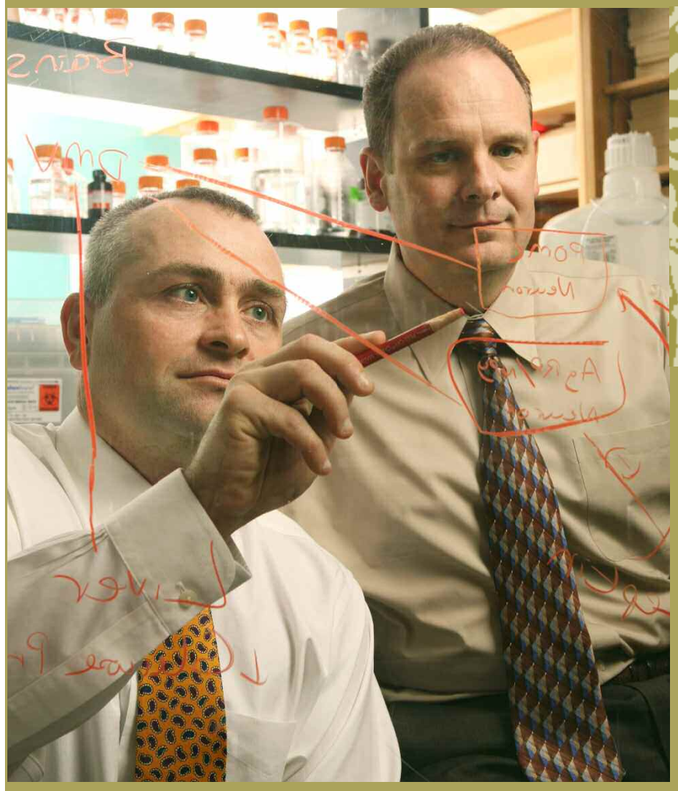
A Big Appetite

A rumble. A growl. A pang.

You might not know how to term it, but you know the message your stomach is trying to convey to your brain when it contracts – you're hungry. Food's sensory appeal, perhaps the aroma of just-out-of-the-oven apple pie, can play a role in this process, as can your body's internal clock, trained to expect food at certain times.

Throw in a body chemical called ghrelin, and you're "starved."

Ghrelin, a hormone discovered in 1999, begins to stockpile in the stomach as one of the major indicators to the brain that it's time to eat, said Dr. Jeffrey Zigman, assistant professor of internal medicine and part of UT Southwestern's hypothalamic research team.



- hypothalamus - Signals - MC4Rs - neurons - seratonin- insulin - leptin - molecular mechanisms -

Dr. Joel Elmquist (left) and Dr. Jay Horton

"Ghrelin levels rise before meals and fall after meals," Dr. Zigman said, "and when ghrelin levels rise, food intake and body weight increases. Ghrelin is an important hunger signal.

"In fact, we have found that mice that can no longer respond to ghrelin because of receptor deletion are lean and resistant to diet-induced obesity."

Researchers aren't exactly sure why fasting spurs ghrelin levels, but important clues may be found in studying people with conditions such as Prader-Willi syndrome, which is marked by sky-high ghrelin levels. This genetic disorder is associated with severe obesity, cognitive dysfunction, hypogonadism and growth hormone deficiency. It is also characterized by a nearly constant state of hunger, a ravenous appetite, binge eating and even eating things that aren't normally considered palatable.

-Leptin - CCK

receptors -

FGF21 - GLP-1

hormones - PYY

Dr. Roger Unger (left)

-cholecystin-

Dr. Philipp Scherer

ghrelin - SIM1

-adiponectin -

"Finding out more about ghrelin – how it affects the brain's molecular circuitry and how it's released – could help fine-tune drugs to treat conditions like Prader-Willi syndrome and other more common forms of obesity," Dr. Zigman said. "It also could help answer the question of why some people are hungrier than others."

The Secret of Satiety

If you weren't already hungry, perhaps reading the phrases "freshly buttered baked potato" or "the aroma of just-out-of-the-oven apple pie" has helped to fuel your appetite.

But do you ever wonder just how your appetite subsides?

When you eat, your stomach and intestines stretch and signal the brain that you're getting full. The intestine produces a chemical called cholecystokinin, or CCK, that signals the brain that a meal is over. That message to stop eating is then firmly reinforced by other hormones such as GLP-1 and PYY, which travel from the gut to the brain. Fat cells release hormones such as leptin to signal the brain whether the body has stored enough fat or needs more.

Leptin is a key in regulating feeding, and humans and mice lacking leptin are in a constant state of perceived starvation. The hormone, first discovered in 1994, is produced by the body's fat cells. Increases and decreases in leptin levels are sensed by several key feeding centers in the hypothalamus and elsewhere in the central nervous system. Leptin levels signal that the body has had enough food by helping to mute the signals of chemicals that stimulate appetite. Leptin also informs the brain on how the body's fat reserves are doing for the long haul.

In theory, if you're fasting or starving, leptin levels are low, and your appetite is increased. If your body has enough energy stores, leptin levels are high, and the urge to eat is at least reduced, Dr. Unger said.

In recent studies, Dr. Unger has found that, in normal mice, a high-fat diet caused massive obesity and enlargement of fat cells. No surprise there. But in mice with a glut of the receptor for leptin, no obesity occurred, despite high-fat diets.

When abundant leptin receptors are present, fat cells don't have the ability to store fat, he said.

"People with naturally high levels of leptin receptors may not gain weight as rapidly over time as people who have low levels of leptin receptors. It could explain why some people can eat more and not gain weight," Dr. Unger said. "If we had a pharmacologic way of manipulating the expression of the leptin receptor, we might be able to control obesity."

Most obese people, however, have high levels of leptin, but they are resistant to leptin's effects. This may be because increased eating creates so much leptin that the receptors it could dock with are full. With no place to dock, the normal appetite-suppressing pathway gets overloaded and shuts down.

Fat Mice, Skinny Mice

At the opposite end of the spectrum, starvation takes its toll on appetite and satiety as well, offering a different kind of insight into the fight against obesity.

Starving mice have the ability to alter their metabolism and enter into a type of hibernation to conserve energy, helping them survive longer without food.

Dr. Steven Kliewer, professor of molecular biology and pharmacology, and Dr. David Mangelsdorf, chairman of pharmacology and a Howard Hughes Medical Institute investigator, recently identified a hormone-receptor pathway as the mechanism responsible for this process.

They discovered that a hormone called fibroblast growth factor 21, or FGF21, interacts with a certain cellular receptor that controls the use of fat as energy. That interaction spurs a metabolic shift to burning stored fats instead of carbohydrates and induces a hibernation-like state of decreased body temperature and physical activity, all geared to promote survival.

In properly fed mice, FGF21 is not normally active; however, when the researchers introduced FGF21 into these mice, the animals' metabolism changed.

"Their metabolism appeared as if they were starved, even after they had just eaten," said Dr. Kliewer, holder of the Nancy B. and Jake L. Hamon Distinguished Chair in Basic Cancer Research. "They burn fat very efficiently. We hope to manipulate this hormone-receptor signaling pathway to craft the next generation of drugs to combat human obesity and other conditions. We want to see if we can get the benefits of eating less without eating less."

Another type of mouse contradicts the notion that overeating leads to obesity *and* health problems.

Mice that lack leptin but have a glut of the hormone adiponectin overeat and get obese, but they don't develop insulin resistance or diabetes, according to a recent study by Dr. Philipp Scherer, professor of internal medicine and director of the Touchstone Center for Diabetes Research.

These mice can store excess calories in fat tissue instead of in liver, heart or muscle tissue – places where excess fat can lead to inflammation and heart disease.

The mice get morbidly obese but have normal blood-glucose levels.

Adiponectin, an insulin-sensitizing hormone released by fat cells, is the key, Dr. Scherer said. A person's adiponectin levels decline as they consume excess calories. Genetically increasing adiponectin levels in overeating mice caused their weight to balloon but made them physiologically skinny.

"The continual firing of adiponectin generated a 'starvation signal' from fat that says it is ready to store more energy," said Dr. Scherer, who holds the Gifford O. Touchstone Jr. and Randolph G. Touchstone Distinguished Chair in Diabetes Research. "The mice became what may be the world's fattest mice, but they have normal fasting glucose levels.

"The inability to appropriately expand fat mass in times of overeating may be an underlying cause of insulin resistance, diabetes and cardiovascular disease."

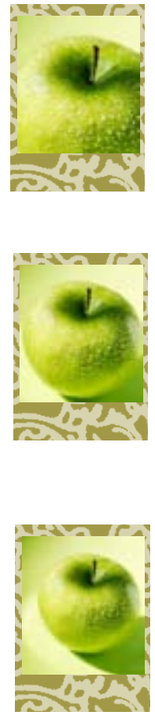
Additional research by Dr. Jonathan Graff, associate professor of developmental biology and molecular biology, shows that a single gene might control whether or not individuals tend to pile on fat, a discovery that may point to new ways to fight obesity and diabetes.

"From worms to mammals, this gene controls fat formation," Dr. Graff said.

Mice with increased activity of the gene, called *adipose*, ate as much or more than normal animals; however, they were leaner, had diabetes-resistant fat cells and were better able to control blood-sugar metabolism. In contrast, animals with reduced *adipose* activity were fatter, less healthy and had diabetes.

Dr. Graff and his colleagues also determined that in fruit flies, various combinations of the gene's variants lead to a range of body types from slim to medium to obese.

The actions of this so-called "skinny gene," which is also found in humans, could help explain why so many people struggle to lose weight and suggests a new direction for developing treatments that address the obesity epidemic, Dr. Graff said.



"If we had a pharmacologic way of manipulating the expression of the leptin receptor, we might be able to control obesity."

— *Dr. Roger Unger*

-Leptin - CCK

receptors - FGF21

- GLP-1 hormones

- PYY - chole-

Dr. Steven Kliewer (right)

cystin- ghrelin -

Dr. David Mangelsdorf

SIM1 hypothalamus

More Genes Related to Obesity

Some people just don't get full.

Consider for example, a young girl who, at age 2, weighed 45 pounds. She always felt hungry, and no diet, fitness plans or medical treatments helped control her weight, which ballooned to 220 pounds by age 12.

Dr. Andrew Zinn, associate professor in the Eugene McDermott Center for Human Growth and Development and internal medicine, began studying this girl in the late 1990s when she was a toddler. He sought to find an explanation for her problem by analyzing her genes. He got a hint from routine prenatal studies that showed that part of the girl's chromosome No. 1 had moved onto chromosome No. 6, and vice versa. When genetic material is intact but moves to a wrong place, a gene may be disrupted in the process.

In the girl's case, Dr. Zinn found a disruption in a gene called *SIM1*.

He and his colleagues obtained a mouse strain with a similar defect and found that the rodents overate and became obese.

"On a low-fat diet, the mice ate about 10 percent to 15 percent more food than their normal littermates and 70 percent more when fed a high-fat diet," Dr. Zinn said. "That's a lot of calories."

Dr. Zinn had hit on a new gene defect that causes obesity.

Dr. Zinn's research group and others at UT Southwestern continue to investigate how *SIM1* works. They've found that *SIM1*, a transcription factor that turns on or off other genes, normally works in the MC4R pathway in the hypothalamus to help control food intake, said Dr. Bassil Kublaoui, assistant professor of pediatrics and internal medicine. MC4R mutations are the most common genetic defect identified in severely obese children, but they still account for only a small percentage of such cases.

In mice completely lacking *SIM1*, a vital area of the hypothalamus, called the paraventricular nucleus, never develops.

In mice lacking one of the two normally present copies of the gene – as in the young girl – the paraventricular nucleus does not function properly, setting the stage for constant hunger and overeating.

"We're now working to find the targets of *SIM1* that control food intake," Dr. Zinn said. "Therapies then could be designed to activate or block those targets."

Dr. Zinn said his work and that of others indicate that the overeating and obesity that runs rampant in America, where 66 percent of adults are overweight or obese, is not simply an issue of inadequate willpower.

"Losing weight or not overeating through willpower is a misperception," Dr. Zinn said. "The drive to eat is really a biological and genetic matter."

The Hungry Worm

While the *Caenorhabditis elegans* worm, which feasts on bacteria, is no larger than a pinhead, the creature is offering significant new insights into the mechanisms of hunger.

Dr. Leon Avery, professor of molecular biology, and Dr. Young-jai You, a postdoctoral researcher in his lab, have identified a series of biochemical reactions that control how *C elegans* eats by contracting and relaxing a large muscle called the pharynx to suck in its prey. When it is starved, *C elegans* reacts by pumping the pharynx harder.

Drs. You and Avery and their colleagues found that activating the worms' muscarinic receptors triggers the same behavior and biochemical response that starvation would.

"When starved worms were put back in the presence of food, their pharynxes had an increased pumping rate compared to well-fed worms, suggesting that the muscle's biochemistry and physiology had altered to enhance food ingestion," said Dr. Avery, holder of the John P. Perkins, Ph.D., Distinguished Professorship in Biomedical Science. "This might aid our understanding of feeding in mammals, which also have muscarinic receptors. When mice, for example, are genetically altered to lack the gene for one type of muscarinic receptor, they eat less and are skinnier than their normal counterparts."

Dr. You is taking the studies of the *C elegans*' hunger another step by examining whether the worms reach satiety and get full. If they do, the worms could be novel vessels to study the molecular signals and processes behind satiety in other animals and humans.

Food as Reward

Another issue further complicates the biochemistry of appetite, especially in humans: Could food be addictive?

Studies are accumulating that show that the brain's "reward center," which mediates reward under normal conditions and addiction under pathological conditions, is rich in receptors for many of the same hormones, including leptin and ghrelin, that affect the hypothalamus to help control appetite and satiety. The reward center includes dopamine-producing neurons in a part of the midbrain called the ventral tegmental area. Those neurons send signals to the nucleus accumbens, part of the brain's limbic system.

This hints that certain types of food, under the right conditions, might have an addictive quality, said Dr. Eric Nestler, chairman of psychiatry. Dr. Nestler and Dr. Michael Lutter, instructor of psychiatry, are exploring the actions of key appetite and satiety hormones in the reward center.

"Leptin, ghrelin and other peptides are active in this reward center, so some of the drive to eat might be mediated through these pathways," said Dr. Nestler, who holds the Lou and Ellen McGinley Distinguished Chair in Psychiatric Research.

Past studies have focused on the deletion of leptin receptors in the reward center of the brains of mice in an attempt to determine whether the rodents will feed more or less if they don't get a feeling of reward or pleasure from eating.

Dr. Nestler and Dr. Lutter, in collaboration with Dr. Elmquist and his team, are investigating whether some of the people who have unexplained obesity might be addicted to food, and whether the relationship between the brain's reward pathways and hunger and satiety peptides could have relevance in treating both depression and addiction.

"We're examining the role of these hormones in reward pathways to see if those hormones might be viable targets for depression or addiction medications," he said.

Best Bet to Enhance Satiety

So what can you do, if anything, to prevent overeating and obesity?

Eating cheese or a boiled egg for breakfast, and not a doughnut, can help you feel fuller longer, said Dr. Jo Ann Carson, professor of clinical nutrition and a nutrition scholar in the Center for Human Nutrition at UT Southwestern.

That's because protein can help enhance satiety.

"Protein and other low-glycemic foods tend to contribute a steady amount of glucose, the body's main source of energy, helping promote a feeling of fullness," Dr. Carson said.

Foods that are high in carbohydrates have an opposite effect. Carbs tend to cause glucose levels to spike, then crash, making you feel hungrier sooner.

Dr. Carson also recommends these tips:

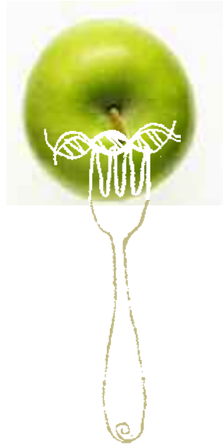
- **Eat slowly**. The satiety signal itself is slow, taking at least a few minutes to get from the intestines to its destination in the brain.
- **Set consistent meal times.** Don't starve all day before a big feast; you'll be less likely to overeat. Don't eat late at night. This can cause the body to store calories.
- **Avoid fast food.**
- **At a party**, socialize away from the buffet table, removing a temptation to overeat.

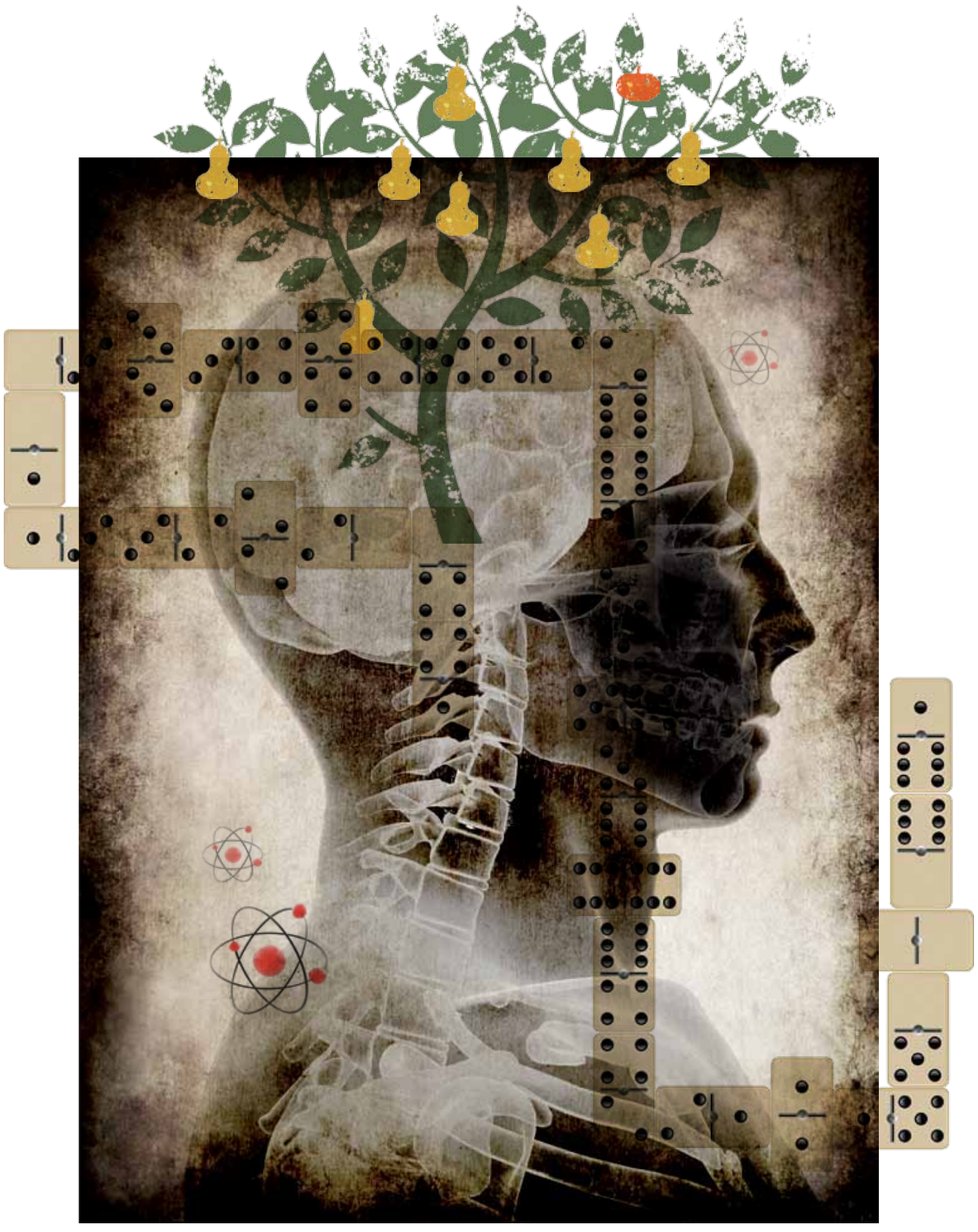
As the work being done to understand appetite and satiety at UT Southwestern continues to gain headway in the battle against obesity, Dr. Carson urges people to remember the seminal rule of a healthy lifestyle:

"Don't consume more calories than you burn," she said. "Exercising and reducing your food intake are the best ways to stave off obesity and stay healthy."

"Losing weight or not overeating through willpower is a misperception. The drive to eat is really a biological and genetic matter."

— *Dr. Andrew Zinn*





SYSTEMS BIOLOGY:

Interpreting Nature's Rules

FROM ATOMS TO ECOSYSTEMS, all of biology is built upon networks of interactions. Molecules link to form proteins within cells; cells cluster and communicate with one another to form tissues; tissues form organs; and organs must function together in a coordinated way to create a living organism. On a grander scale, entire ecosystems are based on an intricate, balanced web of individual species that depend on one another to survive. Scientists long have sought to understand the components of biology by studying their structure and function in isolation – a lone gene or protein, or the behavior of a single species in a tidal pool. But understanding the "pieces" of much larger networks is not enough to predict what will happen when the components hook up and function as a system. For example, what is the smallest "unit" of genes, cells or interactions in the body that can predict whether a person will be good at dribbling a basketball, or be able to learn a foreign language, or develop cancer? Uncovering the most fundamental evolutionary design principles of living systems not only will lead to a better understanding of how nature works in general but is vital to making important strides in diagnosing and treating disease, a state in which systems in our bodies malfunction.

by Amanda Siegfried

At UT Southwestern Medical Center, a cadre of researchers is dedicated to the field of "systems biology," with the ultimate goal of understanding how networks of interactions produce functioning biological systems that are more than the sum of their parts.

A home for systems biology research

Investigators in the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational and Systems Biology at UT Southwestern link basic research on molecules and cells with analysis of how entire biological systems function, both in health and in sickness. The center was established in 2004 and was made possible by a $12.8 million gift from the Cecil and Ida Green Foundation.

Under the leadership of Dr. Alfred Gilman, executive vice president for academic affairs, provost and dean of UT Southwestern Medical School, the Green Comprehensive Center is home to researchers who span various scientific disciplines, including cell biology, neuroscience, structural biology, mathematics and computer science. They work not only as individuals, but also collaboratively in their own "network" to create models of biological systems that consider not only the individual parts but also how those parts react to each other and to changes in their environment.

Dr. Rama Ranganathan, professor of pharmacology at UT Southwestern, is director of the Systems Biology Division of the Green Comprehensive Center. He leads the group of investigators who were recruited in large part because their varied expertise and backgrounds bring crucial skills and perspectives to bear on myriad questions pertaining to systems biology.

"The past several decades have seen an increase in understanding of the individual components that make up cells, tissues and organisms, but this knowledge does not explain even the basic behaviors of these systems taken as a whole," said Dr. Ranganathan, who holds the Cecil H. and Ida M. Green Chair in Biomedical Science. "The central problem now is to understand how the *interactions* among the parts are arranged so that they have identifiable biological meaning."

The concept of studying biological systems is not new; scientists have always sought to understand how whole organisms function. Advances in technology, however, now facilitate the in-depth study of the intricate structure of tiny biological components and the gathering of enormous amounts of data about individual pieces of biological puzzles.

For example, powerful computers combined with X-ray crystallography techniques have made it possible to map and analyze the 3-D crystal structure of numerous proteins, shedding light on how they physically interlock with other molecules. Advances in molecular biology allow researchers to probe interactions among a few components at a time within cells. The mapping of the human genome has provided a bonanza of information to support the study of individual genes.

