2008 Annual Review

SOUTHWESTERN MEDICINE

Transplanting Success:

UT Southwestern's programs make it among the most comprehensive centers in the nation

| SLEEP DISORDERS | GENETICS REVOLUTION | CHEMICAL ATTRACTION

The Magazine of UT Southwestern Medical Center

CONTENTS

BECOMING PODOLSKY 2
Many descriptions – renowned scientist, empathetic clinician, enthusiastic educator, experienced mentor and focused administrator – fit hard-charging Dr. Daniel K. Podolsky, UT Southwestern's new president.

THE GENE SCENE 6
UT Southwestern reserchers are at the forefront of the genetics revolution.

CHEMICAL ATTRACTION 18
At UT Southwestern, chemists work side by side with biologists in a unique collaboration.

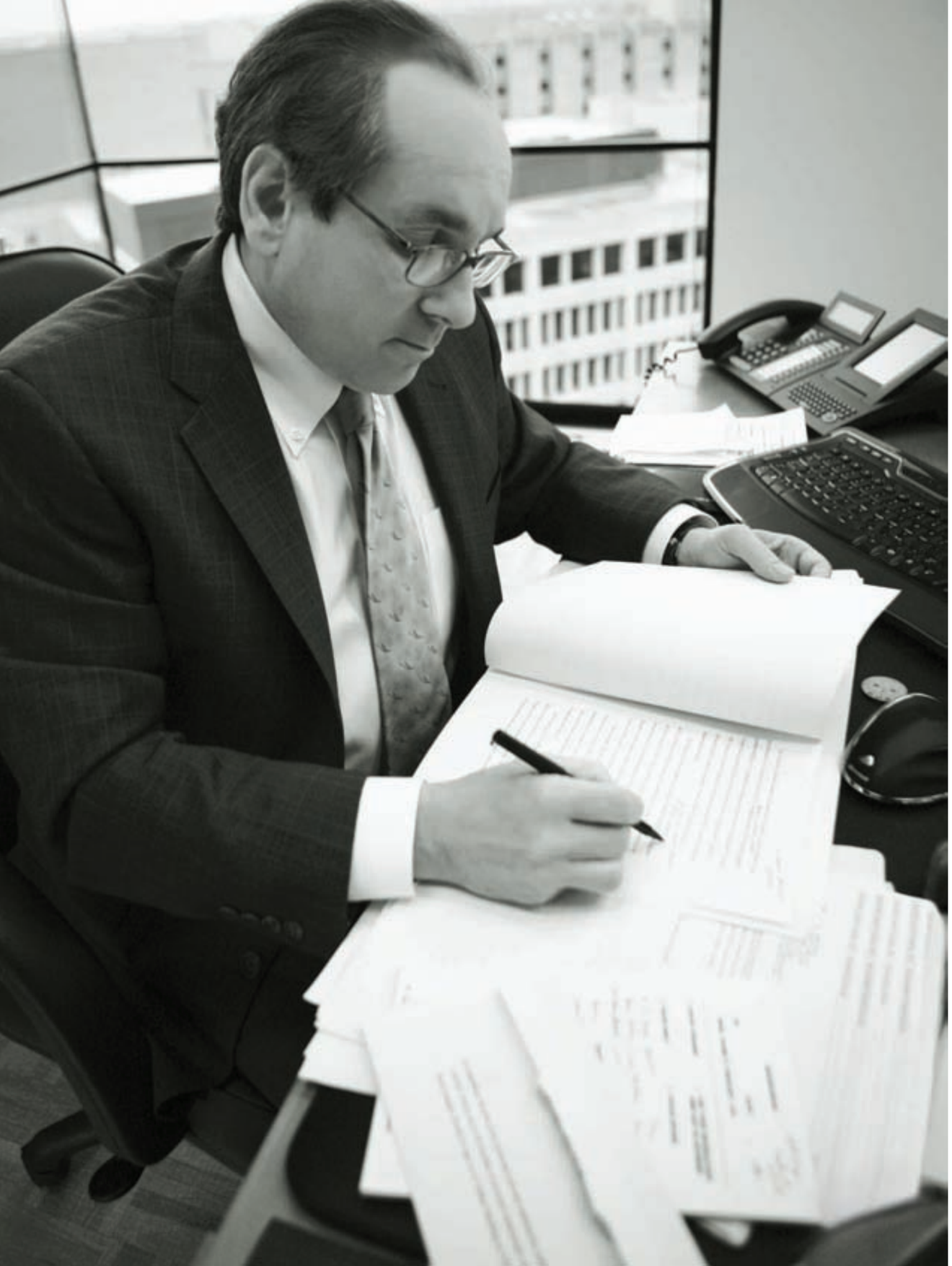
TRANSPLANTING SUCCESS 24
UT Southwestern's programs make it among the most comprehensive centers in the nation.

20 YEARS OF HEART TRANSPLANTS 30
In 1988, Dr. W. Steves Ring moved to Dallas to build a world-class transplant program. Today, UT Southwestern's program has one of the best survival rates in the country.

THE MIGHTY LIVER 42
The liver is one of the most elegantly complicated organs in the human body, performing tasks from cleaning up to regeneration. When something goes wrong, UT Southwestern's liver team takes over.

THE CLINICAL FRONTIER 48
FROM A TO ZZZZZs 48
IN A HEARTBEAT 50

Articles from *Southwestern Medicine* and other news and information from UT Southwestern are available online at www.utsouthwestern.edu.



Becoming Podolsky

By Kristen Holland Shear

Many descriptions – renowned scientist, empathetic clinician, enthusiastic educator, experienced mentor and focused administrator – fit hard-charging Dr. Daniel K. Podolsky, UT Southwestern's new president.

It's dark outside when Dr. Daniel K. Podolsky flips on the light switch to his 12th floor office in the Eugene McDermott Academic Administration Building. His computer's clock reads 5:30 a.m. Dr. Podolsky knows that he has an hour, maybe two, before other lights will begin to flick on around him.

UT Southwestern Medical Center's third president relishes the morning hours, rising early to run most days before driving to work. This tradition of rising early began in high school when he would awake at 3 a.m. every Sunday to deliver bagels to neighbors throughout Southfield, Mich., a suburb of Detroit. Eventually he took up running because, as he says, there's not much else to do at that time of day.

"Although the health benefit is important, it's also a quiet time to think and reflect without distraction," said Dr. Podolsky, whose wife is a pediatrician and two sons and daughter are students at Columbia Law School, Harvard Medical School and Harvard College.

Dr. Podolsky became president of UT Southwestern on Sept. 2, 2008, after a nationwide search. Dr. Kern Wildenthal had announced his retirement as president in October 2007. The new president now holds the Philip O'Bryan Montgomery Jr., M.D., Distinguished Presidential Chair in Academic Administration and the Doris and Bryan Wildenthal Distinguished Chair in Medical Science.

Rising early isn't the only trait Dr. Podolsky picked up from his father, who was a general practitioner back in the days when the position involved everything from surgery to obstetrics and pediatrics. The younger Dr. Podolsky also inherited a love for science and decided to follow his father's example.

Dr. Podolsky's zeal for science paid off when he met Drs. Milton Weiser, recently retired as chief of gastroenterology at the State University of New York in Buffalo, and Kurt Isselbacher, legendary chief of the gastroenterology unit at Massachusetts General Hospital, while looking for a laboratory job. He was in the midst of his first year at Harvard University after being accepted as a sophomore student at the age of 18.

Students from all three schools welcome Dr. Daniel Podolsky to campus on his first day as president.

"Our priorities must … include … innovation that translates biomedical research into new approaches to patient care; quality that provides our patients with consistently safe and efficient care; and a culture that makes each patient feel truly cared for by our attention to them and their families."

— Dr. Daniel K. Podolsky

THOUGH THE RENOWNED PHYSICIANS WERE SKEPTICAL ABOUT LETTING AN UNDERGRADUATE WORK IN THEIR LAB, thinking they seldom remained long enough to undertake a significant project, Dr. Isselbacher finally relented. What followed was a lifelong mentorship that led the young student into a career in gastroenterology.

"Through my early years of college, I always assumed I would pursue a career in science or medicine. When I applied for that first laboratory job, it happened to be in a hospital setting, and I realized that I didn't necessarily have to choose one or the other," Dr. Podolsky said.

Within two years of his going to work in the gastroenterology unit at Massachusetts General, Dr. Podolsky's first published results appeared in the *Journal of Cell Biology*. A year later, he graduated *summa cum laude* from Harvard and continued on to Harvard Medical School, where his research of the human digestive system continued. He completed his residency and fellowship at Massachusetts General and joined the faculty of Harvard and the staff of Massachusetts General in 1981. During his tenure he served as the Mallinckrodt Professor of Medicine and a faculty dean for academic programs at Harvard, as well as chief of gastroenterology at Massachusetts General.

Dr. Isselbacher, now the Mallinckrodt Distinguished Professor of Medicine at Harvard Medical School, said Dr. Podolsky's dedication and insight amazed him from the start.

"He was omnipresent," Dr. Isselbacher said. "It never seemed like he was doing anything else, except he was going to college at the same time. He would come in early in the morning, sometimes around 4:30 a.m., then go to class around 8 or 8:30 a.m. and then come back to the lab."

Dr. Isselbacher said Dr. Podolsky, whom he considers almost a son, is probably one of the greatest scientists with whom he has ever worked.

"He was outstanding when he started with me, and he's just continued to evolve into a very mature, effective scientist and administrator and a very astute clinician," Dr. Isselbacher said. "In addition, Dan has an almost instant recognition of the issue and a penetrating mind that is very analytical. He immediately sees the issue and is able to proceed from there."

Dr. Podolsky credits Dr. Isselbacher, one of the foremost international leaders in gastroenterology, with fueling his interest in studying inflammatory bowel disease. "Even though I learned about many other areas in the course of medical school and found many of them interesting, having the privilege to learn from true giants in the field of gastroenterology made a significant difference."

More than 1 million people in the U.S. suffer from inflammatory bowel disease (IBD), a group of disorders in which the intestines become inflamed. The two major types of IBD are ulcerative colitis and Crohn's disease. Ulcerative colitis is limited to the colon, or large intestine. Crohn's most commonly affects the small intestine and/or the colon, but it can involve any part of the gastrointestinal tract. Both ulcerative colitis and Crohn's disease ebb and flow in the intensity and severity of illness. Unfortunately, no one yet knows for certain what causes IBD nor how to cure or prevent it.

Dr. Podolsky has been searching for those answers since his undergraduate days in Dr. Isselbacher's lab. Through the years, however, Dr. Podolsky's fascination with the human digestive system intensified. He said there are a number of factors that have led him to continue his research.

"One could make the case that the intestine is the site of the most extensive interaction with the outside world," he said. "But then, it's also critically important in the understanding of a number of other conditions. This insight leads to better treatments, cures or preventions for other diseases and disorders, which is clearly why the intestine is of importance and interest."

Dr. Willis Maddrey, executive vice president for clinical affairs at UT Southwestern and an authority on liver diseases, first met Dr. Podolsky early in his career at Massachusetts General Hospital.

"From the time I first met Dr. Podolsky, it was apparent that he was surely one of the most outstanding young investigator/clinicians in the country. As all who knew Dr. Podolsky early in his career expected, he advanced rapidly, succeeding Dr. Isselbacher as chief of the gastroenterology division at Massachusetts General in 1989 at the age of 35. During his tenure as chief, he trained a generation of young physicians who now are emerging as leaders in the digestive disease community, both in the United States and abroad," said Dr. Maddrey, holder of the Adelyn and Edmund M. Hoffman Distinguished Chair in Medical Science and the Arnold N. and Carol S. Ablon Professorship in Biomedical Science. "Dr. Podolsky has outstanding clinical, research and administrative abilities. The research he has done and presented has always been among the best."

Dr. Podolsky's determination hasn't dissipated in the 36 years since he first set foot in Dr. Isselbacher's lab.

His early research focused on intestinal epithelial differentiation and the control of proliferation. He also studied the function of glycoproteins, which led him to discover characteristic changes in patients with ulcerative colitis. This observation paved the way for new ideas about changes to intestinal barrier function that may make someone more vulnerable to developing IBD.

While researching intestinal epithelial differentiation and proliferation, he discovered how various growth factors affected intestinal epithelial differentiation repair in a variety of disorders, including infectious diarrhea, inflammatory bowel disease and peptic ulcer. One of these growth factors was a peptide known as intestinal trefoil factor, a previously unrecognized gene that Dr. Podolsky discovered and later characterized. The protein encoded by this gene is thought to protect the mucosa from injury, stabilizing the mucus layer and affecting the healing of the epithelium. Clinical trials have suggested that it may be effective in treatment of a variety of disorders, including chemotherapy to reduce damage to the gastrointestinal tract.

Dr. Anil Rustgi, the T. Grier Miller Professor of Medicine and Genetics and chief of gastroenterology at the University of Pennsylvania, said Dr. Podolsky's findings, particularly his observations about trefoil factors, have had a huge impact on the field of gastroenterology.

"His research is very rigorous. It is hypothesis-driven, innovative, and his results have been provocative," said Dr. Rustgi, who worked under Dr. Podolsky at Massachusetts General. "There are several aspects of his research dating back even to his college years that have led to paradigm shifts in our understanding of intestinal epithelial biology."

"There is no question that as president of UT Southwestern Dr. Podolsky will continue to develop the research agenda in both the clinical and basic sciences and will build on the excellent foundation that was created during Dr. Wildenthal's presidency."

— Dr. Willis Maddrey

Most recently, Dr. Podolsky's research has focused on exploring how intestinal cells guide immune responses and the body's symbiotic relationship between its own intestinal cells and that of microflora.

The author of more than 300 original research and review articles considers the discovery and follow-up characterization of trefoil factor his finest scientific accomplishment. "Our laboratory was among the first to demonstrate the importance of the epithelium in aiding innate responses and alterations of those responses related to inflammatory bowel disease," Dr. Podolsky said.

Dr. Maddrey said his colleague's research continues to have a profound impact on the field.

"Dr. Podolsky has been active in several national associations including the American Gastroenterological Association. During his tenure as president of the AGA, he was recognized for his promotion of a forward-looking agenda, and it became apparent throughout the digestive disease community that Dr. Podolsky would emerge as a visionary leader," Dr. Maddrey said. "There is no question that as president of UT Southwestern Dr. Podolsky will continue to develop the research agenda in both the clinical and basic sciences and will build on the excellent foundation that was created during Dr. Wildenthal's presidency."

One of Dr. Podolsky's strengths, Dr. Rustgi said, is that he's able to take complex ideas representing completely different directions and synthesize them in a cohesive fashion into a lucid vision.

"Because of his ability to bridge basic science to clinical medicine, he's been a forerunner at looking at mechanistic underpinnings in animal models and in cell culture and understanding how that applies to inflammatory bowel disease in humans," Dr. Rustgi said.

On the basis of his contributions to the field, Dr. Podolsky will be this year's recipient of the Julius Friedenwald Medal for Distinguished Service, the highest honor of the American Gastroenterological Association.

Dr. Kern Wildenthal, who now serves as president of Southwestern Medical Foundation in addition to holding the Carolyn P. and Frank M. Ryburn Jr. Distinguished Chair in Basic Research in Heart Disease at UT Southwestern, said being able to make carefully analyzed and timely decisions is one of Dr. Podolsky's most impressive traits.

"He can take all sorts of input and information, sift through what is relatively unimportant compared to what is crucial, and determine what has the highest priority," Dr. Wildenthal said. "That, along with his great intelligence and interpersonal skills, will ensure that he will be a great success at UT Southwestern."

Continued on page 51

Becoming Podolsky

Continued from page 5

Dr. Alfred Gilman, UT Southwestern's executive vice president for academic affairs, provost and dean of Southwestern Medical School, agrees, saying that Dr. Podolsky's leadership experience makes him well-positioned to take the reins at the medical center.

For the previous three years, Dr. Podolsky served as chief academic officer at Partners HealthCare, which was founded by Massachusetts General and Brigham and Women's Hospital in 1994. Partners is an integrated health care system that includes primary care and specialty physicians, community hospitals, the two founding academic medical centers, specialty facilities, community health centers and other health-related entities.

As chief academic officer, Dr. Podolsky oversaw $1 billion in annual research expenditures, as well as the graduate medical education programs at both Massachusetts General and Brigham and Women's hospitals. More than 50 fellowship graduates who worked in the Podolsky laboratory are now pursuing independent research as faculty members at medical schools nationwide.

"What Dan brings to the table is a wealth of experience leading an enormously successful clinical enterprise and the integration of that enterprise with education and both clinical and basic research," said Dr. Gilman, a Nobel laureate and holder of the Nadine and Tom Craddick Distinguished Chair in Medical Science; the Raymond Willie and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, in Honor of Harold B. Crasilneck, Ph.D.; and the Atticus James Gill, M.D., Chair in Medical Science. "UT Southwestern's basic science research programs remain the foundation of the school, but there are major opportunities here for translational and clinical research."

During the 19 years Dr. Podolsky served as chief of gastroenterology at Massachusetts General, the unit became one of the country's premier sites, hailed for its vibrant research and training programs as well as its comprehensive clinical offerings in gastroenterology. It expanded fifteenfold under his direction to include a high-risk GI cancer center, a liver-biliary-pancreas center and a clinical motility center. The unit is now ranked fourth among all digestive disease programs in *U.S. News & World Report's* honor roll of best hospital specialty services.

Dr. Podolsky also founded the Center for the Study of Inflammatory Bowel Disease, a world-renowned, multidisciplinary program in inflammatory bowel disease that was one of the first funded through the Digestive Disease Centers Program of the National Institute of Diabetes and Digestive and Kidney Diseases. The center has yielded many noteworthy advances since its inception in 1991.

"What Dan brings to the table is a wealth of experience leading an enormously successful clinical enterprise and the integration of that enterprise with education and both clinical and basic research."

— Dr. Alfred Gilman

Former colleagues say that few people can handle the workload of a scientist, clinician, educator, mentor and administrator, but Dr. Podolsky does so with great enthusiasm.

"You don't really find many people who are able to accomplish that many tasks in parallel," Dr. Rustgi said. "It's very impressive."

Dr. Isselbacher said Dr. Podolsky has always made everything look easy. In addition to his scientific ability, he is a superb clinician with a remarkable empathy for patients and a notable memory.

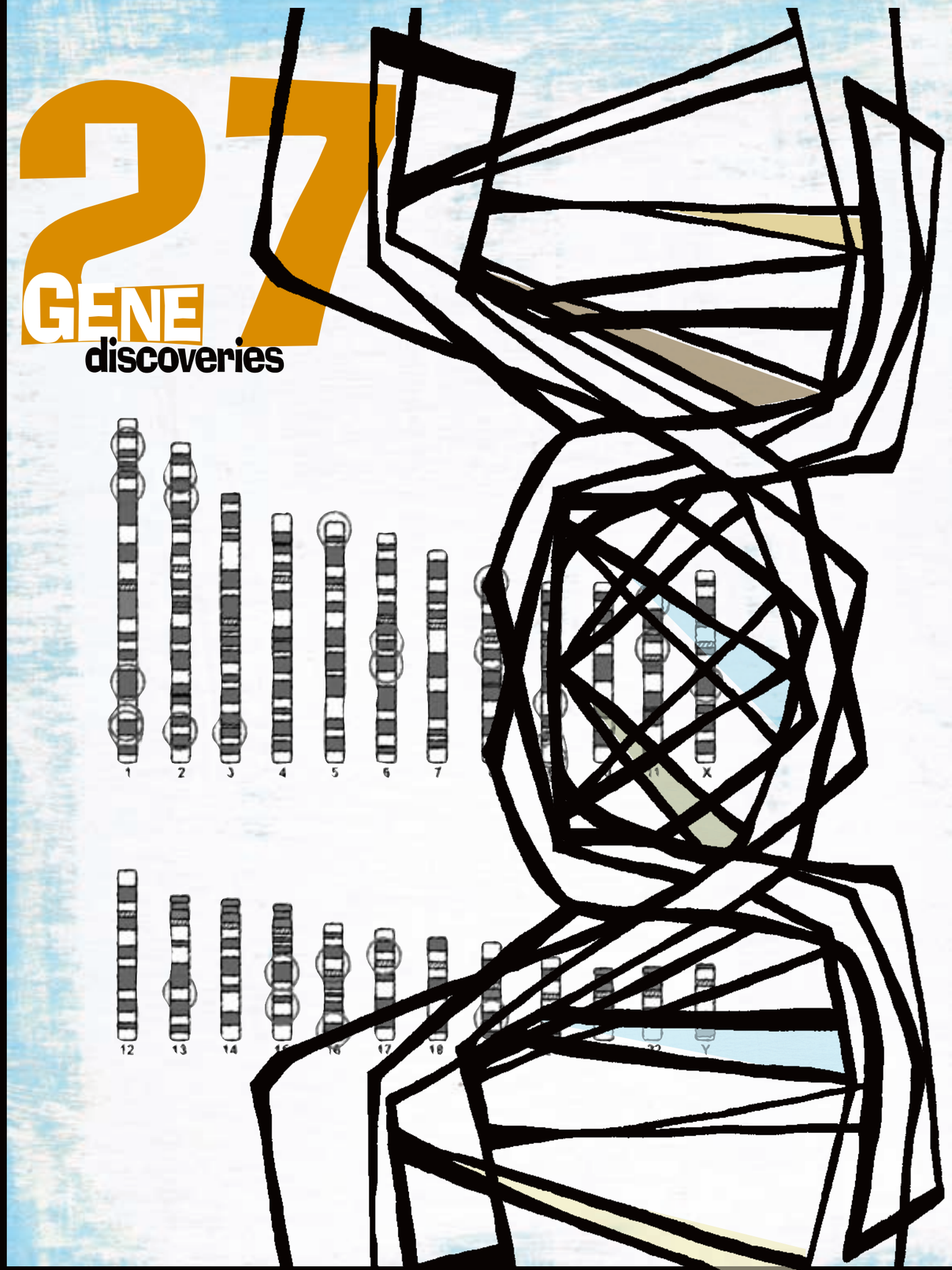
"For many years he used to go to the library every Thursday morning to scan the journals," Dr. Isselbacher said. "Only, for him, scanning the journals meant that he could remember everything he read and be able to recite the contents."

Another one of Dr. Podolsky's strengths, Dr. Wildenthal said, is that he believes in UT Southwestern's longstanding philosophy to focus on excellence, with the conviction that growth will be the natural outcome of quality.

"I have always thought, even back when I was a student here, that UT Southwestern was on a trajectory that would take it to the very top of academic medical centers worldwide," Dr. Wildenthal said. "Our quality is second to none, but we've got a little further to go before we're going to be viewed as equal to the very best in the comprehensive scope of our programs. I think Dan Podolsky is an ideal person to lead our institution to that goal."

For his part, Dr. Podolsky said he is committed to doing everything in his power to ensure that UT Southwestern remains at the forefront in basic science research and at the same time to work to make sure its clinical programs and clinical and translational research are also similarly innovative and of outstanding quality. Taking stock of the education programs offered through the medical school, graduate school and health professions school are also top priorities.

"I look forward to building on the foundation and all that has been accomplished during Dr. Wildenthal's tenure as president and under the leaders who preceded him," Dr. Podolsky said. "Drawing on these historic strengths, our priorities must also include expanding our commitment to clinical excellence in all its dimensions – innovation that translates biomedical research into new approaches to patient care; quality that provides our patients with consistently safe and efficient care; and a culture that makes each patient feel truly cared for by our attention to them and their families." ✳



UT Southwestern researchers are at the forefront of the genetics revolution.

