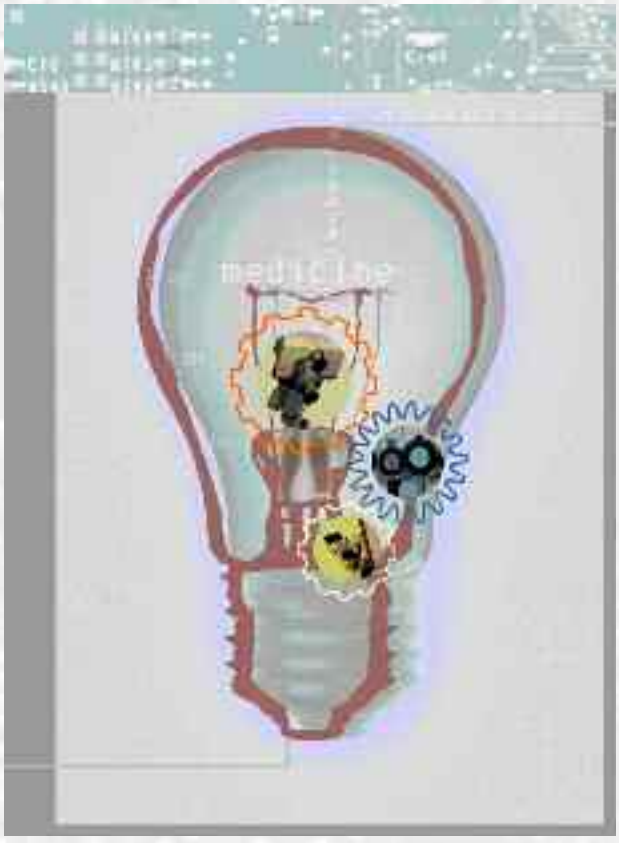
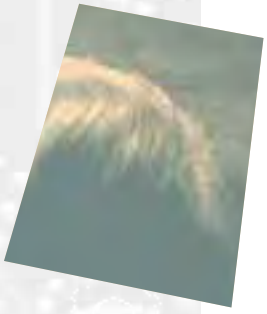
2002 Annual Review

SOUTHWESTERN MEDICINE





Innovations IN Medicine

INSIDE:

Memory

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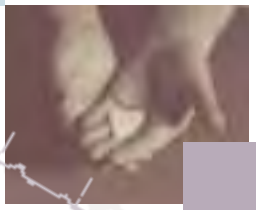
Bioterrorism

Biotechnology

The Magazine of The University of Texas Southwestern Medical Center at Dallas

C O N T E N T S



Articles from *Southwestern Medicine* are available on the World Wide Web at http://www.utsouthwestern.edu.

Alzheimer's Disease
Neurological Disorders
CANCER
heart disease and stroke
pediatric illnesses & birth defects
infectious diseases
immunology and bioterrorism defense
basic molecular research
biostatistics
computational biology
medical imaging,
and BIOTECHNOLOGY

Innovations in Medicine

UT Southwestern's Opportunity to Shape the World of Medical Science

The University of Texas Southwestern Medical Center at Dallas is poised to lead the way in a new era of scientific discovery with its ambitious $450 million *Innovations in Medicine* campaign.

In partnership with the private sector, it can build on the state of Texas' commitment to medical research and technological advancement and seize the opportunity to be at the pinnacle of international medical science and clinical care.

"For UT Southwestern to remain in the forefront of the medical revolution, we must continue expanding the depth and breadth of our research and clinical programs," said UT Southwestern President Dr. Kern Wildenthal. "Our faculty leaders are focused on ensuring that new genetic and molecular discoveries are rapidly applied to the practice of medicine and that the clinical services received by our patients are second-to-none."

"I AGREED TO CHAIR THE COMMITTEE BECAUSE I BELIEVE SO STRONGLY IN THE QUALITY AND DIRECTION OF UT SOUTHWESTERN AND IN THE IMPORTANCE OF THIS CAMPAIGN IN TAKING UT SOUTHWESTERN TO THE NEXT LEVEL."