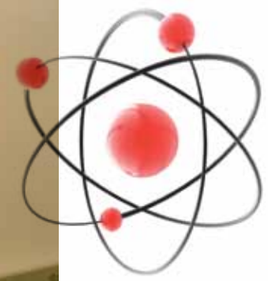
"We're asking the kinds of questions that scientists asked long ago," Dr. Ranganathan said. "But technology has allowed researchers over the past 30 or 40 years to collect details about individual biological units. Given that explosion of data, it is now possible to ask those questions in a more meaningful way."

What is needed, he said, is "circuit theory" for biology – a way of predicting the behavior of networks of components given knowledge about the parts and the mechanisms by which they interact. In physics, for example, natural constants have been found and equations have been derived that describe physical phenomena in an equilibrium state, such as the behavior of a gas in a jar. Such equations predict what will happen when one physical parameter is changed, such as increasing pressure exerted on the jar-enclosed gas.

Biology, however, is not in equilibrium – no such equations have been found to make accurate predictions about outcomes. But that doesn't necessarily mean they're not there.

"Physics is like magic," Dr. Ranganathan said. "Physicists have collected data set after data set, fit a nice equation to it, then used that equation to predict some constant of nature – you get the same number over and over again.

"In biology, we've never done such a thing. To my knowledge, there is no number, no constant, that is some invariable property of biological systems. We don't know if there are such principles in biology that can be derived, but there are some features of biological systems, some commonalities, that make us think such rules might exist."



"We're asking the kinds of questions that scientists asked long ago. But technology has allowed researchers over the past 30 or 40 years to collect details about individual biological units. Given that explosion of data, it is now possible to ask those questions in a more meaningful way."

—Dr. Rama Ranganathan

Going after the answer with a systems biology approach requires not just expertise in biology, but also knowledge and methods from the fields of physics, engineering, math and advanced computer science to design and analyze experiments. Dr. Ranganathan himself brings to the effort a background in bioengineering, a Ph.D. in biology and a medical degree. Other center faculty members have backgrounds in genetics and computational biology, mathematics and software development, and biophysics.

Members of the center ask difficult questions and approach their research often by using simple biological systems, such as fruit flies, yeast and bacteria. These are not as complex as humans, but the basics are the same.

To understand why simple organisms are such important tools in understanding human biology, think of a car, said Dr. Gürol Süel, assistant professor of pharmacology who earned his Ph.D. in molecular biophysics from UT Southwestern and joined the center's faculty in 2006 as a W.W. Caruth Jr. Scholar in Biomedical Research.

"If you just want to understand the basic principles of a car, maybe a car from the 1920s would be best to study," Dr. Süel said. "It's a car, but with fewer gadgets compared to modern-day versions. In our labs, we try to go back to the simple organisms – they are still cars, in essence, and we want to understand how the steering or the brakes work without having to deal with the ABS or the traction control."

Dr. Steve Altschuler, assistant professor of pharmacology, also joined the center in 2005 as a W.W. Caruth Jr. Scholar in Biomedical Research. With an extensive background in mathematics, he takes the car analogy another step.

"We're trying to understand design principles," he said. "So we first remove from the picture details that are unimportant. Even a car from the 1920s is incredibly complex, with thousands of bolts and screws. But as you take it apart, you can start to draw boxes around groups of items. For example, here are the parts that deal with converting gasoline into

energy, and there is the set that transfers energy to the wheels. Similarly, we have been looking at the stochastic nature of biology, trying to understand the smaller systems within larger systems."

The results have been intriguing.

"Certain principles we thought would just apply to simple biochemical signaling systems within cells look like they might apply at smaller scales to molecules and how they polymerize, and at larger scales to how cells communicate with each other and how organisms communicate," Dr. Altschuler said. "In our attempt to look at simple processes, we have stumbled upon principles that have not been applied at other scales."

Biology as a team sport

Another aspect of systems biology requires examining dynamic networks as they play out in time and space. Dr. Süel compares the field of study to trying to understand a familiar pastime – the game of football.

"Let's say a Martian shows up on planet Earth on a Sunday, goes to a stadium and watches a football game in action," Dr. Süel explained. "The alien will be able to understand certain basic principles, such as one team is trying to progress in one direction, and there is a ball being thrown.

"However, if I just showed him snapshots of a team in action in a random order, it would be nearly impossible for him to understand what's happening at all."

To get a firm grasp on the sport of football as a whole, the alien needs to understand more than just the individual players on the field. He needs to know how they interact, both in physical space and over time, as well as the context and environment in which the game is played. Players might act a certain way when their team is down by two points and they have only 15 seconds left in the game to score, or the game may be played differently in the sunshine than it is during an unexpected snowstorm.

Similar issues are involved in understanding biological processes – by nature, they are dynamic, Dr. Süel said.

The common approach of investigating in isolation different components of a biological system – the function of one gene, the structure of one protein, the behavior of one type of cell or one species of insect in a grassy field – doesn't give an accurate or even understandable picture of the biological "game," Dr. Süel said.

"If you really want to understand a team sport – and that's what biology is, with many proteins and genes and cells interacting all the time – you have to make sure you look at what the entire team does as a whole, over time and in various natural elements, rather than just focusing on individual players," he said.

Because of improvements in technology, researchers now have the ability to be like an observer at a football game, watching biology in action and analyzing the game. Imaging technology and resources at UT Southwestern include one of the most powerful scientific instruments used to study the molecules of life. About 15 feet tall, 10 feet across and weighing nearly 4 tons, an 800-megahertz nuclear magnetic resonance (NMR) spectrometer was delivered to the campus in 2003. Funded by a $2 million grant from the National Institutes of Health, the NMR device allows scientists to produce 3-D images of proteins and other biological molecules in solution, which is similar to proteins' natural environment within cells.

"Where the real power comes in studying complex systems is being able to see how things, like proteins, move and change over time," Dr. Ranganathan said. "Large magnets such as this allow us to really look a lot more closely at protein dynamics."

Imaging techniques such as fluorescence microscopy allow Dr. Süel and his colleagues to use a kind of time-lapse photography to put together movies of interacting components within cells. For example, much of Dr. Süel's research focuses on "genetic circuits" found within each living cell. Each of these circuits consists of a distinct set of biochemical reactions that contribute to some biological process.

Using fluorescence microscopy, he labels different parts of a circuit with a glowing molecule, a "tag," that allows him to follow the action inside a cell when certain genes are turned on and off. One of the processes he has observed is the differentiation of a bacteria cell from one state to another, which is akin to the way human stem cells change into a specific tissue type.

This approach has shown how bacteria use random fluctuations in biochemical reactions – so-called cellular "noise" – to make decisions about cellular differentiation. Such noise, technically referred to as stochastic fluctuations, was previously thought to interfere with the reliable operation of biological systems. Dr. Süel's group was the first to demonstrate experimentally that they could regulate cell fate by controlling noise in bacterial cells.

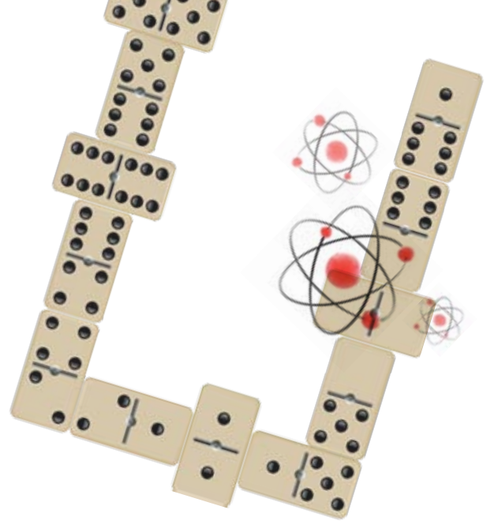
The goal here, as in all systems biology, is to identify basic sets of genes or sets of interactions that result in specific biological functions, such as cell-fate determination, the making of insulin, or the triggering of the immune system against a virus. Armed with a complete picture about these processes, it may then be possible to predict a person's health outcome or their reaction to a given medicine based on his or her genetic makeup or physiology.

Evolution in the driver's seat

The primary constraint on the design and development of biological systems is evolution, Dr. Ranganathan said. Nature is the ultimate laboratory – systems that work well and adapt to changing environments survive, while those that don't work are lost to the ages.

"In our attempt to look at simple processes, we have stumbled upon principles that have not been applied at other scales."

—Dr. Steve Altschuler



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Drs. Lani Wu, Steve Altschuler and Gürol Süel (from left)

"One implication of our work is that the evolutionary protein-design process may not be as complex as was previously thought."

—Dr. Rama Ranganathan

Many biological systems are conserved, meaning they are found in similar forms from the simplest organisms to the most complex. From the formation of proteins to the "wiring" of neurons in the brain, the systems that have survived the test of time are those that are able to withstand random changes in their components or interaction parameters, while at the same time remaining "plastic" enough to allow for variations that allow them to adapt to changing environments.

Those are the systems that are most enticing to the systems biology group.

"In evolved systems, some parts and connections are just more important than others," Dr. Ranganathan said.

By examining how proteins have evolved, Dr. Ranganathan discovered a set of simple "rules" that nature appears to have used to design proteins and to manufacture them from groups of molecules called amino acids. From those rules, he has produced artificial proteins that look and function just like their natural counterparts. He and his colleagues created the proteins based only on information they derived from analyzing a particular family of related natural proteins and certain characteristics those family members have in common with each other.

Dr. Ranganathan said the solutions he built are so close that, at least in a test tube, "we can't tell them apart from natural proteins."

Proteins carry out all the body's life functions and are composed of combinations of amino acids strung together in long chains. These chains curl up and fold back upon themselves in a variety of ways, with the amino acid sequence determining how the chain will be folded.

A major question is: What information contained within that sequence produces the proper 3-D folded structure?

There are only about 20 specific amino acids that can be combined to make a protein. Even for a small protein made up of 100 amino acids, the number of possible combinations of amino acids is staggering, many times more than the number of atoms in the known universe.

"How did nature devise the right sequences that resulted in functioning proteins? Somehow, it found a way," Dr. Ranganathan said. "One implication of our work is that the evolutionary protein-design process may not be as complex as was previously thought."

To test the "rules" he gleaned from the evolutionary record, Dr. Ranganathan fed them into a computer program his lab personnel developed. The program generated sequences of amino acids, which the researchers then "back-translated" to create artificial genes. Once inserted into laboratory bacteria, the genes produced artificial proteins as predicted.

The work suggests that modern-day proteins have likely inherited much of the information specifying their structure and basic aspects of function from their ancestors. The basic ancestral template that Dr. Ranganathan deduced has likely been fine-tuned over time by evolution, resulting in each member of the protein family developing its own idiosyncratic function in specific cells.

A matter of scale

Adding to the complexity of systems biology research, some small-scale biological systems that might seem highly relevant when studied in the lab might not be important at all at the larger scale of the whole organism.

"The ultimate question is what does it mean to be relevant at a particular scale?" said Dr. P. Robin Hiesinger, assistant professor of physiology in the center who joined the faculty in 2006 as a Eugene McDermott Scholar in Medical Research. "There is an idea that relevance is transmitted across scales. If a particular feature at the micron level in the brain is really important, then it will also matter at the tissue level, or organism level. Or maybe at the evolutionary level, there would be a fitness advantage in having this feature there."

One of the traditional lines of thinking that systems biology tries to transcend is the notion that scientists should focus on one spatial scale in their research. The danger of that kind of tunnel vision, Dr. Ranganathan warned, is that researchers concentrate so hard on making discoveries on one scale that they might never ask whether what they are measuring has any relevance.

"It's like asking how long is the coastline of England. The answer is, it depends on the size of your ruler," he said. "You can look at microscopic divots that will increase the length of the coastline, but if you're circumnavigating the island in a ship, you probably don't care about fluctuations at that level."

Dr. P. Robin Hiesinger

The brain under a microscope

Dr. Hiesinger keeps relevance in mind, literally, in his investigations.

"I am interested in a very complicated structure – the brain – and figuring out how to make one," he said. "The brain allows us to think about the organ itself, which is a very weird thing to think about."

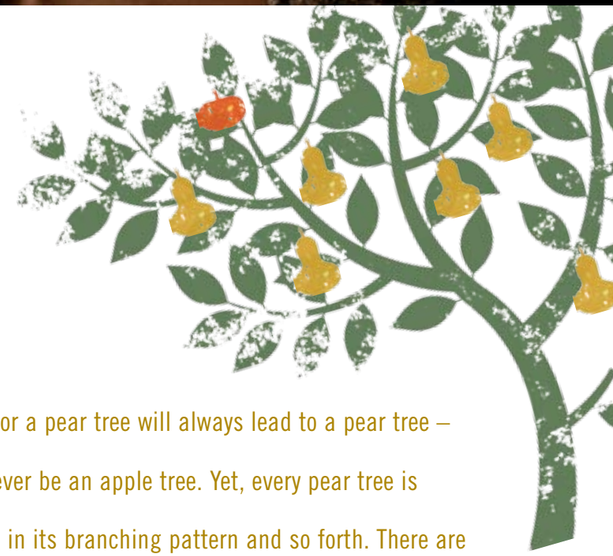
Dr. Hiesinger's field of study is called neurogenetics.

"We are studying how emergent properties of complexity are actually encoded by genes," Dr. Hiesinger said. "A gene does not encode, or directly make, the brain, not even an individual neuron. A gene just encodes a protein, which then goes on and plays its games at a different level, within cells."

Dr. Hiesinger compares the development of the human brain to a fruit tree.

"A seed for a pear tree will always lead to a pear tree – it will never be an apple tree," he said. "Yet, every pear tree is different, in its branching pattern and so forth. There are sets of parameters that will always differ among individuals, but the roots are fundamentally the same. This is also true for our brain."

Just as Dr. Süel examines genetic and cellular circuits, and Dr. Ranganathan studies the core building blocks of proteins, Dr. Hiesinger seeks to understand



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neuronal circuits, the basic wiring pattern in the brain that is largely conserved both within individuals of one species and even across different species.

A number of human diseases are thought to depend on defects in brain wiring, including schizophrenia, autism, bipolar disorder, Tourette syndrome and some forms of epilepsy. By characterizing the dynamics of brain wiring in many individuals within and across related species, researchers hope to capture the fundamental rules involved in brain development and possibly identify promising drug targets.

The brain's wiring diagram is not limited to physical connections between nerve cells, called neurons. The development of the brain's circuitry also involves genes turning on and turning off at specific times over the course of an organism's life; the coordinated movement of different kinds of cells to the right place in the "network" at the right time; and molecular processes that generate and strengthen the spaces between cells, called synapses, where cell-to-cell communication takes place, leading to learning and memory.

Dr. Hiesinger's goal is to use a systems biology approach to understand how all these factors from different scales and different levels of organization come together to create the seemingly complex structure of the brain.

It has been said that if the brain were simple enough for us to understand it, we would be so simple that we couldn't. In the face of such overwhelming complexity, where to start?

Dr. Hiesinger tackles the problem by using a simple organism – the fruit fly.

"Yes, the fly does have a brain, and it is surprisingly complicated. We understand very little about how it works," he said.

Specifically, he focuses on the primary visual system of the fruit fly *Drosophila melanogaster*, one of the workhorse species of the modern laboratory.

The fly brain provides a simpler yet representative example of the neuronal circuitry problem, and the primary visual map in the fly is arguably one of the best characterized brain structures in any organism.

Dr. Hiesinger's approach is twofold. First, he causes mutations in the flies' genes and then looks for specific defects in the insect's brain wiring. Second, he characterizes the developing brain with live imaging.

"The most interesting questions you can ask about what we are doing are: How can so few genes create such a complicated brain, and how much of who we are is predetermined by our genome?"

—Dr. P. Robin Hiesinger

When examining the mutated flies, Dr. Hiesinger looks not only for cells that die or cells that don't form the proper connections, but also for defects that lead to recognizable malfunctions in physiology, such as flies that have problems in their olfactory system, or bugs that perform poorly on visual tasks.

It may be that there are so-called microcircuits in the brain, networks of cells that are well-defined in terms of their input-output relationship.

"Perhaps we can learn something about the kind of function that is being carried out by the piece of the brain that contains such a microcircuit," Dr. Hiesinger said.

No one is expecting that this approach will tell researchers that a particular memory or thought is stored in a particular place in the brain, but Dr. Hiesinger said identifying microcircuits that are related to various functions is a starting point.

"There is a gap between the microstructure of synaptic connections among neurons and the macroscopic map of the brain, where different regions are responsible for language, motor tasks and visual acuity, for example," he said. "The way microcircuits come together and work determines much about the way the brain develops."

There are surprisingly few genes, only a couple of thousand, that underlie brain development, Dr. Hiesinger noted.

"The most interesting questions you can ask about what we are doing are: How can so few genes create such a complicated brain, and how much of who we are is predetermined by our genome?

"The two extremes are genes and cognition. We want to know what happens in between."

Mathematics + biology = drug discovery

When it comes to complexity, a single cell may rival the brain. But that hasn't discouraged intrepid researchers in the Green Comprehensive Center from attempting to deduce the operating principles driving one of the most basic units of life.

Dr. Altschuler and Dr. Lani Wu, who have worked together since graduate school at the University of California, San Diego, combine mathematical modeling with techniques from engineering and biological experimentation to understand the mechanisms at work within cells. Like Dr. Altschuler, Dr. Wu has a doctorate in mathematics. An assistant professor of pharmacology, she joined the center in 2005 as the first Cecil H. and Ida Green Scholar in Biomedical Computational Science.

Her goal is to understand the mechanisms of cell polarity, one of the most fundamental types of cellular organization. The establishment of cell polarity creates an axis of asymmetry required for many cellular processes.

Failure to establish proper cell polarity can lead to abnormalities in cell differentiation, cell movement, neuronal growth and other developmental diseases affecting human health, Dr. Wu said.

To understand how cells respond to stimuli, the scientists use sophisticated robotic technology and high-powered computers to record and analyze data from millions of cells at a time. They can track more than 300 different characteristics of each cell, an achievement that allows them to study, for example, whether all cells respond the same when exposed to a given medication or whether cancer cells respond differently than healthy cells.

The technique has tremendous applications in drug discovery, the researchers say, because the process is automated and allows for the screening of hundreds of drugs in a relatively short amount of time.

The amount of data Drs. Altschuler and Wu generate – and the amount of computer time they consume – is staggering. Analyzing 40 billion data points from a single experiment rivals the processes astronomers use to study the cosmos.

"Like Dr. Süel and Dr. Hiesinger, we look at systems that are not static in time and space, so we have to gather huge amounts of information," Dr. Altschuler said. "Now that the parts of cells have been identified, the goal of our systems biology approach is to build not only descriptive models, but also predictive models."

Much of their work hinges on probability, another concept from mathematics that systems biologists employ. For example, even though it may not be possible to predict how an individual cell is going to behave, looking at the behavior of thousands or millions of cells allows researchers to predict how certain populations of cells are likely to respond to a stimulus.

Complexity from simplicity

An irony not lost on UT Southwestern's systems biology researchers is that in order to find the simplest design principles in nature, they must use the most complicated technology to perform experiments that sometimes are extremely difficult. In many cases, the technology does not yet exist for the experiments they want to do.

"Our equipment often has to be pushed beyond what it was designed to do, or it has to be created in the laboratory using engineering and computer programming expertise," Dr. Ranganathan said.

The one thing shared by all the systems biologists in the Green Comprehensive Center is the inherent belief that ultimately, the underlying rules of biology should be simple, understandable and consistent with evolution.

"Our belief in the existence of basic biological design principles doesn't come out of nowhere," Dr. Altschuler said. "There are so many examples in mathematics of simple equations where a tiny change leads to incredibly complex patterns."

Dr. Hiesinger's perspective is more philosophical.

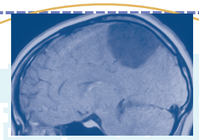
"We all look at systems and observe complex behavior," he said. "Drs. Altschuler and Wu observe unpredictable heterogeneity in cell cultures. Dr. Süel observes unpredicted behavior when his bacteria transform into one or another state. I observe the complexity of the brain, while Dr. Ranganathan studies the complexity of proteins. We all observe these things and ask questions about *how* they work. But it's a completely different question to ask *why* something is built the way it is in nature."

In the realm of biology, the fundamental answer to "why?" is always "evolution."

"This is inevitably a question of understanding the mechanisms and principles of evolution," Dr. Ranganathan said, "the process by which we believe natural things came to be the way they are."

"Our belief in the existence of basic biological design principles doesn't come out of nowhere. There are so many examples in mathematics of simple equations where a tiny change leads to incredibly complex patterns." —Dr. Steve Altschuler

UT Southwestern physicians have formed a "brain trust." Together their talents and vast expertise in every specialty help victims of brain trauma regain



BRAIN POWER

From Permian High School football player Trey Howard's typical week is pretty much like any other 21-year-old's. He watches sports in his spare time, attends church regularly, takes some classes at Odessa College and works daily at his father's contracting business tallying up orders. Except that his routine also involves daily physical therapy to try to regain his sense of balance, and speech therapy that has brought him over the past four years from just being able to say "hi" to humor-filled conversations. He also undergoes cognitive therapies trying to regain his short-term memory – things all lost in a moment during a traffic accident. "I was trying to dodge something and rolled," he said. "I was thrown through the windshield and hit my head on the pavement."

"Life-altering" is often an exaggerated phrase. But for traumatic brain injury patients, it's almost an understatement, insufficiently descriptive of the struggle and work faced by millions like Trey who seek to do the tasks that were once familiar. Brain injuries can affect thinking, sensation, language, emotions and motor skills.

By Russell Rian

Trey, the high-school football player with a beautiful black Camaro and a bright future, fell into a motionless coma for five months.

He was eventually able to swallow on his own, but had no ability to even blink a "yes" or "no" response to questions. There seemed to be a daily struggle to fight off infections, muscle stiffness or a host of other medical problems, and family members heard grim predictions for his survival. Permanent vegetative state was the best scenario often given.

But his mother and father, Becky and Billy Ray Howell Jr., weren't ready to give up. They seized on a glimmer of hope when Trey's physicians pointed them toward UT Southwestern Medical Center's traumatic brain injury program, one of the nation's leading programs for recovery from brain trauma.

"We are unique in that we provide the entire continuum of care, from the intensive care unit to lifelong follow-up."

— *Dr. Karen Kowalske*

"They didn't make any promises. They said it's a daily wait-and-see. But they said they preferred to remain optimistic," Mrs. Howell recalled.

Six months after the accident, on Dec. 15, 2003, as his parents walked into his daily therapy at UT Southwestern University Hospital - Zale Lipshy, to where he was transferred, he turned and said, "Hi."

"It knocked me up against the wall," his mother recalled. "It was the best Christmas ever."

He eventually graduated high school, walking across the stage with assistance from a UT Southwestern physical therapist.

He still struggles to walk on his own.

"Everyday I try to regain my balance, which I have yet to do," he said. "I really want to do that."

Life-Altering Statistics

Life-changing moments like Trey's actually happen every 23 seconds – the average pace at which traumatic brain injuries occur in the U.S.

The National Center for Injury Prevention and Control, part of the Centers for Disease Control and Prevention, reports about 1.4 million people sustain a traumatic brain injury each year in the United States. Of those, about 1.1 million are treated and released from an emergency department; 235,000 are hospitalized; and about 50,000 die.