THE GENE SCENE

The completion of the Human Genome Project early in this decade was heralded as the beginning of a new era in scientific discovery and medical advances. The 13-year endeavor set out to identify all of the approximately 20,000 to 25,000 human genes and determine the sequence of the 3 billion chemical base pairs in human DNA – each letter in the genetic "alphabet" that spells out the instructions for making a person. The massive project promised to provide a basis of knowledge that would aid in the identification of risk factors, disease processes and potential new treatments for common yet complex diseases such as cancer, heart disease and mental illness. At UT Southwestern Medical Center, investigators are delivering on that promise. Armed with advanced technology, they are at the forefront of the genetics revolution, uncovering the function of genes, tracing the causes of many diseases back to genetic variations and mutations, and developing improved and novel genetics-based treatment and diagnostic strategies for illnesses. By the end of 2007, UT Southwestern researchers had identified 27 disease-causing genes, including in 1983 the gene responsible for familial hypercholesterolemia, an inherited condition that causes extremely high levels of cholesterol and heart attacks at an early age. That discovery by Dr. Michael Brown, director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease, and Dr. Joseph Goldstein, chairman of molecular genetics, led to their receiving the Nobel Prize in physiology or medicine for their research uncovering the underlying mechanisms of cholesterol metabolism. A snapshot of research projects from a handful of UT Southwestern laboratories highlights the latest progress and challenges in genetics research.

by amanda siegfried

Genome 101

At its basic level, DNA is a molecule made up of four chemicals called bases: adenine (A), guanine (G), cytosine (C) and thymine (T). Human DNA consists of about 3 billion base pairs strung out in rows of two strands contained in chromosomes, which are located in each cell's nucleus. The bases from one strand pair up with those on the other strand – A always with T and C with G. The base pairs, also called nucleotides, are arranged like rungs on a ladder. The vertical sides of the ladder are made up of sugar and phosphate molecules, and the structure is then twisted and coiled up like a spring to form what is called a double helix.

Humans have 23 pairs of chromosomes, and these are divided up into individual genes. Chromosomes also contain DNA that is not part of the genes. Genes contain the code, or blueprint, for making proteins, which then go on to carry out most of life's functions. When a gene's protein is being made in the body, the gene is said to be "expressed."

More than 99 percent of the genome is the same in each person, but there are areas where the base pairs differ – where the "spelling" of genetic information varies from person to person. Such differences are often key starting points for researchers to identify and investigate genetic links to disease.

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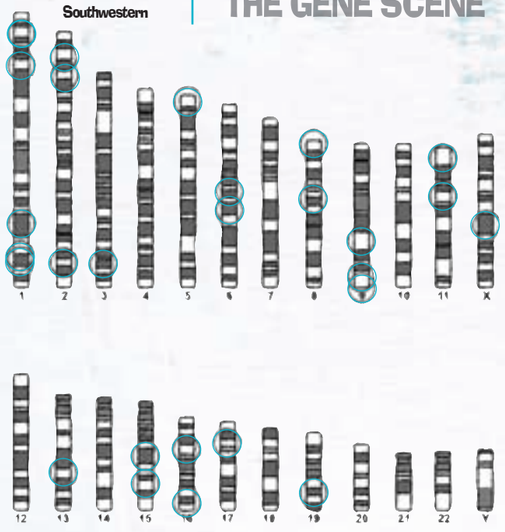
In some cases, there is a particular misspelling or mistake in the DNA itself, which is called a mutation. These errors in the instructions for making proteins can result in partially or completely non-functional proteins – conditions that can lead to disease. Such inherited conditions, or a predisposition to certain conditions, can be passed from generation to generation and include, for example, cystic fibrosis, sickle-cell anemia and some forms of breast cancer. Each can be traced to a mutation in a particular gene. For many such diseases, genetic tests are available to determine whether an individual carries such a mutation.

The genome can vary in other ways that are linked to disease. Natural variations in the sequence of base pairs among individuals – variations that are more common than mutations – are called single nucleotide polymorphisms, or SNPs (pronounced "snips"). There are millions of SNPs in the human genome, places where one person may have a T while another person has a C, for example. One of the major accomplishments of the Human Genome Project was a map detailing exactly where in the genome these SNPs occur.

27 GENE discoveries at UT Southwestern

On the leading edge of

THE GENE SCENE



CHROMOSOME 1:
Autosomal Recessive Hypercholesterolemia (2001) – *cholesterol metabolism*
Dominant Hypobetalipoproteinemia (2005) – *cholesterol metabolism*
Age-Related Macular Degeneration (2005) – *age-related blindness*
Mandibuloacral Dysplasia (2003) – *skeletal development*
Infantile Neuronal Ceroid Lipofuscinosis (1995) – *fatal childhood disorder*

CHROMOSOME 2:
Male Pseudohermaphroditism (1991) – *male sexual development*
Sitosterolemia (2000) – *cholesterol metabolism and heart disease*
Cerebrotendinous Xanthomatosis (1991) – *fat metabolism*

CHROMOSOMES 3 and 5:
Pulmonary Fibrosis (2007) – *lung disease*

CHROMOSOME 6:
Stargardt Disease (2001) – *childhood blindness*
Obesity (2000) – *obesity*

CHROMOSOME 8:
Atrial Septal Defect (2004) – *heart disease*
Progressive Neonatal Cholestasis (1998) – *fat metabolism*

CHROMOSOME 9:
Male Pseudohermaphroditism (1994) – *male sexual development*
Congenital Generalized Lipodystrophy (2002) – *fat metabolism*
Aortic Valve Disease (2005) – *heart disease*

CHROMOSOME 11:
25-Hydroxyvitamin D Deficiency (2004) – *skeletal development*
Multiple Exostoses (1996) – *limb deformities*

CHROMOSOME X:
Choroideremia (1993) – *blindness*

CHROMOSOME 13:
Hirschsprung's (1994) – *nerve development*

CHROMOSOME 15:
Aromatase Deficiency (1993) – *estrogen production*
Papa Syndrome (2002) – *arthritis*

CHROMOSOME 16:
Progressive Intrahepatic Cholestasis (2000) – *childhood liver disease*
Malonyl CoA Decarboxylase Deficiency (1999) – *childhood metabolic disorder*

CHROMOSOME 17:
Spontaneous Pneumothorax (2005) – *lung disorder*

CHROMOSOME 19:
Familial Hypercholesterolemia (1983) – *cholesterol metabolism, heart attack*

Normally, each cell contains two copies of every gene – one inherited from the father, one from the mother – located on each of the chromosome pairs. Another type of variation occurs when an individual's genome contains more (or fewer) than two copies of a given gene. These are called copy number variations, or CNVs. Many SNPs and CNVs have no medical relevance, while others can have profound impact on a person's health or susceptibility to disease.

Over the last few years, technologies have evolved to allow the rapid characterization of variation in the human genome, as well as in animal models, said Dr. Edward Wakeland, chairman of immunology.

Holder of the Edwin L. Cox Distinguished Chair in Immunology and Genetics, Dr. Wakeland heads UT Southwestern's Microarray Core Facility, which provides laboratory services to researchers on the UT Southwestern campus and nationwide.

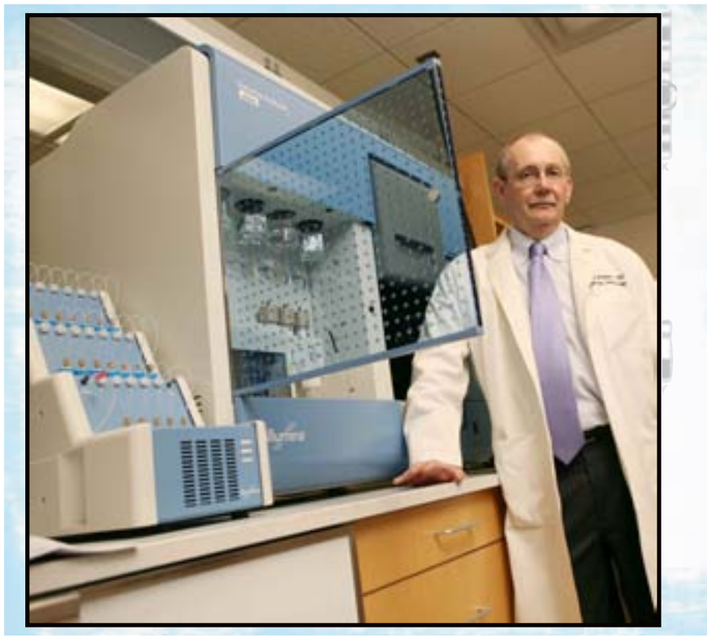
"Our core labs run very sophisticated instruments that allow us to provide genotyping for SNPs and CNVs at an unprecedented rate," said Dr. Wakeland, who also directs the Walter M. and Helen D. Bader Center for Research on Arthritis and Autoimmune Diseases.

Genotyping involves comparing one person's DNA with another person's DNA at millions of positions along the entire length of their respective genomes, allowing researchers to determine where humans are the same and where they are different. Performing such comparisons over and over again, among large populations of people, both sick and healthy, provides clues to where the origins of gene-associated diseases might lurk.

The newest piece of equipment in the core facility – one of the most sophisticated gene sequencers on the planet – provides a tremendous boost to the effort.

"This next-generation technology allows us to re-sequence the entire genomes of hundreds of individuals incredibly rapidly, efficiently and cost-effectively," Dr. Wakeland said. "It is now possible, with a single instrument, in a single experiment over three or four days, to re-sequence 3 billion base pairs in an individual's genome. In terms of raw sequencing power, this is tens of thousands of times greater than even the most sophisticated, standard sequencing instruments."

The technology and services Dr. Wakeland's core facility provides to other investigators also aids his own research, which focuses on understanding the genetic links to systemic lupus erythematosus, a chronic autoimmune disease that afflicts nearly



1.5 million people in the U.S., more than cerebral palsy, multiple sclerosis, sickle-cell anemia and cystic fibrosis combined. Ninety percent of lupus victims are women.

"Lupus clearly has a very strong genetic component," Dr. Wakeland said. As part of a large consortium of institutions, he is performing SNP scans of the entire genome for thousands of patients and healthy controls in an effort to identify particular genes that are associated with susceptibility to this chronic illness. So far, the group has identified 18 different regions of the genome containing genes that increase an individual's susceptibility to lupus.

DNA, Repair Thyself

Most mutation-generating damage to the DNA in our cells is repaired by special enzymes that make up the DNA repair systems of each cell. Each cell has a number of pathways through which these enzymes recognize and repair mistakes in DNA, an important process the body uses to protect itself from disease.

Dr. Errol Friedberg, chairman of pathology and holder of the Senator Betty and Dr. Andy Andujar Distinguished Chairmanship of Pathology, is an expert on DNA repair mechanisms, and his research sheds light on the role misregulated gene repair plays in diseases such as cancer.

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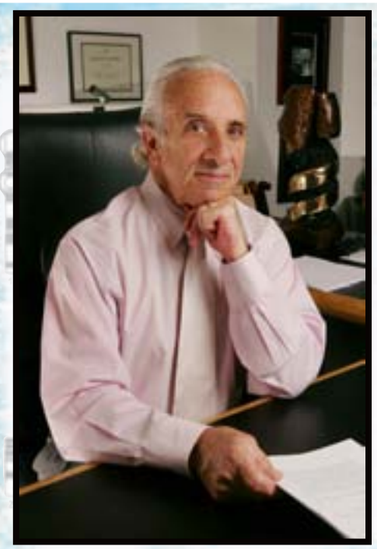
– Dr. Edward Wakeland



"The skin cancer can arise either from a cell's failure to repair sunlight-damaged DNA, or it can arise from a low-fidelity polymerase's inability to bypass the damage accurately."

– Dr. Errol Friedberg

When cells divide, their entire DNA complement must be copied faithfully so that each new cell contains the same genetic information. DNA polymerases with very high accuracy, or high copying fidelity, are the molecules that travel along the genome's length "reading" and copying the sequence of bases. But when a DNA polymerase encounters a site of unrepaired DNA damage, this replication process frequently stops because these polymerases are unable to negotiate the damage.

In recent years, however, researchers have identified a new class of specialized DNA polymerases that are naturally very sloppy at copying DNA; they skip over certain kinds of damage and just carry on. "Evolution might not occur without them," said Dr. Friedberg, whose research group was the first to show that such polymerases exist in mammals.

"This phenomenon promotes survival of the cell," he said. "If replication is completely arrested, the genome cannot be duplicated, and the cell will die. But if a DNA polymerase can bypass damage because of its low fidelity, arrested replication can be avoided, and the cell will divide, even though this process may lead to mutations because of the low copying fidelity. Better to have a mutation, though, than to die. These sorts of mutations also presumably contribute to the genetic plasticity that is required for Darwinian evolution over time."

When such low-fidelity polymerases malfunction, cancer can result. For example, skin cancer is extremely common in a hereditary disease called xeroderma pigmentosum.

"The skin cancer can arise either from a cell's failure to repair sunlight-damaged DNA, or it can arise from a low-fidelity polymerase's inability to bypass the damage accurately," Dr. Friedberg said.

Dr. Friedberg and his colleagues believe that there are nine or 10 such low-fidelity polymerases, and that each one selectively bypasses a specific form of environmentally induced or spontaneous DNA damage.

"Normally a particular low-fidelity DNA polymerase will accurately bypass a particular sunlight-induced lesion [damage] in DNA, thereby avoiding mutations," Dr. Friedberg said. "It's supposed to do that. In some xeroderma pigmentosum patients, however, this DNA polymerase is defective, so one of the other low-fidelity DNA polymerases does the job – inaccurately – and cancer results."

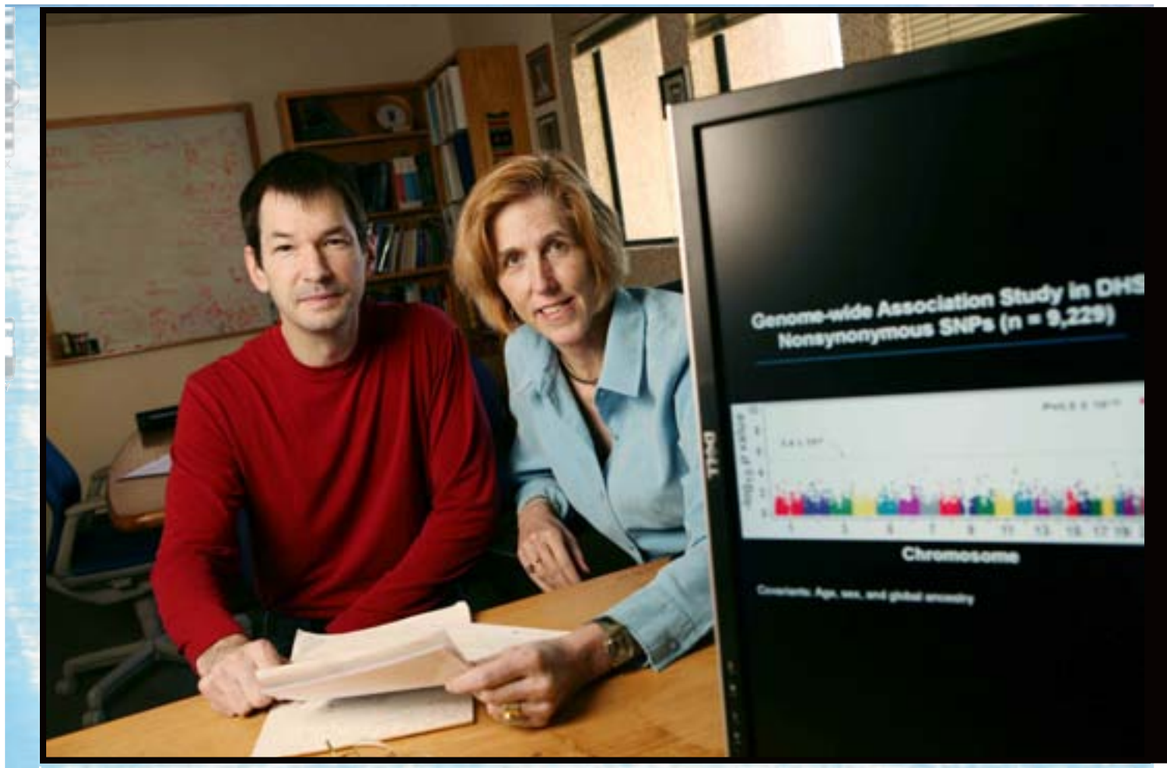
The goal now, Dr. Friedberg said, is to figure out the specific form of damage that each of these specialized low-fidelity DNA polymerases was selected for during evolution.

There is also evidence suggesting that one of these DNA polymerases is overexpressed in lung cancer cells.

"We believe that in some forms of cancer, some of these DNA polymerases might not be working well, so we are screening cancers to see whether that is the case," Dr. Friedberg said. "If true, then it may be possible to target one of these polymerases with a drug in situations where it is overexpressed, offering a potential way to prevent cancer."

Genetics of Heart Disease

Dr. Helen Hobbs, director of the Eugene McDermott Center for Human Growth and Development and of the Donald W. Reynolds Cardiovascular Clinical Research Center and chief of clinical genetics, and her colleague Dr. Jonathan Cohen, professor of internal medicine and an investigator in the Center for Human Nutrition and the McDermott Center, are among the world's leading experts on the genetic factors associated with heart disease. They and their colleagues are not only making tremendous progress in identifying specific genetic links to disease, but also are translating that information from the laboratory to develop strategies to combat heart disease in patients.



Dr. Jonathan Cohen and Dr. Helen Hobbs

Dr. Hobbs and Dr. Cohen, who holds the C. Vincent Prothro Distinguished Chair in Human Nutrition Research, published a study in 2005 showing that humans with mutations in a gene called *PCSK9* had low-density lipoprotein (LDL) cholesterol levels 40 percent lower than individuals without the mutation. That study, based on data gathered from nearly 3,500 participants in the Dallas Heart Study, which Dr. Hobbs leads, determined that individuals with the mutated version of the gene were unable to make normal levels of PCSK9 protein.

In additional studies, they found that people with such cholesterol-lowering genetic mutations were significantly less likely to develop coronary heart disease later in life than those without the variations.

Since Dr. Hobbs's discovery, Dr. Jay Horton, who heads UT Southwestern's Task Force for Obesity Research and holds the Dr. Robert C. and Veronica Atkins Chair in Obesity & Diabetes Research, has been studying just what the PCSK9 protein does in the body, and his research is bringing the findings closer to clinical applications. His studies suggest that inhibiting PCSK9's action may be another route to lowering LDL cholesterol in individuals with high cholesterol, and he has teamed with Alnylam Pharmaceuticals to evaluate use of new therapies to target the protein and lower cholesterol.

"Let's say you have a population of 300 people with coronary artery disease and 300 without it, and at one particular SNP [nucleotide], the C allele is present in 50 of the heart-disease patients, but in only 10 people from the healthy group. Then we say, Ah, this looks interesting."

– Dr. Helen Hobbs

Dr. Hobbs and Dr. Cohen's research has focused in part on performing whole-genome association studies, a research technique that relies on advanced technology and the SNP map produced by the Human Genome Project. Their whole-genome association studies utilize a gene chip, a postage-stamp-sized device that has on its surface tiny wells that each contain one SNP. These SNPs are arranged on the chip in the order that they appear in the genome, from one end of the DNA molecule to the other, from chromosome 1 to chromosome 23. The device allows researchers to examine variations in base pairs from multiple people – both ill and healthy – and uncover possible genetic links to disease.

Here is an example of how this technique works. Dr. Hobbs and her group recently used gene chip technology to examine DNA samples from hundreds of individuals who had coronary heart disease and hundreds who were healthy. Her purpose was to determine where the two groups differed genetically.

Using the SNP gene chip, Dr. Hobbs and Dr. Cohen looked at 100,000 SNP variations occurring at intervals of about 30,000 base pairs.

"Basically what we were asking is, 'What allele does each person have at every one of these SNP locations?'" she explained. An allele is the particular "letter" of the genetic alphabet – A, C, T or G – that a person has at any given location in the genome.

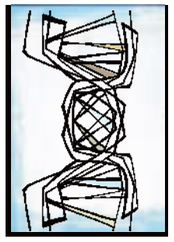
Starting at the beginning of the genome, the researchers looked at the first SNP. There they determined whether individuals who have heart disease tend to exhibit one particular allele more than do healthy people. They then repeated this process for each SNP on the chip.

"Let's say you have a population of 300 people with coronary artery disease and 300 without it, and at one particular SNP, the C allele is present in 50 of the heart-disease patients, but in only 10 people from the healthy group. Then we say, 'Ah, this looks interesting,'" said Dr. Hobbs, who holds the Eugene McDermott Distinguished Chair for the Study of Human Growth and Development and the Dallas Heart Ball Chair in Cardiology Research.

In this study, the group led by Drs. Hobbs and Cohen discovered one SNP variation that is highly associated with coronary heart disease. It lies on chromosome 9. In the next step, the researchers looked more closely at base pairs on either side of this SNP to see how far out into the genome the association extended.

When they examined the surrounding regions, they narrowed down the disease-association region to one consisting of 58,000 base pairs.

"The interesting part is that there's no gene in there," said Dr. Hobbs, an investigator for the Howard Hughes Medical Institute at UT Southwestern. "It's a noncoding region, which means it does not code for a protein. There is probably something else that's in there, some other sequence that's affecting these people. That's a mystery still, but we're looking at that now to figure out what exactly it might do."



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– Dr. Helen Hobbs

Mental Illness Links to Genes

Many diseases and conditions are much more complex than one gene, one disease. More often than not, disease is a result of an intricate system of many genes and their products, and in some cases, as Dr. Hobbs discovered with her heart disease research, a condition traces back to a DNA region that at first blush doesn't seem to be doing anything.

Most psychiatric diseases are hereditary, yet have proved difficult to understand because of these convoluted interactions. At UT Southwestern, Dr. Lisa Monteggia and Dr. Colleen McClung are delving deep into the genetic mechanisms at work in the brain in an effort to understand better how mental illness arises, with the ultimate goal of developing more effective treatments.

"We're working on a problem that's a lot harder than trying to find the genes involved in, say diabetes or even certain types of cancer, because psychiatric diseases are more complex and variable," said Dr. McClung, assistant professor of psychiatry. "It's unlikely that we're going to find a silver bullet – this one gene that causes depression or bipolar disorder. But it's still worth trying to identify genes that are involved in these illnesses so that we can develop more targeted treatments."

It is likely, she said, that such illnesses are the result of a combination of genes and other factors, such as environmental influences.

Dr. Monteggia, assistant professor of psychiatry, is studying a gene that produces a protein in the brain called brain-derived neurotrophic factor, or BDNF. The protein is a type of growth factor, which regulates the division and proliferation of cells in the body.

BDNF is the most prevalent growth factor in the brain, and several studies suggest it might be necessary for antidepressants to work in patients. There is evidence that many of the most-prescribed antidepressant medications increase the expression of BDNF in the brain.

Dr. Monteggia relies on mouse models of depression to investigate the effects of BDNF and other genes. Mice can be altered genetically and conditioned to exhibit behaviors similar to those experienced by patients suffering from psychiatric disorders.

Among her findings, Dr. Monteggia has shown that if BDNF is specifically deleted in the mice's brains, the animals no longer respond to antidepressants. Furthermore, by eliminating BDNF only in specific regions of the brain, she and her colleagues have homed in on a subregion of the hippocampus that is necessary for antidepressant action.

Investigating depression is particularly compelling, Dr. Monteggia added, because everyone knows someone who is affected by depression.

"Many people do not respond to the various treatments for depression. Why? It's a very interesting and dynamic area of research," she said. "We know there is a genetic component, but we don't know what the genes are. That's why we're trying to study this growth factor and how it responds to antidepressants to learn more about the disease and the affected brain regions."

Dr. Monteggia also uses animal models in studies of autism spectrum disorders. For example, she is investigating a condition called Rett syndrome, one of only a small number of neuropsychiatric illnesses that have been conclusively linked to a gene, according to Dr. Monteggia.

When she knocked out a gene called *MeCP2* in particular regions of the mice's brains, the animals exhibited autistic-like behavior, including heightened anxiety, social deficits, and some minor learning and memory deficits.

"We have shown that the loss of this gene triggers an imbalance between excitation and inhibition of nerve cells in the brain, leading either to over-excitation or over-inhibition," Dr. Monteggia said. "Neurons have to maintain this balance, or they can trigger seizures or a number of other problems in information processing, which have been suggested to underlie autism spectrum disorders. Importantly, we are trying to understand how this gene controls neural connectivity leading to the regulation of this balance."

Dr. Monteggia speculates that the gene in question is responsible for making a transcription factor, a type of protein that turns other genes on and off. When this gene is faulty, it inappropriately activates other genes and increases gene expression, resulting in the imbalance.

Dr. McClung also has found in mice that disrupting the gene that regulates biological clocks results in manic behavior. With a mutation in a gene called *CLOCK*, the animals exhibit behavior similar to humans with bipolar disorder. This psychiatric illness causes a dramatic shift in a person's mood, energy and ability to function – much more severe than the normal ups and downs of everyday life. Several million American adults suffer from the condition.

Dr. Lisa Monteggia *(left)* and Dr. Colleen McClung

"This mouse has given us a great opportunity to study what the *CLOCK* gene is doing and why a mutation in it results in a behavioral response that looks so much like mania," Dr. McClung said. "We know, for example, that the CLOCK protein acts as a transcription factor – it controls the expression of other genes. So now we are looking at some of those downstream targets, the genes that CLOCK is regulating, and we found a couple that we are really excited about."

Dr. Monteggia said developing animal models for studying human genetic conditions is a key step in the quest to find more effective treatments. Data from excellent animal models provide important justification when researchers seek approval to test drugs in human patients.

"What Colleen and I do is important in terms of modeling these diseases, because when it comes to drug development, you have to have an animal model to start with.

"With autism spectrum disorder, we have a clear genetic component. With depression, we have a gene that's definitely implicated. But now, what happens downstream from the gene? With the animal models we have a place to start."

"This mouse has given us a great opportunity to study what the *CLOCK* gene is doing and why a mutation in it results in a behavioral response that looks so much like mania."

– Dr. Colleen McClung

Cancer Genetics

When it comes to understanding the myriad complexities of cancer, UT Southwestern researchers in the Harold C. Simmons Comprehensive Cancer Center are on the front lines of the attack against many forms of the disease. Research efforts focusing on the genetics of lung cancer and breast cancer offer two examples of how advanced technology is propelling discovery as well as facilitating translation of scientific findings to patient care.

Dr. John Minna and Dr. Adi Gazdar have spent the past 30 years trying to understand the genetic and epigenetic changes associated with the development and treatment of lung cancer. Their work seeks to discover these changes and use them as biomarkers – molecular signatures of disease – both to detect lung cancer earlier and to develop new therapies. Their approach also bodes well for so-called personalized medicine, which aims to target the unique characteristics of an individual's tumor with the best current therapies.

As part of this effort, Dr. Minna leads UT Southwestern's prestigious Specialized Program in Research Excellence (SPORE) grant from the National Cancer Institute (NCI), a dedicated effort focused on lung-cancer research. The award is shared with UT M.D. Anderson Cancer Center and involves collaborations with Vanderbilt University, Harvard University, the University of Pittsburgh, Johns Hopkins University and the University of Colorado.

In addition, Drs. Minna and Gazdar have been part of the Genetic Epidemiology of Lung Cancer Consortium, funded by an NCI grant. That group identified a region of the genome – a gene yet to be identified but located on chromosome 23 – whose inheritance greatly increases the risk of developing lung cancer.

Although it is well-established that smoking greatly increases an individual's chances of getting lung cancer – one in 10 heavy smokers eventually develops the disease – about 15 percent of lung cancers occur in people who have never smoked. According to the NCI, more than 200,000 new cases of lung cancer are diagnosed each year, so 15 percent translates into about 30,000 cases among never-smokers. What is the underlying cause of cancer in these individuals?

"Lung cancer among never-smokers is really an ignored disease, yet it is such a major killer," said Dr. Gazdar, professor of pathology in UT Southwestern's Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research.

"There are hundreds of these changes in lung cancer. In fact, the molecular changes in tumors that develop in smokers compared to those in never-smokers are like night and day. It's difficult to understand why these changes are so dramatically different between these two types of lung cancer."

– Dr. Adi Gazdar

In 2005 Dr. Gazdar and Dr. Minna, director of the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics and the Hamon Center, helped make a key discovery. They found that lung-cancer patients who have never smoked are much more likely than smokers to harbor one of three mutations in the epidermal growth factor receptor (*EGFR*) gene. In addition, they found that such mutations are more common in women and in people of Asian ancestry.

While some gene-linked diseases are caused by mutations in DNA itself, another type of genetic alteration, called an epigenetic change, does not alter the underlying DNA sequence at all. Instead, epigenetic forces cause genes to be expressed differently in different cells. For example, each cell in the body contains the instructions – the genes – for making hair, but these genes are not normally expressed in heart cells. Epigenetic factors control such selectivity, and when those factors go awry, disease can result.

Dr. Gazdar is one of the pioneers who first discovered epigenetic changes that are associated with lung cancer.

"There are hundreds of these changes in lung cancer," said Dr. Gazdar, who holds the W. Ray Wallace Distinguished Chair in Molecular Oncology Research. In fact, the molecular changes in tumors that develop in smokers compared to those in never-smokers "are like night and day," he said. "It's difficult to understand why these changes are so dramatically different between these two types of lung cancer."

Dr. Gazdar is a principal investigator for the NCI's Early Detection Research Network (EDRN), a large collaboration of research scientists at more than 30 institutions nationwide devoted to developing and testing biological markers to aid in the early detection of cancer. Dr. Gazdar's group concentrates on lung cancer.

Dr. Gazdar approached both the EDRN and the Canary Foundation, a nonprofit organization dedicated to detecting cancer in patients earlier, to jointly fund a large multi-institutional project to study lung cancer in never-smokers. With $2 million available for the first year of the study, Dr. Gazdar will lead the research, to be performed at six sites. The effort is aimed at identifying molecular changes that occur in never-smokers who develop cancer, with the ultimate goal of developing a test to catch these changes early.

Such a test could help smokers and non-smokers alike.

Dr. Adi Gazdar and Dr. John Minna

"About 10 to 15 years after someone has stopped smoking, their cancer more closely resembles cancers from never-smokers than from smokers," Dr. Gazdar said. "Ideally what we would like is to take a DNA sample from the patient's blood and see not only whether they have an epigenetic predisposition for lung cancer, but also whether cells in their lungs already have some of these changes. It may be that if we had such a test, it might also apply to long-term former smokers."

Dr. Minna also is pioneering new approaches to studying lung-cancer genetics. Together with Dr. Jerry Shay, professor of cell biology and holder of the Southland Financial Corp. Distinguished Chair in Geriatrics, he developed continuously growing normal lung epithelial cells that live indefinitely in cell culture, a feat that researchers had been trying to achieve for more than 30 years. Now, using those cells, he systematically studies the effects of altering one gene at a time, or in groups, in order to study the importance of each gene in the progression toward lung cancer.

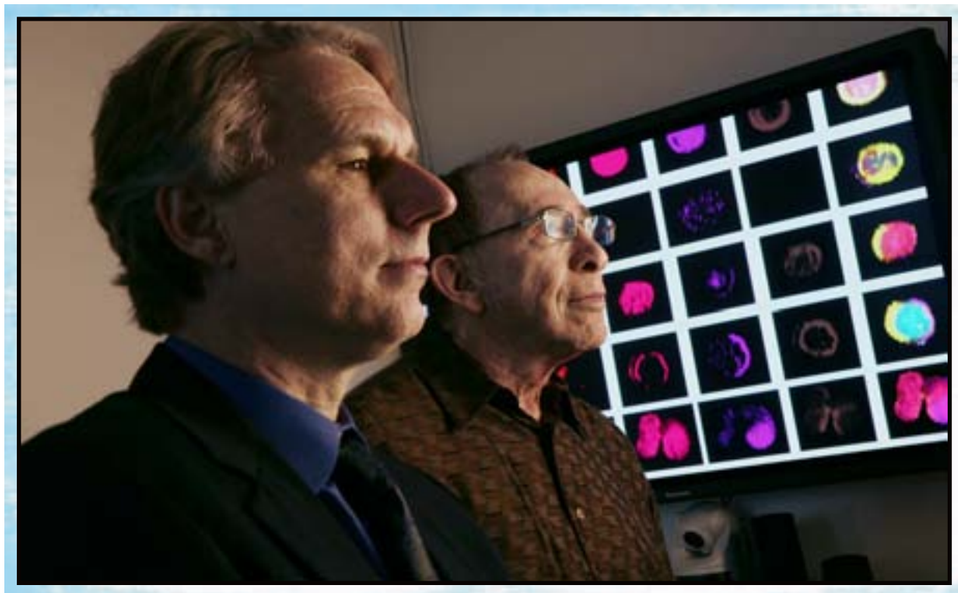
"Virtually everyone in the world working on lung-cancer research is using this panel of 300 or so lung-cancer lines that we started."

– Dr. John Minna

"We can look at a cell that has just one cancer-causing gene and compare its characteristics with the exact same normal cell that has not been changed," Dr. Minna said.

He and his research group now are working to verify this approach as a potential new cancer diagnostic tool for identifying patients' lung cells that exhibit tell-tale genetic signatures of cancer. Dr. Minna and Dr. Gazdar also have developed more than 300 different lung-cancer cell lines for use in experiments by their own team as well as others' research.

"Virtually everyone in the world working on lung-cancer research is using this panel of 300 or so lung-cancer lines that we started," said Dr. Minna, who holds the Sarah M. and Charles E. Seay Distinguished Chair in Cancer Research and the Max L. Thomas Distinguished Chair in Molecular Pulmonary Oncology. "Because we know the clinical details of the patients from whom these lung-cancer lines were derived, and we have genome-wide knowledge of each tumor's genetic profile, we can examine the effects of genetic and epigenetic changes on the behavior of each lung cancer, including its response to specific therapies."



Dr. Harold "Skip"Garner and Dr. Jonathan Uhr

Dr. Minna also has worked in collaboration with Dr. Michael White, professor of cell biology and associate director for basic science at UT Southwestern's Harold C. Simmons Comprehensive Cancer Center; Dr. Michael Roth, professor of biochemistry who leads the center's High Throughput Screening System, holds the Diane and Hal Brierly Distinguished Chair in Biomedical Research and is associate dean of UT Southwestern Graduate School of Biomedical Sciences; and Dr. Xian-Jin Xie, assistant professor of clinical sciences in the Simmons Cancer Center. The team recently combined Dr. Minna's lung-cancer cell lines with a massive genome-wide screening technology that one by one knocked down, or reduced the expression of, each of the 25,000 human genes in the cancer cells. The researchers then treated the cells with a very low dose of the chemotherapy drug paclitaxel (Taxol) in an effort to see if turning down any of the genes made the tumor cells more sensitive to the medication. They isolated 74 such genes, some of which made the cells 10,000 times more sensitive to the drug. The results are important because the ability to lower the dose of chemotherapy medications without compromising effectiveness reduces debilitating side effects.

"The proteins these genes produce are now new drug targets," Dr. Minna said. "If we could develop a drug that has the same effect as these knockdowns, then we could take a tumor that is just a little bit sensitive to Taxol and make it exquisitely sensitive."

"Dr. Garner is a brilliant physicist. He has taken a telescope developed by NASA and has made it into a microscope. This instrument has wonderful properties in terms of examining light, far beyond a normal microscope's capacity."

– Dr. Jonathan Uhr

Breast Cancer Mysteries

Dr. Jonathan Uhr has been an immunology researcher at UT Southwestern since 1972, when he joined the faculty as chairman of microbiology. He stepped down from the chairmanship in 1997 and moved to the Cancer Immunobiology Center, where he investigates some of the enigmas of breast cancer.

About 10 years ago, Dr. Uhr developed a technique to detect cancer cells that are shed from a primary tumor and go on to circulate in the blood. The test has been commercialized and now is used routinely in laboratories to pluck circulating cancer cells selectively out of the bloodstream for further analysis and characterization. The test also has helped Dr. Uhr identify a puzzling aspect of some breast cancers.

Breast-cancer patients who carry multiple copies of a particular gene – a condition also known as gene amplification – tend to have a poor prognosis. It was thought that if a patient's tumor initially was found to not have amplification of the *HER-2* gene, and the cancer recurred after treatment, that the recurring cancer would always be *HER-2* negative. Patients who test positive for *HER-2* amplification are often candidates for treatment with a drug called Herceptin.

Dr. Uhr, however, tracked patients whose primary tumor was initially *HER-2* negative, and in about 20 percent of the cases in which cancer recurred after treatment, he found that their tumors had shed into the bloodstream cells that had acquired *HER-2* amplification. The results have potential clinical significance because patients with *HER-2* negative primary tumors who have recurrent breast cancer are not candidates for treatment with Herceptin, said Dr. Uhr, who holds the Raymond Willie and Ellen Willie Distinguished Chair in Cancer Research, in Honor of Laverne and Raymond Willie Sr.

Telescope-Turned-Microscope

For as long as Dr. Uhr has been at UT Southwestern, NASA's Landsat satellites have collected information about Earth from space. The instruments on board detect and distinguish unique frequencies of light that reflect from such objects as vegetation and man-made structures. Scientists then interpret that data to monitor urban growth, agricultural irrigation and deforestation and to evaluate environmental change over time.

Now, the same technology that has helped to improve our understanding of Earth is being used to improve our understanding of genetics, as well as provide a potential new way to catch cancer early.

Dr. Uhr has teamed with Dr. Harold "Skip" Garner, professor of biochemistry and internal medicine and in the McDermott Center, who has adapted the technology, called hyperspectral imaging, to biology.

"Dr. Garner is a brilliant physicist," Dr. Uhr said. "He has taken a telescope developed by NASA and has made it into a microscope. This instrument has wonderful properties in terms of examining light, far beyond a normal microscope's capacity."

The researchers use fluorescent markers, or chemicals that emit different colors of light, to "tag" various components of cancer cells, such as the HER-2 protein and other cancer-related molecules. Then, using Dr. Garner's patented Hyperspectral Imaging Cytogenetics Microscope, the researchers can track how much of a given molecule is present.

"We can tag a set of 10 different biomarkers and precisely quantify the molecular signature of a given cancer cell," Dr. Uhr said. "And, because these proteins are encoded by genes, we're basically looking indirectly at the genetics of cancer cells. We can also look for specific mutations associated with the development and progression of cancer."

Knowing exactly what genes are active in a patient's particular cancer could improve diagnosis and treatment of the disease. In addition the technology might identify new patterns or combinations of gene expression that occur early in the disease process.

"Today, pathology labs can perform one test at a time, and the results are often interpreted subjectively based on individual pathologists' experience," Dr. Garner said. "We can look at 10 biomarkers at a time on one cell, and if we do that multiple times, we can examine 20 or 30 or 40 markers per cell. That information goes directly into an intelligent database."

With this tool, pathologists can compare their patient's sample with every other sample in the database.

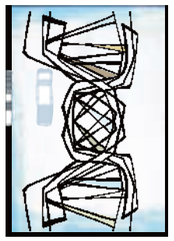
"All those samples can be linked to patient diagnosis, treatments and outcomes. When the database pulls up a sample similar to the one the pathologist is looking at, he'll have a better idea of what he's dealing with and how to proceed, based on actual clinical outcomes of similar patients," said Dr. Garner, who holds the Philip O'Bryan Montgomery Jr., M.D., Distinguished Chair in Developmental Biology.

Dr. Uhr said he is very optimistic about a new project in which he and Dr. Garner are attempting to use the hyperspectral imaging microscope in conjunction with capturing circulating cancer cells (CTCs). The pair is working with a nanotechnology research group at UT Austin to develop a microchip device that will not only capture CTCs with far greater sensitivity than the commercial instrument, but also will analyze the cells with a hyperspectral imaging device.

"CTCs in the blood are present early in the life history of a tumor," Dr. Uhr explained. "When we find a cell in the blood that is a cancer cell, all these tumor markers can be evaluated on the basis of a simple blood test by an automated instrument in a clinical pathology lab. That sounds like a wild dream, but it really is not. It's based on very solid preliminary data that we have obtained from this microscope combined with the microchip device.

"I can't think of a more exciting development than the use of this telescope-turned-microscope for detecting cancer early, because early detection should translate into a higher cure rate."

Dr. Uhr's enthusiasm for his work translates into an urgency that perhaps all biomedical researchers share – a hopefulness that one day their laboratory work ultimately will benefit the patient. Even as new technologies and techniques continue to transform the practice of medicine at an accelerating rate, it is the patient's own genes – and the UT Southwestern researchers who study them – that continue to revolutionize approaches to combating disease.✳



"I can't think of a more exciting development than the use of this telescope-turned-microscope for detecting cancer early, because early detection should translate into a higher cure rate."

– Dr. Jonathan Uhr

Chemical Attraction

By Aline McKenzie

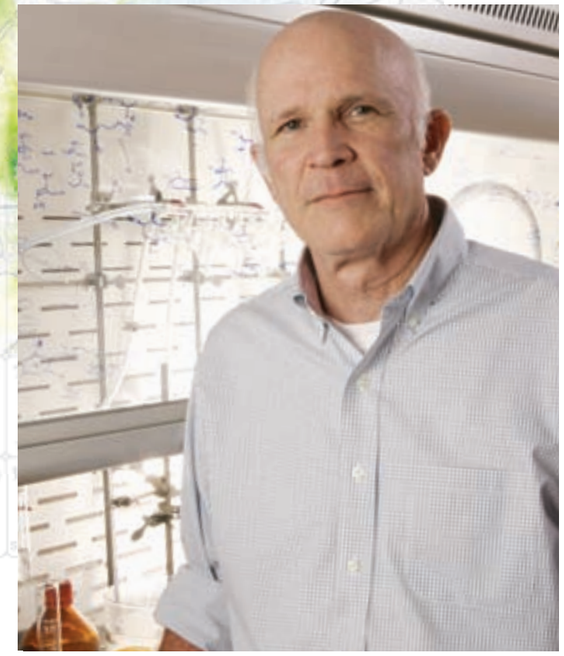
On the fourth floor of a building on UT Southwestern Medical Center's South Campus, a strange vinegary smell permeates the air. It's an odor found almost nowhere else at the medical center.

The acrid odor, caused by acid used in chemical reactions, stems from a unique program at UT Southwestern – full-time faculty chemists working side by side with biologists.

UT Southwestern was the first academic biomedical center to create a "pure" chemistry program, which focuses on analyzing, synthesizing and modifying molecules that might have promise for the future treatment of human diseases.

"It's unusual to have research capabilities in hard-core chemistry in a medical center, and yet I think the opportunity for chemistry to impact medicine is tremendous," said Dr. Steven McKnight, chairman of biochemistry and the driving force behind the program.

The difference between UT Southwestern and a more traditional chemistry department is that the chemical compounds discovered and studied here are prioritized for biological activity – one may show promise in killing cancer cells, another may be a potential antibiotic.



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>
> — Dr. Steven McKnight

In a traditional program, chemical reactions might be so exotic as to be studied only by mathematicians and physical chemists. At UT Southwestern, after a chemist's work is done, a biologist applies the discoveries to real-life situations.

Chemists and biologists work next door to each other, so exchanging ideas means walking a few yards. Sometimes a chemist discovers an interesting molecule from, say, a marine bacterium, and wants to know how it affects cells. Sometimes a biologist has an active molecule that doesn't dissolve well in water or is weak and needs to be modified so it's more usable or more potent.

"Without the chemists, it would be folly for us to pursue new drug leads," said Dr. McKnight, holder of the Distinguished Chair in Basic Biomedical Research and the Sam G. Winstead and F. Andrew Bell Distinguished Chair in Biochemistry. "It would never work.

"The chemists don't come here solely to give us additional ways of studying biology. They themselves have their own fields."

Dr. Alfred Gilman, executive vice president for academic affairs, provost, and dean of UT Southwestern Medical School, said, "Steven McKnight has been able to attract a group of really exciting young chemists who appreciate being here. It can be like being in a candy store, rather than being in a traditional department of chemistry.

"Putting chemists next door to biologists is particularly important," said Dr. Gilman, holder of the Nadine and Tom Craddick Distinguished Chair in Medical Science; the Atticus James Gill, M.D., Chair in Medical Science; and the Raymond Willie and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, in Honor of Harold B. Crasilneck, Ph.D.

"If they're not rubbing elbows, they don't have the opportunity to say, 'Hey, I can help you with that; I can see a way to do that,'" said Dr. Gilman, who also directs the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational and Systems Biology.

Dr. Jef De Brabander, one of the first chemists to join the program, said the communication and talent of the two groups of scientists was what appealed to him, as he made a risky career jump into an untried program 10 years ago. He is a professor of biochemistry and a member of the Harold C. Simmons Comprehensive Cancer Center.

"Dr. McKnight calls it bringing chemistry back into biochemistry," Dr. De Brabander said. "It comes down to how things function – that's a chemical problem."

Dr. De Brabander's work focuses on re-creating molecules found in marine sponges, soil bacteria and other species.

"Our passion is 'How do I make this?'" he said.

There are several reasons to try to synthesize a biologically active molecule, rather than just purify it from its source. Primarily, the original organism may be too rare or difficult to gather to provide enough of the compound.

This was the case of two molecules with possible actions against cancer and osteoporosis that Dr. De Brabander was studying. His laboratory was the first to create the molecules in the lab from scratch.

In addition to their rarity, one of the compounds came from animals in Antarctica called sea squirts. International treaties forbid harvesting for profit in Antarctica, so the compound *must* be created in the lab.

"You can take a sponge, grind it up, isolate the compounds, but then you have no more source," said Dr. Chuo Chen, assistant professor of biochemistry, who works primarily with marine organisms.

The researchers' interest in the sea squirts was rooted in previous work on a compound from sponges that killed cancer cells. Biologists from UT Southwestern found that the substance acted on a molecule that pumps protons out of solid tumors, presumably to prevent them from building up acid. Unfortunately, the compound from sponges proved to have toxic side effects in the brain.

The compound from the sea squirts acts on the same pump, but so far, no side effects have been noted.

"We know now we have a new lead," Dr. De Brabander said. "We were working with some of the best biologists around to see how it really functioned. You can only do that if there's really a back-and-forth of people addressing problems together."