About half of all traumatic brain injuries result from traffic accidents involving cars, motorcycles, bicycles and pedestrians. Traffic accidents are the major cause of traumatic brain injury for those under 75, while falls are the major cause for those 75 and older. Children ages 0 to 4 and teens 15 to 19 are at highest risk for traumatic brain injuries. About 20 percent of traumatic brain injuries result from violence, such as assaults or child abuse; 3 percent are due to sports injuries. They occur more frequently in men than women, and African-Americans have the highest risk of death from traumatic brain injuries.

These injuries typically happen in one of two ways: a direct blow to the head, such as hitting a windshield or pavement after being thrown, or an indirect slam of the brain inside the skull, said Dr. Karen Kowalske, chairman of physical medicine and rehabilitation and director of the Kimberly-Clark Center for Physical Medicine and Rehabilitation Research at UT Southwestern.

"Even if you don't go through the windshield, just how quickly the head moves up and back can cause the brain to fly forward then hit the back of the skull. So even if you don't hit your head on anything, just the whiplash of your neck can cause brain damage," Dr. Kowalske said.

That is why using vehicle restraint systems is key to preventing brain injury in the first place, she noted. Between the airbag, seat belt and headrest in a vehicle, your neck can't go back and forth.

Nationally Recognized Expertise

UT Southwestern physicians make up the eventual recovery team for brain injury patients brought into Parkland Memorial Hospital's Level 1 trauma center, where many North Texas traffic accident victims end up.

"We are unique in that we provide the entire continuum of care, from the intensive care unit to lifelong follow-up," said Dr. Kowalske, who holds the Charles and Peggy Galvin Professorship in Physical Medicine. "We intervene early on. We can start the interventions, both therapeutic and pharmacologic, from the day of injury. We bring them to the inpatient rehabilitation unit at University Hospital - Zale Lipshy as soon as they are medically stable, even if they are still in a coma, because there are some mechanisms of coma stimulation you can use to facilitate getting people out of a coma – both drug and therapy."

UT Southwestern pools the efforts and talents of a multitude of departments and divisions, including neurological surgery, neurology, physical medicine and rehabilitation, psychiatry and neuropsychiatry, and neuroradiology, to tackle these types of injuries. They are among the most complex and least understood that confront doctors.

"To an experienced clinician, experienced neurologist, psychiatrist or neurosurgeon, the patient that presents with these typical types of complaints and problems that are common to brain injuries are not hard to diagnose," said Dr. Ramon Diaz-Arrastia, professor of neurology. "On the other hand, medical professionals who don't have as much experience with it frequently misdiagnose."

UT Southwestern's traumatic brain injury program has grown from a small operation with a shoestring budget to one of eight U.S. centers selected by the National Institutes of Health to be part of the Traumatic Brain Injury Clinical Trials Network.

UT Southwestern also has become home to the North Texas Traumatic Brain Injury Model System, one of 16 select centers throughout the U.S. awarded grants by the Department of Education's National Institute on Disability and Rehabilitation Research to conduct in-depth research on traumatic brain injuries. UT Southwestern's grant, for which Dr. Diaz-Arrastia serves as principal investigator, was recently renewed for five more years. The major aims of the network are to reduce the rates of death, vegetative states and cognitive dysfunction after moderate to severe traumatic brain injury and to evaluate acute and rehabilitative interventions for efficacy, safety and cost-effectiveness.

Medical Care for Brain Injuries

The signs and symptoms of a mild brain injury can include headaches, confusion, mood swings, dizziness or concentration problems. More severe injuries can result in persistent headaches, vomiting or nausea, seizures, slurred speech, weakness or numbness in extremities, and increased confusion and agitation.

Consultations among experienced physicians in UT Southwestern's hospital-based program are a critical first step in forging a successful treatment that targets the specific problems for each patient.

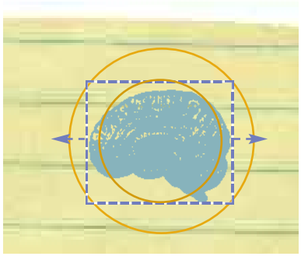
"Part of the advantage here is that you're treated by doctors who are very experienced in treating patients with these kinds of injuries, and we also have access to the latest research and the latest approach to medication intervention and procedural intervention," Dr. Kowalske said.

Imaging plays a crucial first role in identifying which areas of the brain have been damaged and determining which connections still work.

Soft-tissue injuries to areas such as the brain don't lend themselves well to traditional X-rays. A major breakthrough for brain-injury treatment came with the introduction of computed tomography scans in the late 1970s and early 1980s. But even CT scans, among the most commonly used images, aren't ideal. Magnetic resonance imaging can offer a better picture, but may also need to be supplemented with positron emission tomography scans. In addition, UT Southwestern is studying cutting-edge technology like diffuser tensor imaging, a special type of MRI that reveals damage unique in the human brain.

Medications also can play a critical front-line role in bringing someone out of a coma, as well as dealing with post-accident pain or cognitive impairment. The good news is that physicians have a much better array of medications these days to help restore brain functions.

Six months after the accident, on Dec. 15, 2003, as his parents walked into his daily therapy at UT Southwestern University Hospital - Zale Lipshy, to where [Trey Howell] was transferred, he turned and said, "Hi."



"We're just starting to understand which areas of the brain can substitute for function, and as we gain better awareness of that, we'll actually use these techniques to see if a particular exercise helps a particular area adjust better."

— *Dr. Karen Kowalske*

There are several medications that help improve outcome and improve the efficiency of rehabilitation.

Patients get better overall, and they get better over a shorter period of time," Dr. Kowalske said. "So we're very aggressive with pharmacologic agents to maximize recovery as well. They actually help the brain cells recover. That's something we didn't know 10 years ago. We thought that brain cells didn't have any potential to recover, and it turns out that's not true."

Neurostimulants work at the cellular level to help the brain reconstruct damaged neurological connections and encourage the formation of new connections.

"They can generate more neural connections, mostly in an adaptive mode of other neurons taking over for the neurons that aren't working. The neurons that are sluggish work better, and the neurons that aren't working at all then have other neurons that can substitute," she said.

Behavioral modifying drugs and spasticity and sleep medications assist with alterations in mood and sleep patterns or muscle control.

"We're just starting to understand which areas of the brain can substitute for function, and as we gain better awareness of that, we'll actually use these techniques to see if a particular exercise helps a particular area adjust better," she said. "We're not quite there in tailoring our program specifically to the area involved, but we're making progress."

Rehabilitation and Therapy

UT Southwestern's doctors also tap into the university's expansive rehabilitation program, which sets up individualized programs for each patient to get them back as close as possible to their pre-accident condition.

"From studies, we know that activity and con - centrated therapy helps recovery," said Dr. Kowalske, who oversees the rehabilitation clinic that annually handles more than 1,100 visits from patients with traumatic brain injuries. "We are on the cutting edge for medication intervention and therapy intervention."

Occupational therapies, such as dressing, bathing, grooming and eating, are aimed at achieving maximum independence in daily living, while recreational therapy targets skills for specific activities, such as tennis or drawing, that a patient enjoyed previously, said Dr. Anne Hudak, assistant professor of physical medicine and rehabilitation.

Physical therapies seek to bring the patients to the peak of their post-trauma mobility, whether in a wheelchair or learning to walk again. For some that involves shifting from a bed to a wheelchair. For others, like Trey Howell, it means learning to regain balance. Therapists use everything from electrical stimulation for the muscles, to special electronics that offer feedback on balance.

Speech, language and hearing therapies are available to circumvent damage involving swallowing, speaking and listening. Some of the more recent innovations involve electrical stimulation for swallowing, which is critical for self-feeding.

Cognitive therapies often involve strategies for remembering – making lists, repeating objectives and names, or carrying a bill, perhaps, to remind someone they got up to get their checkbook.

Therapy is not limited to physical and cognitive arenas either. A critical part of recovery involves psychological and social counseling.

"If I say for the next two months you're going to sit in the hospital, it would completely disrupt your entire life," said Dr. Kowalske. "And if you add on top of that a functional limitation, not being able to swallow or walk or talk, it would obviously be devastating. So our psychologists work very closely with patients and families."

Usually the mental, cognitive and emotional piece of this is more difficult than the physical, said Dr. Hudak.

"It takes people time to accept their physical limitations, but it's a very concrete thing, and because it is so concrete, they usually get it. The cognitive, behavioral aspects are much more difficult," Dr. Hudak said.

Recovery isn't all about the patient either. Family support is often a critical factor in the patient's recovery.

They have to learn how to care for the patient at home, such as transferring them from bed to wheelchair, perhaps, or caring for wounds, or ensuring medication regimens and exercise programs are followed.

"Family is a tremendous part of the healing process," Dr. Hudak said. "I always tell my patients, this injury not only happened to them, but also to their family. Families go through night after night in the ICU, and they go through all the time in acute care, all the time in rehab. It puts a lot of stress and strain on the family dynamics."

Researching Causes and Cures

How to better care for, diagnose and treat traumatic brain injury patients is always on the minds of doctors caring for these patients, but giving the best care also requires research into what works and what influences recovery, such as genetic factors.

"How the brain functions normally is still a black box, and then you've got a broken black box, which makes it that much harder," said Dr. Hudak.

Will a patient be part of the lucky 10 percent to 20 percent who fully recover and lead the life they had before or among the 80 percent to 90 percent who will need new ways to adapt and accomplish the otherwise ordinary tasks of life?

The Centers for Disease Control and Prevention estimates that at least 5.3 million Americans currently have a long-term or lifelong need for help to perform activities of daily living as a result of a traumatic brain injury.

"The way a patient will recover after a brain injury is very difficult to predict clinically," Dr. Hudak said. "Some people look pretty good in the ER and ICU, but nevertheless end up with a very severe impairment to the point that they cannot go back to work or school or fulfill family responsibilities. On the other hand, there are people who look terrible in the ER or ICU, and you're wondering whether you should be counseling the family about possible death, and they surprise you and turn around and a few months later, if not completely back to normal, are very functional. They go back to work or school and are pretty darn close to leading a normal life. That's been a real conundrum clinically for a long time."

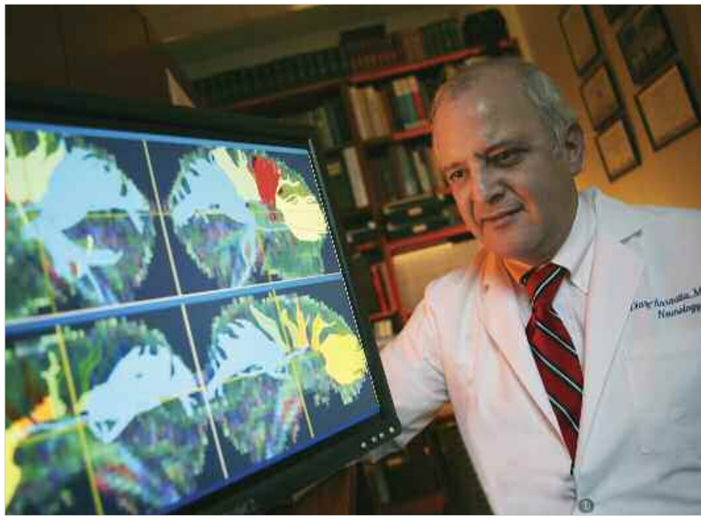
But researchers at UT Southwestern are starting to uncover some clues.

"It is likely that at least some of the explanation for that variability in outcome is due to genetic factors, differences in the way that the brain tissue reacts to injury," Dr. Diaz-Arrastia said.

Controlled experiments, for example, demonstrate that the same type of injury in different strains of rats, even some with only a few different genes, can have different results in terms of outcome.

When the Human Genome Project began, Dr. Diaz-Arrastia realized the potential for identifying genes affecting traumatic brain injury recovery for humans.

"So we started collecting a great deal of clinical information early on – details of the injury, details of patients' hospital course in the ICU. Then we would contact them six months after their injury to gauge the degree of their recovery," he said. "By now, we have more than 1,000 patients who have enrolled in our study, and we have identified some very interesting genetic variances that appear to influence outcome. We are just on the cusp of doing a much larger study."



"We have more than 1,000 patients who have enrolled in our study, and we have identified some very interesting genetic variances that appear to influence outcome."

— *Dr. Ramon Diaz-Arrastia*

Down the Road

Both Trey Howell and his UT Southwestern physicians are optimistic about the future.

"Rehab is difficult, but it's worth it," said Mr. Howell, who hopes to eventually attend college full time.

Said Dr. Diaz-Arrastia: "I think there have been some very great advances in the past several decades. One thing that has clearly happened is that the mortality is way down, from about 40 percent in the 1980s to about 20 percent in the last several years.

"It's hard to compare those two eras because a lot of other things have happened – better cars, more use of seatbelts and airbags. But my sense is that most of that decrease in mortality is actually due to improved care in trauma, in neurosurgery and in the ICU as well as in rehabilitation.

"We're working on it very hard, although we still have a long way to go. I don't think there's going to be any one magic bullet."

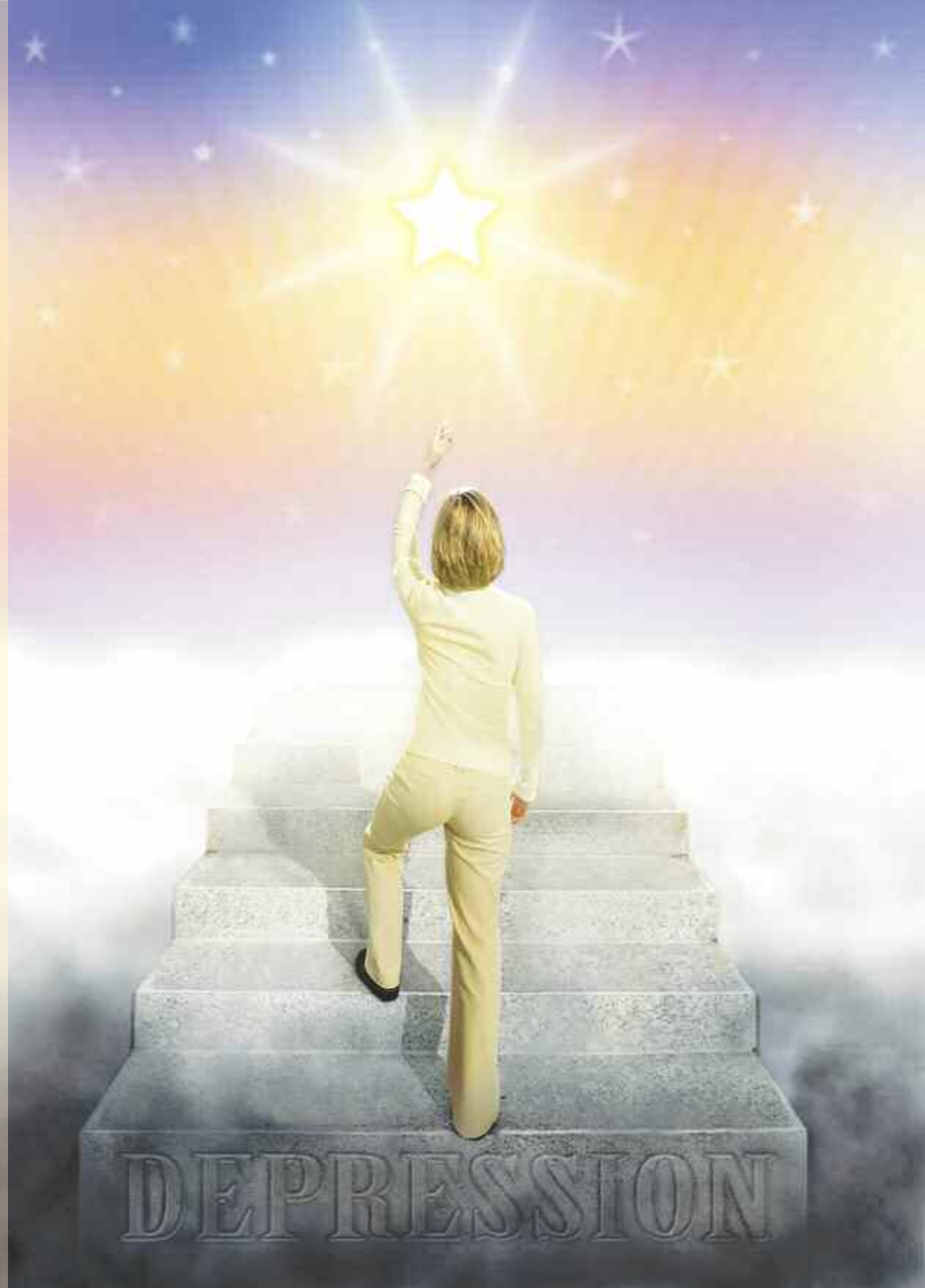
For more information on traumatic brain injury, please call 214-645-2080, or visit www.utsouthwestern.edu/patientcare/medicalservices/rehab.html.

STAR★D

Step-by-step toward a brighter future

By Donna Steph Hansard

Kasey Thompson has her life back, thanks to a landmark study on depression led by researchers at UT Southwestern Medical Center. ★ Four years ago, the 42-year-old senior administrative associate in UT Southwestern's Department of Neuroscience realized she was more than just a little sad. ★ "The big catalyst for me was that I started feeling suicidal," said Ms. Thompson. "And it wasn't as if I wanted to die. I just didn't care about being here anymore." ★ She'd been at a fall festival, touting her handmade jewelry, and what should have been a fun afternoon with friends instead brought thoughts of despair. ★ "There were all these precious children walking around in their cute costumes, and I was doing very well selling jewelry. I was with my friends. It was a beautiful day. And I was miserable. Just miserable," she said. "I didn't want to go on any longer. ★ "I went home and had all these scary thoughts. And I called my best friend and said: 'There's something wrong here. I don't want to feel like this anymore. It's got to stop.'" ★ For Ms. Thompson, acknowledging that her depression was more than simply "feeling down" was the first step in reaching out for help. ★ "I needed someone else to know how I was feeling because if it becomes known, it becomes less frightening. And once you admit it, you have to do something about it."



Depression was not new for Ms. Thompson. She'd experienced it before and had been prescribed antidepressants, but she had abandoned the medication when she began feeling a bit better. Plus her friends and family had questioned why such a "happy person" would need drugs to keep her life on track.

"There's a stigma attached to being on antidepressants and being depressed, although there shouldn't be," she said. "I explain to people now that it's like diabetes. You would never criticize a diabetic for taking insulin. It's the same with someone who takes high blood pressure medication."

After that fall day, Ms. Thompson knew that her depressive episode demanded attention.

"There was nothing particularly wrong. I didn't have any major crisis in my life. But when there's nothing wrong, and you're still unhappy, and then you get to the point that you're *very* unhappy for no particular reason, you've got to get help."

The following Monday, Ms. Thompson called her doctor, who told her about research being conducted in UT Southwestern's Department of Psychiatry.

The study, the largest ever on treatments for depression, today is considered a benchmark in the field of depression research, offering step-by-step guidelines for measuring and treating the symptoms of major depressive disorder, or MDD.

Designed and led by UT Southwestern researchers, the six-year, $33 million study initially included more than 4,000 patients at 41 primary-care and psychiatric clinics across the country, with participants representative of the U.S. census. Funded by the National Institute of Mental Health (NIMH), the study included individuals who had been diagnosed and were being treated for depression in "real-world" settings, rather than symptomatic volunteers who responded to advertisements, as often is the case in clinical trials. In addition to suffering from MDD, most participants also had other coexisting general medical and psychiatric conditions.

Results of the study, designated STAR*D (Sequenced Treatment Alternatives to Relieve Depression), since have been published as more than 60 peer-reviewed articles in numerous medical journals, including the prestigious *Journal of the American Medical Association*, *The New England Journal of Medicine* and the *American Journal of Psychiatry*. These, in turn, have spawned media reports in hundreds of print and television outlets around the world during the past several years.

Different from other clinical trials on depression, STAR*D set its objective higher. Rather than simply trying to achieve a "response" from participants – that they improved – the study aimed for remission – getting them completely well and symptom-free.

UT Southwestern psychiatrists Drs. A. John Rush and Madhukar Trivedi designed the study to incorporate specific step-by-step medication treatment guidelines based on patients' symptoms and possible medication side effects. Participants and clinicians answered a list of specific questions on each visit that allowed them to keep track of whether depressive symptoms had improved since the last visit. This "measurement-based care" approach was used to make decisions on whether or not to continue medication, change medication, add medication or add cognitive therapy – in a predetermined sequential fashion. Participant preferences also were considered.

STAR*D is the first definitive study to provide solid, scientific-based evidence regarding which next treatment steps are best for treatment-resistant depression. Depression, like other chronic medical illnesses, can be considered treatment-resistant when at least one or two adequately delivered treatments are not followed by remission of symptoms.

UT Southwestern was selected by the NIMH as the coordinating study center, with Dr. Rush as principal investigator, after a lengthy and competitive bidding process. Also included in the original investigative group were researchers from Massachusetts General Hospital, University of Pittsburgh and Columbia University.

A recent World Health Organization report ranked depression as the fourth-most disabling medical condition worldwide and predicted it will be the second-most disabling condition worldwide by 2020.

Each year, about 21 million American adults – or 9.5 percent of the population – struggle with depression, a chronic and recurring disease, which frequently returns for two or more episodes, many of those lasting two years or more. About one in 20 teens also suffers from depression, labeled one of the most common disorders of adolescence by the NIMH.

The lifetime risk of depression is 7 percent to 12 percent for men and 20 percent to 25 percent for women. Its annual cost was estimated at $83.1 billion in the United States alone for the year 2000, including $26 billion in costs of treatment and $57 billion in losses due to factors such as absenteeism, reduced productivity at work and the value of lifetime earnings due to suicide-related deaths. Depression is responsible for up to 70 percent of psychiatric hospitalizations and about 40 percent of suicides.

"Depression is a disabling condition just like any other medical condition – like diabetes or congestive heart failure – and should be treated as such," said Dr. Rush, vice chairman of clinical sciences and professor of psychiatry. "STAR*D is important because it represents the largest group of moderately to severely depressed patients studied, most of whom had either chronic or recurrent major depression, and the majority of whom also had concurrent other general medical or psychiatric disorders."

"Depression is a disabling condition just like any other medical condition – like diabetes or congestive heart failure – and should be treated as such,"

~ Dr. A. John Rush

"What's also important is that nearly half of these patients significantly benefited from and showed a response to the medication, with one in three of those achieving a symptom-free state after the first round of medication," said Dr. Rush, who holds the Betty Jo Hay Distinguished Chair in Mental Health and the Rosewood Corporation Chair in Biomedical Science.

"The take-home message from the study is that patients need to hang in there and stay in treatment, even if several steps and various medications must be tried," he said. "Be patient and willing to tell your doctor if a medication isn't working, if the dosage is bothering you or if you're having side effects. Collaborate with your physician to find the right medication and dosage, and stay on it long enough to give it a chance to work."

Dr. Trivedi, professor of psychiatry and director of UT Southwestern's mood disorders research program and clinic, said STAR*D represents a summary of all the steps and a comprehensive road map of outcomes from the largest depression trial ever conducted.

"It offers clear evidence of what happens step-by-step and gives us a good idea of longer-term outcomes a year after treatment," said Dr. Trivedi, holder of the Lydia Bryant Test Professorship in Psychiatric Research.

"What's also exciting about STAR*D is that it's the first large clinical trial where we entered into the community of practitioners who were routinely treating patients with depression, both in primary care and specialty care," he said. "Rather than evaluating people who volunteer for studies – usually conducted for the purpose of Food and Drug Administration approval of a medication – these studies used patients seeking treatment for depression in their respective clinics and often having other general medical illnesses and psychiatric conditions. The results from this study can thus easily be applied to routine clinical practice in both primary and specialty care."