Dr. Omid Soltani, now a chemist at a pharmaceutical company, was one of the first graduate students to join the program. Having grown up in the Dallas-Fort Worth area, he was familiar with UT Southwestern and was eager to join the new program.

"I knew the quality of the research in general at UT Southwestern was quite high, so if chemistry was going to be done, it was going to be quite high as well," Dr. Soltani said. "Knowing this, I didn't feel it was a great risk joining a nontraditional chemistry program."

> Being able to walk down the hall and talk to someone is different than at other universities.
>
> — Dr. Jennifer Kohler

Dr. Soltani worked several years to synthesize a compound found in yeast. Then, working with researchers in internal medicine, physiology and cell biology, he was able to study its properties as a carrier of protons and metal ions and as a promotor of cholesterol uptake.

Working in a brand-new program "was very intense and fast-paced," he said. "We wanted to make our presence felt among chemistry researchers elsewhere and to establish ourselves as excellent students within UT Southwestern."

Dr. Jennifer Kohler, assistant professor of internal medicine and biochemistry, studies how carbohydrates on cell surfaces interact during immune reactions and other processes.

These interactions are fleeting and chemically weak, so her work involves variations of the molecules that can lock onto each other, so the researchers can then analyze them.

But while she understands and can make the variations needed, the biology requires input – where exactly in the cell are these molecules? What controls the molecules to which the cell binds?

"Being able to walk down the hall and talk to someone is different than at other universities," Dr. Kohler said. "We don't know all the biology techniques."

The collaboration between the chemists and the biologists allows them to take two different approaches, Dr. McKnight said.

> Dr. McKnight calls it bringing chemistry back into biochemistry. It comes down to how things function – that's a chemical problem.
>
> — Dr. Jef De Brabander

> Novel bacteria will yield novel molecules. That's when the chemistry begins. We have to determine the structure of these molecules – that's what we spend our time doing.
>
> — Dr. John MacMillan

53

In some cases, the researchers already know what cell system they're interested in – for example, they might want to look for compounds that affect the brain receptors involved in sleep. A chemist might help them develop variations of existing compounds in this case.

Several times, UT Southwestern chemists have studied a compound whose structure was believed to have been known and found that previous reports had been incorrect. Correcting this information provides a base for better chemistry and modification of the compounds.

In other situations, the scientists might take a novel compound, perhaps harvested from marine bacteria, and find what cellular process it affects, Dr. McKnight said.

"At the outset of almost every project, we don't know how the compound's working," he said. "It's a black box.

"Very rarely, a compound could be medically useful," Dr. McKnight said, but that's not the department's only goal. Several current and former faculty members have, however, formed companies to further develop compounds they've created. In some instances, department members have formed associations with companies to carry out complex, expensive clinical trials that are beyond the reach of the Department of Biochemistry.

Dr. John MacMillan, assistant professor of biochemistry and the Chilton/Bell Scholar in Biochemistry Research points out that studying compounds made naturally by living organisms follows a centuries-old tradition. Many folk cures, some of which led to modern treatments, came from plants. In addition, bacteria or molds have proven a reliable source of many antibiotics, such as penicillin.

"Scientists would go out and collect dirt to find new organisms to study," he said.

Now he continues that tradition, except he goes out to sea to hunt organisms.

"Until recently, the microbial environment of the ocean was not well understood," Dr. MacMillan said. "We can now collect sediments in a biologically friendly way. There's no reason to think that microbial natural products won't continue to play a role in antibiotic development.

"Novel bacteria will yield novel molecules. That's when the chemistry begins. We have to determine the structure of these molecules – that's what we spend our time doing."

Once a year Dr. MacMillan goes out on a research vessel funded by the National Science Foundation, which carries 27 researchers from a variety of fields and from 10 nations.

He uses a device called a "mud missile," which can go down 3,000 meters and collect sediment using remote-controlled jaws. A plain electric fishing reel then pulls it up.

Once back at the lab, part of his work is figuring out how to keep the bacteria alive in culture – a very different thing than culturing bacteria that live on the land. "So far, we've been pretty lucky," he said.

Dr. McKnight said, "John is like an oil prospector. He goes out; he collects all these samples. He comes back here to UT Southwestern; he cultures them. He extracts; he looks for a new activity that perhaps might be a new molecule that would stop bacteria from growing. It might be an antibiotic, or it might be a new molecule that would stop cancer cells from growing."

Part of the chemist's work is to find ways to make biologically active compounds easier to make. It's one thing to make one-half milligram of something, using expensive ingredients and possibly risky steps.

"It's another thing to try to make it in bulk quantities," Dr. De Brabander said. The chemists sometimes must find a new way to synthesize the compound using less expensive and more environmentally friendly ingredients, perhaps even discovering a way that uses far fewer steps.

"We call that 'more elegant,'" he said.

Dr. McKnight said, "If you have a very complex molecule, it's not trivial to say, 'How do I put this together from its basic components?' It might take 20 or 30 or 40 steps.

"The foundation of being able to use chemistry at UT Southwestern rests on having world-class chemists on our faculty."

Several core support programs work with both chemists and biologists on campus: the Small Molecule Library, the High Throughput Screening System and the Synthetic Chemistry Core Facility.

The Small Molecule Library consists of more than 200,000 commercially available compounds, carefully selected for their possible biological actions.

Researchers can select which ones they'd like to test in an experiment, or all 200,000 compounds can be tested, using the technique of High Throughput Screening (HTS).

In a typical HTS experiment, cells are put into each of 384 small wells in a plate, and an automated system delivers a single compound to each well. The system can then look for signs of a reaction between a compound and a cell, such as the activation of a green fluorescent molecule implanted in the cells.

"Experiments can be as specialized as detecting a change in a single molecule, or as general as a change in a cell's behavior," said Dr. Michael Roth, professor of biochemistry and head of the High Throughput Screening System. Once the screen is completed, chemists then step in, because typically the compounds found in the screen are not active enough.

> These small molecules may become the first-ever drugs specifically designed to enhance the human heart's natural repair mechanism, helping the heart rebuild muscle after a heart attack.
>
> — Dr. Jay Schneider, with Dr. Jenny Hsieh

> Experiments can be as specialized as detecting a change in a single molecule, or as general as a change in a cell's behavior.
>
> — Dr. Michael Roth

Sometimes an initial screening of the full 200,000-compound library can be narrowed down quickly to just a handful of compounds to pursue for further study.

The Synthetic Chemistry Core Facility assists other researchers in creating variations of promising lead compounds that have shown biological activity.

The facility also provides researchers at UT Southwestern with the latest in synthetic, medicinal and analytical chemistry as an in-house service that is unique among medical centers in the United States, Dr. McKnight said. This service means that researchers can work where biology and chemistry intersect without having to outsource.

Continued on page 52

Chemical Attraction

Continued from page 23

Collaborations already have been established with researchers from internal medicine, cardiology and developmental biology.

The researchers can also draw on a device called a LC-SPE-NMR, a mouthful but one that combines three types of analytical methods – liquid chromatography, solid phase extraction, and nuclear magnetic resonance – into one device, providing a powerful tool for unraveling the structure of a molecule. UT Southwestern is one of only two U.S. universities that have this device, Dr. MacMillan said. "It's going to be extremely powerful for us."

Dr. Jenny Hsieh, assistant professor of molecular biology and in the Cecil H. and Ida Green Center for Reproductive Biology Sciences, was an early beneficiary of the core resources available at UT Southwestern. She and Dr. Jay Schneider, assistant professor of internal medicine, found by accident that a substance called isoxazole-9 nudged immature stem cells into becoming more mature nerve cells. This discovery came as they were looking for compounds that would prompt stem cells into becoming heart cells.

"Isoxazole small molecules were safe and well tolerated by mice and have great potential as drugs for humans," Dr. Schneider said. "These small molecules may become the first-ever drugs specifically designed to enhance the human heart's natural repair mechanism, helping the heart rebuild muscle after a heart attack.

"This is very exciting, and chemistry was the key."

Dr. Hsieh said the chemists were fully engaged from the start.

"If certain molecules were more potent in triggering neurogenesis [creation of nerve cells], the chemists would use it as a guide to make further modifications and additional variations," she said. "They'd make 10 molecules at a time. It would take us two weeks to test them; then we'd meet again."

Isoxazole-9 was not the original compound that triggered their interest. Instead, it's a variation that is more potent and dissolves more easily in water.

> The real hope and dream is that it will lead to candidates for therapeutic compounds, going beyond the initial step of getting hits in high-throughput screening that show preliminary effects on a cell.
>
> — Dr. Alfred Gilman

In the original study, Dr. Schneider and his colleagues screened hundreds of thousands of molecules to see whether any could transform pluripotent embryonic stem cells into a form resembling immature heart cells. Again, the original promising molecules were modified into more active and useful forms.

When the researchers implanted blood stem cells activated by this compound into injured rodent hearts, the cells took root and improved the animals' heart function.

"This is exactly what this program is designed to do," Dr. Gilman said. "The real hope and dream is that it will lead to candidates for therapeutic compounds, going beyond the initial step of getting hits in high-throughput screening that show preliminary effects on a cell." ✳

Transplanting Success:

UT Southwestern's programs make it among the most comprehensive centers in the nation.

"IT WAS VERY SCARY looking death in its eyes, but I am still alive by the grace of God, prayers from many, and a staff that I would put up against any in the world. I can now look forward to seeing as many sunrises and sunsets as I wish. I can look forward to spending many years with the woman I love, my brothers and sisters, and the greatest parents in the world as well as my children." — *KEN KLEINMAN, A FEW WEEKS AFTER A KIDNEY-LIVER TRANSPLANT AT UT SOUTHWESTERN UNIVERSITY HOSPITAL*

By Russell Rian

There are no ordinary stories among transplant recipients, just a common thread.

Each has a poignant tale of facing death. Each year, they celebrate living. Among them are:

› A brother and sister who cast away sibling rivalries to become recipient and donor;

› A mother's college roommate who stepped forward to donate an organ for her friend's baby;

› A chef who could no longer stand long enough to cook who's now anxiously waiting to get back to his kitchen;

› A man in need of a double transplant and repeatedly told illness of one organ disqualified him for transplant of the other; and

› Two who share the lungs of a teen they'll never meet and who are gratefully honoring the youth by travels never before taken and by snuggling with their grandchildren.

Each is part of a close-knit family in the nationally recognized solid organ transplant programs at UT Southwestern, encompassing livers, kidneys, pancreases, hearts and lungs.

"I was within days of death. My family was thinking, 'Would he look better in a pinstripe or solid suit?' It was grim."

—Ken Kleinman, patient

"Chronic illness takes a toll on people emotionally," said April Morgan, a social worker with the program. "Typically our patients had fulfilling careers, hobbies and other pursuits prior to transplant, and their chronic illnesses have derailed them from being able to experience these things to their fullest. After a transplant, we are able to see patients return to their jobs, spend more time with their families and resume the lives they had previously built for themselves. It is a wonderful experience to be able to provide them with relief of those stressors and see patients enjoying the things most of us take for granted."

Mr. Kleinman explains the toll it took on him this way: "I was within days of death. My family was thinking, 'Would he look better in a pinstripe or solid suit?' There was a cemetery that I wanted to be buried in, and my mom was working on trying to secure a lot there. It was grim. I was staring death in its face. I always thought I would be a lot stronger. But nope. You get death right in front of you, it's a mind trip."

Laying new groundwork

UT Southwestern's transplant doctors and their team are working in innovative ways to improve the chances of everyone who needs a transplant.

New among this year's family of survivors are nearly two dozen liver transplant patients and several multi-organ liver-kidney transplant patients, including Mr. Kleinman, thanks to the addition of liver transplants to UT Southwestern's established transplant services.

Already renowned for its Heart and Lung Transplant Program, UT Southwestern recently took another step for its patients and created a Division of Surgical Transplantation.

Dr. Juan Arenas, a highly respected multi-organ transplant surgeon, was recruited from the University of Michigan and Henry Ford Hospital to be chief of the new division and surgical director of the liver transplant program at UT Southwestern.

He specializes in living-donor liver transplantation, laparoscopic liver surgery, donation after cardiac death and extracorporeal circulatory support.

Dr. Arenas, in turn, recruited surgeons from established programs around the nation. He now has forged a 12-member team of top physicians from surgery, nephrology and hepatology to evaluate and track patients.

"I think what attracted me and others who have joined this program is the ability to consolidate all that expertise and knowledge and translate it into clinical outcomes for real patients," said Dr. Meelie DebRoy, assistant professor of surgery and surgical director for kidney transplants.

In addition, the team can tap into the medical center's gold mine of resources in other fields such as oncology, radiology, pathology, endocrinology, psychiatry, rehabilitation or ophthalmology for added support to handle the wide variety of potential issues that can arise in transplantation care.

"The key competence of the UT Southwestern program has really been the support we've received from the university in establishing that multidisciplinary approach," Dr. DebRoy said. "The multidisciplinary approach is key to the success of any transplant program. A lot of programs that have not been successful have really tried to follow the surgeon-heavy or medicine-heavy approach. Until there's an equal representation and equal buy-in to the process, it's very difficult to establish success."

This approach is convenient for physicians and patients alike because doctors are able to consult at will about issues that may arise, and it minimizes the number of appointments that patients, who are often extremely ill, have to attend.

"These patients see almost the entire gamut of clinical services, so transplant patients generate a lot of internal consultation and clinical service," Dr. Arenas said.

The program covers the comprehensive ongoing medical management and care needed for patients awaiting a transplant as well as the post-care and follow-up for those who have received one. In addition, inside its laboratories, UT Southwestern physicians test for the proper match and continue to evaluate what factors are at play when a transplanted organ is rejected.

The comprehensive philosophy of the program is not limited to just transplantation surgery.

"We strive to provide each of our patients with a personalized approach to treatment," said Landon Ware, administrative director of the kidney-liver-pancreas program.

UT Southwestern staffs its transplantation team with specially trained nurses for care; financial coordinators to help patients navigate insurance and find assistance; social workers who focus on patients' emotional, social and psychological well-being; and clinical coordinators to make sure it all runs smoothly and everyone is communicating with one another. Services range from pharmacists to explain the medication routines to nutritionists who assist with dietary decisions.

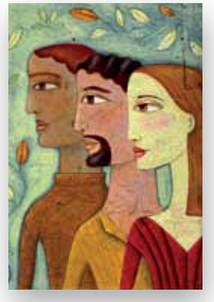
In all, some 50 people tackle the whirlwind of issues swirling about UT Southwestern's transplant recipients.

Ms. Morgan, the transplant social worker, said each patient receives a thorough evaluation to screen for any psychosocial contraindications to transplant surgery and to ensure that the patients have the necessary support and resources available to help them through the transplant process, including emotional support and crisis intervention for patients and families struggling to cope. The staff helps identify community resources and charitable organizations that can benefit the patients as well as alternative funding sources.

"A transplant social worker's primary focus is the patient's emotional, social and psychological well-being," Ms. Morgan said. "Everyone who works in this division does so for the gratification of seeing people improve their quality of life through a transplant."

UT Southwestern also has a mentor program to connect past and upcoming recipients, and a support group to meet the emotional needs of the patients. Housing resources are available through the Guest House for patients and their families from out of the area.

"The hospital helps you with everything from day one," said Greg Sommers, 46, who received a dual kidney-liver transplant in May 2008. "I



"I think what attracted me and others who have joined this program is the ability to consolidate all that expertise and knowledge and translate it into clinical outcomes for real patients."

—Dr. Meelie DebRoy

didn't have health insurance, and they walked me through that. Afterward, they gave me a list of contacts that help people like me. And they helped me retain my benefits, so I don't lose the care I'm getting when I get a job.

"As far as the medication to make sure the body is not rejecting it, they keep on top of it. You go in, and they take blood and make adjustments. They stay on top of all of it. They are just great."

Matchmaking goes high-tech

Behind the scenes, UT Southwestern's Division of Transplant Immunology is contributing its own expertise to the process.

The division, under the direction of Dr. Peter Stastny, provides round-the-clock service to match compatible organs and tissue and to flag potential diseases, all done through high-resolution human leukocyte antigen (HLA) matching and gene sequencing.

HLAs are proteins that the body uses to flag cells that don't belong. A close match reduces the risk of a recipient's immune cells attacking the new organ.

Well-matched transplants do better, require less immunosuppressive treatment and are less likely to become sensitized and develop antibodies against HLA.

Not all organs must be matched exactly. Identical blood types are the only absolute requirement for liver transplants. Even organs that don't require detailed matching still require some testing to ensure they are accepted by the recipient's immune system.

The division does testing not only for UT Southwestern University Hospital, but also for Parkland Memorial Hospital, Children's Medical Center Dallas and the Dallas Veterans Affairs Medical Center, along with a cooperative transplant program in El Paso.

The number of transplants from all the hospitals has more than doubled since 2004 and now exceeds 150 per year.

"The bottom line is that the data suggest that failure of otherwise well-matched kidneys may be caused by these antibodies."

—Dr. Peter Stastny

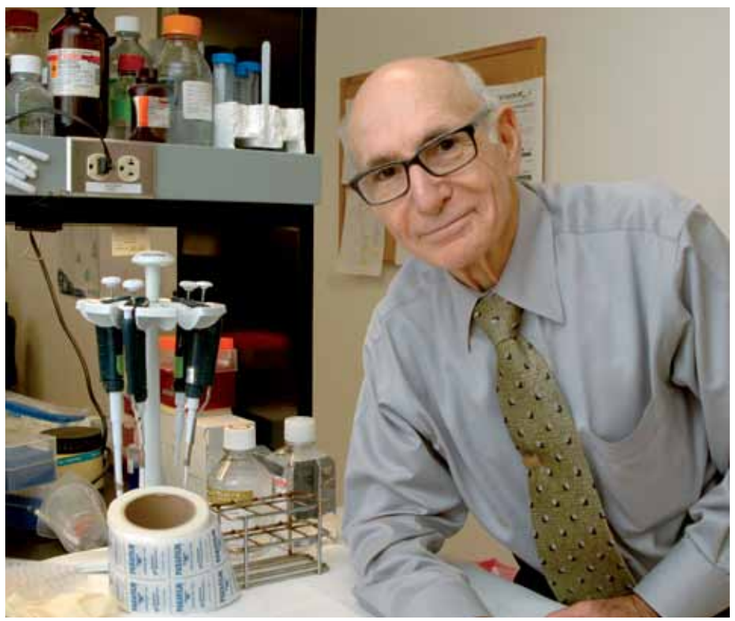
In addition to the tried-and-true methods, the lab is advancing beyond conventional testing with new methods that may allow researchers to predict whether a recipient will develop antibodies rejecting the transplant, said Dr. Stastny.

The division has been breaking new ground on the basic science front as well. Most recently, Dr. Stastny, collaborating with colleagues in Germany, for the first time identified antibodies associated with transplant rejection of otherwise healthy kidneys, research that appeared in *The New England Journal of Medicine*.

For years physicians have been perplexed as to why some seemingly well-matched kidneys were still rejected, and the research turned up a likely culprit – antibodies that aren't targeted by current testing methods.

"The bottom line is that the data suggest that failure of otherwise well-matched kidneys may be caused by these antibodies," Dr. Stastny said.

More research will be needed to show whether this is the sole cause, but the results offer critical direction in finding new explanations of why good transplants go bad and discovering potential new avenues for screening to prevent rejection of transplanted kidneys.



Transplant – a growing need

According to statistics from the Organ Procurement and Transplantation Network, the number of transplants nationally has increased about 11 percent since 2003, and deaths while waiting for a transplant organ have declined each year. Texas ranks third among states in the number of transplants performed. Texas surgeons performed more than 31,000 operations, accounting for about 7 percent of the national total of more than 440,000 transplants since 1988, when results were first tallied.

The waiting list for those in need of an organ, however, surpassed 100,000 for the first time in October 2008.

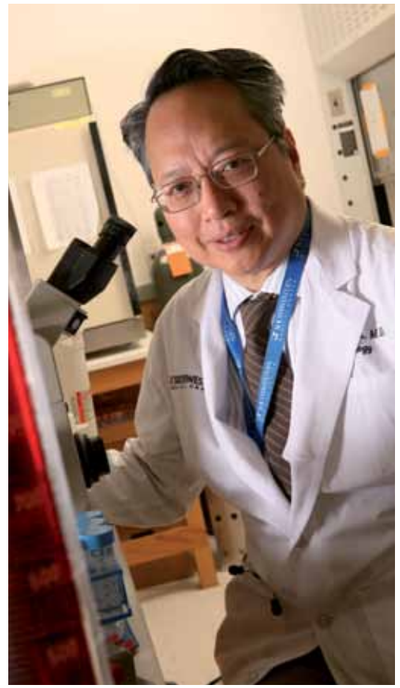
In 2007 there were 28,358 transplants for all organs, nearly 600 fewer than in 2006, and some 6,700 people died awaiting a transplant.

Patients awaiting kidneys and livers account for about 95 percent of everyone on waiting lists. Nearly three-quarters of those waiting for a transplant need a kidney, and about 16 percent need a liver. A pancreas is most often transplanted with a kidney, but pancreases still account for less than 2 percent of the need. Those waiting for hearts and/or lungs account for about 5 percent.

Demand for transplanted organs is not likely to diminish. Because kidney and liver diseases are associated with the growing obesity epidemic, the need for these organs is almost certain to rise.

Kidney-failure successes

"You can lose probably half, maybe two-thirds, of your kidney function and not know it, so it's very sneaky and insidious," said Dr. Christopher Lu, medical director of the kidney transplant service at UT Southwestern and the 2008 president of the Texas Transplantation Society. "The only way to know is to get a checkup and get your blood pressure checked."



"You can lose probably half, maybe two-thirds, of your kidney function and not know it, so it's very sneaky and insidious."

—Dr. Christopher Lu

Kidneys, which come in pairs, are located below the diaphragm, on either side of the spine. They remove wastes from the body, which are excreted as urine. They also help regulate blood pressure, blood volume and chemicals in the blood.

Kidney disease often progresses slowly from an asymptomatic stage, when patients feel well and do not know their kidneys are sick, to a stage when the damaged kidney causes high blood pressure, which produces swelling, difficulty breathing and heart failure. Finally, the kidneys fail completely. At or before that final stage, patients may be treated with dialysis, which involves cleansing the blood by running it through a machine. Or, there may be a need to perform a kidney transplant. Transplants can involve one or two kidneys, but usually involve only one. The donor can be living or deceased.

"We have a large number of patients who require either dialysis or transplant to sustain life," said Dr. Lu, professor of internal medicine. "The number is growing rapidly because the most common causes of kidney disease are diabetes and hypertension. So as we have more and more people with metabolic syndrome, or obesity, who often have complications, we have more and more patients with end-stage renal disease."

Kidney transplantation is the best treatment for many patients with end-stage renal disease. Transplants are performed on only a small percentage of patients whose kidneys fail, largely because of a shortage of organs. In addition, for some patients, the risk of transplant surgery is very high due to their severe heart disease or other medical conditions. These high-risk patients, said Dr. Lu, often can survive well on dialysis if they are not suitable candidates for transplants.

"What most people don't know is that kidney patients on dialysis spend three to five hours, three times a week in dialysis. The ability to lift that burden through transplant is awesome," said social worker Ms. Morgan.

Dr. Lu said people do live longer with a kidney transplant, "but the caveats are you have to be a good candidate for surgery, and you have to comply with your medication. It's important for people to understand that there is a choice. For most patients, if you don't get a transplant today or tomorrow or next month, then you can live on dialysis, and life can be quite good."

UT Southwestern is widely recognized as one of the nation's leading clinical and research centers for treating all stages of kidney disease. The nephrology division, which treats kidney disease and is listed among the top programs in the country by *U.S. News & World Report*, has been instrumental in developing some of the leading tests, treatments and research into kidney disease. UT Southwestern nephrologists have led and participated in research initiatives funded by the National Institutes of Health and other prominent organizations. These initiatives have led to the creation of reliable diagnostic tests to determine a person's risk for developing kidney stones, development of the world's most prescribed medication to treat kidney stones and development of better methods of hemodialysis.

UT Southwestern's top-tier kidney care and experience flows into the transplant arena as well. The program was among the first to use anti-lymphocyte antibodies to prevent and treat rejection, calcium channel blockers to improve early function of a kidney transplant, and molecular biology to match kidneys with patients more successfully.

UT Southwestern's transplant surgeons have performed more than 1,700 kidney transplants since performing the first kidney transplant in Texas in the 1960s. More than 60 pancreas transplants have been done since that program started in 1989.

"Most people think of cirrhosis as being from alcohol, but there are at least 10 to 15 or more causes that are genetic or autoimmune, and all kinds of liver disease can progress to cirrhosis."

—Dr. Anne Larson

Boosting liver transplants

"Most people think of cirrhosis as being a result of alcohol, but there are more than a dozen causes that are genetic or autoimmune. All kinds of liver disease can progress to cirrhosis. Eventually, usually eight to 10 years after development of cirrhosis, the liver has lost enough of its cell mass that it starts to fail. It simply can't keep up with what the body needs it to do. That's when you need a liver transplant," said Dr. Anne Larson, associate professor of internal medicine and medical director of liver transplantation.

The liver is the body's largest organ and is positioned just below the diaphragm atop the stomach, right kidney and intestines. The liver's function is to separate nutrients from food and process carbohydrates, fats and proteins needed by the body. It also produces bile and helps clear toxins from the blood.

Transplanted livers are generally taken from deceased donors, although living donors can give portions of their liver in some cases.

The addition of a liver-transplant component completes UT Southwestern's comprehensive liver-care programs, considered some of the strongest in the country, Dr. Larson said. The medical center's collaborative approach incorporates gastroenterologists, hepatologists, radiologists, hepatobiliary surgeons and pathologists.

UT Southwestern physicians treat liver disease in conjunction with ongoing research programs, allowing them to offer patients the most advanced diagnostic evaluations and treatments available, including immunosuppressant medications, advanced procedures to treat portal hypertension and ascites (complications of cirrhosis), and chemoembolization, which delivers chemotherapy to cancerous liver tumors without exposing other parts of the body to the treatment.

UT Southwestern's addition to the select list of liver transplant programs, which also includes dual liver-kidney transplants, gives patients and referring physicians a valuable additional regional resource to which they may turn.

"If you look back over the past 10 years, the number of people on the wait list for livers has nearly doubled, but the number of transplant operations has remained fairly constant," said Mr. Ware, the program's administrative director. "So our program means more opportunity for these critical cases."

Currently, about 17,000 people are approved nationally for liver transplants and waiting for donated livers to become available, according to the American Liver Foundation. In 2008 5,273 liver transplants were performed in the U.S., while more than 1,200 patients died waiting for a donated liver.

UT Southwestern has now completed about two dozen liver transplants and a few dual liver-kidney transplants. Surgeons expect eventually to be able to perform around 60 such transplants annually.

"I was on dialysis for nearly 13 years before I came here, and they finally gave me a transplant. I got a kidney for my birthday and a liver for Christmas."

—Kevin Young, patient, with Dr. Juan Arenas

One man's story

Kevin Young first noticed something was wrong in 1996. The Kentucky resident began gaining weight quickly, though he hadn't changed his diet and wasn't overeating. Nor could he work it off.

"I was cramping up all the time. My blood pressure stayed high. So I knew it was something. And then they told me my kidney was going out. I thought they could just do an operation or something. I didn't know it was going to be life-changing. Turns out, I had a bad liver, too.

"At that time, they said my liver was not quite bad enough to get a new liver, but it was too bad for me to get a kidney, so I was stuck," Mr. Young said.

The medication that would have been needed to keep him from rejecting his kidney would have likely affected his liver, so he was placed on dialysis, unable to even get on the waiting list. While dialysis staved off kidney failure, his liver was getting progressively worse.

Mr. Young's liver and kidney problems seemed to be peaking just as Dr. Arenas arrived at UT Southwestern to launch the new program, a fortuitous opportunity for Mr. Young and for Dr. Arenas' blossoming new program.

"I was on dialysis for nearly 13 years before I came here, and they finally gave me a transplant," said Mr. Young, whose Dec. 6, 2007, operation coincided with his birthday. "I got a kidney for my birthday and a liver for Christmas."

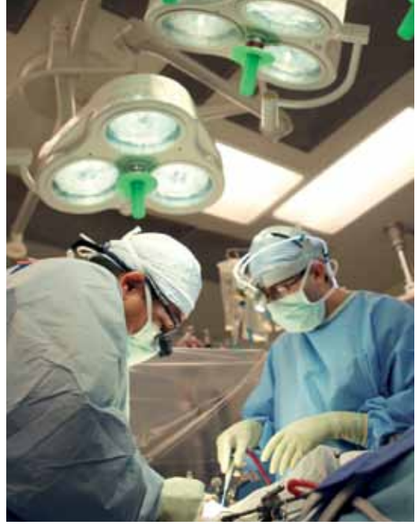
The future

The successful addition of liver transplants rounds out UT Southwestern's nationally recognized and repeatedly honored transplant program, which is among the most select and comprehensive in the nation with transplants for all major organs – heart, lung, kidney, pancreas and liver – along with bone marrow, corneas, skin and bone transplants. In addition, the medical center operates a regional tissue bank.

Dr. Arenas, who was recently named one of the top transplant surgeons in *D Magazine's Best Doctors Guide*, and his team continue to acquire honors for the program.

He performed the area's first robotically assisted kidney removal from a donor. Robotic laparoscopy offers more precision for surgeons and helps diminish recovery time for donors.

Dr. Juan Arenas, who was recently named one of the top transplant surgeons in D Magazine's Best Doctors Guide, and his team continue to acquire honors for the program.



Dr. Arenas, Dr. DebRoy and the team also performed the area's first liver transplant from a donor who died from heart disease. Most deceased donor transplants result from brain-death cases, so the addition of obtaining livers from donors after cardiac death can increase the supply of needed organs.

Improving organ donations is among the immediate goals and priorities of the division, which has already made notable strides toward this objective.

The program received the Department of Health and Human Services' Medal of Honor for Organ Donation for achieving and sustaining a donation rate of 75 percent or more of eligible donors. The Southwest Transplant Alliance also recently recognized UT Southwestern University Hospital for its donor rate.

UT Southwestern's program is a participant in the "daisy chain" for kidney donors, in which willing donors who don't match their friend or family member join the chain, offering their organ to another in the chain who is a match. The recently launched system has potential to further extend the reach and opportunities for those willing to make the sacrifice.

Eventually, physicians in the program hope to gain new insights on transplant longevity from tracking the progress of their patients through the various stages of care before, during and after transplantation.

In addition, transplant officials hope to extend their reach in Texas and beyond through cooperative transplant programs, particularly in areas where transplant surgery is not available, but pre- and postoperative care would be.

UT Southwestern has already paired with Sierra Medical Center Transplant Clinic in El Paso to provide kidney transplants to patients in that region, which currently has no facilities for performing transplants. Kidney transplant patients receive medical care by Sierra Medical Center nephrologists before and after transplant surgery, while UT Southwestern doctors perform the surgeries in Dallas. Officials hope to forge similar agreements with other outlying areas.

The future for the new transplant services means helping more patients facing disabling illnesses or even death, like Mr. Kleinman.

When Mr. Kleinman's health started to deteriorate about five years ago, he was able to treat the problems he faced with pharmaceuticals only briefly.

"I think my body just started to give up on the pharmaceuticals, and, at that point, everything went haywire," he said. It was quite a bumpy road. The days I felt halfway decent, I still couldn't get up and do anything. I couldn't make it up a flight of stairs because it felt like I was climbing a mountain."

Then it got worse.

At one point, he was hospitalized for 63 straight days, watching ambulances and helicopters come in daily, wondering whether one carried the organs he needed.

Then he received a transplant at UT Southwestern.

"For me to have a liver, somebody had to die. And that donor's family doesn't have that person any more. I have tremendous respect for that person, for their family and for what they were able to do for me. I could never begin to repay that," he said with tears in his eyes.

"I get to live my life. Since the surgery, these people have been angels that I can't even describe. It's been a miracle from day one.

"I think about it every day. I assure you that the sky is bluer; the moon is brighter; the grass is greener. It truly is." ✳

For more information about UT Southwestern's transplant program, please call 214-645-1919.

Tissues heal lives, restore sight & function

THE WORD "TRANSPLANT" usually conjures dramatic images of a struggle between life and death and the arduous wait for an organ that's a perfect match. › But solid organs aren't the only types of transplants saving and improving lives. Tissue transplants, performed more frequently than organ transplants, are quietly restoring the quality of life for thousands of people every day. › A tiny piece of corneal tissue can restore sight; a valve can jump start a heart; and a little more than a sliver of skin can heal the wounds of a burn victim. › At UT Southwestern, the Transplant Services Center has been providing second chances for patients for more than three decades.

By Connie Piloto

"Skin grafts may literally save lives. And other tissues that we provide – such as bones and corneas – enhance the quality of life caused by many illnesses and traumas for so many patients," said Ellen Heck, director of UT Southwestern's Transplant Services Center. "Tissue transplants are truly life-enhancing."

"Skin grafts may literally save lives. And other tissues that we provide – such as bones and corneas – enhance the quality of life caused by many illnesses and traumas for so many patients."
— ELLEN HECK

Organ transplants often get more attention because of the critical shortage compared to the great demand, but some tissues also are in short supply – including skin and corneas.

One of the differences between organ and tissue donation is that far more people are eligible to donate tissues than organs because tissues do not have to be collected immediately after a donors' death and can be harvested outside a hospital setting, Ms. Heck said.

Located in the northwest corner of the UT Southwestern campus, the Transplant Services Center procures, processes, stores and distributes tissue grafts for hospitals and physicians throughout Texas as well as across the nation.

In addition to skin, the center stores corneas, tendons for knee surgeries and heart valves, as well as bone grafts that include bone

processed into chips and paste for multiple orthopaedic surgeries.

Since its inception in 1972, the center has supplied more than 200,000 grafts for transplantation, including corneas, skin, musculoskeletal and cardiovascular valves and vessels. Today, the Transplant Services Center supplies tissues to more than 170 hospitals and surgery centers in North Texas.

"The tissue bank is essential for research and for patient care," said Dr. Dwight Cavanagh, associate dean for clinical affairs at UT Southwestern, vice chairman of ophthalmology and holder of the Dr. W. Maxwell Thomas Chair in Ophthalmology. "Our cornea bank does great work. We also provide bone for hundreds of orthopaedic procedures, and we preserve heart valves to be used for children with heart defects. Perhaps it's not as glamorous as a heart transplant, but what we're doing is allowing someone to get their sight back or to live through a major burn or to get their heart repaired. The work is critical."

"What we're doing is allowing someone to get their sight back or to live through a major burn or to get their heart repaired. The work is critical."

— DR. DWIGHT CAVANAGH

The Transplant Services Center, Dr. Cavanagh said, is a UT Southwestern success story, and many of the developments of tissue banking around the country were developed here first.

Initially created by renowned UT Southwestern burn specialist Dr. Charles Baxter as a repository for human skin at Parkland Memorial Hospital, the Transplant Services Center was founded when the skin bank and UT Southwestern were asked to provide services for the Lions Club Eye Bank in Dallas.

Considered one of the pioneering tissue banks in the country, the Transplant Services Center was for years the only civilian tissue bank supplying skin to treat burn patients in other states.

"In the modern care of a burn patient, the transplantation of skin, which we call homograft – or from another person – is vital," said Dr. Gary Purdue, professor of burn/trauma/critical care at UT Southwestern and a nationally recognized burn surgeon. "For small burns we don't use a lot of it, but for large burns it's absolutely necessary."

Dr. Purdue says that one of the advantages of being associated with the Transplant Services Center is the ability to access skin that has not been frozen previously, which has proved to provide better outcomes for patients.

"One of the most important factors in the survival of patients with big burns is the ability of a hospital or physician to have a cooperative relationship with a skin bank, in this case the Transplant Services Center," Dr. Purdue said.

Often, the Transplant Services Center is called upon to aid burn centers located outside the United States, although reserves are always kept to provide for local patients. And when a major disaster strikes, it is often the first to be contacted.

Hours after the Sept. 11, 2001, terrorist attack on the Pentagon, two Transplant Services Center employees drove across the country (because air traffic was suspended) to provide 70 square feet of skin for burn victims being treated at the Washington Hospital Burn Center.

More recently and closer to home, the center has supplied skin and other tissues to Brooke Army Medical Center in San Antonio for injured soldiers.

Tissue to heal a life

Firefighter Chase Frost, 22, who suffered burns over 60 percent of his body during a fire near Philadelphia in the summer of 2007, said human skin from donors saved his life.

The Colleyville resident was attending Widener University in Chester, Pa., while also working as a firefighter, when a roof collapsed as he and another firefighter were battling a blaze inside a row house.

Mr. Frost was eventually transferred to Parkland's burn unit in hopes that UT Southwestern burn specialists could save larger portions of his left arm and his right leg before amputation. He also wanted to be closer to his family while he recuperated.

Sitting on a table in the rehabilitation room at UT Southwestern University Hospital, Mr. Frost was learning how to use a prosthetic leg specifically designed for running, and practicing motions with his robotic hand.

"Doctors grafted artificial as well as human skin throughout most of my body. Had people not made skin donations, my wounds would have been exposed, and my risk for infection would have increased. Basically, I would not have survived."

— CHASE FROST

"Doctors grafted artificial as well as human skin throughout most of my body," said Mr. Frost, who today is planning to return to college, where he was seeking a nursing degree as an Army cadet. "Had people not made skin donations, my wounds would have been exposed, and my risk for infection would have increased. Basically, I would not have survived."

Regaining a life and giving back

For Barbara Daniels, the cornea transplants she received in both her eyes have allowed her to regain the life she once knew.

As her vision deteriorated, Mrs. Daniels, 75, struggled to accomplish her daily routine. She couldn't drive. An avid reader, she couldn't make out the letters on a page or work on a crossword or jigsaw puzzle.

Mrs. Daniels was a bit apprehensive about surgery, so she first only allowed doctors to perform a cornea transplant on her right eye. Then, she had a transplant on her left eye a year later.

Now, three years after surgery, Mrs. Daniels is ecstatic about the results. She enjoys doing artwork, crocheting and is reading – a lot.

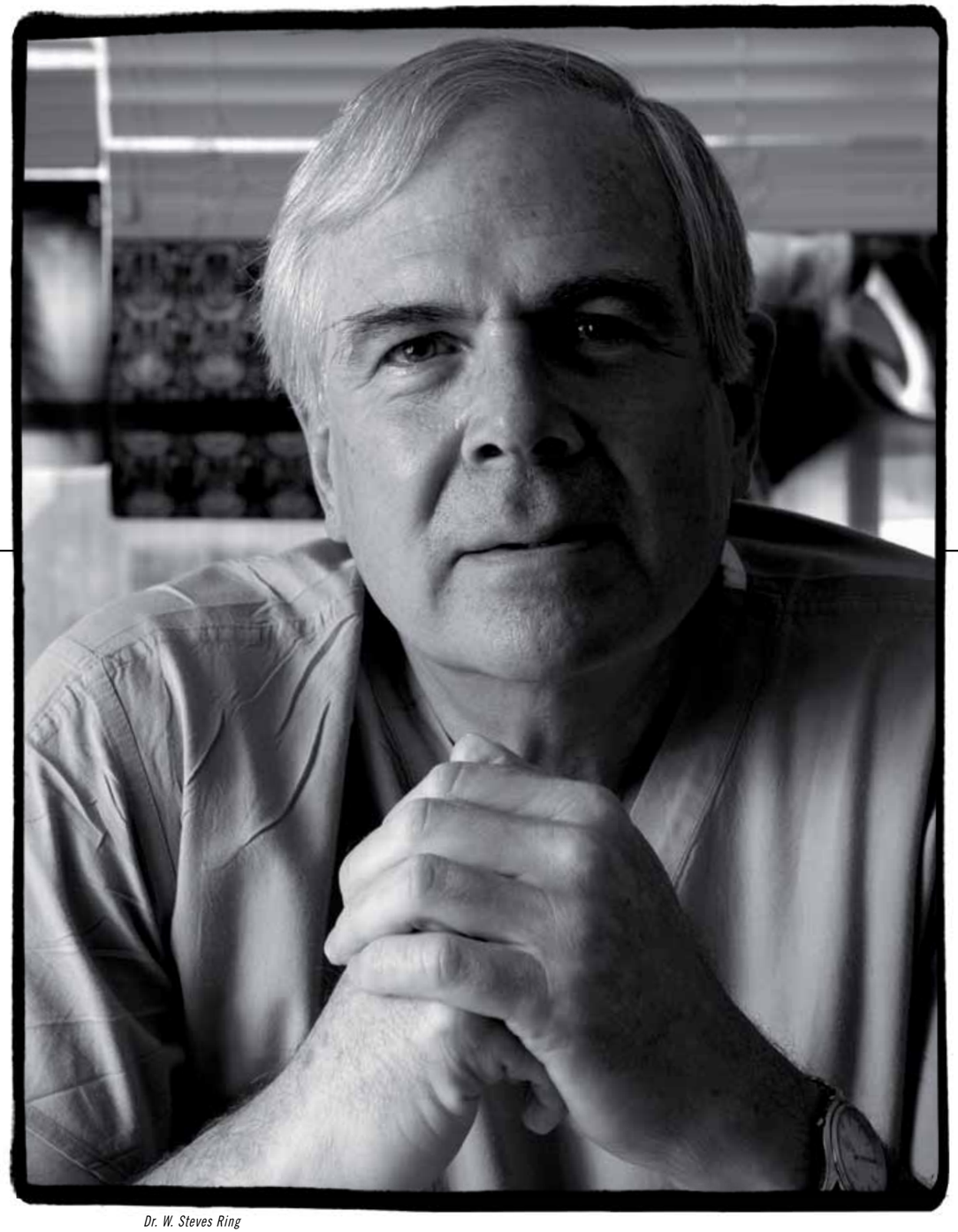
"My quality of life has improved tremendously," said Mrs. Daniels, who lives in Greenville and helps take care of her four grandchildren and one great-grandchild. "Everything I could do before I lost my sight, I can do now."

Mrs. Daniels and her family say they are thankful to the donors whose gifts allowed her sight to be restored. Recently, they did their part to repay those gifts.

When Mrs. Daniels' son-in-law, Ron Helvey, was killed in an accident, his family donated his organs and tissues.

"He had been with me through both eye surgeries," said Mrs. Daniels, who called it "his way of giving back." ✳

For more information about tissue donation, contact the Transplant Services Center at 214-648-2609.



1988

Dr. W. Steves Ring

2008

20 Years of Heart Transplants

In 1988 area newspapers and radio and television stations heralded the arrival of a new doctor in town. > Dallas-Fort Worth, then with a population approaching 2 million, seemed a conspicuously large metropolitan area to have so much press dedicated to the arrival of a single physician. > But this particular physician brought with him the promise of something Dallas had never had locally, or even regionally. Dr. William Steves Ring, one of the nation's most active heart transplant surgeons, made the momentous decision to accept a post at UT Southwestern Medical Center with the goal of building a world-class heart transplant program from the ground up. >

By Katherine Morales

Prior to his arrival,

Dallas had yet to harness the needed talent or experience necessary to make it a major transplant center the way other cities such as Houston had. Dr. Ring had directed the heart transplant program at the University of Minnesota from 1984 to 1987, where he performed more than 100 heart transplants in that three-year period.

His goal, he said, was to move Dallas out of the shadow of Houston and establish a major referral center for heart transplantation. Not only would his team treat patients at UT Southwestern University Hospital (at that time known as St. Paul Medical Center), he also would oversee transplants for patients at Parkland Memorial Hospital, the Dallas Veterans Affairs Medical Center, Children's Medical Center Dallas, and Baylor University Medical Center.

Dr. Ring said he saw it as an opportunity not only to develop the transplant component, but also to establish a comprehensive program for cardiovascular and thoracic surgery.

"I wanted to help put UT Southwestern's program on the map," said Dr. Ring, who holds the Frank M. Ryburn Jr. Distinguished Chair in Cardiothoracic Surgery and Transplantation.

In the first few months of Dr. Ring's tenure at UT Southwestern, he performed two high-profile surgeries. The first was a pediatric heart transplant – the first to be completed in Dallas. The second was an adult heart transplant on A.C. Greene, a prominent Dallas author and historian.

The program marked its 20th anniversary in April 2008 and is nationally recognized as having one of the best post-transplant survival rates in the country, according to the United Network for Organ Sharing.

The UT Southwestern Heart Transplant Program remains the leader in Texas in terms of survival, with one-, five-, and 10-year survival rates for adults at 92 percent, 81 percent and 68 percent, respectively, for adult heart transplant recipients compared to the national averages of 85 percent, 70 percent and 47 percent.

Since 1988, Dr. Ring and his team have performed more than 700 heart transplants and more than 375 lung transplants.

The volume and success, he said, began with the initial enthusiasm and support from the administration, including former UT Southwestern President Dr. Kern Wildenthal and former dean of UT Southwestern Medical School, Dr. William Neaves. Another critical component of the program's success, Dr. Ring said, is the talent of the physicians and staff.

"One thing that has been notable about our program is its consistency and the longevity of our faculty," Dr. Ring said. "Many of our doctors have been here for 18 years or more."

All, he said, are dedicated to working in the unique world of academic medicine, where the workload encompasses not only patient care, but teaching and research.

"The rewards of the job are seeing the enormous impact you have on people's lives," Dr. Ring said. "Some are on ventilators, unable to have a decent quality of life, and after transplantation, they can do almost anything they want."

Defying expectations

Tommy Jones, 49, experienced the profound change unique to transplant patients following a lifetime of illness. A native of Dallas, Mr. Jones said he never knew a time when he wasn't sick. He was born with a heart defect called transposition of the great vessels, where the two major vessels that carry blood away from the heart – the aorta and the pulmonary artery – are switched. As a result, too little oxygen in the blood gets from the heart to the rest of the body.

"Doctors told my parents I'd only live to be about 12 or 13," Mr. Jones said.

But he defied their expectations. At 18, he was only 5 feet tall and 90 pounds, and his health was declining. He had a hole in his heart that needed to be repaired if he was going to survive. He went to Alabama for the surgery and in a short period of time, he grew nearly a foot and gained 90 pounds.

"I finally felt a little better and tried to get on with my life," he said.

But his health problems continued to plague him, and, at 36, he was diagnosed with congestive heart failure.

"My doctor at the time was at another hospital, and he knew I was in bad shape so he suggested I try to get in and see Dr. Ring," Mr. Jones said.