STAR*D was conducted in four phases using the following medications, prescribed in a step-by-step fashion, sometimes used separately and sometimes combining two. Cognitive therapy also was an option.

- Citalopram (Celexa)
- Sertraline (Zoloft)
- Bupropion SR (Wellbutrin SR)
- Venlafaxine XR (Effexor XR)
- Buspirone (BuSpar)
- Mirtazapine (Remeron)
- Triiodthyronine (T3) (Cytomel)
- Nortriptyline (Pamelor, Aventyl)
- Tranylcypromine (Parnate)
- Lithium (Eskalith, Lithobid)

These particular medications were selected because they are among the safest, easiest to take and most frequently prescribed. They also were chosen to test specific theories about which medication would be the most effective. There were no placebo treatments used in the study.

In the first phase of STAR*D, all participants were given the same antidepressant, citalopram (Celexa) for up to 14 weeks. Those who didn't experience remission or couldn't tolerate the medication were strongly encouraged to proceed to phase two, where they were randomized to various groups receiving subsequent treatments, including cognitive therapy alone or in combination with medication, as well as several different antidepressants used alone or in combination. Phases three and four worked similarly.

After each level of treatment, patients whose depression did not go away were encouraged to go on to the next phase. Participants who got somewhat better, but did not become symptom-free also were asked to go to the next step.

Once patients were in remission or decided to stay with their current treatment, they entered a 12-month follow-up, during which their long-term outcomes were monitored.

Some of the major findings from STAR*D include the following:

- A third of individuals with depression can fully recover from their symptoms after their first treatment with an antidepressant.
- Half of people with depression can reach remission after changing or adding an antidepressant.
- The fewer steps it takes a person to achieve remission, the lower the chance for relapse. Conversely, the more steps it takes to achieve remission, the more likely a patient will relapse.
- Patients suffering from depression responded similarly whether treated by a primary-care doctor or a psychiatrist when both followed the same high-quality, measurement-based treatment approach.

The study also found that the highest response and remission rates after the first treatment step came from Caucasian, female participants who were employed and had higher levels of education or income. Participants with socioeconomic disadvantages, more psychiatric conditions and minority status were more likely to drop out of treatment, while those who had prior experience with depressive episodes were more likely to stay in treatment.

Continued on page 57

"It's a myth that you can't measure depression. Our study showed that patients can expect good outcomes using step-by-step measurement of symptoms and medication side effects and by planning the next step, if the first doesn't work."

~ Dr. Madhukar Trivedi

STAR*D

Continued from page 35

Children whose mothers are depressed are more likely to suffer from anxiety, mental-health problems and disruptive behavior than those whose mothers aren't. Children whose mothers are successfully treated for depression show significant improvement themselves, without any additional intervention or treatment of their own.

There are few differences between which medications help patients achieve remission, as long as they are carefully delivered for a long enough time period. Patients tend to do better if they stay on a medication for a greater length of time, up to 12 weeks, before changing to another.

There may be genetic propensities to achieving a better outcome with antidepressant treatments, as well as to having suicidal ideas and thoughts.

"One-third of patients with major depressive disorder can expect to achieve remission, with all or almost all symptoms gone, with the first treatment, and one-half of patients with a second treatment," said Dr. Trivedi. "Compared with other clinical diseases, this outcome is quite exciting."

One of the more surprising results of the study, said Dr. Rush, was that there was little difference between medications used to treat depression.

"To the surprise of a lot of pharmacologists, which drug was used for treatment did not turn out to make much difference in terms of clinical outcomes," he said. "That tells us that, given the drugs we have, it may be that it is more important to use diligently whatever medication the doctor picks than to become convinced that a particular drug is uniquely good for a particular person."

STAR*D provides step-by-step guidelines for treating depression that any physician can follow, Dr. Rush said.

"We found that primary-care doctors in busy practices can measure symptoms and side effects at every visit and follow guidelines that show how to accurately dose and safely manage patients with depression. STAR*D provides a tool that is now available in the public domain (www.star-d.org) to help all doctors treat depression optimally."

Also on the Web site are rating scales that can easily be used to measure depressive symptoms, giving patients and clinicians a way to determine if symptoms are improving or not.

"It's a myth that you can't measure depression," said Dr. Trivedi. "Our study showed that patients can expect good outcomes using step-by-step measurement of symptoms and medication side effects and by planning the next step, if the first doesn't work. STAR*D showed that the use of measurement-based care is quite important."

"I feel like I have myself back. It's more than just your life. It's who you are. It's your entire being. You don't have yourself at all when you're depressed."

~ Kasey Thompson

Kasey Thompson agrees.

"I think a lot of people give you medication and then ask how you're doing, and you say 'fine,' " she said. "The big thing about STAR*D was the questions. There were specific things they would ask you to break down, and I realized that I wasn't sleeping well; I wasn't eating well; I didn't care about things I normally would have. The questions made me realize I might be feeling a little better, but that I could be doing a lot better."

Ms. Thompson began improving after a few weeks of treatment, but it took a combination of two medications and about six months before she felt completely well, she said.

"My turning point was when they added a second medication and also addressed the fact that I still wasn't sleeping well," Ms. Thompson said. "For me, it was twofold. One medication helps with depressed thoughts, and the other does well for helping with the anxiety issues."

While STAR*D answered numerous questions about treating depression, it also raised more. As a result, UT Southwestern has been selected by the NIMH to head a large $10 million follow-up study scheduled to begin enrolling patients in early 2008. The Combination of Drugs to Enhance Outcomes of Depression, or COMED, study will use combinations of antidepressants to battle depression with the goal of helping more patients reach remission faster and stay in remission longer.

"The thought is that if one out of three people hits remission, and it takes about 12 weeks to get there, that's too few and too slow," said Dr. Rush, principal investigator on the second study as well. "Why not give them two antidepressants right off the bat, like you do for hypertension or congestive heart failure? Give them two drugs and see if that gets more people into remission sooner rather than later."

Ms. Thompson is still on the same two medications today and credits STAR*D with her recovery.

"I feel like I have myself back," she said. "It's more than just your life. It's who you are. It's your entire being. You don't have yourself at all when you're depressed."

For more information on treatment for depression at UT Southwestern, please call 214-645-8500, or visit www.utsouthwestern.edu/patientcare/medicalservices/psych.html.

Fighting Infectious Diseases

In the growing battle against high-profile, outbreak-prone diseases, researchers and physicians at UT Southwestern are at the forefront in working to understand, treat and combat their spread.

By Katherine Morales

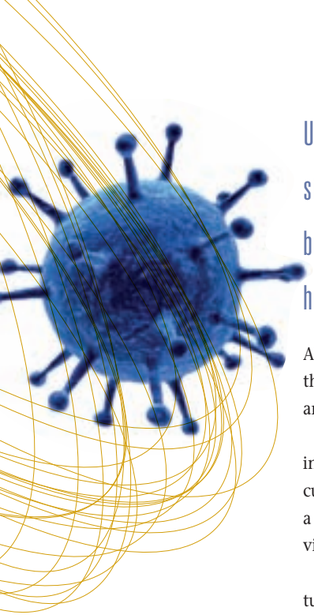
The news reports started quietly enough in May 2007.

Most were just short items in newspapers and brief reports on television stating that federal health officials were looking for people who had recently traveled on two trans-Atlantic flights with an American passenger who may have had extensively drug-resistant tuberculosis.

Within a week, however, that trickle of news reports turned into a flood, becoming a top international story as people raptly followed the complicated travel path of the man dubbed "TB Guy." Some wondered how one person could evade so many lines of defense designed to protect the public from dangerous, contagious illnesses.

The answers proved more complicated as the story continued to unfold during the subsequent months. But the incident highlighted Americans' susceptibility to a variety of diseases as travel, trade and even the speed of information make the world a smaller place.

In the growing battle against high-profile, outbreak-prone diseases, researchers and physicians at UT Southwestern Medical Center are at the forefront in working to understand, treat and combat their spread. ›



UT Southwestern researchers study not only new and exotic diseases, but also diseases that have been with humanity for millenniums.

AS THESE DISEASES have become drug-resistant, they have increased humans' susceptibility to them and weakened existing treatments.

Dr. Tawanda Gumbo, assistant professor of internal medicine at UT Southwestern, studies tuberculosis and extensively drug-resistant tuberculosis, a newly identified strain of TB that leaves patients virtually untreatable using existing anti-TB drugs.

Dr. Gumbo became interested in the study of tuberculosis because of its global prevalence and its ability to adapt to and overcome standard treatments. Up to one-third of the world's population has been exposed to the bacterium that causes tuberculosis.

"TB is one of the most important chronic infectious diseases worldwide, and it has been for the last 10,000 years. It has evolved with humanity, and even new treatments are becoming obsolete," Dr. Gumbo said.

"We have had therapy for many decades, but now, drug-resistant TB is hurting our efforts to eradicate the disease. Travel and movement of people across borders has certainly contributed to increases in new infections." —Dr. Tawanda Gumbo

As the case of the TB traveler highlighted, drug-resistant TB has the potential to spread rapidly.

Not every infected person develops the full-blown disease, so latent TB infection is common, even endemic in some areas of the world. When latent infections become active infections, however, the untreated disease kills up to two-thirds of its victims.

The bacterium that causes TB was first identified in 1882, but it wasn't until 1946 that the discovery of targeted antibiotics effectively treated the disease. Antibiotics continued to keep the disease in check until the 1980s, when the disease's resurgence became a global concern. By 1993 the World Health Organization declared the disease a world-health emergency.

"We have had therapy for many decades, but now, drug-resistant TB is hurting our efforts to eradicate the disease. Travel and movement of people across borders has certainly contributed to increases in new infections," Dr. Gumbo said.

He explained that public health authorities in countries like the United States have had better success in managing tuberculosis treatments – which involves taking a cocktail of antibiotics for several months – than other countries where public-health initiatives are not as well-supported.

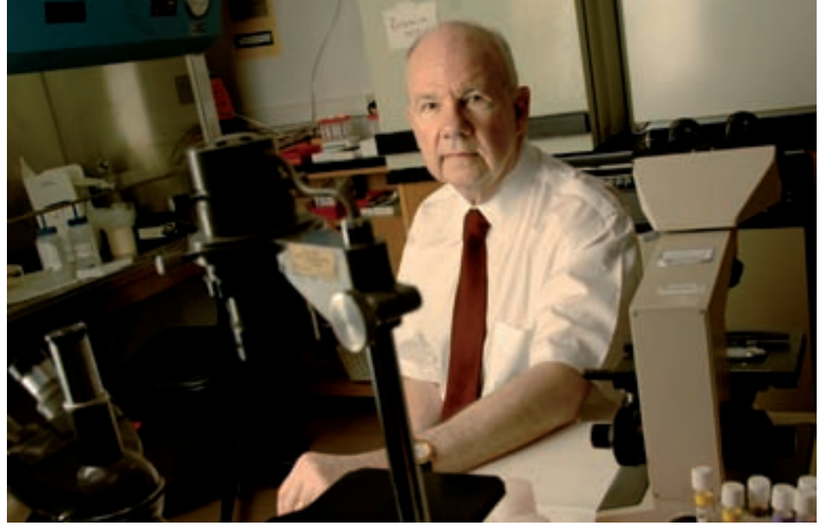
Deadly strains can still appear anywhere, regardless of public-health protection, he said.

"Resistance will always occur, that's evolution. These bacteria are trying to survive, and noncompliance among people who are taking treatments is common," Dr. Gumbo said.

New research into this old disease includes discovering new treatments with shorter regimens that patients can easily follow, even in rural and remote parts of the world. Treatment for the disease can take several months and must be closely monitored by public-health authorities.

In his laboratory, Dr. Gumbo measures how antimicrobial drugs behave and how microbes react to those drug concentrations. His aim is to use the information to slow or stop new strains of TB from erupting.

"We are working to develop concepts for short-term therapy and resistance suppression," Dr. Gumbo said. "I think we have an obligation to create new, shorter treatments and develop more palatable therapies."



Influenza

Influenza, another ancient disease, has killed millions of people worldwide for hundreds of years. Arriving in seasonal epidemics, it has created tremendous public-health threats in years when it reached epidemic proportions. In the 20th century alone, there have been three major flu pandemics caused by distinctly different strains of the influenza A virus.

Dr. James Luby, professor of internal medicine at UT Southwestern and former chief of infectious diseases for more than two decades, is an expert in clinical virology. He has experience with two of the pandemics. Influenza, he said, is a particular challenge because it mutates quickly and can spread very fast. The flu is one of a specialized set of viruses that use ribonucleic acid, or RNA, rather than DNA, for storing genetic information.

"The virus itself changes character very quickly. RNA viruses in general mutate all of the time. When pandemic flu occurs, a new strain of virus comes into existence generally by re-assortment between a current human strain and a circulating bird strain," Dr. Luby said. "We have more control than ever over viral infections. Conventional vaccines, a new live virus vaccine and new anti-viral drugs are effective at preventing and treating influenza."

He warned that even in years when there is no flu pandemic, the disease still kills thousands of people in the U.S. Those who are very young, very old or who have compromised immune systems are at a much higher risk of becoming critically ill.

Seasonal flu vaccines are the best way of protecting public health, Dr. Luby said, because they are created annually to protect people against the most common strains of flu. Not only do they provide protection for those vaccinated, but wide-scale public vaccination programs also offer some community protection for those who have not received the vaccine.

"RNA viruses in general mutate all of the time. When pandemic flu occurs, a new strain of virus comes into existence generally by re-assortment between a current human strain and a circulating bird strain." —Dr. James Luby

Vaccines

Seasonal influenza highlights the importance of vaccines. Vaccines, in fact, are among the most highly effective protections against illnesses. Researchers at UT Southwestern are contributing to the effort of finding new vaccines by examining host response to infections and performing cutting-edge studies of the pathogenesis of diseases – the way infectious agents cause disease within the body.

Dr. Jane Siegel, professor of pediatrics and a specialist in pediatric infectious disease at UT Southwestern, points out that effective vaccine programs have eradicated smallpox and greatly diminished the incidence of polio – a disease that once reached epidemic proportions in the early 20th century.

"Our experience is that when an individual gets infected, the severity of the disease is determined by many different factors – underlying disease, subtle immune deficiencies, and others. But we can't always predict how well antibiotics or other treatments will work; that's why vaccines are so effective. Treatments for a disease become obsolete if you can prevent it in the first place," Dr. Siegel said.

Developing vaccines is an expensive process. Much research must be done, and clinical trials are paramount in gauging the safety and efficacy of any new drug. When approved, vaccines are continually monitored by public-health officials to ensure their success and safety.

"We, as clinicians and researchers, are always walking the fine line of determining risk of disease versus risk of vaccines, and we are constantly doing surveillance to see if there are any vaccines causing adverse effects," Dr. Siegel said. "We've been so successful with vaccines that some people don't have a feel for how detrimental it would be if there weren't vaccines in place. Vaccines have stood the test of time; they are safe and effective; and they are the best way of preventing the spread of disease."

E coli

Uncovering the ways in which bacteria behave in the body and learning how they reproduce are other ways researchers at UT Southwestern are combating diseases – research they hope can speed development of new treatments.

Escherichia coli is usually transmitted through contaminated food. Recent outbreaks in the United States have originated from ground beef and spinach. The illness can cause painful symptoms in healthy adults and can be fatal to young children, the elderly and those with compromised immune systems.

Dr. Vanessa Sperandio, associate professor of microbiology at UT Southwestern, studies the way strains of *E coli* react inside the human body.

Recently, Dr. Sperandio and her team discovered a receptor inside the *E coli* bacterium that receives signals from natural flora and hormones inside the human body, spurring it to infect cells. Since they identified the receptor, work has begun on testing the effectiveness of existing medications on blocking the receptor.

"You can get infected by only a few bacteria that enter through your mouth. When those bacteria get to your large intestine, they get signals from the host and know they are in the right place. Receptors then send signals, and they begin to activate aggressive virulence genes," Dr. Sperandio said. "This receptor is found in many different pathogens, so we can use this knowledge to design specific antagonists to block bacterial infections."

Cattle are the primary source for most *E coli* infections in the United States. When cattle waste reaches water sources near food crops, contamination can occur. Unsanitary slaughtering of cattle can also lead to cross-contamination of the beef itself, and shipment of infected food speeds the rate at which the public can become ill.

Diminishing the amount of *E coli* shed by cattle may reduce infection of human food sources, so Dr. Sperandio and her colleagues are currently looking for ways to diminish the amount of bacteria in cattle. She recently received funding through UT Southwestern's High Impact/High Risk Research Program to study treatments of bacterial infections such as *E coli*.

"We're working on a way to change the way *E coli* reacts in the cattle's intestine," Dr. Sperandio said. "If you kill it in cattle, you get it out of the environment."

HIV

Animals are an easy vector through which diseases spread to humans. But humans have always been very efficient at spreading diseases to one another.

"We, as clinicians and researchers, are always walking the fine line of determining risk of disease versus risk of vaccines, and we are constantly doing surveillance to see if there are any vaccines causing adverse effects."

—Dr. Jane Siegel

A recent scourge highlighting the speed at which a virtually unknown, localized disease can explode into a worldwide pandemic has been the progression of the human immunodeficiency virus, which causes AIDs. The most widely accepted theory of its origin is that the virus originated in chimpanzees and made the jump to humans sometime in the 20th century. As people began traveling from rural areas to larger towns and cities, they spread the disease to one another.

The small, localized infection spread easily across geopolitical borders, spilled across oceans and entrenched itself globally. Huge leaps in scientific knowledge over the past 25 years have led to a much better understanding of the complex disease. Preventing its spread has proved much more challenging, however.

"In the U.S., advances in treatment have made HIV more of a chronic disease, but the number of new infections still continues to go up every year," said Dr. Doug Hardy, associate professor of internal medicine and pediatrics at UT Southwestern.

Dr. Hardy works with HIV-positive patients in Dallas, where treatments have significantly improved the life span and quality of life for many. But there are chasms separating the quality of life for patients here and patients in countries where treatment is scarce and education about the disease is sorely lacking.

"HIV carries much more of a societal stigma in South Africa. People really don't want to get tested because they are ostracized, and people who seek treatment also are very suspicious of Western medicine. The HIV problem in Africa is very daunting, but I think ultimately it's such a crucial issue that we will find ways to take positive steps to address it."

—Dr. Doug Hardy

In an effort to change these conditions, Dr. Hardy has helped establish a clinical fellowship program in South Africa, where one in three women of childbearing age is infected with HIV.

In 2006 UT Southwestern philanthropists Linda W. Hart and Milledge A. Hart III provided $150,000 to begin funding the program after returning from a trip to South Africa, where they heard a presentation on the Waterberg Welfare Society Hospice House clinic. This facility, which serves hundreds of South African patients who otherwise would have no means of receiving medical care, is funded by the Wilson Education Foundation, established by Dallas interior designer Trisha Wilson. In 2007 the Harold Simmons Foundation contributed $1 million to enable the program to expand dramatically.

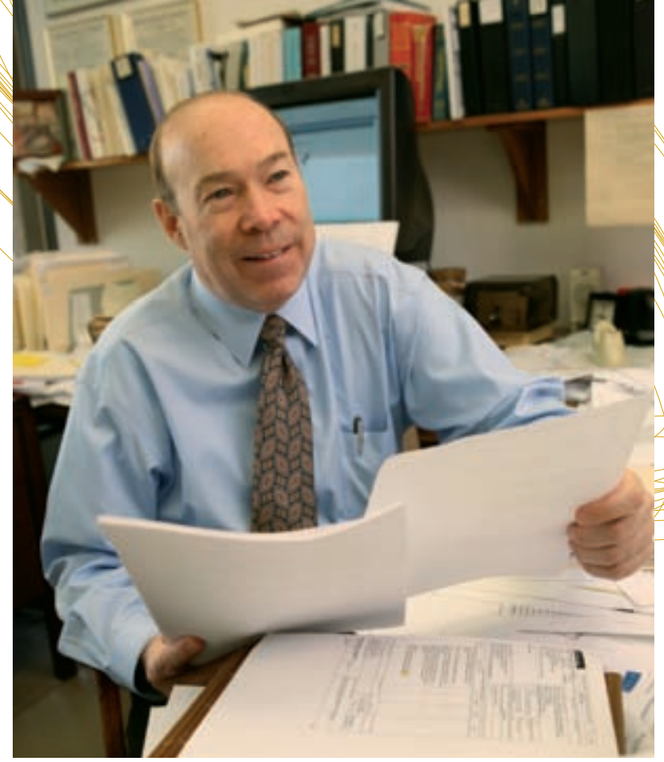
UT Southwestern participating physicians from the departments of Pediatrics, Internal Medicine or Family and Community Medicine are stationed in South Africa for three to six months and treat HIV-positive patients.

"HIV carries much more of a societal stigma in South Africa. People really don't want to get tested because they are ostracized, and people who seek treatment also are very suspicious of Western medicine," said Dr. Hardy. "The scope of the problem makes it so important and valuable to get residents interested in doing a fellowship like this. The HIV problem in Africa is very daunting, but I think ultimately it's such a crucial issue that we will find ways to take positive steps to address it."

With no prospects of an effective vaccine on the horizon for HIV, discovering new treatments and ways to prevent its spread presents a major challenge for researchers at UT Southwestern.

HIV mutates at a very rapid rate within each individual patient and can develop resistance to existing treatments very quickly. Dr. J. Victor Garcia, professor of internal medicine at UT Southwestern, has developed a novel approach to rapidly test potential treatments for HIV and AIDS. He and his colleagues have developed a new type of laboratory mouse engineered to be susceptible to certain infections that only afflict humans and for which there are no accessible models to evaluate clinical interventions.

Normal mice are not susceptible to human-specific viruses, such as HIV. These limitations make it extremely difficult to study and develop therapies that target these viruses.



"The bottom line is that in order to know whether or not something really works, you have to test it. You have to give any drug as close to a real-world test as possible," Dr. Garcia said. "In the case of HIV, it is so unique to humans that it doesn't infect anything else in quite the same way."

Dr. Garcia's mouse model allows a parallel model for human infection by essentially "humanizing" the mice using human blood stem cells.

"It gets us as close as possible to mimicking human infection. All of the target cells relative to infection by a human pathogen like HIV are present in the mouse," he said.

The model enables scientists to test and discard ineffective treatments faster and to speed the implementation of promising treatments. It also allows scientists to see how infection occurs once HIV is introduced.

"In the absence of a vaccine, you can treat infections in people, but it would be better to prevent new infections in the first place," Dr. Garcia said. "One fascinating aspect of our humanized mouse model is the fact that it recapitulates the same routes of infection used by the virus to infect human."

What this represents to scientists is an opportunity to test novel approaches aimed at preventing the further spread of AIDS in a highly relevant in vivo setting.

"We are now evaluating pre-exposure prophylactic measures, such as widely available antiviral drugs or novel microbicides [substances that can be used topically] to prevent HIV transmission in humans," he said. "That is the value of these animal models. Time is critical, and the model allows us to study pathogens accurately, to abandon therapies that don't work or that can potentially cause harm, and to implement those with the best promise for success."

West Nile Virus

Despite tremendous medical advances in creating vaccines and treatments, diseases continue to mutate and spread. Just as smallpox arrived in the Americas from Europe centuries ago, physicians and epidemiologists are seeing new outbreaks of illnesses native to other areas of the world. Less than a decade ago, West Nile virus arrived here in the blood of birds and mosquitoes, probably on shipments of cargo from areas where the disease originated. Recent outbreaks of the disease have resulted in deeper, more thorough studies of the disease and its prevalence. There is currently no vaccine, and the disease can cause encephalitis and death.

"Natural selection has bred special strains of *Staph aureus* that are resistant to antibiotics and very virulent. We used to see these only in hospitals, but they are now becoming more common in the community."

—Dr. Robert Haley

"The incidence of West Nile in Texas is high. We are routinely one of the top states for West Nile infections," said Dr. Roger Bedimo, assistant professor of internal medicine at UT Southwestern and chief of infectious disease at the Veterans Affairs North Texas Health Care System. "Little is known about the long-term effects of infection, and, without a vaccine, treatments are our best option. We want to expand our knowledge of West Nile and aid in the design of better therapies."

UT Southwestern recently joined a national clinical trial network to identify the long-term health effects of West Nile virus infection and to learn more about the disease's progression, symptoms and mortality.

The trial, initiated by the National Institutes of Health Clinical Center, includes 13 sites where researchers are observing the natural course of the virus over a year in people who have either a fever or neurological diseases due to West Nile infection.

"The emergence of these diseases is greatly facilitated by travel and the shipment of goods. That is why we want to track trends in the rise of complications due to West Nile infection," Dr. Bedimo said. "Various manifestations of the disease have been well-documented. But we are seeing neuroinvasive forms of the disease, such as meningitis, encephalitis and myelitis – which can cause paralysis – in younger patients and in different populations."

Because serious complications are rare, tracking the disease poses a unique challenge to investigators. Microbiologists at UT Southwestern are now studying the North American strain of the virus to see how the disease functions inside the body and how it slips through the immune systems to create such havoc.

"This disease was first discovered in Uganda and has since caused many sporadic outbreaks in Europe, the Middle East and Asia, but not in the Western Hemisphere until recently," Dr. Bedimo said. "But the disease doesn't always present symptoms in the same way, and we are also seeing infections in younger people. We don't know why."

Halting New Killers

Monitoring the spread of diseases is crucial in alerting health experts to new pathogens and protecting public health. Epidemiologists examine the spread of disease and coordinate plans with public-health officials to stop or slow the spread of pathogens.

UT Southwestern routinely collaborates with county and regional health agencies. Because UT Southwestern faculty members work in some of the largest hospitals in the area, tracking diseases and working with infectious disease specialists improve patient outcomes.

"There is a constant need for surveillance so we can quickly understand and develop countermeasures to disease," said Dr. Robert Haley, chief of epidemiology at UT Southwestern and holder of the U.S. Armed Forces Veterans Distinguished Chair for Medical Research, Honoring America's Gulf War Veterans.

Local health departments, hospitals and medical centers play a key role in protecting public health and disseminating information quickly and accurately. When severe acute respiratory syndrome, or SARS, first broke out in 2002, global health networks picked up reports of what was described as a flu outbreak in China.

Within a few months the World Health Organization set up a network for doctors and scientists researching SARS. Quarantines were implemented, and the virus genome was sequenced shortly thereafter.

"You can't keep information about infectious disease bottled up. It has to get out to the right people. We're at a point now where the world community does not tolerate roadblocks to world health reporting." —Dr. Robert Haley

"The faster we can disseminate knowledge about new diseases, containment becomes so much easier," Dr. Haley said.

The slow, but steady spread of MRSA (methicillin-resistant *Staphylococcus aureus*) is also being closely watched by public-health officials, who first reported the skin infections among intravenous drug users in 1981. It has since become the most common cause of emergency room visits for patients with skin and soft-tissue infections.

"There are two kinds of *Staph* that live on humans: *Staph aureus* and *Staph epidermidis*. *Staph epidermidis* is on every millimeter of skin on your body and doesn't generally cause disease," Dr. Haley said. "*Staph aureus* in a healthy person is usually just inside the nose, on the scalp, or in a wound or sore. Most people who have it, never have a problem with it. But natural selection has bred special strains of *Staph aureus* that are resistant to antibiotics and very virulent. We used to see these only in hospitals, but they are now becoming more common in the community."

Like so many other pathogens, *Staph aureus* poses a greater threat to those with compromised immune systems. Since the resistant *Staph* germs can circumvent routine hygiene measures, conducting public-health surveillance to chart changes in the number of infections pinpoints where strong prevention measures are needed to halt their spread.

Notifying other health organizations about new infections keeps health-care workers abreast of any suspicious rise in new or existing diseases.

"You can't keep information about infectious disease bottled up. It has to get out to the right people," Dr. Haley said. "Collaboration among agencies like local and state health departments, the Centers for Disease Control and Prevention, and the World Health Organization spreads public-health knowledge and makes containment possible. We're at a point now where the world community does not tolerate roadblocks to world health reporting."

To learn more about clinical services in infectious disease, please visit http://www.utsouthwestern.edu/patientcare/medicalservices/infectious.html.

mother & child

For five decades, the Department of Obstetrics and Gynecology at UT Southwestern has embraced evidence-based medicine, which uses strict scientific methods to ensure improved care.

These faculty members not only lead the country in numbers of babies delivered annually, but their philosophy has also made them national leaders in raising the standard of care for all pregnant women.

BY ALINE MCKENZIE

A woman in labor lies in bed, an electronic device attached to her abdomen to keep track of the unborn baby's heartbeat.

Since the 1960s, this has been a routine procedure. The technology was introduced because it seemed like a good idea, and it became an entrenched part of obstetrical practice, despite lack of proof that its benefits, such as detecting a baby in distress, would outweigh risks, such as false alarms that might lead to unnecessary Caesarean sections.

Decades later, another device was invented to measure the level of oxygen in the baby's blood during birth. Again, the rationale was that this technique might alert clinicians to a baby in distress.

But this time a nationwide team, led by UT Southwestern Medical Center, did a study involving more than 5,000 women. The researchers proved that the technique, called fetal pulse oximetry, had little effect on the rate of Caesarean deliveries, complications or overall health of the babies.

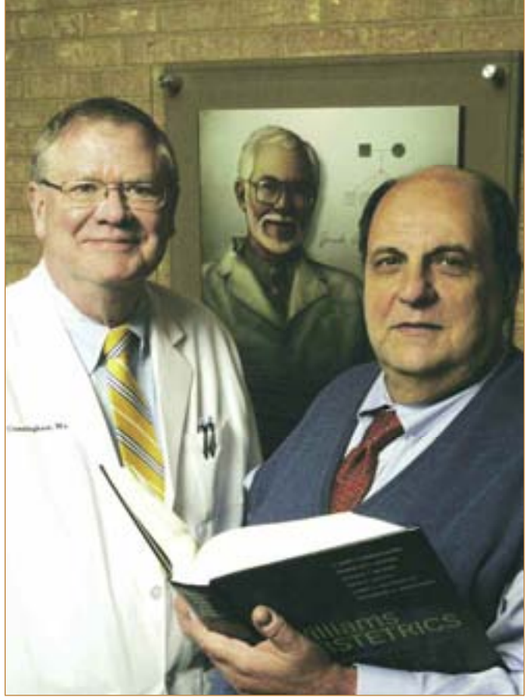
The device, which would have added cost and physical intrusion to labor, was subsequently taken off the market.

"Fetal oximetry was based on the rationale that you could measure fetal oxygen saturation. The thought was if you could know that, you would be able to determine the baby's condition – a very logical rationale," said Dr. Steven Bloom, chairman of obstetrics and gynecology, the study's senior author and holder of the Mary Dees McDermott Hicks Chair in Medical Science at UT Southwestern.

Co-investigator Dr. Kenneth Leveno, professor of obstetrics and gynecology and holder of the Jack A. Pritchard, M.D., Chair in Obstetrics and Gynecology, said, "The evidence we acquired here, however, was that it didn't improve the outcome."

This philosophy – that nothing should be added to routine obstetrical care without first being carefully studied – has characterized the Department of Obstetrics and Gynecology at UT Southwestern for five decades.

CUNNINGHAM



LEVENO

"This department has published research that provides the impetus for a lot of the evidence in this book [Williams Obstetrics], *chapter by chapter."*

—Dr. Kenneth Leveno, with Dr. Gary Cunningham, in front of a portrait of Dr. Jack Pritchard

Under its guidance, Parkland Memorial Hospital manages about 16,000 deliveries a year using a standardized-care approach to ensure that routine births don't get unnecessary care, while complicated ones get the focus they deserve.

"Our colleagues have described us as the conscience of American obstetrics," said Dr. Leveno, who calls it conservatism.

About half of the obstetrician-gynecologists in Dallas trained at Parkland, where many of the pregnancies are high-risk, under the excellent tutelage of UT Southwestern faculty, said Dr. Gary Cunningham, former chairman of obstetrics and gynecology and holder of the Beatrice and Miguel Elias Distinguished Chair in Obstetrics and Gynecology. That expertise has, in turn, translated to better outcomes for Parkland's patients and has made UT Southwestern a referral center for high-risk pregnancies.

"You can use the scientific principles with which we run our clinical services in probably almost every practice in the country," Dr. Cunningham said. "The excellent outcomes seen here are transferable to the Massachusetts General Hospital in Boston, or the Mayo Clinic in Minnesota, or to hospitals in the Dallas area."

At UT Southwestern University Hospital-St. Paul, obstetricians handle some extremely complex cases, such as pregnancy in women who have had heart or lung transplants, and they are developing surgical procedures for fetuses still in the womb.

"This is *Star Wars*," Dr. Cunningham said. "Our doctors take some of the sickest of the sick."

The department's illustrious reputation is underscored by the fact that the most widely used textbook in the field, *Williams Obstetrics*, and its companion volume, *Williams Manual of Obstetrics*, is almost completely written by UT Southwestern doctors. The department's clinician-researchers are currently revising the textbook for its 23rd edition.

"This department has published research that provides the impetus for a lot of the evidence in this book, chapter by chapter," Dr. Leveno said. "So I am always struck by the realization that practice of obstetrics is governed by our rather large commitment to the publication of evidence."

Since the days of one of its early chairmen, Dr. Jack Pritchard, the department has been devoted to "evidence-based medicine" – clinical practice based on scientific study. Dr. Pritchard took what was medical dogma of the day and replaced untested medical practices with science.

Dr. Pritchard was particularly interested in the use of magnesium sulfate to treat preeclampsia, a serious condition that can lead to convulsions and death during labor in women with high blood pressure. Now, this treatment has become standard therapy worldwide.

"Our legacy goes back 50 years," Dr. Leveno said. "The tradition has been here that patient management should be governed by evidence. We persevere in this approach.

"You can't practice medicine without measuring what you do."

The very term "evidence-based medicine" may seem surprising to some, said Dr. Jodi Dashe, associate professor of obstetrics and gynecology.

"One would hope all the treatments prescribed by doctors are based on scientific evidence."

Historically, medicine has been more art than science. The Ancient Greek physician Hippocrates said, *ars longa, vita brevis* – "art is long, life is short." He went on to say *experimentum periculosum* – "experiment treacherous."

But the OB-GYNs at UT Southwestern embrace experiment, in the form of planned, controlled, randomized trials to test their questions and theories.

In line with this approach to medicine, UT Southwestern has been part of the Maternal-Fetal Medicine Units Network since 1996. The network was founded in 1986 by the National Institute of Child Health and Human Development to use scientifically sound medical trials to improve care and health of pregnant women and their babies, and to test whether new treatments are effective, safe and cost-efficient.

"The network is at the forefront of clinical research in obstetrics and is helping provide the evidence to guide our practice," Dr. Bloom said. "Some of the most important clinical research in all of obstetrics is being conducted in the network."

The network consists of 14 medical centers and a data-coordinating center. More than 30 studies or registries have been conducted or created nationwide since its inception.

"The network was created for the express purpose of gathering evidence in obstetrical management and maternal-fetal medicine," said Dr. Leveno, who is UT Southwestern's principal investigator for the network. "For us to join it was suitable philosophically.

"One of the reasons American health care is so expensive is there's a lot of medicine that's not evidence-based. I think most people would admit that. But to some extent, it's not fair to cast aspersion on people who practice medicine based on rationale, because the studies necessary to do clinically based medicine are extremely expensive, and there aren't very many of those. The network is one example of where the National Institutes of Health is providing the resources necessary to do these kinds of multicenter studies."

"The network is at the forefront of clinical research in obstetrics and is helping provide the evidence to guide our practice. Some of the most important clinical research in all of obstetrics is being conducted in the network."

—Dr. Steven Bloom

Laboring over new studies

Dr. James Alexander, associate professor of obstetrics and gynecology and chief of obstetrics at Parkland, has been particularly interested in Caesarean delivery. Along with 12 other centers in the network, he studied more than 37,000 Caesarean births and found that associated fetal injuries were uncommon, occurring in about 1 percent of cases. Most of these were lacerations from scalpel injuries. Other rare injuries included broken bones, injury to facial nerves and injury to nerves running from the spine to the arm.

"The question is all about patient safety," Dr. Alexander said.

BLOOM

CASEY

"Our primary goal here at UT Southwestern is to look constantly at ways to improve the care of our patients."

—Dr. Brian Casey

While Caesarean deliveries are relatively safe, it is still important to provide solid facts to the expectant mothers about potential risks, he said.

UT Southwestern OB-GYNs have also influenced other trials that have been performed by the entire network.

Dr. Brian Casey, associate professor of obstetrics and gynecology, has been studying how mild cases of an underactive thyroid – called hypothyroidism – could affect fetal development.

"We found that subclinical (nonsymptomatic) hypothyroidism was associated with preterm birth and placental abruption," Dr. Casey said. "It unleashed a tremendous response from several endocrinological groups about how important it was to identify this group during pregnancy."

The study began with a small team of UT Southwestern doctors, who looked at subclinical hypothyroidism in 17,000 women who gave birth at Parkland. The results of this study were pivotal in developing a national study funded by the NIH network.

Now, researchers are looking at whether treat - ment with thyroid hormones can stave off those problems, as well as help the children. The $27 million study will include 120,000 women nationwide.

"We're going to test their babies five years out and get an IQ test to see if the treatment had a benefit," Dr. Casey said.

This NIH study is a classic case of taking an idea that makes sense – a rationale – and doing a rigorous study to ensure that it really makes a difference – the evidence, he said.

"Despite the fact that there's a rationale, there's currently no good evidence that identifying pregnant women with subclinical hypothyroidism and treating them will make a difference," he said. "Although the rationale is very important, it's most important to get evidence for what we think is the right answer."

Preventing preterm birth is another major focus of the department, as well as the network.

Several faculty members have been studying a derivative of progesterone called 17-alphahydroxy-progesterone caproate, or 17P. This substance has been shown to reduce preterm birth in women who have had previous preterm deliveries, but it's not known if it's effective under other conditions.

Situations undergoing study in the network include women who have short cervixes, as measured by ultrasound, or who are carrying twins, both conditions associated with preterm birth.

"If 17P could be shown to be effective in preventing preterm birth, this would be evidence-based medicine that could change practice in the United States," Dr. Dashe said. "Preterm birth is such a public-health problem. It's the major cause of infant mortality.

"But if the study comes out negative, that's also helpful. Clinicians will know that this is something that should not be offered, so women will not be given a weekly injection that will not help them or their babies."

Dr. Casey, in addition to studying thyroid disorders, also examines gestational diabetes. About 5 percent of pregnant women have diabetes, most a result of the pregnancy itself.

Dr. Casey suspects that when these women aren't pregnant, their pancreases are just barely able to keep up with their bodies' demand for insulin. But when they become pregnant, their pancreases fall behind.

"In a normal, healthy woman, the pancreas is up to the challenge," he said. "But with the rate of obesity increasing in the United States, more and more women are already pre-diabetic."

While it may go away right after the baby comes, gestational diabetes continues to lurk in the background.

"The diabetes they had in pregnancy is a harbinger of things to come," Dr. Casey said. "Fifty percent of those women will develop diabetes later in life."

Diabetes in pregnancy also affects the fetus. The increased sugar in the mother's blood crosses the placenta, and as a result, the fetus grows larger. An overly large baby is at risk of birth trauma, may require a Caesarean delivery and may have other neonatal complications.

UT Southwestern is currently the lead center for a network trial studying gestational diabetes. The clinician-researchers divide women with mild hypoglycemia into two groups. One group gets routine prenatal care, while the other receives glucose monitors and nutrition counseling.

Another area of interest is preeclampsia. Dr. Jeanne Sheffield, associate professor of obstetrics and gynecology and director of the UT Southwestern maternal-fetal medicine fellowship program, oversees the department's work on a network study that seeks to find out whether giving vitamins C and E during pregnancy can prevent this condition, which causes a sharp rise in blood pressure during the third trimester of pregnancy and can be a sign of serious problems. Preliminary studies with small numbers of women have shown some benefit, but the power of the network can bring in 10,000 women to provide stronger data.

"If we're going to make a major change that affects the obstetrics world, we study it first," Dr. Sheffield said. "Very little gets changed here without evaluating it. We put a lot of resources in our division behind the network studies.

"Vitamin C and vitamin E are two vitamins people commonly take already," she said. "If we could lower the rates of preeclampsia, we would do the country – we would do the world – a service."

The clinician-researchers are also studying whether there are ways to predict who is at risk for preeclampsia. They're looking at factors such as blood pressure, protein in the urine and Doppler ultrasound images of uterine arteries.

"Preeclampsia is something that's international; everyone would like to know how to prevent it, and how to predict it," she said.

Dr. Casey said, "Our primary goal here at UT Southwestern is to look constantly at ways to improve the care of our patients. And if we alter care of our patients, we measure the impact of that alteration, and then we report it in manuscript form.

"We've followed it; we've measured it; we can report to the world that it's beneficial; and then we can change our practice and provide better care for our patients."

For more information on obstetrics and gynecology at UT Southwestern, please call 214-645-3838, or visit www.utsouthwestern.edu/patientcare/medicalservices/obgyn.html.

"If we could lower the rates of preeclampsia, we would do the country – we would do the world – a service."

—Dr. Jeanne Sheffield

SHEFFIELD

At UT Southwestern, scientists are trying to understand the blood supply lines that nourish malignant tumors. Understanding this process – and finding ways to interrupt it – is key in the fight against cancer.

ANGIOGENESIS
the cancer connection

The mysteries surrounding cancer, the uncontrolled growth of abnormal cells, have confounded scientists for years. Despite remarkable advances in the laboratory and the development of treatments, researchers still don't know what triggers many forms of this life-threatening disease. At UT Southwestern Medical Center, scientists are building upon the lessons learned from past progress for new discoveries.

One of those lessons is that cancerous tumors, in order to expand, somehow trigger the growth of new blood vessels – supply lines that allow tumor cells to grow and to eventually move out and spread.

The process is called angiogenesis, and it occurs in normal tissues during growth and development as well as in wound healing. It is a fundamental step in the transition of tumors from a dormant to a malignant state. Understanding what controls angiogenesis is key to unlocking the mechanism by which cancerous tumors grow and spread.

BY CONNIE PILOTO

At UT Southwestern, researchers from an array of disciplines – molecular biology to pharmacology to surgery – are investigating this process and developing drugs aimed at attacking not the tumors themselves, but their life-support systems – the blood vessels.

Each is investigating different questions: How do cells communicate with each other to pattern new blood vessels? What controls the process of angiogenesis? How can it be targeted for therapy?

Their research has been fruitful. Scientists have found a way to cut off nutrients to a tumor by coagulating its blood supply – in essence, giving it a "stroke." A technique that tests the effectiveness of anti-angiogenic therapy was demonstrated at UT Southwestern for the first time. And anti-angiogenic drugs discovered here, including one currently being tested in humans, are showing promising results against cancer as well as other deadly diseases.

Cellular Communication

Dr. Ondine Cleaver's interest in angiogenesis arose out of a general interest in understanding interdependent development of embryonic tissues. As a graduate student, her focus was on decoding DNA and figuring out how it was transcribed and interpreted by differentiating cells.

While trying to clone a gene in the inner layer of the heart, she was distracted.

"I saw these speckled little things," Dr. Cleaver recalled. "I realized they were cells that had not joined together to form a blood vessel yet."

That moment led to a cascade of events that would fuel Dr. Cleaver's interest and point her toward a career devoted to the study of how cells communicate, the signals they exchange at precise times and the locations where they form new blood vessels.

"Blood vessels don't just go anywhere because they want to," said Dr. Cleaver, assistant professor of molecular biology. "They go places because a growth factor – a signaling protein – tells them exactly where to go and how to organize."

One of those signaling proteins is called VEGF, or vascular endothelial growth factor. It is responsible for communication between embryonic tissues and endothelial cells, which line the interior surface of all blood vessels from the heart to the smallest capillary. VEGF also triggers the development of blood vessels that deliver nutrients and oxygen to tumors, enabling them to grow and spread.

Although VEGF is one of the most widely studied growth factors and one to which endothelial cells respond strongly, Dr. Cleaver suspects that there may

> **"I saw these speckled little things. I realized they were cells that had not joined together to form a blood vessel yet."**
>
> – Dr. Ondine Cleaver

be a host of other proteins that send cues to the endothelial cells and affect the way blood vessels form.

"Nobody is an island, not humans and not cells," Dr. Cleaver said. "Everybody that is around you will affect you in some way. If you want to attack tumors, you want to find all the angiogenic factors that are making the blood vessels grow into the tumor, and you have to know both what the positive and the negative signals are."

If Dr. Cleaver and her colleagues could find out exactly how blood vessel formation is initiated, clues would reveal the signals that tumors send to drive the attraction and the growth of blood vessels into the tumor. This work might elucidate quicker and less toxic ways to attack tumor vessels by using anti-angiogenesis therapies.

"One of my goals is to understand the following problem: How and why does a simple blood vessel form?" Dr. Cleaver said. "If we can understand how a single blood vessel forms and why it forms at a specific spot, I think we can attack tumor vessels, starve the tumor and make a significant impact on cancer treatment."

Seek and Destroy

Designing an agent to attack solid cancer tumors – which make up about 90 percent of all cancers – has been Dr. Philip Thorpe's focus for more than a decade.

While most cancer drugs target the tumors themselves, Dr. Thorpe has developed a way to attack and destroy the existing blood vessels that feed a cancer. His research has led to a new approach in fighting the disease: killing tumors by starving them or giving them a "stroke."

"Basically, most of what we do is aimed at finding neat ways to destroy tumor blood vessels and starve tumors to death," said Dr. Thorpe, professor of pharmacology and holder of the Serena S. Simmons Distinguished Chair in Cancer Immunopharmacology in the Harold C. Simmons Comprehensive Cancer Center.

In the course of his research, Dr. Thorpe noticed something odd about the membranes of endothelial cells in the blood vessels that feed tumors. It was a discovery that led him to develop a way to attack the tumors' food supply.

In normal cells, a major component of the cell membrane, known as phosphatidylserine, is positioned on the internal surface.

In cells that have become malignant or infected by a virus, however, stressors created by disease release reactive molecules that cause the phosphatidylserine to flip from the inside to the outside surface of the tumor blood vessels. So, unlike any other blood vessels in the body, these cancer blood vessels have phosphatidylserine exposed on their surface.

In order to attack the blood vessels in cancers, Dr. Thorpe created a drug that binds to the exposed phospholipids. The drug, called bavituximab, circulates in the body through the blood until it gets into the cancer blood vessels. When it finds the flipped-out phospholipids, it binds to them. The binding raises a red flag to the body's immune system, forcing the deployment of the defensive white cells, which home in on and destroy the cancer tumor's blood vessels.