By 1996, he knew that a heart transplant was likely, and by 2007, he was so sick that he spent the entire year in UT Southwestern University Hospital.

"That year, we celebrated all of our birthdays – my wife's, my kids, and mine – in the hospital," he said. "We had Thanksgiving there, too. At that point it was getting really bad, and my doctors kept saying they hoped a heart would come in."

By the end of 2007, he was too weak and far too sick to even get out of bed. Finally, the news he'd been waiting for arrived. The doctors had found a good match for Mr. Jones, and he would be transplanted that day.

"It was the best news I'd ever heard," he said. The surgery went well, although he suffered from a variety of post-surgery ailments. He continued to work at regaining his strength and within a few weeks, Mr. Jones returned home to Red Oak. In November 2008, he celebrated the one-year anniversary of his heart transplant.

"I've never had a life like this," Mr. Jones said. "I never knew I could feel this healthy."

Mastering a formative specialty

With the success of the heart transplant program at UT Southwestern in the late 1980s and early 1990s, another critical element was added in 1991 – the lung transplant program. The first successful single-lung transplant in the world had only been performed eight years before at Toronto General Hospital.

Dr. Randall Rosenblatt, a specialist in pulmonary disease, began his career at UT Southwestern as an intern in internal medicine, and he completed his training as a fellow in pulmonary disease. Now professor of internal medicine and director of the lung transplant program, he was very enthusiastic about heading up this new initiative and working with Dr. Ring.

"Initially, there were major challenges in developing the lung component of the transplant program. It was a relatively new therapy for patients with terminal lung disease and only a few centers were actually performing lung transplants at that time," Dr. Rosenblatt said. "We were fortunate, however, to have very bright, enthusiastic and knowledgeable people who shared a common goal of developing a program with excellent results. Furthermore, we wanted our clinical program to match the high standards set by the research programs at UT Southwestern."

> "I've never had a life like this. I never knew I could feel this healthy."
>
> —Tommy Jones, heart transplant recipient

Providing care for chronically ill transplant patients can present both enormous challenges and opportunities, particularly in the arena of lung transplantation, a fact Dr. Rosenblatt knows well. He often receives cards from patients and their families. Two cards sitting on Dr. Rosenblatt's desk illustrate the contrasting realities of lives affected by lung disease.

One card is from a patient who received new lungs and thanked him for the care received. The second is from the family of a patient who died waiting for lungs that never came.

"Certainly we are limited in our ability to perform more transplants by the lack of lungs available for transplantation," Dr. Rosenblatt said. "We are working on ways of increasing the number of transplants by both increasing awareness of the need for life-saving organ donations and by examining new techniques that could make more lungs usable for transplantation."

Dr. Rosenblatt and his colleagues continue to evaluate new immunosuppressive regimes to lower the likelihood of organ rejection. Lungs, in particular, present challenges that other solid organs do not. They are more delicate and fragile, and only about 18 percent of the donated lungs are able to be used.

Dr. Rosenblatt also established and directs the adult cystic fibrosis clinic at UT Southwestern, now acknowledged as a center experienced in performing lung transplants for these patients. Within his career, he has seen huge progress against the disease that can cause progressive disability and death.

When Dr. Rosenblatt finished medical school in 1973, the median life expectancy for cystic fibrosis patients hovered around 13 years. Now it is approaching 40 years, and patients born today are expected to live into their 50s and 60s or longer.

"I've come to recognize that those who were fortunate enough to have a transplant would not

1988

have had a chance of being alive without it," Dr. Rosenblatt said. "One of the rewards of being a physician is knowing that we have given these patients more time – time that spouses can spend with each other, time that a parent can spend with a child, time that would not have happened without a transplant."

Weaving a fragile tapestry

The sacrifices parents make to save the lives of their children are never more apparent than in the cases handled by surgeons in the Division of Pediatric Cardiothoracic Surgery at UT Southwestern.

The division has grown to become one of the most prestigious transplant centers in the region.

Now under the direction of Dr. Joseph Forbess, chief of the division and holder of the Pogue Distinguished Chair in Pediatric Cardiac Surgery Research, surgeons perform hundreds of cardiac operations a year at Children's Medical Center, in addition to transplants. Dr. Forbess' area of expertise is in high-risk newborn heart surgery. He says he considers such procedures a privilege because he intervenes in the most critical first hours of a child's life.

He came to UT Southwestern in 2004 from Emory University School of Medicine in Atlanta, where he served as an assistant professor of surgery and vice chairman of cardiothoracic surgery at Children's Healthcare of Atlanta.

Dr. Forbess, like his colleagues, said he values the relationships forged with children and their families as central to his role as a physician. "I enjoy this work. It is difficult, but it is rewarding and gratifying to have the opportunity to help families emerge from these difficult situations."

Each child becomes part of the tapestry of a physician's life. This is evident in the photos that adorn the office of Dr. Kristine Guleserian, assistant professor of pediatric cardiovascular surgery and director of the pediatric heart transplant program at Children's Medical Center Dallas.

Smiling faces of children gaze from every wall. In a way, they are her children as well as their parents'. She knows about their hobbies, their interests and how they are faring.

"I feel very privileged because, as a surgeon, I can make such a difference in their lives and their families' lives," she said. "You get to know all of them and form these complex and rewarding relationships."

"One of the rewards of being a physician is knowing that we have given these patients more time – time that spouses can spend with each other, time that a parent can spend with a child, time that would not have happened without a transplant."

—Dr. Randall Rosenblatt

One of the more high-profile examples of the unique relationship between pediatric patient and surgeon occurred two years ago when Dr. Guleserian transplanted Andrew Madden in the summer of 2006 when he was 13 years old. Andrew's mother, Lauri Wemmer, visited Andrew's pediatrician in their hometown of Odessa earlier that year for a routine check on a heart condition called idiopathic dilated cardiomyopathy – a genetic disorder with which Andrew was born.

"He'd been very stable on medication up until that time," Ms. Wemmer said. "Our doctor spoke with the doctors at Children's, and they flew us to Dallas that day."

Ms. Wemmer and Andrew learned shortly thereafter that he would need a heart transplant. At Children's Medical Center, the two met Dr. Guleserian and formed a fast friendship.

"There are some patients who affect you deeply, and Andrew is one of those patients," Dr. Guleserian said.

In the course of their conversations, Andrew and Dr. Guleserian hit upon common ground – both were avid fans of the Boston Red Sox. Later on during his nail-biting wait for a matching heart, Dr. Guleserian gave him a Red Sox cap for luck. Soon after, the good luck charm paid off, and Andrew was transplanted by Dr. Guleserian. Both wore their Red Sox caps into the operating room, and after his recovery both attended a World Series Red Sox game together, where Andrew threw out the opening pitch.

"Forever now," Ms. Wemmer said, "we'll look back on this experience not as the time that Andrew almost died, but as the time he got to experience his dream."

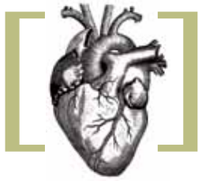
Far-ranging research, far-flung patients

Recently, the department celebrated a surgical milestone representing the marriage of basic science research and the treatment of patients.

More than 1,300 miles away, a baby in Miami, Florida, was born with a one-in-a-million genetic disease called familial hypercholesterolemia (FH).

Born in 2001, Jessica Nichols began showing strange symptoms when she was a few months old.

2008



"I feel very privileged because, as a surgeon, I can make such a difference in their lives and their families' lives. You get to know all of them and form these complex and rewarding relationships."

—Dr. Kristine Guleserian

Her parents saw that she had scabs on her ankles – a hallmark of the disease, which inhibits the body's ability to rid itself of low-density lipoprotein (LDL) cholesterol.

By the time Jessica was 1 year old, her blood cholesterol levels were eight times the normal range.

What her family didn't know at the time was that Jessica's condition had been exhaustively studied at UT Southwestern. In the 1970s, Drs. Joseph Goldstein and Michael Brown, who won the 1985 Nobel Prize in physiology or medicine for their work, discovered the LDL receptor and determined that familial hypercholesterolemia was caused by an autosomal dominant mutation. Dr. Goldstein is chairman of molecular genetics at UT Southwestern, and Dr. Brown is director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease.

Physicians at UT Southwestern had clinical experience treating the rare disease as well. In 1984, a girl named Stormie Jones was treated for FH and received the world's first successful liver and heart transplant at Pittsburg Children's Hospital.

Ultimately, Stormie died in 1990 from organ rejection complications, but her path led the way for future advances in treatment of the disease and transplantation.

Jessica's family traveled from Florida to Texas for treatment.

"The doctors told us she would have to have a liver transplant, but then she had a heart attack," said Roy Nichols, Jessica's father. "After that, we were told she would have to have a new heart, too."

Although the heart attack damaged 70 percent of her heart muscle, the arteries and veins in her heart were also suffering from the inordinate amount of LDL cholesterol buildup. Miraculously, within two days, Jessica had an organ match and underwent the marathon heart and liver transplant in 2006.

"I'm very conservative when it comes to choosing a match," Dr. Guleserian said. "I want to make sure we have really good hearts because there are so many things that can complicate the process."

The only reminder of Jessica's tremendous ordeal is a faint scar that extends a few centimeters above the collar of her shirt.

"She is a firecracker," Dr. Guleserian said. "She's doing great."

The beat goes on

New research in the heart transplant program includes innovative strategies – from mechanical support systems that assist in the function of the heart prior to transplant to more aggressive immunosuppressive drug therapy after transplant – to provide superior care and improve surgical outcomes.

Transplant physicians also have conducted new studies with a cardiac magnetic resonance imaging system to detect, identify and enhance the diagnosis of rejection and of coronary artery disease in heart-transplant patients.

"We also have an active basic-science research laboratory where we investigate new approaches to long-term preservation of the heart for transplantation," Dr. Ring said. "One of these is a device used to perfuse the heart and keep it viable longer prior to transplantation."

The ventricular assist device program has expanded the clinical use of devices to bridge the gap to transplantation. Mechanical assistance such as left-ventricular assist devices help patients survive longer while they wait for a transplant, and some patients are implanted with the devices as a long-term treatment for heart failure and other ailments.

UT Southwestern is also one of only 10 pilot programs in the country to test a new left ventricular assist device designed for children.

As the department continues to expand and grow, Dr. Ring doesn't linger on the past too long. He said his primary goals are to increase the volume of transplants, offer the best new treatments and perform the most cutting-edge techniques available.

"It's been an exciting time these past 20 years. I didn't know completely how everything would unfold, but I'm happy with the progress," he said. "The pool of private referring physicians who have supported us has been tremendous, and the community has been wonderful." ✳

For more information on UT Southwestern's Heart and Lung Transplant Program, please call 214-645-5505.

The Mighty Liver

It is one of the most elegantly complicated organs in the human body, performing tasks from cleaning up to regeneration. When something goes wrong, UT Southwestern's liver team takes over.

By LaKisha Ladson

DONNA DAVIDSON of Frisco checked into a hospital weighing nearly 190 pounds. She had so much fluid around her abdomen that she couldn't eat and had difficulty breathing. When she left seven days later, she weighed only 130 pounds. › She was suffering from a condition called ascites. Ascites is a side effect of cirrhosis, which in her case was due to hepatitis C, a virus that infects the liver. It had taken 10 years from her initial diagnosis for her to develop recognizable symptoms of the disease. › At the hospital, as she watched bottle after bottle fill with fluid drawn from her abdomen, Ms. Davidson could no longer deny her reality. › "Suddenly hepatitis was in my face," she said. "I knew that I had serious problems and that I had to pay attention from now on. I realized I was ill and needed to take control." › It would be another decade before Ms. Davidson would find a longer-term solution to the complications of her hepatitis C: liver transplantation. ›

Patient Donna Davidson

UT Southwestern Medical Center

has a long-standing reputation for leadership

in research and treatment of liver disease, especially in the areas of chronic viral hepatitis B and C. An important expansion of the UT Southwestern capabilities in this area has been the development of a liver transplantation program. With the institution of the liver transplantation program, UT Southwestern doctors now offer patients with advanced chronic liver disease transplantation as a treatment option.

"The liver transplantation program at UT Southwestern University Hospital will allow us to provide a continuum of service for patients with liver disease, beginning with a focus on prevention of viral hepatitis and cirrhosis and the treatment of hepatitis B and C," said Dr. Willis Maddrey, executive vice president for clinical affairs and holder of the Adelyn and Edmund M. Hoffman Distinguished Chair in Medical Science and the Arnold N. and Carol S. Ablon Professorship in Biomedical Science.

Dr. Maddrey's experience with liver transplantation dates back to the early 1980s, when he was part of a liver transplantation unit in Philadelphia. Dr. Maddrey has since written and edited several books on liver transplantation.

"At UT Southwestern, we are able to care for patients with advanced liver disease with the knowledge that when the time comes for transplantation, we are fully able to provide the treatment," he said.

More than 20 liver transplants have been completed in the first year of the program with excellent results.

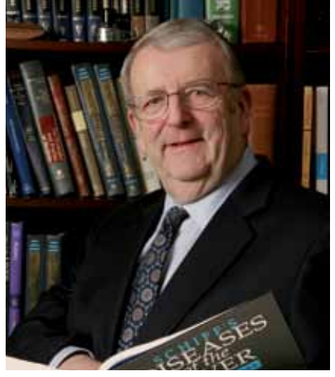
The liver is the body's "jack-of-all-trades." It removes or neutralizes toxins, germs and bacteria from the blood. It produces immune agents to control infection, proteins to regulate blood clotting, and bile to absorb fat and fat-soluble vitamins. It stores and releases energy when the body needs it. It is the site of cholesterol synthesis, which is significant because cholesterol is important in fat and energy metabolism and is also the principal molecular building block of many hormones.

As if it knows its own significance, a healthy liver is capable of regrowing to fully normal size from only 20 percent of its original mass.

Located centrally in the body, it has two dedicated blood supplies from the intestines and from the aorta. The liver is the second-most common site in the body for metastases originating from diseased organs.

"The clinical disease pathophysiology and the functions of the liver are fascinating," said Dr. William Lee, professor of internal medicine, head of the clinical center for liver diseases and holder of the Meredith Mosle Chair in Liver Disease. "If someone has severe liver failure, a main symptom can be altered mental status, from mild drowsiness to confusion or coma. If your liver isn't detoxifying things in the bloodstream, they can get into the brain, put you to sleep and make the brain swell."

UT Southwestern was one of the first centers in the nation to recognize hepatology as a separate division of internal medicine and has since attracted some of the leading minds in the field to perform basic research and conduct clinical trials to find treatments for liver disease.



"At UT Southwestern, we are able to care for patients with advanced liver disease with the knowledge that when the time comes for transplantation, we are fully able to provide the treatment." —Dr. Willis Maddrey

"To me, Dr. Lee is the hepatitis guru. He is a wonderful doctor. He has studied hepatitis; he was well-informed. I knew if Dr. Lee was connected with the program and put the team together, that it would be stellar."

—Donna Davidson with Dr. William Lee

Transplants are used to overcome chronic end-stage liver disease and also are lifesaving for patients with acute liver failure (ALF), a medical emergency in which the liver cells die in a short period of time and most of the liver's function is lost.

Dr. Lee is the founder and principal investigator of the Acute Liver Failure Study Group, and Dr. Anne Larson, associate professor of internal medicine, medical director of liver transplantation and director of clinical hepatology at UT Southwestern University Hospital, has taken the lead in writing some of the projects sponsored by the group.

They found that unintentional acetaminophen overdoses account for about 50 percent of acute liver failure in the United States. Dr. Lee has testified before the Food and Drug Administration, leading the FDA to recommend stronger warning labels on over-the-counter pain medications and cold-and-cough remedies containing acetaminophen.

"The liver processes all drugs because everything from the gut goes first to the liver; basically any foreign substance that enters the body has to be processed by the liver," Dr. Larson said.

More than 60 other studies have been initiated by the group as well as outside investigators using the group's biological samples, and more than 30 papers have already been published.

Dr. Don Rockey, chief of digestive and liver diseases and holder of the Dr. Carey G. King Jr. and Dr. Henry M. Winans Sr. Chair in Internal Medicine, has been actively involved in the investigation of mechanisms underlying chronic liver disease. In particular, he and his group wish to understand how the liver becomes cirrhotic.

Liver disease starts with an injury that leads to inflammation, and ongoing or recurrent inflammation leads to a wound-healing process that ultimately causes scarring, and then cirrhosis.

The liver injury could be caused by alcohol abuse, hepatitis, a genetic disease, iron overload or other reasons. Ultimately, if not identified and treated, it can lead to cirrhosis.

Work in Dr. Rockey's laboratory has been funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for the last 15 years. He and his co-workers have identified cells known as stellate cells, which, when activated, result in synthesis of scar tissue.

"Every day we're isolating these cells, and we can study them in primary and pure culture to answer questions about the wound-healing process," Dr. Rockey said.

Among the unique features of stellate cell activation is the release of proinflammatory cytokines – proteins that regulate the intensity and duration of the immune response and mediate cell communication. When cytokines are overexpressed, it leads to scarring, or fibrosis. Each activation site is a potential target for therapy.

"We're working to find a novel therapy to stop and even reverse the wound-healing process," Dr. Rockey said.

As more scar tissue blocks blood flow, eventually the organ reaches a stage in liver disease called cirrhosis, in which scarring can't be reversed and blood flow is blocked so significantly that the liver cannot function efficiently. Cirrhosis is the 12th-leading cause of death by disease in the U.S., killing about 26,000 people each year.

Dr. Rockey has also been part of NIDDK's Drug-Induced Liver Injury (DILI) network for the last six years. The network was created in 2002 to research causes of drug-induced liver injury. Now with a recent NIDDK grant, UT Southwestern is one of eight centers involved in the network. Eventually, their work could help the FDA by monitoring side effects of drugs already on the market.

"What we're trying to do is establish a registry," Dr. Lee said, "to learn how many people out there are impacted by a drug-induced liver injury and to try and figure out the mechanism or mechanisms that cause this. It's important because there are so many drugs that are getting approved nowadays, and no one ever fully understands the drug until it's on the market."

Chronic hepatitis C often leads to liver cirrhosis and is caused by contact with blood

Dr. Don Rockey, chief of digestive and liver diseases, and his group wish to understand how the liver becomes cirrhotic.

that contains the virus that is the most frequent cause of transportation of the disease in the U.S. Worldwide, hepatitis B virus, contracted through contact with blood or fluids of an infected person, also is a major cause.

"There are good therapies for hepatitis B," Dr. Lee said. "We're treating it much the way HIV is treated now. You have to keep monitoring the suppressive medication because sometimes the virus will escape from the drug's effect. At that point, you have to switch to another drug. There is a skill and learning curve to treating hepatitis B."

Dr. Dwain Thiele, professor of internal medicine, is an expert on autoimmune hepatitis and immune mechanisms of liver injury.

"Inflammation injury in the liver with hepatitis B and C is caused by a person's immune system attacking the infected cells," Dr. Thiele said. "As we better understand that process, we gain insight into how to identify patients at different stages of the disease and better concepts on how to treat and manage the disease."

Dr. Maddrey has had a long and active interest in the prevention and treatment of chronic viral hepatitis.

"Physicians and clinical investigators at UT Southwestern, led by Dr. Lee, have participated in many of the trials of new drugs for the treatment of viral hepatitis in the last 20 years. Our physicians have played roles in development of new treatments for hepatitis B and C," Dr. Maddrey said.

Dr. Thiele's research also has led to the identification of an enzyme responsible for cytotoxic lymphocytes, or destructive white blood cells, which kill infected target cells.

His work identified a way to inhibit enzymes within the liver called serpins, which are important in liver injury and cell death.

Many of these processes occur without recognizable symptoms. Cirrhosis often develops without signs or can be discovered accidentally through elevated liver enzyme levels during routine blood tests.

That's what happened with Ms. Davidson. Her doctor ordered routine blood work and found she had hepatitis. She believes she contracted the disease from a blood transfusion in the late 1970s, before donated blood was screened routinely.

Ms. Davidson became a patient of Dr. Lee's and saw him on a regular basis. She suffered through the flu-like side effects of the drug interferon,

"As we better understand the process [of inflammation injury in the liver with hepatitis B and C], we gain insight into how to identify patients at different stages of the disease and better concepts on how to treat and manage the disease."

—Dr. Dwain Thiele

but it never completely knocked the virus into remission. After several years, she first developed edema, fluid in the feet, and then ascites.

Because of her fluctuating weight, she bought pants with elastic bands and kept several sizes of clothes in her closet. Her fluid buildup would become worse when she traveled out of town for business, so it became routine for her to go to hospitals to be drained of the fluid.

"Every place I'd travel I'd get off the airplane and go to the hospital," Ms. Davidson said.

When complications of cirrhosis can't be controlled or the liver is so damaged that it has stopped functioning, transplantation becomes necessary. Ms. Davidson, a mother of two daughters, got to the point that she needed to be drained of fluid twice a week.

In 2000 she went through intense transplant orientation where she met with doctors and other sufferers of the disease. Then her ascites went into remission for several years, and she was dropped off the transplant waiting list.

"I didn't have water problems," she said. "I don't know what happened."

Meanwhile, UT Southwestern was developing its liver transplantation program. Dr. Larson was recruited, and Dr. Juan Arenas was chosen to become chief of surgical transplantation and the surgical director of the liver transplant program at UT Southwestern.

"Drs. Arenas, Larson and their colleagues have developed a first-class team," Dr. Maddrey said. "Dr. Larson is an extremely dedicated and brilliant hepatologist. Dr. Arenas and his surgical colleagues Dr. Meelie DebRoy [assistant professor of surgery] and Dr. Dev Desai [associate professor of surgery] are extremely dedicated and capable. They are off to an excellent start."

Dr. Arenas has been performing liver transplantations for more than a decade.

"The fact that the program is at a leading academic institution gives it a lot of strength because at any given time you've got the brainpower to tackle any issue you might encounter," Dr. Arenas said. "You can consult internally."

Before joining UT Southwestern, Dr. Larson came from a program that performed 125 liver transplants annually. "Though the program at UT Southwestern is new, the doctors involved have a lot of pooled experiences with liver care, from the general hepatologist to the transplant surgeons. We have a really comprehensive, well-rounded group with expertise in every portion of liver care now. The transplant team has closed the loop," she said.

Because of the increasing numbers of people living with hepatitis and because of better screening for cancer, a complication of the disease, UT Southwestern physicians say they expect to see a rising demand for liver transplants.

Meanwhile, Ms. Davidson eventually developed hepatocellular carcinoma. It was found early enough, and the cancer was small enough, that she was put back on the waiting list for liver transplantation.

On Nov. 27, 2007, she became the second patient transplanted by the UT Southwestern liver team. Ms. Davidson said she was grateful that UT Southwestern's transplantation program was in place at the time she needed it.

"To me, Dr. Lee is the hepatitis guru. He is a wonderful doctor. He has studied hepatitis; he is well-informed," she said. "I knew if Dr. Lee was connected with the program and put the team together, that it would be stellar."

Dr. Arenas performed the surgery, and Ms. Davidson was out of the hospital in just five days.

"The level of service was unbelievable," she said. "I wasn't scared; I wasn't frightened; everything the transplant team did and said was perfect. They took every fear away from me."

Not all liver cancer is a result of hepatitis or other liver damage, and that's where the multidisciplinary approach to liver cancer at UT Southwestern comes into play. Tumors from other parts of the body metastasize to the liver more often than liver cells themselves become cancerous.

Getting a patient to a group of experts who can offer multispecialty care is key, said Dr. Roderich Schwarz, head of the GI cancer disease-oriented team within UT Southwestern's Harold C. Simmons Comprehensive Cancer Center.

"If a spot is found on the liver, patients need a multidisciplinary approach before any decisions are made to avoid unnecessary and counterproductive treatment or tests being performed," said Dr. Schwarz, chief of surgical oncology and holder of the Mark and Jane Gibson Distinguished Professorship in Cancer Research. "These are very challenging cancers, and treatment can be rather risky. They are among the top three or four lethal cancers that exist, so it's a large challenge.

"We want not only to deliver the best multidisciplinary treatment for each individual patient, but also to develop new treatments that are more promising than the ones we currently have."

The complexity and location of the liver make finding the right treatment options difficult and require doctors to be creative. Whereas an organ such as the brain can be immobilized for surgery or targeted radiation, the liver provides greater challenges. Each time a person breathes, the liver moves.

"There are very sophisticated procedures we can do at UT Southwestern that other places are unable to do," Dr. Schwarz said.

For sufferers of chronic liver disease, physicians and patients know that transplantation is not a panacea.

"We're not curing them; we're trading an incurable disease for a manageable one," Dr. Larson said.

For Ms. Davidson, who dubbed her new liver "Juan Lee" after Drs. Arenas and Lee, freedom from ascites is worth it. Since her transplant, she's starting to live a full life again, including spending time with her five grandchildren. She has traveled to Nevada, Massachusetts, Alabama, Japan and Guam since her procedure.

She takes comfort in the fact that the transplant team is experiencing her recovery with her.

"When they give me my follow-up blood work and call to tell me I'm OK, they're just as excited as I am," she said. "I had this huge surgery, and I don't feel alone. The service and attention I received was impeccable. I didn't have time to be afraid; I didn't have time to be worried. Somebody was always there to answer any questions."✳

For more information about UT Southwestern's comprehensive liver care program, please call 214-645-0595.

"There are very sophisticated procedures we can do at UT Southwestern that other places are unable to do."

—Dr. Roderich Schwarz

From A to ZZZZZs

By Russell Rian

Sleep disorders disrupt the lives of 70 million Americans each year. The 100 or so distinct sleep disorders are among the most diverse of medical problems. They range from breathing disturbances and psychological stresses to rare disorders like narcolepsy.

Yet all share the power to make life a nightmare.

"Sleep disorders have the ability to disrupt nearly every aspect of a person's life," said Dr. Nilesh Davé, assistant professor of internal medicine and medical director of the UT Southwestern Sleep and Breathing Disorders Center. "Poor sleep not only affects performance and behavior at school, work and home, but it also has been tied to health issues such as obesity and high blood pressure."

Sleep problems also are associated with increased risk for diabetes, depression, stroke and heart attack, and they are linked with nearly 20 percent of all serious motor vehicle crashes. These disorders cost hundreds of billions of dollars annually in direct medical costs for doctor visits, hospital services and medications, according to the Institute of Medicine, which has identified sleep disorders as a major unmet public-health problem.

The wide range of factors causing the disorders can make diagnoses and treatment plans tricky. Some patients may need to tap pulmonologists like Dr. Davé, who specialize in sleep-related breathing problems; others may need a psychiatrist to address psychological factors. Once diagnosed, resolving problems may demand still more medical talent – from surgeons to neurologists.

So when UT Southwestern physicians banded together to examine the best strategies, they quickly concluded that patients' needs could best be met in a multidisciplinary center where patients with sleep disorders of all causes and diagnoses could access the broad base of medical expertise needed for that not-so-simple good night's sleep.

UT Southwestern assembled its dream team, a comprehensive collection of experts in pulmonary medicine, neurology, psychiatry, pediatrics, oto - laryngology, and oral and maxillofacial surgery to work and consult with one another to launch the Sleep and Breathing Disorders Center.

The 6,000-square-foot center, located on the second floor of Professional Office Building 2 on the West Campus, is among the most advanced in the nation and one of the first in the Southwest to encompass the management of all sleep problems – including sleep apnea, insomnia, restless leg syndrome, narcolepsy, circadian rhythm disorders and parasomnias (which include sleepwalking and night terrors), snoring, and breathing difficulties due to neurological and musculoskeletal disorders such as amyotrophic lateral sclerosis (ALS) and muscular dystrophy.

Some sleep disorders are straightforward, but many are interrelated with other health issues and demand a coordinated review. Such was the case for Neil Kaden, a 54-year-old McKinney consultant.

Mr. Kaden, who advises start-up businesses, struggled to balance medications prescribed for issues ranging from allergies and Parkinson's disease to insomnia before being directed to the UT Southwestern sleep center.

"It got so bad that for several weeks, I couldn't fall asleep at all. Medications had me sleepwalking or didn't work at all. Sometimes I would get some sleep, but never restful sleep," said Mr. Kaden, who also lost, then gained, 30 pounds during that time. His lack of sleep also was triggering late-stage Parkinson's-related problems.

"I had no muscle tone," he said. "I had trouble getting in and out of chairs. I couldn't sit comfortably in most chairs. I was exhausted much of the time. I was in bad shape."

Dr. Davé ran a battery of tests and determined Mr. Kaden had a very treatable form of sleep apnea, which affects an estimated 18 million Americans.

"The great thing is that Dr. Davé really cared about me. He's not just a sleep doctor. He's a pulmonologist, which I needed," Mr. Kaden said.

Dr. Davé also conferred with Dr. Shilpa Chitnis, assistant professor of neurology at UT Southwestern, to coordinate Mr. Kaden's treatments for Parkinson's.

"He and Dr. Chitnis got me into physical therapy to recover my muscle tone and to improve my balance. They determined I didn't have asthma and began sorting through several of my medications to reduce interactions," Mr. Kaden said. "Dr. Davé looked at all the medications I was taking and figured out that some were likely interfering with others."

Dr. Davé placed him on a regimen involving a special breathing device, which allowed Mr. Kaden to stop taking sleep and asthma medications. After years of suffering, he responded quickly to the treatments.

"As a result of all this, there's a medication for my Parkinson's that has a chance of halting the progression of the disease. I can take that now because I got off some other medications," Mr. Kaden said.

Prevalent data suggest that 80 percent to 90 percent of adults with clinically significant sleep-disordered breathing remain undiagnosed, and there are estimates that as many as 40 million Americans suffer from some undiagnosed sleep disorder.

Dr. Davé said it is important to be focused on the individual and the complexity of issues each faces when diagnosing sleep-related problems. Strategies for care need to address the severity of symptoms, the patient's lifestyle and the specific goals for each patient's therapy.

"Our physicians can craft a specially tailored approach for each and every patient coming through the center, thanks to the diverse medical talent on hand," said Dr. Davé. "We especially want our neuromuscular patients with breathing problems to maintain their autonomy and reduce the number of times they have to return to the hospital due to respiratory failure. The goal is to empower patients and their families to lead as normal a life as possible."

Six specially designed rooms are available for Sleep and Breathing Disorders Center physicians and staff to conduct in-house sleep studies in order to diagnose and evaluate disorders. The center features the latest, state-of-the-art diagnostic and treatment equipment and techniques, including:

- Polysomnograms – These devices are used for overnight sleep studies, in which sensors are attached to the head, face, chest and legs. These sensors chart brain waves, heart rhythms, breathing, eye and leg movements, even muscle tension.
- Continuous and Bilevel Positive Airway Pressure (CPAP and BPAP, respectively) machines – These devices are considered the initial and often best treatment for obstructive sleep apnea, a condition in which the patient awakens hundreds of times during the night due to inadequate air flow.
- Light therapy – This is used to help adjust the body's internal clock for a patient experiencing circadian rhythm problems and seasonal affective disorder.

- Medications and behavioral therapies – These include changing dietary and nutritional habits or chronotherapy (altering bedtime) and are among treatments that can help people who are having trouble with insomnia.
- Surgeries – These are performed to widen a patient's airway by removing excess tissue in the throat or directly increasing its size.

Many of UT Southwestern's notable researchers are involved in sleep physiology and biology, Dr. Davé said. In other labs, UT Southwestern researchers are actively pursuing the genes that regulate the daily rhythms of life and tracking electrical and chemical activity in the brain during sleep.

"Very few institutions," Dr. Davé said, "can provide state-of-the-art care in this area as well as UT Southwestern can, while offering patients results from some of the field's best-known researchers."✳

For more information on the Sleep and Breathing Disorders Center, please call 214-645-5337.

> **"Poor sleep ... has been tied to health issues such as obesity and high blood pressure."**
> *– Dr. Nilesh Davé*

In a heartbeat

By Katherine Morales

Consider the complexity of a single heartbeat.

A signal is initiated in the upper part of the heart as an electrical impulse, which then spreads throughout the heart's four chambers, causing them to contract and pump blood through the body.

A cluster of medical conditions, however, can disrupt the heart's electrical current and cause havoc, even in otherwise healthy people. These disruptions, known as cardiac arrhythmias, cause the heart to beat wildly out of control, at more than 230 beats per minute, or slow to dangerous levels.

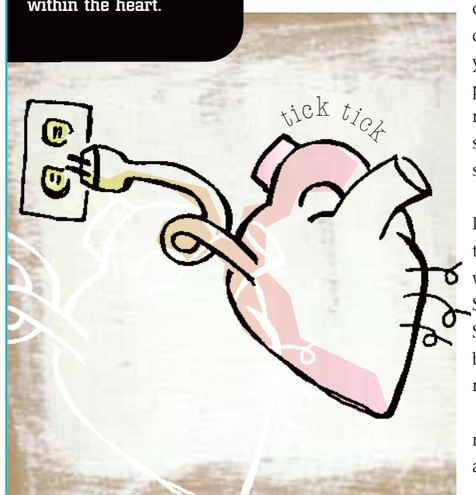
Other kinds of electrical discord can make the heart quiver in place rather than effectively pushing out blood to the body. Such changes can be deadly.

While cures for arrhythmias are often not possible, UT Southwestern physicians are at the vanguard of research into and treatment for these conditions.

The physicians and other health-care professionals who treat arrhythmias regard their work as analogous to electricians fixing electrical problems, by rewiring the heart, modifying its functions with medications or implanting devices to keep it beating normally.

Joel Thompson, a 26-year-old Utah native, said his heart began beating out of control 15 years ago.

He eventually was diagnosed with hypertrophic cardiomyopathy, a rare congenital condition that makes the heart muscle thicker and is a leading cause of sudden cardiac death, particularly in young athletes. His physician prescribed medication, and that seemed to mitigate the symptoms for a while.



After moving to Dallas in August 2006 to attend UT Southwestern Graduate School of Biomedical Sciences, Mr. Thompson began having more trouble.

"I remember running to catch the train, and the next thing I remember is waking up in the hospital," he said.

At UT Southwestern University Hospital, Dr. Jose Joglar, associate professor of internal medicine and holder of the Elizabeth Thaxton Page and Ellis Batten Page Professorship in Cardiac Electrophysiology Research, took a closer look at Mr. Thompson's medical history and the regimen of medication he was taking.

"It turned out that my medicine could cause some serious side effects," he said.

Dr. Joglar changed Mr. Thompson's anti-arrythmic medication and implanted a cardioverter-defibrillator. It resembles a pacemaker but is programmed to detect cardiac arrhythmia and correct it by delivering a jolt of electricity.

At UT Southwestern, Dr. Joglar and his team have dedicated electrophysiology labs, complete with computerized equipment that helps them gather data from within the heart. Because cardiac arrhythmias have different kinds of footprints, diagnosing and treating them can be complex.

"It's a very procedure-oriented specialty," said Dr. Charles Lampe, assistant professor of internal medicine. "This is also a very technologically advanced field, and I think we all like the challenges and the ability to provide definitive therapies."

In addition to surgery to implant devices, doctors in the center perform procedures, such as ablation, in which portions of the heart tissue that cause abnormal heart rhythm are destroyed. Such was the case for Nancy Cardona, 30, whose alarming symptoms began in 2007.

After visiting her cardiologist, the mother of three young children was referred to Dr. Richard Wu, associate professor of internal medicine who specializes in electrophysiology.

Dr. Wu put Mrs. Cardona on a 24-hour monitor that detects changes in the heartbeat. Eventually, her heart began beating well over 200 beats per minute.

After monitoring her heart for a month, Dr. Wu admitted her to the clinic for a cardiac ablation.

Mrs. Cardona still undergoes regular treatment at UT Southwestern because of the complexity of her heart arrhythmia. She also has had a second cardiac ablation.

"I really like Dr. Wu because he actually sits down with me and explains everything that is going on," she said.✳

For more information on cardiac electrophysiology, please call 214-645-8000.

Dr. Joglar and his team have dedicated electrophysiology labs, complete with computerized equipment that helps them gather data from within the heart.

2008

ANNUAL REVIEW

54 HIGHLIGHTS OF THE YEAR

65 FINANCIAL STATEMENT

68 GIFT REPORT

HIGHLIGHTS
of the year

FALL 2007

PARADA, LEVINE RECEIVE HONORS

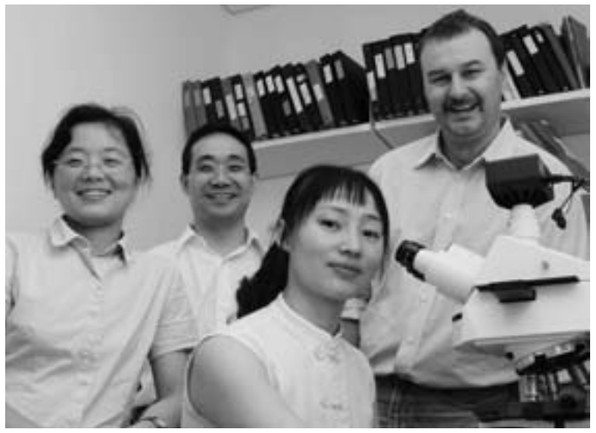
Dr. Luis Parada, chairman of developmental biology, was elected to the Institute of Medicine, and Dr. Beth Levine, chief of infectious diseases, was named a Howard Hughes Medical Institute investigator.

Dr. Parada's election brings the number of current UT Southwestern faculty members inducted into the institute, a component of the National Academy of Sciences, to 18, more than any other institution in the southwestern region of the U.S. His research has provided insights into brain development and cancer biology and has led to the identification of molecules that inhibit nerve regeneration after injury.

Dr. Levine was one of 15 researchers nationwide chosen to join the Howard Hughes Medical Institute, a philanthropic organization that promotes biomedical research. Her laboratory identified the first known mammalian autophagy gene and discovered that defects in the gene contribute to cancer, aging, neurodegenerative diseases such as Alzheimer's, and infectious diseases.

DR. LUIS PARADA

DR. BETH LEVINE



THE RESEARCH TEAM OF DR. ILYA BEZPROZVANNY (RIGHT) INCLUDES DRS. XI CHEN, TIE-SHAN TANG AND JING LIU. THEIR FINDINGS ON HUNTINGTON'S DISEASE SHEDS LIGHT ON THE BIOCHEMICAL MECHANISMS INVOLVED IN THE NEUROLOGICAL CONDITION.

DRUG MAY SHIELD BRAIN CELLS FROM HUNTINGTON'S DISEASE

A drug used in some countries to treat the symptoms of Huntington's disease prevents death of brain cells in mice genetically engineered to mimic the hereditary condition, scientists led by Dr. Ilya Bezprozvanny, professor of physiology, have discovered.

The drug, called tetrabenazine (TBZ), blocks the action of dopamine, a compound that some nerve cells use to signal others. TBZ is approved for use in several countries, but not the U.S., to treat uncontrollable muscle movements in Huntington's and other neurological conditions. Huntington's patients suffer jerky, uncontrollable movements called chorea and deterioration of reasoning abilities and personality, which begin after numerous brain cells have died.

The research, reported in *The Journal of Neuroscience,* sheds light on the biochemical mechanisms involved in the disease and suggests new avenues of study for preventing brain-cell death in at-risk people before symptoms appear.

'SKINNY' GENE EXISTS, MAY BE KEY IN DIABETES FIGHT

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

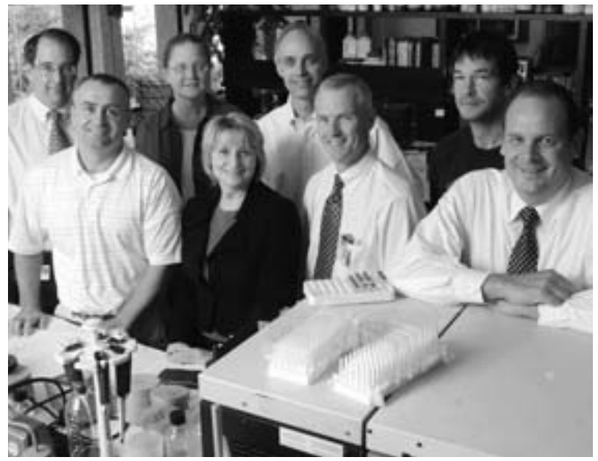
The researchers manipulated the gene *adipose* in various animals, turning the gene on and off at different stages in the animals' lives and in various parts of their bodies. It was discovered that the gene, which is also present in humans, is likely to be a master switch that tells the body whether to accumulate or burn fat, the investigators reported in the journal *Cell Metabolism.*

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

$22 MILLION TO FUND TASK FORCE FOR OBESITY RESEARCH

The National Institutes of Health awarded UT Southwestern a $22 million grant to enhance the medical center's groundbreaking efforts to attack obesity from every angle, including studying fat cells and developing new medicines.

Researchers, who will receive the funds over the next five years, make up one of only nine interdisciplinary research consortia sponsored by the NIH Roadmap for Medical Research. These groups seek to solve difficult problems by blending approaches from multiple biomedical research disciplines. UT Southwestern's group is the only one focused on obesity.



RESEARCHERS ON THE TASK FORCE FOR OBESITY RESEARCH INCLUDE (LEFT TO RIGHT): DRS. CRAIG MALLOY, JOEL ELMQUIST, JOYCE REPA, ELIZABETH PARKS, DAVID MANGELSDORF, DAVID RUSSELL, JONATHAN COHEN AND JAY HORTON.

The Dallas group comprises 29 scientists from different backgrounds, including genetics, endocrinology, nutrition, neurology, lipid metabolism, psychiatry and epidemiology – a combination aimed at better understanding the processes that lead to obesity and associated metabolic disorders, according to Dr. Jay Horton, professor of internal medicine and molecular genetics and coordinating investigator for the grant.

WINTER 2008

INNOVATIONS IN MEDICINE CAMPAIGN SETS RECORD

UT Southwestern's *Innovations in Medicine* campaign, officially launched in April 2002, was the most ambitious fundraising effort in Dallas history. At its close – Dec. 31, 2007 – almost $773 million had been given or pledged by more than 700 generous donors.

The largest previous fundraising drive by UT Southwestern was for its *Fund for Molecular Research,* which ran from 1992 to 1995. It surpassed its $150 million goal by $15 million. At the time it was the largest fundraising effort for research ever undertaken by an American medical school and the largest private-donor campaign ever conducted in Dallas.

The latest campaign was chaired by William T. Solomon. Honorary chairs included Amy and Lee Fikes, Nancy B. Hamon, Mrs. Eugene McDermott, Deborah and Tex Moncrief, Edith and Peter O'Donnell Jr., Margot and Ross Perot, Margaret and Bob Rogers, Sarah and Charles E. Seay (who died in 2009), Annette and Harold Simmons, and Cecil H. Green (who died shortly after the campaign began).

A total of 130 donors each contributed $1 million or more to the campaign, with 25 of these donating at least $5 million. Four gave $50 million or more to the campaign, including a record-setting $125 million commitment from Mr. and Mrs. Harold Simmons and

ANNETTE AND HAROLD SIMMONS (LEFT) ARE JOINED BY DR. KERN WILDENTHAL AND PAUL M. BASS JR. AT THE ANNOUNCEMENT OF THE COUPLE'S $50 MILLION COMMITMENT TO UT SOUTHWESTERN'S *INNOVATIONS IN MEDICINE* CAMPAIGN, RAISING THE LEGENDARY PHILANTHROPISTS' TOTAL CONTRIBUTIONS FOR THE CAMPAIGN TO A RECORD-SETTING $125 MILLION.

the Harold Simmons Foundation. Other contributors at the $50 million level included the Perot Foundation, the T. Boone Pickens Foundation and an anonymous donor.

EVEN PATIENTS NOT MORBIDLY OBESE MAY NEED SURGERY

The existing criteria for obesity surgery – based on a patient's body-mass index or weight-to-height ratio – often excludes a group of obese patients at high risk for cardiovascular disease, UT Southwestern researchers led by Dr. Edward Livingston, chief of GI/endocrine surgery, have found.

The study, appearing in the journal *Surgery for Obesity and Related Diseases*, is among the first to evaluate the risk-factor relationship between body mass index (BMI) and cardiovascular disease as it relates to bariatric surgery criteria. It found cardiovascular risk factors do not necessarily worsen with increasing obesity, and the findings also support the concept that obesity, by itself, doesn't trigger an adverse cardiovascular risk profile or increased risk of death.

Persons with a BMI of 40 or more are at least 100 pounds over their recommended weight and are considered morbidly obese. Bariatric weight-loss surgery is currently recommended for patients with a BMI greater than 40, as well as for patients with a BMI greater than 35 who suffer from life-threatening illnesses.

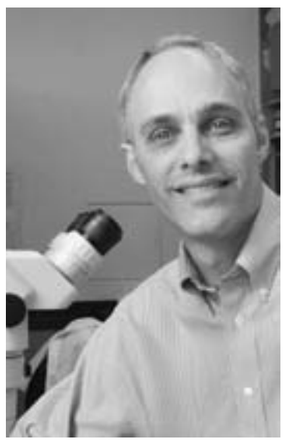
SPRING 2008

MANGELSDORF ELECTED TO NAS

Dr. David Mangelsdorf, chairman of pharmacology and a Howard Hughes Medical Institute investigator, was elected to the National Academy of Sciences. With his election, UT Southwestern now has 17 faculty members currently serving in the academy, more than two-thirds of all the medical members in Texas.

An internationally prominent researcher in lipid biology, Dr. Mangelsdorf has made major contributions to the understanding of the mechanisms that control cholesterol and bile acid metabolism. His work complements the Nobel Prize-winning research carried out at UT Southwestern by Dr. Michael Brown, director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease, and Dr. Joseph Goldstein, chairman of molecular genetics.

Dr. Mangelsdorf's research focuses on nuclear receptors that serve as sensors in protecting human cells against unusually high and possibly toxic levels of lipids, such as cholesterol and fatty acids. He has discovered several new molecules, called ligands, that activate so-called orphan nuclear receptors. Dr. Mangelsdorf has defined the critical role these receptors and ligands play in the regulation of lipid and bile acid metabolism and the governance of cholesterol, which could lead researchers to the development of new cholesterol-fighting drugs.



DR. DAVID MANGELSDORF

DR. PHIL EVANS AND HIS CLINICAL STAFF OFFER THE NEWEST TECHNOLOGY IN BREAST IMAGING – A FULLY AUTOMATED DEVICE THAT USES SOUND WAVES TO MAKE IMAGES OF THE TISSUES INSIDE THE BREAST.