"The tumor cells die away because they no longer have a supply of oxygen and nutrients," Dr. Thorpe said. "You can think of it as a drug that tricks the body into redirecting its immune cells to destroy the cancer blood vessels."

> **"Basically, most of what we do is aimed at finding neat ways to destroy tumor blood vessels and starve tumors to death."**
>
> – Dr. Philip Thorpe

By targeting the host's blood vessels instead of the cancer cells directly, therapy using bavituximab avoids the propensity of cancer cells to mutate until they become drug-resistant.

In the laboratory, bavituximab has been remarkably effective in reducing and in some cases eliminating several types of human cancers in mice, including breast, prostate, lung and pancreatic tumors.

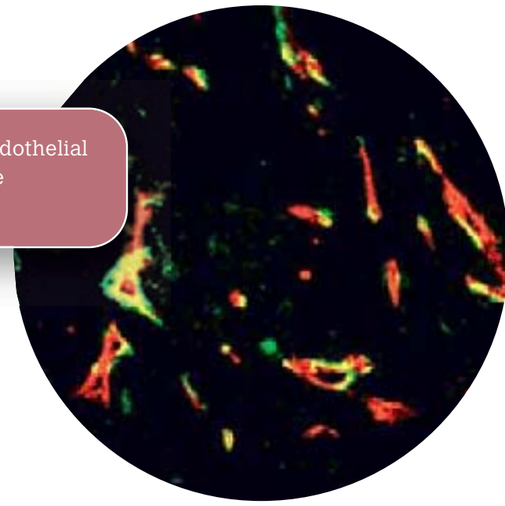
It is currently being tested in clinical trials in the U.S. and India for its effectiveness against solid-tumor cancers. Peregrine Pharmaceuticals has exclusively licensed the drug from UT Southwestern. Dr. Thorpe has a long-standing collaboration with the California-based company to take his discoveries from the lab into clinical trials.

Although bavituximab was created for cancer therapy, it also has been shown in clinical tests to work against viruses, including the hepatitis C virus. In the lab, it is being tested against viruses that cause tropical diseases, such as hemorrhagic fevers and certain strains of flu.

Dr. Thorpe says the anti-virus mechanism is similar to the anti-angiogenesis effect, in which the drug targets phospholipids on the outside of the virus' outer cover, which in turn alerts the immune system to destroy the virus-infected cell.

"It's one of those amazing situations in which you develop something for cancer and, lo and behold, it works for virus diseases, too," Dr. Thorpe said. "Clinical trials have shown that the treatment is safe for patients with hepatitis C. We're also seeing reductions in their blood virus load, which is very encouraging news."

While clinical trials are under way, Dr. Thorpe continues to explore how bavituximab and other vascular targeting agents developed in his lab can be paired with conventional therapies to develop new treatment strategies.



An example of endothelial cells and pericyte co-localization.

Bavituximab is particularly well-suited to be used in combination with other types of cancer treatments, such as radiation and chemotherapy, because these therapies induce flipping of the phospholipids on the tumor vessels, enlarging the target for attack and increasing the effectiveness of the treatment.

"In our years of research, we have established that bavituximab is effective in treating different types of cancers in animals. It is also effective against metastases, and it works well when combined with chemotherapy and radiation therapies," Dr. Thorpe said. "If all those facts translate into human beings, then we are indeed looking at a breakthrough."

Following Anti-Cancer Agents

In Dr. Rolf Brekken's laboratory, half of his research team concentrates on answering basic questions about how the microenvironment surrounding tumors controls angiogenesis; the other half is focused on developing therapeutic interventions.

Their target: pancreatic cancer.

"It's one of the deadliest cancers," said Dr. Brekken, assistant professor of surgery and pharmacology and a recipient of the Effie Marie Cain Research Scholar award for studies of angiogenesis. "The primary tumor is very bad, but there are very talented surgeons now who can take out primary tumors; however, we still have a problem. In most cases, by the time the tumor is removed, the cancer has already metastasized to the liver."

When cancer spreads to the liver, it does so via the blood and the circulatory system, which means that the pancreatic tumor cells invaded the blood vessels that fed the tumor, and the blood vessels provided an escape route for metastatic tumor cells. Cancer cells then travel all over the body and, for some reason, preferentially grow in the liver.

"That's one of the things that we'd like to try to control," Dr. Brekken said "How can we stop those *original* blood vessels from reaching the tumor? Or better yet, how do you destroy them outright?"

While investigating those strategies, Dr. Brekken and his research team discovered a way to monitor a patient's response to anti-angiogenesis therapy.

Dr. Brekken used an inexpensive tracing agent in combination with ultrasound to demonstrate for the first time that they could pinpoint how effectively drugs targeted pancreatic cancer.

The study, involving human pancreatic tumor cells implanted in mice, opened a new avenue for real-time imaging of a patient's response to cancer therapies.

The research team examined how pancreatic tumor cells respond to an experimental anti-cancer agent that targets VEGF, the protein responsible for triggering the development of blood vessels that keep tumors alive.

> **"How can we stop those original blood vessels from reaching the tumor? Or better yet, how do you destroy them outright?"**
>
> – Dr. Rolf Brekken

To track the drug's effectiveness, the research team employed a commonly used contrast, or tracing agent, called microbubbles. Each tiny bubble measures about one to two microns in diameter – about one-hundredth the width of a human hair – and consists of albumin, sugar and an inert gas. Microbubbles are used routinely in echocardiography, for example, to allow cardiologists to see how efficiently and how much blood the heart pumps.

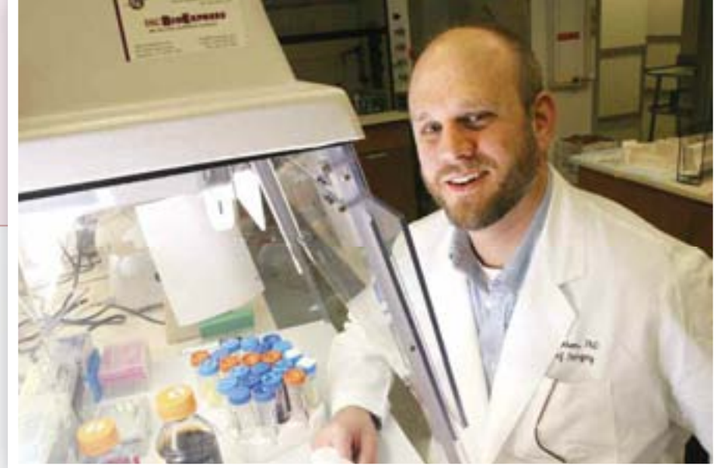
The experimental drug Dr. Brekken used in the study was one that he had created when he was a graduate student training in Dr. Thorpe's laboratory. It has yet to be named and is still in the early stages of testing, but it is similar to a Food and Drug Administration-approved anti-angiogenesis drug called bevacizumab (Avastin), which is currently being used to treat colon cancer.

Dr. Brekken and his team linked the microbubbles to the targeting agents that are then used to monitor the effect of the drug. The harmless microbubbles bound to blood vessels in the tumor and allowed researchers to use ultrasound to get a crisp picture of how the drug impacted blood vessels that fed the tumor.

What they saw in the animals indicated that the drug did indeed choke tumor growth vessels that were feeding the cancer. In one of the studies, blocking VEGF activity achieved a 40 percent reduction in mean tumor size after four treatments over a two-week period, a significant control of tumor growth, Dr. Brekken said.

Dr. Brekken and his colleagues are pursuing approval from the FDA for use of the monitoring method in humans.

"It has been difficult to assess whether anti-angiogenic drugs are having an impact on tumors in human patients," Dr. Brekken said. "The sooner we can measure the effectiveness of the treatment, the earlier we can intervene to change anti-cancer agents if a particular drug has no effect. This could be a lifesaving approach in patients with a rapidly fatal disease."



Managing Growth

A focus of study in Dr. Fiemu Nwariaku's laboratory is on finding a mechanism that interrupts the growth of new blood vessels in thyroid cancer, especially an aggressive type called anaplastic thyroid cancer, which doesn't respond well to present treatments and kills swiftly.

A surgeon-scientist, Dr. Nwariaku says most thyroid cancers are curable with surgery. The prognosis, however, is not as good for patients with recurrent thyroid cancer or anaplastic thyroid tumors because chemotherapy and radiation are not effective.

"These tumors kill through rapid local growth and invasion of local structures, such as the airway," said Dr. Nwariaku, vice chairman for surgical research, associate professor of GI/endocrine surgery and holder of the Malcolm O. Perry, M.D., Professorship in Surgery. "The strategy we've taken is to try to look at ways of starving the tumor of its blood supply and, thus, preventing it from growing."

Dr. Nwariaku recently made strides when he found that an existing cancer drug that blocks the growth of tumor blood vessels slowed the growth of anaplastic thyroid tumors in mice.

The drug, called TNP-470, had previously proved effective against the growth of tumor vessels, and Dr. Nwariaku wanted to test it in thyroid cancer. He found that the drug slowed tumor growth and increased survival in animals with thyroid cancer. While the results suggest that the drug keeps the growth of the thyroid cancer in check, it's also possible that it may shrink the tumor at higher doses.

"If the tumor stays the same size, it is less likely to kill the host in a short period of time," Dr. Nwariaku said.

Dr. Nwariaku and his team also discovered a potential mechanism by which TNP-470 works. During the angiogenic process, endothelial cells that line existing blood vessels migrate into the tumor. TNP-470 appears to stop those cells from migrating by preventing the activation of a protein called Rac, which is important in cell migration.

Researchers have not determined if TNP-470 would help in human patients with thyroid cancer yet because the drug is currently not approved for this disease; however, they continue to work on similar strategies in these patients. The next step for researchers is to examine similar drugs and develop a better animal model for the cancer.

> **"The strategy we've taken is to try to look at ways of starving the tumor of its blood supply and, thus, preventing it from growing."**
>
> – Dr. Fiemu Nwariaku

In the Clinic

Dr. Roderich Schwarz is interested in the use of anti-angiogenesis agents in combination with current chemotherapeutic therapies to target upper gastrointestinal cancers, which aren't responsive to usual treatments.

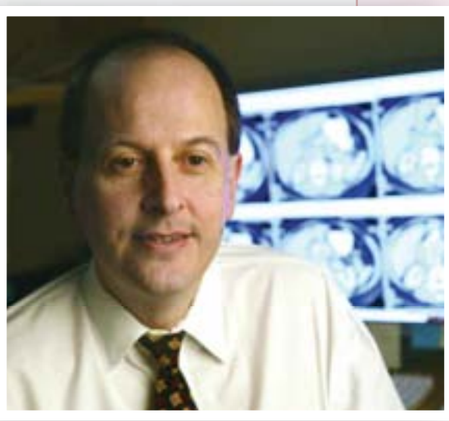
"It is painfully obvious that traditional therapies don't work sufficiently," said Dr. Schwarz, chief of surgical oncology, associate director of surgical oncology at the Simmons Comprehensive Cancer Center and holder of the Mark and Jane Gibson Professorship in Cancer Research. "Because of it, there is a pressing need to explore treatments that follow a different pathway."

Angiogenesis inhibition is one of those promising paths. Dr. Schwarz is testing how mice injected with pancreatic tumor cells respond to a combination of three agents: gemcitabine, the main chemotherapy drug used to treat pancreatic cancer; bevacizumab; and a protein called EMAP II, which blocks endothelial cell division.

Used alone, the agents had a minimal effect in attacking the tumor cells. Gemcitabine and bevacizumab used together did not provide a significant benefit, either. But when Dr. Schwarz paired the two drugs and added EMAP II, he saw much more potent effects.

"The tumors didn't grow, or they grew very slowly," Dr. Schwarz said.

Dr. Schwarz suspects that EMAP II blocks the binding of several proteins necessary for cell attachment and migration and that it also enhances the ability of the anti-angiogenic agent to block



“The major push in the next five to 10 years is in finding avenues to slow down the growth of the cancer – to turn this threat into a chronic disease that patients can live with.”

– Dr. Roderich Schwarz

VEGF signaling, thus stopping the proliferation of tumor blood vessel growth. The next steps are to elucidate the EMAP II mechanism, to design an agent with similar effects, and to conduct further preclinical studies.

“The major push in the next five to 10 years is in finding avenues to slow down the growth of the cancer – to turn this threat into a chronic disease that patients can live with,” Dr. Schwarz said. “I think, with the use of more refined anti-angiogenesis treatment, that is achievable.”

Impact Across Disciplines

Research in angiogenesis and the development of anti-angiogenesis factors has impact across medical disciplines. Understanding the process may prove effective as a treatment not only for cancer but also for a wide range of entirely different conditions, such as cardiovascular disease. While researchers want to find ways to suppress blood vessel growth as a means to attack cancer, they also want to learn how to *promote* blood vessel growth in order to treat cardiovascular disease.

Other research efforts on angiogenesis by UT Southwestern faculty include:

■ Dr. Philip Shaul, professor of pediatrics and holder of the Lowe Foundation Professorship in Pediatric Critical Care Research, studies the role of endothelial cells in cardiovascular disease. In addition to their role in the formation of new blood vessels, endothelial cells serve as the guardians of existing blood vessels. They normally prevent inflammatory cells from adhering to the vascular wall. They prevent blood clotting and combat multiple other events that lead to atherosclerosis. Dr. Shaul and his research team have discovered the processes by which well-recognized risk factors for cardiovascular disease directly govern the behavior of endothelial cells.

“Now, the challenge is to determine how to harness these multiple processes to provide novel means to combat cardiovascular disease,” Dr. Shaul said.

■ Dr. Hiromi Yanagisawa, assistant professor of molecular biology, studies how tumor cells behave in their microenvironment and how they interact with the extracellular matrix, proteins located outside the cells that provide support for cells and aid in blood vessel growth. She pays particular attention to the interaction between ECM proteins and endothelial cells, especially in pancreatic tumor cells.

“We want to manipulate the environment surrounding the tumors and inhibit their growth,” Dr. Yanagisawa said. “I want every ECM molecule that supports tumor growth and angiogenesis to be under our control. Finding that control switch is our goal.”

■ Dr. Michelle Tallquist, assistant professor of molecular biology, studies the developmental processes that lead to the formation of coronary arteries, the vessels that supply blood to the heart muscle. One of the goals in her laboratory is to identify the mechanisms that would trigger growth of new blood vessels in the heart, thus opening a fresh blood supply into the damaged muscle.

“While blockage of the coronary arteries is the most common cause of death in America, failure to revascularize the damaged heart muscle is a significant complication,” Dr. Tallquist said. “Generating new blood vessels could improve the clinical outcome of patients who suffer from heart attacks.”

At UT Southwestern, researchers across campus are focused on understanding angiogenesis, that intricate process that triggers the growth of new blood vessels.

Decoding the signals that cells exchange in order to convince established blood vessels to generate new vasculature is one of the avenues being studied. Developing and testing new targeting agents that interfere with the blood supply tumors need is also an aim.

As researchers wait to see how the agents they developed in the laboratory respond to the cancers of patients being treated in clinical trials, new explorations continue.

For more information on cancer treatment at UT Southwestern, please call 214-645-4673, or visit www.utsouthwestern.edu/patientcare/medicalservices/cancer.html.

Technology targets tumors

By Connie Piloto

A former amateur rodeo star, Donald Croxton has had his share of medical issues.

In 1989, he was paralyzed when he fell from a bull during his hometown's annual rodeo. Nine months later, Mr. Croxton walked out of a rehabilitation center with the aid of a cane. A cascade of problems stemming from the injuries followed him for years.

Then, in 2005 he was diagnosed with something unrelated to his previous injuries – brain cancer.

During a lengthy and difficult operation, surgeons gingerly removed a cancerous tumor lodged under Mr. Croxton's brain. He underwent radiation, and the cancer was gone.

Two years later, the nose bleeds Mr. Croxton had suffered shortly before he was first diagnosed with cancer returned. Doctors confirmed his suspicions: The cancer was back.

This time, a malignant tumor had developed in the sinus cavity between Mr. Croxton's eyes, and it was pushing out along the bridge of his nose toward his right eye. Operating would require surgeons to remove Mr. Croxton's eye and eye socket.

"I wanted to save my eye," said Mr. Croxton, 45, who lives in Bowie. "I didn't care if I lost my eyesight, but I didn't want my eye removed."

His doctors at UT Southwestern Medical Center decided to forego surgery and instead tried stereotactic radiosurgery. The noninvasive technique concentrates high doses of radiation directly on tumors that would be especially hard to reach using traditional surgery. In Mr. Croxton's case, the tool of choice was the CyberKnife.

"Due to the scarring produced by Mr. Croxton's previous surgical procedure, it would be difficult to find the margins of the recurrent tumor surgically," said Dr. Bruce Mickey, professor of neurological surgery and otolaryngology-head and neck surgery, director of the Annette G. Strauss Center in Neuro-Oncology and holder of the William Kemp Clark Chair in Neurological Surgery at UT Southwestern. "On the other hand, the CyberKnife could precisely target the tumor and its margins with the aid of the digital information provided on his CT [computed tomography] and MRI [magnetic resonance imaging] scans."

In the Annette Simmons Stereotactic Treatment Center at UT Southwestern University Hospital - Zale Lipshy, radiation oncologists use high-tech, image-guided radiation tools such as the CyberKnife and a related system called the Gamma Knife to target tumors and offer breakthrough radiation treatments.

"We have paired our state-of-the-art technology and our research capabilities with a team of world-renowned radiosurgery experts to provide our patients with the latest advancements in cancer treatment," said Dr. Hak Choy, chairman of radiation oncology and holder of the Nancy B. and Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research.

Stereotactic therapy delivers high-dose radiation beams to a tumor in a concentrated, extremely precise manner. Many beams of radiation – often more than 100 – are directed at the tumor. Each of these beams is relatively weak and causes very little damage when traveling through the patient's body.

When all the beams converge at the target, however, their cumulative effect adds up to an extremely potent dose aimed at destroying the target cells with great precision.

At UT Southwestern, the CyberKnife is most commonly used to treat primary or metastatic brain tumors, which are those that have spread to the brain from other parts of the body. It is also the therapy of choice for treating other tumors of the head and neck, base of the skull, cervical spine and the lungs and liver.

The CyberKnife system features sophisticated tracking software and a linear accelerator that is mounted on a robotic arm. The robotic arm is coupled with two orthogonal X-ray imaging cameras, which are used to locate the position of the tumor. The flexibility of this robotic arm makes it possible to treat certain areas of the body, such as the spine and spinal cord, that cannot be reached by conventional radiotherapy techniques.

Before UT Southwestern radiation oncologists treated Mr. Croxton with the CyberKnife, doctors first took MRI and CT scans of Mr. Croxton's tumor. The scans provided three-dimensional images of the tumor and allowed physicians to configure the radiation beams to target precisely its unique shape.

"We decided to use the CyberKnife to give a highly focused radiation boost to the tumor and to try to control it without surgery," said Dr. Robert Timmerman, professor of radiation oncology and holder of the Effie Marie Cain Distinguished Chair in Cancer Therapy Research. "We gave Mr. Croxton's tumor five separate high-dose treatments on the CyberKnife and paid special attention to minimize the dose to the optic pathways in hopes that he would be able to retain his vision."

Mr. Croxton's eyesight has remained intact, and while the tumor has shrunk considerably, Dr. Timmerman and Mr. Croxton's surgeons are monitoring it closely. They might yet have to perform surgery, but they would be removing a much smaller tumor than the one initially discovered before undergoing treatment with the CyberKnife.

Another high-tech radiation tool called the Gamma Knife also uses highly focused and targeted radiation to treat vascular malformations, cancer and benign tumors in the brain when conventional surgery can't be done.

In addition to treating brain disorders and tumors, the Gamma Knife's accuracy and pinpoint precision have helped many people recover from the constant and debilitating pain of more uncommon functional disorders like trigeminal neuralgia.

Ken Hardin's pain started out of the blue one spring day in 2005. Every time he touched the left side of his face – to rub an eye or touch his upper lip – a bolt of intense pain would shoot through his face.

"Sometimes the pain would last 2 seconds, sometimes up to 30 seconds," Mr. Hardin said.

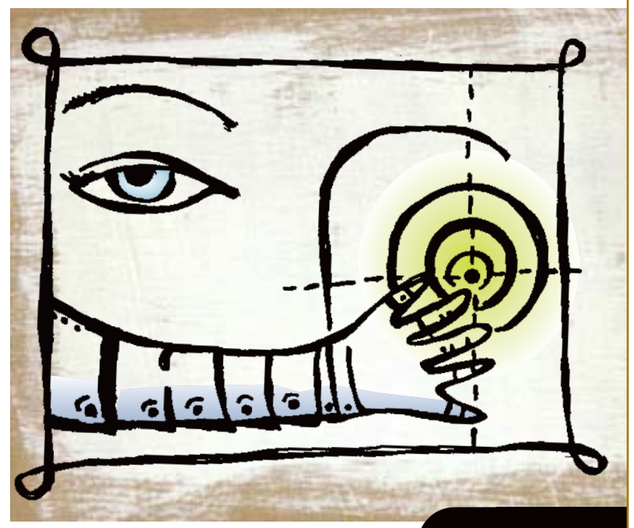
Mr. Hardin, 75, of Arlington, did his own research and consulted with several neurologists who determined he was suffering from trigeminal neuralgia, a chronic pain condition that causes extreme, sporadic, sudden burning or shock-like face pain.

The condition is often treated with medication that can make patients feel tired and sleepy. There were other treatment options, but most included surgery, he found. Then, he read about radiosurgery using the Gamma Knife system.

Mr. Hardin's neurologist referred him to Dr. Timmerman at UT Southwestern.

"I was a little anxious about the treatments, but when I read about the Gamma Knife, I knew that if it was an option for me, that was the way to go," Mr. Hardin said. "It was not invasive at all."

At UT Southwestern, Mr. Hardin was fitted with a special helmet that kept his skull from moving during the treatment. Then, 201 separate beams of cobalt-60 radiation were targeted on Mr. Hardin's brain stem during a treatment that lasted less than an hour.



"We have paired our state-of-the-art technology and our research capabilities with a team of world-renowned radiosurgery experts to provide our patients with the latest advancements in cancer treatment."
–Dr. Hak Choy

"The helmet allows us to have the mechanical accuracy of one-tenth of a millimeter. You could hardly hold your fingers that far apart. Then, we treat the nerve as it comes out of the brain stem," Dr. Timmerman explained. "It's a 4 millimeter section of the nerve right as it exits the brain stem, and it's in a very critical area."

Surgery would have required physicians to drill through the hardest bone in the body – the temporal bone, which controls hearing and facial functions.

"We can relieve the pain substantially in about 80 percent of patients," Dr. Timmerman said. "About half of them will get complete relief within a week or two of the treatments."

That's what happened to Mr. Hardin. A week later he started feeling less pain. Two weeks later, the pain was gone.

"Day to day living without pain, discomfort or medication is wonderful," Mr. Hardin said. "I am much more productive, and I am less of a burden physically and emotionally to those close to me."

For more information on CyberKnife or Gamma Knife treatments, please call 214-645-6455, or to learn more about radiation oncology, visit www.utsouthwestern.edu/patientcare/medicalservices/radonc.html.

Stent strikes down strokes

By Aline McKenzie

Bob Ritchie hadn't had a massive stroke – yet – but the signs were there that one might be in his near future. In late 2007, he began suffering a series of short-lived but frightening symptoms.

"I'd lose my vision or have blurred vision, or there would be a tingling around my mouth or down to my right hand," said Mr. Ritchie, 75, a retired truck driver who lives in Wichita Falls. "It was very scary."

> "I think it's a beautiful surgical procedure. You have all the time in the world."
>
> *—Dr. Babu Welch*

Eventually, Mr. Ritchie was referred to Dr. Lee Pride, associate professor of radiology at UT Southwestern Medical Center, who performed a procedure designed to prevent, rather than treat, strokes.

Mr. Ritchie is one of the first patients to have been treated with a specially designed brain stent – a thin tubular mesh that holds open a blood vessel that's been narrowed by atherosclerosis. UT Southwestern is one of a few centers in the United States participating in a registry to operate on patients and track the success of the procedure.

The commercially developed system, called Wingspan, uses a balloon to expand the vessel and then leaves the stent behind to keep it open. It was approved by the Food and Drug Administration in 2005 under a program called a Humanitarian Device Exemption, which encourages development of treatments that affect fewer than 4,000 people in the U.S. each year.

Before the cranial stent was available, UT Southwestern neurointerventional surgeons used stents designed for vessels around the heart, but these devices were made for tougher vessels and were less suitable for the more delicate vessels of the brain.

"Overall, the new stents have been much safer than anything we've had before for treating narrowed arteries in the brain," said Dr. Pride, who described the stents as gentler on patients.

Since his surgery, Mr. Ritchie said he feels only minor dizziness from time to time.

"I feel much safer," he said. "I think it's prolonged my life."

Another treatment for defective blood vessels in the brain is also in the works at UT Southwestern. Excimer Laser-Assisted Nonocclusive Anastomosis, or ELANA, uses a laser to create a connection between arteries without the need to stop blood flow to the brain.

With the success of this technique, surgeons will be able to replace or bypass diseased portions of a critical brain artery while significantly reducing the risk of stroke, said Dr. Babu Welch, associate professor of neurological surgery and radiology.

Bypass surgery in the brain is trickier than in other parts of the body. Clamping off an artery for even a few minutes could cause some people to suffer a massive stroke, Dr. Welch said.

With the ELANA technique, one end of the replacement vessel is attached to an artery "downstream" of the portion that is to be removed. A tiny laser is then fed through a slit in the graft, and the free end of the graft is sewn to the vessel beyond the point of the defective area. The laser then burns a tiny hole through the vessel wall, and blood begins flowing directly from the carotid artery through the graft.

With a blood supply guaranteed to the brain, the defective portion of the vessel can then be clamped off at both ends and removed with no haste required.

ELANA, developed in the Netherlands, is used only in rare cases when an enormous tangle of malformed vessels called an aneurysm that can't be treated with normal methods must be removed, or when removal of a tumor would tear a blood vessel.

UT Southwestern's reputation as a world-class center for neurovascular surgery opened the door for Dr. Welch and Dr. Duke Samson, chairman of neurological surgery, to travel to Europe, where they learned the surgery from its inventor.

UT Southwestern is now fully equipped to perform the operation, which was approved by the FDA in summer 2007.

"I think it's a beautiful surgical procedure," Dr. Welch said. "You have all the time in the world."

For more information about neurological surgery, please call 214-645-2300, or visit www.utsouthwestern.edu/patientcare/medicalservices/neuro.html.

Seeing MS clearly

By Aline McKenzie

Multiple sclerosis has traditionally been difficult to diagnose because its symptoms can be variable and attacks might be separated by years. As technology has developed, however, accurate early diagnosis has become easier and doctors can begin treatment in the vital early stages.

Now, one of the fastest and simplest methods to track damage in the central nervous system is available at UT Southwestern Medical Center. Called Optical Coherence Tomography, or OCT, it measures the thickness of the layer of nerves in the retina of the eye.

The device sits on a small tabletop and is a bit larger than a microwave oven. A patient puts his or her chin on a rest, and two quick flashes of light probe the retina. On the computer screen, a speckled strip of colors shows the depth of the retina.

Patient Julie Marwitz has undergone both magnetic resonance imaging and spinal taps for monitoring her MS.

"This is a lot simpler," said Ms. Marwitz, an office accounting manager. "All I have to do is take my contact lenses out. The only bad part is trying to hold your eyes open without blinking."

OCT is a relatively new way of monitoring MS, said Dr. Elliot Frohman, professor of neurology and ophthalmology and director of the Multiple Sclerosis Program and Clinical Center at UT Southwestern.

"To look at something as delicate as the retina in a few seconds with a resolution of 8 microns [micrometers] – I was blown away," said Dr. Frohman, recalling his first view of the images.

"The beauty of OCT is it's really a stand-alone method to be able to measure the structural architecture of nerve cells and their axons within the retina," he said.

An axon is the long arm of a nerve cell, along which the electrical signal travels before triggering the next nerve cell.

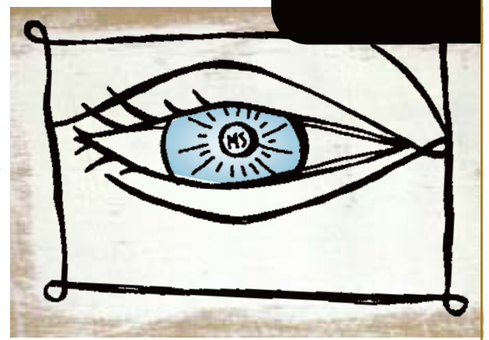
In the retina, axons converge behind the eye to form the optic nerve, which then travels into the brain.

Collaborative studies between Dr. Frohman and his colleagues Dr. Laura Balcer from the University of Pennsylvania and Dr. Peter Calabresi from Johns Hopkins University show a striking relationship between the integrity of the retina and changes in both vision and the brain over time. The researcher-clinicians hope this technology can be used to help identify and prove the ability of new drugs to protect both the eye and the brain from the ravages of MS. A number of clinical trials of novel drug therapies to both protect and restore nerve function are in the planning stages and will be spearheaded by Dr. Frohman.

"OCT's ability to monitor axonal nerve damage in MS may introduce a new tool to understand and find treatments," said Dr. Frohman, who holds the Irene Wadel and Robert I. Atha Distinguished Chair in Neurology and the Kenney Marie Dixon-Pickens Distinguished Professorship in Multiple Sclerosis Research.

MS is caused by an autoimmune reaction in which the body attacks its own myelin, the fatty-insulating layer that surrounds nerve cells. Without myelin, nerve cells can't conduct electrical signals as quickly, and their axons, the long, thin branches that stretch to their target cells, become scarred and damaged.

> "We may now have the ability to really look at neurons, their preservation, and perhaps even their restoration within the eye."
>
> *—Dr. Elliot Frohman*



Brain damage can be tracked with MRI, and researchers have developed some mathematical models to quantify the loss of brain tissue and link it with patients' symptoms, but with mixed success, according to Dr. Frohman.

Thus, if OCT turned out to be a reliable measure of brain atrophy and the disease's progression, doctors would have an inexpensive, easy technique that can be performed in the office.

"We may now have the ability to really look at neurons, their preservation, and perhaps even their restoration within the eye," Dr. Frohman said.

For more information about multiple sclerosis, please call 214-645-8800, or visit www.utsouthwestern.edu/patientcare/medicalservices/neuro.html.

Keep a healthy heart

By Katherine Morales

It wasn't until his second year in medical school that Dr. Casey Pollard pieced together his family's history of heart disease – a history so rife with cardiovascular disease, he thought he could be at risk, too.

"The more I started learning and thinking about my health, the more I realized I needed to be proactive about it," he said.

After Dr. Pollard moved to Dallas for a radiology residency at UT Southwestern Medical Center, he continued to wonder whether he would soon suffer the same battles with heart disease as other men in his family.

"Everyone in the family on my dad's side has had diabetes and heart problems from an early age," Dr. Pollard said. "I started digging deeper and asking questions of my family. My dad had an angioplasty and had several stents put in. He was also diagnosed with diabetes when he was 28."

Dr. Pollard, 28, decided to try a new approach to protect his health.

"One of my friends told me that his wife worked as a physician assistant at the preventive heart clinic at UT Southwestern. He said he knew the perfect person to help me," Dr. Pollard said.

The perfect person turned out to be Dr. Amit Khera, head of the preventive cardiology program and assistant professor of internal medicine at UT Southwestern.

> "Success is when a patient never develops a chronic disease rather than treating it after it develops."
>
> *–Dr. Amit Khera*

A relatively new addition to the division of cardiology, Dr. Khera and his team help prevent chronic disease from developing in patients who have complex risk factors for heart disease.

"I see many patients who don't actually have diagnosed heart disease, but who are at increased risk due to very strong family histories of heart disease," Dr. Khera said. "Some patients, like Dr. Pollard, also have uncontrolled risk factors, and it's very important for them to address these problems as soon as possible."

In addition to genetic risk factors, Dr. Khera looks at traditional risk factors and lifestyle habits. Those with a genetic predisposition to heart disease may be compounding their problems by not exercising or not eating the right foods. Patients who come to the clinic also meet with a dietitian, who advises them on ways to improve or augment their diet.

"Early intervention is critical, as are lifestyle changes. We also try to assess whether advanced testing is needed and whether drug therapies would be useful," Dr. Khera said.

In some cases, patients may not need any intervention, he added.

"We are very judicious in treatment and understand that some people don't necessarily need to take a pill every day for the rest of their lives. A lot of people we see are very young, so if they don't need drug therapies, we avoid that. In some cases, modest lifestyle modification is the best solution," Dr. Khera said.

Although preventive cardiology is not new, it is a rare specialty in private practice. It is more common in academic medical institutions like UT Southwestern, where the collaborative scope of patient care provides broader expertise.

"As a physician, I've always felt that it makes more sense to avoid a potential chronic health problem before it develops and affects a patient's quality of life," Dr. Khera said. "Success is when a patient never develops a chronic disease rather than treating it after it develops."

Dr. Pollard strives to be one of those success stories.

"The damage accumulates over the years, and I told my wife that my family is an example of what happens if you don't step in early," Dr. Pollard said. "I want to measure the success of preventive medicine for myself."

For more information on preventive cardiology, please call 214-645-7500, or visit www.utsouthwestern.edu/patientcare/medicalservices/hlv.html.

Stopping the migraine trigger

By Donna Steph Hansard

Three years ago, Sharon Schafer Bennett suffered from migraines so severe that the headaches were disrupting her life.

The 46-year-old mother of two said she felt like she was constantly "canceling everything" because the headaches – often two or three per week – would put her flat on her back.

Now, thanks to an innovative surgical technique performed by a UT Southwestern Medical Center plastic surgeon who helped pioneer the procedure, the frequency and intensity of the Houston-area native's migraines have diminished dramatically.

"I can't even begin to tell you what a change this has made in my life," said Mrs. Bennett, who had the procedure in May 2005. "For the first time in years, I can live like a normal human being and do all the normal 'mom' and 'wife' things that the migraines physically prevented me from doing."

The technique – performed by only a handful of plastic surgeons in the U.S. – uses the anti-wrinkle drug Botox to pinpoint which of several specific muscles in the forehead, back of the head or temple areas may be serving as "trigger points" to compress, irritate or entrap nerves causing the migraine. Because Botox temporarily paralyzes muscles, usually for about three months, it can be used as a litmus test to see if headaches go away or become less intense while the Botox's effects last, said Dr. Jeffrey Janis, assistant professor of plastic surgery.

If the Botox is successful in preventing migraines or lessening their severity, then surgery to remove the targeted muscle is likely to accomplish the same result, but on a longer-term and possibly permanent basis, he said.

"Many neurologists are using Botox to treat migraines, but they are making the injections in a 'headband-like' circle around the forehead, temple and skull," Dr. Janis said. "They are not looking at finding the specific location of the headache's trigger point. While patients may get temporary relief, after the Botox wears off they will have to go back and get more injections or continue medications for migraines.

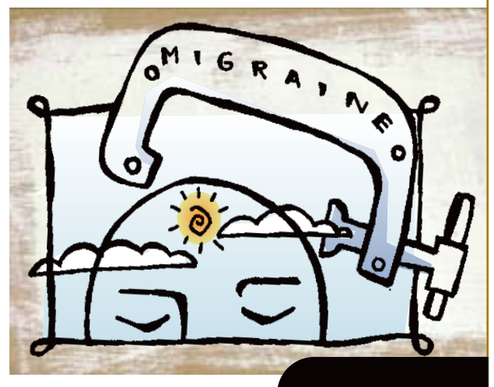
"I inject the Botox into one trigger point at a time and leave the others alone."

Approximately 28 million Americans, 75 percent of those women, suffer from migraines, according to the National Institutes of Health.

"A migraine is something you can't explain to someone who hasn't had one," said Mrs. Bennett, who began suffering monthly migraines as a teenager. As she grew older, the headaches become more frequent and unpredictable.

"This surgery has made a huge difference in my life," she said.

Dr. Janis began collaborating more than five years ago with Dr. Bahman Guyuron, a plastic surgeon at Case Western Reserve University and the first to explore using surgery to relieve migraines, following the revelation by several of his patients that their migraines had disappeared after they had cosmetic brow lifts. Dr. Janis has assisted his colleague by performing anatomical studies on cadavers to explore the nerves and pathways that might cause migraines. Together they have identified four specific trigger points and developed a treatment algorithm that includes using Botox prior to deciding whether to perform surgery.



Dr. Janis sees only patients who have been diagnosed with recurring migraines by a neurologist and have tried other treatments that have failed.

"Plastic surgeons are not in the business of diagnosing and treating headaches," he said. "This is a novel method of treatment that is proving to be effective and potentially more long-lasting than other things used before. But it is still in its infancy."

For more information about migraine treatments, please call 214-645-2353, or visit www.utsouthwestern.edu/patientcare/medicalservices/plastics.html.

> "This is a novel method of treatment that is proving to be effective and potentially more long-lasting than other things used before."
>
> *–Dr. Jeffrey Janis*

This is spinal tech

By Russell Rian

Stanton Laraway wasn't willing to give up racquetball and other activities as he turned 60, but his chronic back pain was growing worse.

"It just deteriorated through the years," the Allen resident said. "For years and years it bothered me. I was really uncomfortable. I was in constant pain."

He tried the traditional routines – aspirin, exercise therapy, muscle relaxers – but nothing helped.

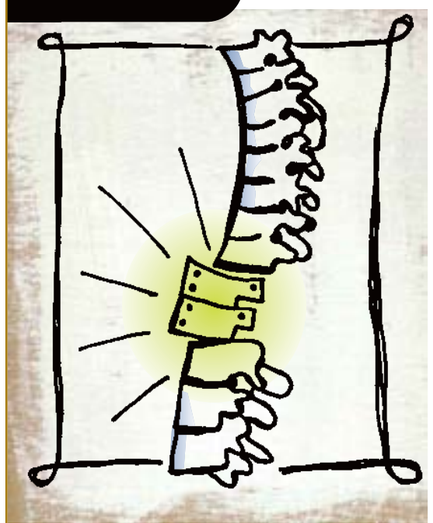
So after being steered to UT Southwestern Medical Center's Dr. Kevin Gill, one of the top spine surgeons in the nation, Mr. Laraway consented to take part in a new trend – mobility surgery – and had an artificial disc inserted in his spine.

"Three weeks later I was swimming and went back to work," said Mr. Laraway, a technical manager for AT&T. "Now, I have no pain at all. I walk, jump, run, climb trees, lots of things I shouldn't be doing. I play racquetball once a week for a couple of hours. I take a great deal of pleasure in feeling like a younger man."

Mr. Laraway reflects a growing population of back-pain sufferers who are finding fresh lives through new innovations for back surgery.

Dr. Gill, professor of orthopaedic surgery, Dr. Kevin Morrill, assistant professor of nuerological surgery, and Dr. Samuel Bierner, associate professor of physical medicine and rehabilitation, serve as co-directors of UT Southwestern's new Spine Center. The center brings together experts in orthopaedic surgery, neurological surgery, neuro - radiology, rheumatology and physical therapy to forge a comprehensive treatment plan individualized for each patient.

> "I guess you could say we are in the mobility business."
>
> —Dr. Kevin Gill



From testing new artificial discs and flexible rods in the spine to employing new bone materials that lessen recovery time, UT Southwestern is establishing itself as a frontline leader in efforts to correct long-standing back pain.

The technology boom for damaged discs encompasses a wide range of devices designed to maintain flexibility, including replacing the damaged discs with prosthetic devices, as in Mr. Laraway's case.

For unpinching nerves, technologies are emerging that use more flexible rod systems and spacers to keep vertebrae separated. Cutting-edge bone cement materials help repair fractured vertebrae.

Gene therapies to preserve the disc, to prevent degenerative disc diseases, to avoid cartilage deterioration and to allow nerve healing also are under study.

Even traditional surgeries that fuse vertebrae together have improved. Surgeons can now use a protein that stimulates bone formation to generate new tissue. The protein compound, called bone morphogenetic protein, or BMP, has been approved by the Food and Drug Administration for several procedures to heal and strengthen bones.

"To achieve a fusion you have to get the bones to grow together," explained Dr. Morrill, who specializes in multilevel fusion operations for deformities and tumor-spinal-cord compression. "So now we have these things that can help us achieve that fusion without having to take the bone from some other part of the body. That reduces pain. It improves recovery time. It improves the rates of achieving a fusion."

As the population ages, the prevalence of back pain continues to climb. And the surgical field reflects that, with spinal surgeries shifting from single-digit to double-digit growth rates over the past decade, Dr. Gill said.

"I think you're going to find that more and more people want their spine problem taken care of; they want to be more active," he said. "I guess you could say we are in the mobility business. We don't save lives, we save lifestyles."

For more information about the Spine Center, please call 214-645-6455, or visit www.utsouthwestern.edu/patientcare/medicalservices/spine.html.

2007

ANNUAL REVIEW

LETTER FROM THE PRESIDENT

Dear Friends,

As many of you know, I announced in October 2007 that I would be retiring as president of UT Southwestern Medical Center effective September 2008. I will be continuing on the faculty after that time, as well as increasing my involvement with Southwestern Medical Foundation in support of UT Southwestern's mission.

KERN WILDENTHAL, M.D., PH.D.

It has been a great honor to serve as UT Southwestern's president since 1986, as a dean for 10 years prior to that, as a faculty member since 1970, and as a student and resident in the 1960s. During that time, I have been privileged to have the opportunity to work with countless talented and dedicated leaders. I deeply appreciate the important contributions made not only by my colleagues here at the medical center and our associates throughout the international biomedical profession, but also by our many civic, philanthropic and political supporters. With unprecedented help from our community friends and state leaders, UT Southwestern has been able to excel in every category by which academic medical centers are judged.

Over the past two decades, our supporters' faith in this institution has enabled UT Southwestern's endowment to increase from $40 million in 1986 to more than $1.4 billion. Annual private donations to support operations and research, endowment and capital construction at the medical center increased from $11 million in 1986 to a record-setting $166 million in the 2007 fiscal year.

UT Southwestern is enormously grateful to the philanthropic community, whose generosity has set new funding records through our *Innovations in Medicine* campaign. The campaign, which began earlier this decade as a $450 million effort, has now surpassed the $740 million mark. This phenomenal result for the most ambitious fundraising effort in Dallas history would not have been possible without generous gifts from more than 600 contributors. The leadership of campaign chairman William T. Solomon, Southwestern Medical Foundation chairman Paul M. Bass, and the 120 volunteer members of the Leadership Council was exceptional.

It should always be remembered, of course, that the ultimate success of a fundraising drive is not merely the dollars *raised*, but how effectively the dollars are *used*. The hallmark of UT Southwestern's success has been and will remain the exceptional quality of the internationally renowned physicians, researchers and teachers whom we have been able to recruit and retain, and who are advancing mankind's understanding of health and disease, educating the next generation of professionals, and providing superlative medical care to hundreds of thousands of patients each year.

During the past two decades, the physical size of the medical center has more than tripled – from 2.5 million square feet to more than 8 million square feet of space on land that has increased from 65 acres to 231 acres. But the source of our greatest pride is not our physical growth, but the growth in the quality of our institution. The impact an institution such as ours can have on people's lives through education, research and clinical care is extraordinary. I believe that UT Southwestern is now recognized broadly throughout our community and across the nation as one of Dallas', Texas' and America's crown jewels.

UT Southwestern's progress – the stellar faculty and staff, the outstanding student body, the buildings, the medical breakthroughs, the lives saved – would not have been possible without major private philanthropy to supplement the growing support we have received from state and federal government sources. I hope that the extraordinarily generous private citizens of Dallas and our entire region, as well as our elected officials, feel gratified that their investments in UT Southwestern have been worthwhile. Their farsightedness and generosity are greatly appreciated by all of us at the medical center, for we simply could not have succeeded without their help.

When I decided in 2006 that 2008 was the right time for me to turn the reins over to a new president, one of the principal reasons I felt sure of the timing was the total confidence I have in our entire leadership team. There is no better academic and administrative executive group in the country. Under the new president, they will continue to ensure that UT Southwestern is at the pinnacle of the nation's academic medical centers.

It has been a great privilege to be part of UT Southwestern's administration for the past three decades and to be able to participate in the institution's progress. I inherited a wonderful base to start from, and I've had the pleasure of working with many fantastic people at the medical center, in the community, at the UT System, and in government.

I know that you will join me in the years ahead as we do our best to ensure that UT Southwestern continues to grow and thrive.

Thank you very much for your confidence and trust.

Kern Wildenthal, M.D., Ph.D.

HIGHLIGHTS
of the year

FALL 2006

LISTER, VITETTA JOIN INSTITUTE OF MEDICINE

Dr. George Lister, chairman of pediatrics, and Dr. Ellen Vitetta, director of the Cancer Immunobiology Center, were elected to the Institute of Medicine, a component of the prestigious National Academy of Sciences.

They bring the total number of current UT Southwestern faculty members inducted into the institute to 19, the largest representation for any university in Texas and surrounding states.

Dr. Lister's work on oxygen transport during postnatal development provided a rational basis for the care of critically ill children. He also led a national program to study home monitoring for sudden infant death syndrome, a program that changed national policy for management of infants at risk.

One of the most highly cited researchers in the country, Dr. Vitetta is internationally recognized for her immunology research. She is a pioneer in immunotoxin therapies that find cancer cells and destroy them without hurting normal surrounding cells or tissue. She also developed and completed the first human clinical trial of a recombinant vaccine for ricin, a deadly toxin and a potential bioterror threat.

FORMER GOV. BILL CLEMENTS AND UT SYSTEM REGENT RITA CLEMENTS WIELD THE RIBBON-CUTTING SCISSORS, WITH THE HELP OF DR. KERN WILDENTHAL (CENTER), AT THE DEDICATION OF THE BILL AND RITA CLEMENTS ADVANCED MEDICAL IMAGING BUILDING.

DR. GEORGE LISTER

DR. ELLEN VITETTA

CLEMENTS BUILDING DELIVERS LATEST IMAGING TECHNOLOGIES

UT Southwestern and UT System dignitaries joined in the dedication of the Bill and Rita Clements Advanced Medical Imaging Building – a state-of-the-art facility equipped with cutting-edge scientific tools that will enable researchers to peer deep inside the human body and learn more about the disease processes of diabetes, Alzheimer's, schizophrenia and many other illnesses.

Former Texas Gov. William P. "Bill" Clements Jr. donated $10 million to Southwestern Medical Foundation to complete construction and equip the research and clinical building, which features the most powerful imaging technologies in the world.