ULTRASOUND HELPS DETECT BREAST CANCER

For women at high risk of developing breast cancer, breast ultrasound combined with mammography may detect more cancers than mammography alone, UT Southwestern clinicians and researchers, including Dr. W. Phil Evans, director of the UT Southwestern Center for Breast Care, have shown.

More than 2,800 women at high risk of developing breast cancer participated in the multicenter trial, whose results were presented in the *Journal of the American Medical Association*. The median age of the participants was 55 years, and more than half had a personal history of breast cancer.

Breast ultrasound is a non-invasive procedure that uses sound waves to make a picture of the tissues inside the breast. A fully automated 3-D breast ultrasound machine – the newest technology in breast imaging – is used at the Center for Breast Care, the first site in Dallas and Fort Worth to obtain the equipment. Data can be captured in three dimensions as opposed to a flat image, and physicians can review images from any angle, uncovering areas that previously might have remained unseen.

DEPRESSED TEENS RESPOND TO COMBO THERAPY

More than half of teenagers with the most debilitating forms of depression who do not respond to treatment with selective serotonin reuptake inhibitors (SSRIs) show improvement after switching to a different medication combined with cognitive behavioral therapy, researchers at UT Southwestern and colleagues reported.

Dr. Graham Emslie, professor of psychiatry and pediatrics and principal Dallas investigator in the multicenter study, helped to demonstrate that if an adolescent hasn't responded to an initial course of treatment, switching treatments may be effective. The study, which involved 334 teenagers with moderate to severe major depressive disorder, was published in the *Journal of the American Medical Association*. Historically, these types of patients have the worst treatment outcomes and may have suicidal ideation.

The researchers found that nearly 55 percent of teenagers who failed to respond to SSRIs improved when they switched to a different antidepressant and participated in cognitive behavioral therapy. The study also found that about 41 percent of participants responded after switching to either a different SSRI or to venlafaxine, a different kind of antidepression medication.

DR. GRAHAM EMSLIE

DR. DANIEL SCOTT

SINGLE-INCISION WEIGHT-LOSS SURGERY COMPLETED

UT Southwestern surgeons completed the first single-incision Lap-Band weight-loss surgery in Texas. Rather than the standard five small incisions used for traditional laparoscopic gastric banding surgery, surgeons used a single 8-centimeter incision, reducing future scarring and accelerating healing.

Drs. Daniel Scott and Homero Rivas, associate professor and assistant professor of surgery, respectively, completed the 2½-hour procedure at UT Southwestern University Hospital - Zale Lipshy. They used a special camera to see around obstructions and special graspers with a curved tip.

UT Southwestern surgeons were the first in a three-state area to perform laparoscopic gastric-bypass surgeries in the late 1990s. They also performed the region's first Lap-Band procedures.

SUMMER 2008

NEW HOWARD HUGHES INVESTIGATORS BEGAN AS ENDOWED SCHOLARS

Three researchers who originally joined the UT Southwestern faculty as part of the institution's acclaimed Endowed Scholars Program in Medical Science were selected to become Howard Hughes Medical Institute investigators.

Dr. Lora Hooper, assistant professor of immunology and microbiology; Dr. Youxing Jiang, associate professor of physiology; and Dr. Hongtao Yu, professor of pharmacology; were named as new investigators by the institute. Their appointments bring the number of HHMI investigators who are UT Southwestern faculty members to 12, a number that ranks in the top 10 in the country.

Dr. Hooper joined the UT Southwestern faculty in 2003 as the Nancy Cain and Jeffrey A. Marcus Scholar in Medical Research, in Honor of Dr. Bill S. Vowell. Dr. Jiang, a W.W. Caruth Jr. Scholar in Biomedical Research, also joined the faculty in 2003, and Dr. Yu joined the faculty as the Michael L. Rosenberg Scholar in Medical Research in 1998.

LESS FRUCTOSE MAY BOOST WEIGHT-LOSS

One of the reasons people on low-carbohydrate diets may lose weight is that they reduce their intake of fructose, a type of sugar that can be made into body fat quickly, according to researchers led by Dr. Elizabeth Parks, associate professor of clinical nutrition.

UT SOUTHWESTERN RESEARCHERS NAMED HOWARD HUGHES MEDICAL INSTITUTE INVESTIGATORS IN 2008 ARE (TOP TO BOTTOM) DR. LORA HOOPER, DR. YOUXING JIANG AND DR. HONGTAO YU.

DR. ELIZABETH PARKS

Dr. Parks said her team's findings suggest that eating the right type of carbohydrates may be just as important in weight control as the number of calories a person eats.

Current guidelines suggest that limiting processed carbohydrates, many of which contain high-fructose corn syrup, may help prevent weight gain, and the new data on fructose clearly support this. The study, reported in the *Journal of Nutrition,* shows for the first time the surprising speed with which humans make body fat from fructose.

HOSPITAL SECURES TOP RANKINGS

UT Southwestern has been named in *U.S. News & World Report's* America's Best Hospitals 2008 as one of only three hospitals in North Texas to achieve top rankings in one or more specialties.

The America's Best Hospitals guide identifies 170 out of more than 5,000 medical centers nationwide that excelled in one or more of 16 specialties.

The UT Southwestern specialties and their ranks on the list include: neurology and neurosurgery at 18th; urology at 25th; kidney disease at 36th; and gynecology at 48th.

385 EARN DEGREES FROM THREE SCHOOLS

Diplomas were received by 218 UT Southwestern Medical School students and 47 UT Southwestern Graduate School of Biomedical Sciences students at May 31 commencement ceremonies.

Dr. William H. Cunningham, holder of the James L. Bayless Chair for Free Enterprise in the Red McCombs School of Business at UT Austin, gave the commencement address.

Southwestern Medical Foundation's Ho Din Award, the top award given annually to UT Southwestern Medical School graduates, was presented to Drs. Sara Lindsey and Joshua Mitchell by William T. Solomon, chairman of Southwestern Medical Foundation.

Rodney Infante received the 2008 Nominata Award, given to the outstanding graduate student.

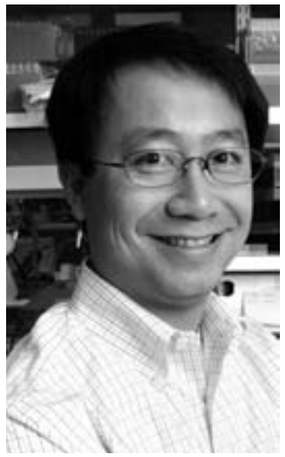
UT Southwestern Allied Health Sciences School conferred degrees on 120 students. Another 70 students received degrees at August graduation exercises.

PRC PRESENTS TWO DISTINGUISHED AWARDS

The President's Research Council presented its 2008 Distinguished Young Researcher Award to a pair of outstanding UT Southwestern scientists. The recipients – Dr. Ralph DeBerardinis and Dr. Lu Le – each received a $70,000 award.

Dr. DeBerardinis, assistant professor of pediatrics and a member of the Eugene McDermott

CARMEN ORDONEZ, CLINICAL NUTRITION GRADUATE, RECEIVES HER DIPLOMA FROM DR. KERN WILDENTHAL, WHO RETIRED AS PRESIDENT OF UT SOUTHWESTERN IN AUGUST 2008.

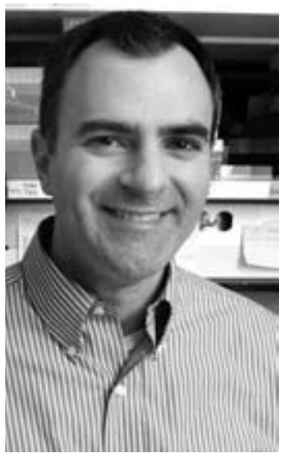


DR. LU LE

Center for Human Growth and Development, is studying the metabolic activities that support cell growth and proliferation. He is also investigating genetic diseases that affect metabolism in children.

Dr. Le, assistant professor of dermatology and developmental biology, is investigating how genetic and other microenvironmental cues regulate tumor formation in the peripheral nervous system. His research focuses on elucidating the biology of neurofibromatosis type I, a common, tumor-causing, disfiguring human genetic disorder. Dr. Le's research has led to the hypothesis that neural stem cells in the skin may play an important role in the pathogenesis of this disease.

The Distinguished Young Researcher Award is presented annually by the PRC, a group of community leaders who are interested in advancing medical research at UT Southwestern.



DR. RALPH DEBERARDINIS

APPOINTMENTS FOR 2007-2008

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

- Dr. Richard Auchus, to the Charles A. and Elizabeth Ann Sanders Chair in Translational Research.
- Dr. James Chen, to the Robert McLemore Professorship in Medical Science.
- Dr. Rody Cox, to the Rody P. Cox, M.D., Professorship in Internal Medicine.
- Dr. Sophie Fletcher, to the Felecia Cain Fellowship in Urology.
- Dr. Rebecca Gruchalla, to the William A. Sellars, M.D., and Joyce M. Sellars Distinguished Chair in Allergy and Immunology.
- Dr. Robert Hammer, to the Graydon Heartsill Professorship in Medical Science.
- Dr. Eric Hansen, to the Lorraine Sulkin Schein Distinguished Professorship in Microbial Pathogenesis.
- Dr. Makoto Kuro-o, to the Kern and Marnie Wildenthal President's Research Council Professorship in Medical Science.
- Dr. David Mangelsdorf, to the Beatrice and Miguel Elias Distinguished Chair in Biomedical Science.
- Dr. Kimberly Mezera, to the R. Wofford Cain Distinguished Chair in Bone and Joint Disease Research.
- Dr. Madelyn Pollock, to the Stanley Gilbert, M.D., Professorship in Family Practice.
- Dr. W. Gary Reed, to the Sinor/Pritchard (Katy Sinor and Kay Pritchard) Professorship in Medical Education, Honoring Donald W. Seldin, M.D.
- Dr. Shelley Roaten Jr., to the Carla and Paul Bass Professorship in Medical Education, Honoring Charles C. Sprague, M.D.
- Dr. Michael Roth, to the Diane and Hal Brierley Distinguished Chair in Biomedical Research.
- Dr. Roderich Schwarz, to the Mark and Jane Gibson Professorship in Cancer Research.
- Dr. Daniel Scott, to the Frank H. Kidd Jr., M.D., Distinguished Professorship in Surgery.
- Dr. Timothy Solberg, to the Barbara Crittenden Professorship in Cancer Research.
- Dr. R. James Valentine, to the Alvin Baldwin Jr. Chair in Surgery.
- Dr. Keith Wharton, named associate dean for undergraduate medical education and basic science curriculum at the medical school.
- Dr. Michael White, to the Hortense L. and Morton H. Sanger Professorship in Oncology.
- Dr. Joseph Zhou, to the Drs. George and Anne Race Distinguished Professorship in Pathology.
- Dr. Andrew Zinn, named associate dean of the Medical Scientist Training Program.

MAJOR GIFTS IN 2007-2008

Philanthropists continued to demonstrate their commitment to UT Southwestern in 2007-2008, providing support for a variety of research and clinical programs.

Major new pledges and gifts received in the 2007-2008 fiscal year included:

- $23,302,000 from the Perot Foundation for ongoing multiyear support of research programs, for the Medical Scientist Training Program for M.D./Ph.D. students, and to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.
- $20,000,000 from community supporters and UT Southwestern faculty members and staff to establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence for the medical center's clinical, research and educational programs; major individual donors to this fund are cited elsewhere within this list.
- $3,000,000 from the Harry W. Bass Jr. Foundation to Southwestern Medical Foundation to name the Heart, Lung and Vascular Center at UT Southwestern University Hospital - St. Paul.
- $2,000,000 from Mrs. Florence Doswell to establish and support the Houston J. and Florence A. Doswell Center for the Development of New Approaches for the Treatment of Hypertension.
- $1,900,000 from the Cain Foundation to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence and to further support the Felecia Cain Fellowship in Urology.
- $1,500,000 from Bea and W. Ray Wallace to create the Bea and Ray Wallace Fund for Endowed Scholars in Urologic Disease, in Honor of John McConnell, M.D.
- $1,406,804 from the 2008 Sweetheart Ball to support research in the prevention and treatment of cardiovascular disease.
- $1,112,548 from Helen Dupies Bader, through a bequest, to increase funding for the Walter M. and Helen D. Bader Center for Research on Arthritis and Autoimmune Diseases.
- $1,100,000 from Mrs. Ute Schwarz Haberecht and Dr. Rolf Haberecht and their children, Caroline Haberecht Moore and Michael Haberecht, M.D., Ph.D., to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence and to support the *Innovations in Medicine* campaign.
- $1,000,000 from Mr. and Mrs. Louis A. Beecherl Jr. to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.
- $1,000,000 from the Dedman Foundation and the Dedman family to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.
- $1,000,000 from Mr. and Mrs. Thomas J. Engibous to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.
- $1,000,000 from Mr. and Mrs. S.T. Harris to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.
- $1,000,000 from Ms. Linda W. Hart and Mr. Milledge A. Hart III to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.
- $1,000,000 from the Hoblitzelle Foundation in support of the medical center's Program for New Scholars in Medical Research.
- $1,000,000 from the Lowe Foundation to establish and support the Erma Lowe Laboratory for Research on Alzheimer's disease.
- $1,000,000 from the Eugene McDermott Foundation to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.
- $1,000,000 from Mr. and Mrs. W.A. "Tex" Moncrief Jr. to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.
- $1,000,000 from Mr. and Mrs. John G. Penson to establish the Nancy P. and John G. Penson Fund in Urology, in Honor of Claus G. Roehrborn, M.D.
- $1,000,000 bequests from Mary Kathleen "Kitty" Phillips and her daughter, Kathleen Anne Phillips, to establish the Sam H. Phillips Jr., M.D., Distinguished Chair in Surgery, in memory of Kitty Phillips' husband and Kathleen Anne Phillips' father; the Sam H. Phillips Jr., M.D., Visiting Professorship in Internal Medicine, in Honor of Dr. Jack Edwards and Dr. Billy B. Oliver; the Sam H. Phillips Jr., M.D., Visiting Professorship in Endocrinology, in Honor of Dr. Sam Marynick; and the Sam H. Phillips Jr., M.D., Visiting Professorship in Surgery, in honor of Dr. David Vanderpool and Dr. Jim Carrico.
- $1,000,000 from Mr. and Mrs. Robert B. Rowling to support the *Innovations in Medicine* campaign.
- $1,000,000 from Suzy Ruff/Ruff Family Foundation Fund of Communities Foundation of Texas for a fund to establish the Ruff Family Distinguished Chair for Wound Healing in the Department of Plastic Surgery.

■ $1,000,000 from Dr. William and Joyce Sellars to create the William A. Sellars, M.D., and Joyce M. Sellars Distinguished Chair in Allergy and Immunology.

■ $1,000,000 from the Diana K. and Richard C. Strauss Foundation to establish the Diana K. and Richard C. Strauss Fund for Medical Excellence, in Honor of Willis C. Maddrey, M.D.

■ $875,000 from the Crystal Charity Ball to support the medical center's part of a $1.4 million grant for a collaborative program between UT Southwestern and UT Dallas to conduct research and provide comprehensive multidisciplinary clinical programs for children with autism.

■ $750,000 from Mrs. Elaine D. Sammons to further support the Elaine D. Sammons Cancer Research Program under the direction of Dr. Eugene P. Frenkel, and to upgrade the Elaine Dewey Sammons Chair in Pulmonary Research, in Honor of John E. Fitzgerald, M.D., to a distinguished chair.

■ $600,000 from Gil and Tricia Besing to support clinical care and research programs.

■ $600,000 from Benjamin and Selma Parrill, through a bequest, to establish the Ben and Selma Parrill Endowment Fund in General Medicine, in honor of Dr. Gary Reed; the Ben and Selma Parrill Endowment Fund in Cardiology, in honor of Dr. Sharon Reimold; and to endow the Flora Miller Award Fund to help medical students.

■ $595,000 from the Hartwell Foundation to support medical research, with particular emphasis on pediatric diseases.

■ $537,407 from Clarence Thomas Hill Jr., through a bequest, to establish the Clarence Thomas Hill Jr., M.D., Scholarship Fund.

■ $500,000 from Crow Holdings, L.L.C./The Harlan R. Crow Family/The Trammell S. Crow Family/The Stuart M. Crow Family to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.

■ $500,000 from Lorraine Sulkin Schein, through a bequest, to fund a visiting lectureship in geriatrics as well as to support education, research and clinical programs.

■ $448,685 from the Sparrow Foundation to support UT Southwestern's portion of the Center for Advanced ADHD Research, Treatment and Education (CAARTE) initiative – a joint project with UT Dallas' Center for Brain Health and the Shelton School.

■ $400,000 from the Amon G. Carter Foundation to continue support of Dr. James Amatruda's genetically based research to discover treatments for childhood cancer and to support Dr. Matthew Porteus' work in gene therapy research for pediatric genetic diseases.

■ $400,000 from the David M. Crowley Foundation to support the Spinal Cord Injury Laboratory and to foster research into peripheral nerve pain management and Parkinson's disease.

■ $380,000 from an anonymous foundation to support research on multiple sclerosis and ovarian cancer.

■ $377,843 bequest from Hortense Sanger to create the Hortense L. and Morton H. Sanger Professorship in Oncology and to support geriatric programs.

■ $337,277 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.

■ $322,625 from the ALS Evening of Hope for research on Lou Gehrig's disease.

■ $305,578 from Mr. and Mrs. C.B. Hudson for further support of clinical enhancement programs.

Generous contributions and pledges of $100,000 to $250,000 were received from a number of additional donors, including the following new commitments from:

■ Mr. and Mrs. Edward M. Ackerman to support a variety of programs at UT Southwestern.

■ Mrs. Claude C. Albritton III to establish the Susan H. Albritton in Memory of Jane W. and James D. Heldt Research Fund to support stem cell research.

■ Anonymous through Southwestern Medical Foundation to underwrite special development programs.

■ Mary Kay Ash Charitable Foundation to support research on cervical cancer.

■ Austin Industries owner-employees, in honor of William T. Solomon and his family, for a three-piece granite sculpture "Sun Disc Triptych" by artist Jesus Moroles.

■ Geraldine Sears Beddow, through a bequest, to establish the Geraldine S. Beddow Heart Research Fund and the Geraldine S. Beddow Cancer Research Fund.

■ Mrs. Ben R. Briggs to support activities in internal medicine, given in honor of Dr. R. Ellwood Jones III.

■ Dr. and Mrs. Michael S. Brown to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.

■ W. Plack Carr Jr. and Cissy Carr to create two professorships – the Carla and Paul Bass Professorship in Medical Education, Honoring Charles C. Sprague, M.D., and the Sinor/Pritchard (Katy Sinor and Kay Pritchard) Professorship in Medical Education, Honoring Donald W. Seldin, M.D.

■ Mr. and Mrs. Leland W. Carter to support clinical programs at UT Southwestern University Hospital - Zale Lipshy and to support medical research.

■ Jean H. Craver, through a bequest, to support diabetes research.

■ Peter and Charron Denker to create the Charron and Peter Denker Fund for Medical Excellence, in Honor of Steven Leach, M.D.

■ Mr. Louis Dorfman Sr. and Dr. Sam Y. Dorfman Jr. to support clinical research and UT Southwestern's spine program.

■ Mr. and Mrs. James S. Dubose and Mr. and Mrs. James E. Dubose to support pulmonary research in honor of Gwynne D. Keyland.

■ Mr. and Mrs. John F. Eulich to support the 2008 Crystal Charity Ball Coordinated Program for Research and Treatment of Autism.

■ Eye Ball 2008, to support ophthalmology research.

■ Mr. and Mrs. Stanford C. Finney Jr. to create the Stan and Mary Clare Finney Neuro-Oncology Research Fund to support glioma and CNS lymphoma research.

■ The Hon. and Mrs. Richard W. Fisher to establish the Fisher Family Professorship in Women's Mental Health Studies.

■ Gayden Foundation to provide unrestricted support for UT Southwestern.

■ Dr. and Mrs. Alfred G. Gilman to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.

■ Mr. and Mrs. Irwin J. Grossman to support diabetes research.

■ Mr. and Mrs. Ron W. Haddock to support the *Innovations in Medicine* campaign.

■ Mr. and Mrs. S. Roger Horchow to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.

■ Gayle Ann W. Hysinger, through a bequest, to support medical education, research and patient care at UT Southwestern.

■ Dr. and Mrs. Norman M. Kaplan to increase the endowment of the Norman and Audrey Kaplan Chair in Hypertension.

■ J. Luther King Jr. and Teresa C. King, along with Luther King Capital Management, to foster medical research, teaching and patient care programs.

■ Mr. and Mrs. Donald P. Kivowitz to establish the Stacey & Donald Kivowitz Charitable Foundation Fund for Urology under the direction of Drs. Margaret Pearle and Claus Roehrborn.

■ LeukemiaTexas to support a leukemia research project under the direction of Dr. Pier Paolo Scaglioni.

■ Mr. and Mrs. Tom B. Medders III, given in honor of Drs. Elizabeth A. Maher and Bruce E. Mickey, to support genetics research and anaplastic astrocytomas treatment.

■ Harry S. Moss Heart Trust for additional support of cardiovascular research in the Harry S. Moss Heart Center.

■ John R. and Kelley Murrell to support geriatric research, education and clinical care.

■ Once Upon a Time… to support clinical research in surgery and projects in neonatal care.

■ Dr. and Mrs. Charles Y.C. Pak to further support the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research.

■ Dr. David and Anabel Pillow, and Dr. David Pillow Jr. and Sunny K. Pillow, to establish the Pillow Family Medical Student Scholarship Fund.

■ Charles W. Plum, through a bequest in memory of his wife, Margaret McCollister Plum, to support Alzheimer's disease programs.

■ President's Research Council members to establish the Kern and Marnie Wildenthal President's Research Council Professorship in Medical Science.

■ Caren H. Prothro to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.

■ Mr. and Mrs. Lee R. Raymond to support the study of the cellular mechanisms underlying asthma's pathogenesis.

■ Mr. and Mrs. Robert D. Rogers, through the DGBB Foundation, to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.

■ Rudman Foundation to support the Josephine Rudman Laboratory for Alzheimer's Disease Research.

■ Sammons Dallas Foundation to support the Heart, Lung and Vascular Center at UT Southwestern University Hospital – St. Paul.

■ Anne Craddock Schoellkopf, through a bequest, to create the Anne C. Schoellkopf Scholarship Fund for medical students.

■ Mr. and Mrs. William T. Solomon to help establish the Kern Wildenthal, M.D., Ph.D., Fund for Medical Excellence.

■ Eleanor Pierce M. Stevens Trust to support UT Southwestern.

■ Mr. and Mrs. T. Peter Townsend to upgrade the Peter and Joanna Townsend Family Fund for Scholars in Research on Autism Spectrum Disorders to the Peter and Joanna Townsend Family Distinguished Chair in Research on Autism Spectrum Disorders.

■ Mr. Henry Van Beber to support Alzheimer's disease research under the direction of Dr. Craig M. Powell.

■ Olean U. Vincent, through a bequest, to support research on Alzheimer's disease, osteosarcomas and glioblastomas.

■ The Hon. Alan Walne to establish the Walne Family Trust Fund for Alzheimer's Disease Research.

■ Mr. and Mrs. Phillip F. Wiggins to support activities in the Department of Neurosurgery.

■ Mr. and Mrs. Joel T. Williams Jr. to support clinical and research activities.