The building also houses the newly established Advanced Imaging Research Center, which receives state funding, as well as income from major endowments contributed by Dallas philanthropists.

BIOLOGY, BIOCHEMISTRY EXPERTISE LAUDED

An independent analysis of the impact of U.S. institutions' scientific research named UT Southwestern among the top 10 American institutions in four of seven biomedical fields and ranked it No.1 in biology and biochemistry.

The medical center's impact in biology and biochemistry was stronger than any other U.S. university or medical center, according to *Science Watch*, an independent publication that reports on trends and performance in basic research. UT Southwestern also ranked third in psychiatry, seventh in neurosciences and behavior research, and eighth in molecular biology and genetics. *Science Watch* bases its survey on papers published and then cited by other researchers during a five-year period. The latest report covered 2001-2005.

Only three institutions appeared in more categories than UT Southwestern.

WINTER 2007

OUTPATIENT FACILITY TRANSFORMS GROWING WEST CAMPUS

The Outpatient Building, the first of a series of towers that will usher the medical center's hospital and clinical operations into a new era, opened in December 2006.

The seven-story, 210,000-square-foot building houses world-class facilities that include a surgical center, radiology-imaging services and overnight guest suites, in addition to clinics, physician offices and diagnostic services. The $75 million facility also includes clinics and academic offices for orthopaedic surgery, plastic surgery, general surgery, and digestive and liver diseases.

THE SEVEN-STORY OUTPATIENT BUILDING PROVIDES CLINIC AND OFFICE SPACE FOR A NUMBER OF DEPARTMENTS, IN ADDITION TO A SURGICAL CENTER.

BODY-CLOCK RESEARCH AIDS UNDERSTANDING OF BIPOLAR DISORDER

UT Southwestern researchers, led by Dr. Colleen McClung, assistant professor of psychiatry, demonstrated in mice that disrupting the gene that regulates their biological clocks causes mice to exhibit behaviors similar to humans with bipolar disorder.

In a study in the *Proceedings of the National Academy of Sciences*, scientists showed that the *Clock* gene, which controls the body's circadian rhythms, may be integrally involved in the development of bipolar disorder. Circadian rhythms include the daily ups-and-downs of waking, eating and other processes such as body temperature, hormone levels, blood pressure and heart activity.

The study included putting the mutant mice through a series of tests, during which they displayed hyperactivity, decreased sleep, decreased anxiety levels, a greater willingness to engage in "risky" activities, lower levels of depression-like behavior and increased sensitivity to the rewarding effects of substances such as cocaine and sugar.

SEA CREATURE'S TOXIN MAY AID CANCER BATTLE

UT Southwestern researchers, inspired by a toxin derived from a reclusive sea creature resembling a translucent doughnut, have developed a related compound that

DR. PATRICK HARRAN

shows promise as a cancer treatment.

In a study appearing in the *Proceedings of the National Academy of Sciences*, the scientists – led by Dr. Patrick Harran, professor of biochemistry – detail how the toxin blocks uninhibited reproduction of cultured human cancer cells while leaving healthy cells unaffected. In preclinical trials, a synthetic form of the toxin reduced human tumors implanted in mice without the harmful side effects seen using other cancer drugs.

The animal, *Diazona angulata*, is a sea squirt a few inches wide that lives in colonies anchored to rocks. Its toxin proved to kill cancer cells in culture, but so little of its natural form was available that a race soon began to synthesize it in the laboratory. A chemical structure for the toxin, called diazonamide A, was published in 1991, but in 2001 Dr. Harran's research group showed that initial report to be incorrect, and uncovered the correct structure. Dr. Harran and his co-workers have since synthesized several variants of diazonamide A in order to pin down how it prevents cancer cells from dividing.

SPRING 2007

HOBBS ELECTED TO NAS

Dr. Helen Hobbs, director of the Eugene McDermott Center for Human Growth and Development and a Howard Hughes Medical Institute investigator, was elected to the National Academy of Sciences. UT Southwestern now has 17 faculty members currently serving in the esteemed organization, more than 70 percent of the total of the 23 NAS members from Texas academic medical institutions.

Dr. Hobbs, as director of the Donald W. Reynolds Cardiovascular Clinical Research Center, leads the Dallas Heart Study, a multiyear, multimillion dollar project aimed at learning more about the hidden causes of heart disease and finding new treatments. Her research focuses on identifying genetic factors that contribute to variations in the levels of cholesterol in the blood, especially low-density lipoproteins.

DR. HELEN HOBBS

YOUNG DRUG-USERS FACE HIGHER RISK FOR STROKES

Researchers at UT Southwestern reported that increasing rates of amphetamine and cocaine usage by young adults significantly boosts their risk of stroke.

In the *Archives of General Psychiatry*, the physicians described their research, which examined more than 8,300 stroke patients – ranging in age from 18 to 44 – at more than 400 Texas hospitals from 2000 through 2003. An analysis of risk factors and trends among stroke victims in this age group pointed to an increase in substance abuse as a major danger, particularly in the abuse of methamphetamines.

Dr. Arthur Westover, assistant professor of psychiatry, led the study, which showed young people who abuse amphetamines are five times more likely to have a hemorrhagic stroke than nonabusers. If cocaine is abused, the person's likelihood of having either a hemorrhagic or an ischemic stroke more than doubles.

'SMARTER' MICE MAY REVEAL NEUROLOGICAL TREATMENT PATHWAY

Mice genetically engineered to lack a single enzyme in their brains are more adept at learning than their normal cousins and are quicker to figure out that their environment has changed, a UT Southwestern research team, led by Dr. James Bibb, assistant professor of psychiatry, found.

The results, which appeared in *Nature Neuroscience*, revealed a new mechanism of learning in the brain that may serve as a target for treating disorders such as post-traumatic stress disorder, Alzheimer's disease or drug addiction in humans.

DR. JAMES BIBB WITH GENETICALLY ENGINEERED 'SMARTER' MICE

The engineered mice were more adept at learning to navigate a water maze and remembering that being in a certain box involves a mild shock. Even when a situation changed, such as the water maze being rearranged, the engineered mice were much faster to realize that things were different and work out the new route.

PARADA NAMED TO AMERICAN ACADEMY OF ARTS, SCIENCES

The American Academy of Arts and Sciences elected Dr. Luis Parada, chairman of developmental biology, to membership. With his election, UT Southwestern now has 14 faculty members currently serving in the organization.

Dr. Parada, who directs the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration, discovered the genes for TRK receptors, which interact with organic molecules known as neurotrophins to signal embryonic nerve cells to survive or die. Scientific journal articles documenting his research into this cellular-survival-signaling mechanism have been so widely quoted that Dr. Parada is among the most cited biologists in the world.

Dr. Parada's current research focuses on how stem cells develop into nerve cells in the hippocampus, an area of the brain associated with learning and memory.

SUMMER 2007

PRC PRESENTS TWO DISTINGUISHED AWARDS

The President's Research Council presented its 2007 Distinguished Young Researcher Award to a pair of outstanding UT Southwestern scientists. The recipients – Dr. Colleen McClung, assistant professor of psychiatry, and Dr. Julie Pfeiffer, assistant professor of microbiology – each received a $75,000 award.

Dr. McClung is studying the role of circadian rhythms in the development and treatment of psychiatric disorders.

Dr. Pfeiffer is investigating certain viruses in order to combat treatment failures and develop new vaccines. In particular, she is examining why treatment fails for about half of the 4 million people in the U.S. who are infected with the hepatitis C virus.

The Distinguished Young Researcher Award is presented annually by the PRC, which is made up of community leaders who are interested in learning about and advancing medical research at UT Southwestern.

DR. COLLEEN MCCLUNG

DR. JULIE PFEIFFER

DR. JAMES CUTRELL, 2007 RECIPIENT OF THE HO DIN AWARD

401 EARN DEGREES FROM THREE SCHOOLS

Diplomas were awarded to 227 UT Southwestern Medical School students and 50 UT Southwestern Graduate School of Biomedical Sciences students at June 2 commencement ceremonies.

Richard Fisher, president and chief executive officer of the Federal Reserve Bank of Dallas, gave the commencement address.

The top award to a graduating medical student, Southwestern Medical Foundation's Ho Din Award, was presented to Dr. James "Brad" Cutrell by Ron W. Haddock, a foundation trustee.

Ryan Potts received the Nominata Award, given to the outstanding graduate school student.

At winter commencement, UT Southwestern Allied Health Sciences School conferred degrees on 59 students. Another 65 students received degrees at August gradua - tion exercises.

GOVERNOR SIGNS HISTORIC CANCER RESEARCH BILL

Gov. Rick Perry selected UT Southwestern and UT M.D. Anderson Cancer Center to be the two sites at which he officially signed House Bill 14, the historic cancer bill that will create one of the largest cancer research initiatives in the nation.

Before hundreds of UT Southwestern students, physicians, faculty members and statewide guests, Gov. Perry culminated a six-month push to create the Cancer Prevention and Research Institute of Texas, a multibillion dollar cancer research trust fund.

In November 2007 Texas voters approved the fund, which Gov. Perry said will allow the state to put an additional $3 billion into the fight against cancer.

TEXAS GOV. RICK PERRY SIGNS HOUSE BILL 14, WITNESSED BY STATE REP. JIM KEFFER; LANCE ARMSTRONG; STATE SEN. JANE NELSON; AND DR. KERN WILDENTHAL.

APPOINTMENTS FOR 2006-2007

The following individuals were appointed to endowed positions or to major leadership positions at UT Southwestern during the past fiscal year.

- Dr. Juan Arenas, to serve as chief of surgical transplantation.
- Dr. Douglas Baker, to the Sarah M. and Charles E. Seay Distinguished Chair in Pediatric Medicine.
- Dr. Joseph Borrelli Jr., to serve as chairman of orthopaedic surgery and to the Doctor Charles F. Gregory Chair in Orthopaedic Surgery.
- Dr. Dennis Burns, to the Jane B. and Edwin P. Jenevein, M.D., Chair in Pathology.
- Dr. Alison Dobbie, to serve as chair of family and community medicine and to hold the Perry E. Gross, M.D., Distinguished Chair in Family Medicine.
- Dr. Mark Drazner, to the James M. Wooten Chair in Cardiology.
- Dr. Phil Evans, to serve as associate vice president for clinical imaging services.
- Dr. John Fitzgerald, to the Elaine Dewey Sammons Chair in Pulmonary Research, in Honor of John E. Fitzgerald, M.D.
- Dr. Glenn Flores, to the Judith and Charles Ginsburg Chair in Pediatrics.
- Dr. Kevin Gardner, to the Virginia Lazenby O'Hara Chair in Biochemistry.
- Dr. Robert Greene, to the Sherry Gold Knopf Crasilneck Distinguished Chair in Psychiatry, in Honor of Mollie and Murray Gold.
- Dr. Barbara Haley, to the Charles Cameron Sprague, M.D., Chair in Clinical Oncology.
- Dr. Patricia Hicks, to the Harry W. Bass Jr. Professorship in Pediatric Education.
- Dr. Elizabeth Holper, to the Dallas Heart Ball Chair for Research on Heart Disease in Women.
- Dr. Jay Horton, to the Dr. Robert C. and Veronica Atkins Chair in Obesity & Diabetes Research.
- Dr. Jer-Tsong Hsieh, to the Dr. John McConnell Distinguished Chair in Prostate Cancer Research.
- Dr. Michael Jessen, to the Robert Tucker Hayes Foundation Distinguished Chair in Cardio-thoracic Surgery.
- Dr. Nitin Karandikar, to the Vernie A. Stembridge, M.D., Distinguished Chair in Pathology.
- Dr. John McClay, to the John W. and Rhonda K. Pate Professorship in Otolaryngology and Head and Neck Surgery.
- Dr. Bruce A. Meyer, to serve as vice president for medical affairs.
- Dr. Allen Morey, to the Paul C. Peters, M.D., Chair in Urology.
- Dr. Schmuel Muallem, to the Ruth S. Harrell Professorship in Medical Research.
- Dr. Eric Olson, to the Pogue Distinguished Chair in Research on Cardiac Birth Defects.
- Dr. Rama Ranganathan, to the Cecil H. and Ida M. Green Chair in Biomedical Science.
- Dr. Michael Rosen, to the Carolyn R. Bacon Professorship in Medical Science and Education.
- Dr. John Sadler, to the Daniel W. Foster, M.D., Professorship in Medical Ethics.
- Dr. Rashmin Savani, to the William Buchanan Chair in Pediatrics.
- Dr. Philipp Scherer, to serve as director of the Touchstone Center for Diabetes Research and to hold the Gifford O. Touchstone Jr. and Randolph G. Touchstone Distinguished Chair in Diabetes Research.
- Dr. John Schorge, to the Amy and Vernon E. Faulconer Distinguished Chair in Medical Science.
- Dr. Roderich Schwarz, to serve as chief of surgical oncology in the Harold C. Simmons Comprehensive Cancer Center and to hold the Mark and Jane Gibson Professorship in Cancer Research.
- Dr. Madhukar Trivedi, to the Betty Jo Hay Distinguished Chair in Mental Health.
- Dr. William Turner Jr., to the Ernest Poulos, M.D., Distinguished Chair in Surgery.
- Dr. Francisco Velazquez, to serve as associate vice president for clinical laboratory services.
- Dr. Charles White III, to the Nancy R. McCune Distinguished Chair in Alzheimer's Disease Research.
- Dr. Kim B. Yancey, to serve as chairman of dermatology and to hold the Mary Kay Inc. Distinguished Chair in Dermatology.

MAJOR GIFTS IN 2006-2007

Philanthropists continued to demonstrate their commitment to UT Southwestern in 2006-07, providing support for a variety of research, clinical and educational programs.

Major new pledges and gifts received in the 2006-07 fiscal year included:

- $52,000,000 from Mr. and Mrs. Harold C. Simmons to create the Harold and Annette Simmons Comprehensive Center for Research and Treatment in Brain and Neurological Disorders, to establish the Annette Simmons Stereotactic Treatment Center at UT Southwestern University Hospital - Zale Lipshy, and to support UT Southwestern's participation in an innovative clinical program for indigent patients in South Africa.

■ $50,250,000 from the T. Boone Pickens Foundation to support the *Innovations in Medicine* campaign and to name the T. Boone Pickens Biomedical Building.

■ $12,000,000 from the Dedman Foundation to establish and endow a new Program for Endowed Clinical Scholars, designed to recruit a steady stream of outstanding young physicians who will be the future leaders of UT Southwestern's clinical studies of new therapies and in the provision of exemplary clinical care and service.

■ $5,000,000 from Mrs. Edmund M. Hoffman to establish and endow the Hoffman Family Center in Genetics and Epidemiology.

■ $4,750,000 from Dorothy H. Middleton, through a bequest, to establish an endowment for research on paralysis and paralytic diseases.

■ $4,222,000 from the Perot Foundation for continued support of research programs and for the Medical Scientist Training Program for M.D./Ph.D. students.

■ $2,100,000 from Mission Pharmacal Co. to establish and endow the Neill Walsdorf Sr. Biotechnology Center in Mineral Metabolism.

■ $2,000,000 from an anony - mous foundation to support heart research.

■ $1,500,000 from the Lucille G. Murchison Foundation to establish the Lucille Murchison Endowed Fund for Scholars in Clinical Research.

■ $1,477,000 from an anonymous foundation to provide funds for the recruitment of exceptional new faculty members and to support novel high-risk/high-gain research projects.

■ $1,406,760 from proceeds of the 2007 Sweetheart Ball for heart research.

■ $1,100,000 from the Cain Foundation to support the Cain/Denius Comprehensive Center in Mobility Research and to endow the Felecia Cain Fellowship in Urology.

■ $1,050,000 from the Hawn Foundation to support the *Innovations in Medicine* campaign.

■ $1,000,000 from an anonymous couple to provide funding for the recruitment of exceptional new medical researchers.

■ $1,000,000 from Mrs. Sherry Knopf Crasilneck to establish and endow the Sherry Gold Knopf Crasilneck Distinguished Chair in Psychiatry, in Honor of Mollie and Murray Gold.

■ $1,000,000 from Mr. and Mrs. Vernon E. Faulconer to establish and endow the Amy and Vernon E. Faulconer Distinguished Chair in Medical Science.

■ $1,000,000 from Mr. and Mrs. John Ridings Lee, through a life insurance policy, for the *Innovations in Medicine* campaign.

■ $1,000,000 from the McKenzie Foundation to establish two endowed chairs in psychiatry.

■ $1,000,000 from Dr. and Mrs. Charles Y.C. Pak to support the Charles Y.C. Pak and Donald W. Seldin Center for Metabolic Research.

■ $1,000,000 from Mr. and Mrs. Bernard Rapoport to establish and endow the Audre and Bernard Rapoport Distinguished Chair in Clinical Care and Research.

■ $800,000 from Gayle W. Hysinger, through a bequest, to endow programs in medical education, research and patient care.

■ $766,000 from Mr. and Mrs. T. Peter Townsend to establish the Peter and Joanna Townsend Family Fund for Research on Autism Spectrum Disorders.

■ $750,000 from Drs. Debra L. Caudy and Clay M. Heighten to establish the Jon Heighten Endowed Scholars Fund for Research on Autism Spectrum Disorders.

■ $700,000 from the A.L. Chilton Foundation to support the Chilton/Bell Scholar in Biochemistry, the Chilton/Bell Fellowship Award in Biochemistry, the A.L. Chilton Distinguished Visiting Professorship in Biochemistry, and clinical programs at UT Southwestern University Hospitals.

■ $700,000 from the Hartwell Foundation to support research on pediatric diseases through Hartwell Individual Biomedical Research Awards.

■ $600,000 from Once Upon a Time … for clinical care and clinical research programs.

■ $500,000 from Mr. and Mrs. Harold M. Brierley to upgrade the Diane and Hal Brierley Chair in Biomedical Research to a Distinguished Chair.

■ $500,000 from the Constantin Foundation to support the *Innova - tions in Medicine* campaign in honor of longtime board member Joel T. Williams Jr., and to equip a cardiac laboratory at UT Southwestern University Hospital - St. Paul.

■ $500,000 from John P. Harbin and Linda Harbin Robuck to be added to the Dorothy L. and John P. Harbin Center for Alzheimer's Disease Research and the Dorothy L. and John P. Harbin Chair in Alzheimer's Disease Research.

■ $500,000 from the Ted Nash Long Life Foundation to support medical research projects on aging.

■ $500,000 from Elaine D. Sammons to establish the Elaine Dewey Sammons Chair in Pulmonary Research, in Honor of John E. Fitzgerald, M.D., and to provide further support to the Elaine Dewey Sammons Distinguished Chair in Cancer Research, in Honor of Eugene P. Frenkel, M.D.

■ $500,000 from Dr. and Mrs. Charles A. Sanders to establish the Charles A. and Elizabeth Ann Sanders Chair in Translational Research.

■ $350,000 from Mr. and Mrs. Edward M. Ackerman for additional support to the *Innovations in Medicine* campaign through the Edward and Wilhelmina Ackerman Endowment Fund.

■ $330,000 from proceeds of the 2007 ALS Evening of Hope for research on Lou Gehrig's disease.

■ $320,000 from Mr. and Mrs. C.B. Hudson for further support of clinical priorities in the *Innovations in Medicine* campaign.

■ $300,000 from Shirley G. Alweis, through a bequest, to establish the Shirley and Norman Alweis Endowment Fund for Macular Degeneration Research.

■ A sculpture titled "Undulating X" by New Mexico artist Ali Baudoin, valued at $300,000, from Mr. and Mrs. Dan Cook to enhance the UT Southwestern campus.

■ $300,000 from the David M. Crowley Foundation to support research on spinal cord injury, Alzheimer's disease, and Parkinson's disease.

■ $250,000 from JPMorgan Chase to support the Science Teacher Access to Resources at Southwestern (STARS) program.

■ $250,000 from NCH Corp., Irvin L. Levy, Lester A. Levy and Walter M. Levy to support the *Innovations in Medicine* campaign.

Generous contributions and pledges of $100,000 to $250,000 were received from a number of additional donors, including new commitments from:

■ The Alcon Foundation, Inc. to support educational programs for ophthalmology residents.

■ An anonymous foundation for the support of multiple sclerosis research, in honor of Dr. Elliott Frohman.

■ The Mary Kay Ash Charitable Foundation to support cancer research.

■ The Barrett Family Foundation Fund of Communities Foundation of Texas to establish the Barrett Family Professorship in Cancer Research.

■ Biogen Idec to support multiple sclerosis research.

■ Barbara J. Bottjer, through a bequest, to support research on spinal-cord injuries.

■ The Amon G. Carter Foundation to support research in pediatric oncology.

■ The Lizanell and Colbert Coldwell Foundation to support research projects in biochemistry and microbiology.

■ The Crowley-Carter Foundation to support pediatric neuro - logical research activities.

■ Mr. and Mrs. Robert W. Decherd to establish the Decherd Family Fund for Medical Research in support of programs related to leukemia and bone marrow transplantation.

■ Mr. and Mrs. James R. Elliott, III, to establish the J.R. Elliott, III, Family Fund in support of the *Innovations in Medicine* campaign.

■ The 2007 Eye Gala to support research on macular degeneration.

■ Mr. and Mrs. Gerald Frankel to support cancer research and clinical activities.

■ Mr. and Mrs. Mark D. Gibson to establish the Mark and Jane Gibson Fund for Cancer Research.

■ Mr. and Mrs. Irwin J. Gross - man for further support of diabetes research.

■ Dr. Rolf R. Haberecht and Mrs. Ute Schwarz Haberecht for further support of the *Innovations in Medicine* campaign.

■ Mr. and Mrs. Stanford C. Finney Jr. to support research and clinical programs in neuro-oncology.

■ Mr. and Mrs. Richard Fisher and the Collins Fisher Foundation to establish the Fisher Family Professorship in Women's Mental Health Studies.

■ Susan Metz Hawkins to establish the Dr. M. Hill and Dorothy Metz Scholarship Fund.

■ The M.R. and Evelyn Hudson Foundation to support genetic/genomic research and educational programs for radiology residents.

■ Mr. and Mrs. Dee Kelly for the *Innovations in Medicine* campaign, in honor of Dr. Willis Maddrey.

■ David M. Marshall to support prostate and bone cancer research, in honor of Dr. John C. Bagwell.

■ Mrs. Donald M. Matter, in memory of Mr. and Mrs. Charles Fugitt, to support clinical programs at UT Southwestern University Hospital - Zale Lipshy.

■ The Harry S. Moss Heart Trust for additional support of heart research in UT Southwestern's Harry S. Moss Heart Center.

■ Mr. and Mrs. John R. Murrell and the Murrell Foundation for programs in geriatric medicine.

■ Mr. Raymond Nasher and the Nasher Foundation to support cancer research, in honor of Dr. Eugene Frenkel.

■ The Margot Rosenberg Pulitzer Foundation to support breast-cancer research activities.

■ The Rudman Foundation to support the Josephine Rudman Laboratory for Alzheimer's Disease Research.

■ Anne C. Schoellkopf, through a bequest, to support medical re - search.

■ Bryan F. Smith, through a fund established at the Catholic Foundation, to support clinical programs.

■ Mr. and Mrs. Gifford Touchstone to support research in the Touchstone Center for Diabetes Research.

■ Dr. and Mrs. William L. Watson to endow the William L. Watson, M.D., and Patricia Watson Southwestern Academy of Teachers Fund.

■ Mr. and Mrs. Joel T. Williams Jr. to support medical research.