— William T. Solomon

"THE CAMPAIGN

is off to an exceptionally strong start with a significant number of major lead gifts during the 'quiet phase' of the effort," Wildenthal continued.

Major gifts early in the campaign included four donations totaling more than $64 million: a $25 million distribution from a trust established by Bulah M. Luse; $20 million from the Howard Hughes Medical Institute; $11.7 million from the Harry S. Moss Trust for the Prevention and Cure of Heart Disease; and $7.5 million from Deborah and W.A. "Tex" Moncrief Jr.

William T. Solomon, chairman of Austin Industries, is leading more than 100 prominent civic and business leaders who have volunteered to serve on the campaign's leadership council.

"I agreed to chair the committee because I believe so strongly in the quality and direction of UT Southwestern and in the importance of this campaign in taking UT Southwestern to the next level," said Solomon, who has been on the board of Southwestern Medical Foundation since 1981.

"Serving on the Foundation's board has better enabled me to track the progress of UT Southwestern and to be able to appreciate the results the scientists and researchers there have attained," he said.

Physicians and researchers around the world have been given the blueprint for human life with the completion of the Human Genome Project. Genetic discoveries are yielding new insights into diseases — both common and rare — that afflict millions. Biotechnology — the use of basic-science breakthroughs to create new and better treatments and diagnostic tools — will be a major economic growth area in the future, predicts Wildenthal.

Most of the funds raised in the campaign will be directed toward endowments and project support for research on major diseases, for which breakthroughs are probable over the next few years and decades, and for enhancement of clinical care programs.

The following areas are included among the campaign priorities:

ALZHEIMER'S AND OTHER NEUROLOGICAL DISORDERS. Researchers at UT Southwestern are making significant strides in understanding Alzheimer's. They are also unlocking the mysteries of Parkinson's, epilepsy, visual and hearing disorders, and paralyzing afflictions such as multiple sclerosis, muscular dystrophy, ALS (Lou Gehrig's disease) and spinal injury. Discoveries about genetic and molecular control of brain-cell function are revealing the underlying causes of many neurological diseases, including mental illnesses and substance abuse.

CANCER. UT Southwestern is a leader in research and treatment for a variety of cancers — breast, prostate, lung, ovarian, intestinal, skin and brain, as well as leukemia, lymphomas and pediatric malignancies. New ways to predict genetic susceptibility are being developed, and fresh insights on the regulation of cell division and programmed cell death are providing novel approaches for treatment.

HEART DISEASE AND STROKE. Today, the world's most advanced research endeavor on the underlying causes of heart attacks, heart failure, high blood pressure and stroke is based at UT Southwestern. The Dallas Heart Disease Prevention Project is gathering the most comprehensive data ever assembled on an American population. At the same time, our clinical advances in cardiac transplantation and in the treatment of heart failure are setting national standards. Our work on the genetic and environmental control of risk factors for cardiovascular disease is revolutionizing medicine.

PEDIATRIC ILLNESSES, BIRTH DEFECTS AND INHERITED DISORDERS. Knowledge of the genetic code has opened the way to prevent and cure a host of pediatric diseases. Many illnesses that strike at an early age have genetic influences — congenital heart diseases and other birth defects; sickle-cell disease; cystic fibrosis and other pulmonary diseases; diabetes, rheumatoid arthritis and lupus erythematosus; Crohn's disease and ulcerative colitis; and many forms of pediatric cancers. For these and related diseases, whether they appear in childhood or later in life, basic and clinical research is rapidly leading to new strategies for cures and preventions.

INFECTIOUS DISEASES, IMMUNOLOGY AND BIOTERRORISM DEFENSE. UT Southwestern scientists are working aggressively to develop better vaccines to prevent infections and more potent medicines to treat them. Immunological studies are revealing the body's natural defense mechanisms, how they can go awry and how they may be enhanced. And while we are seeking new ways to neutralize and defeat biological agents that might be used by terrorists, we are accelerating our battle against conventional infectious diseases such as meningitis, hepatitis and AIDS.

BASIC MOLECULAR RESEARCH, BIOSTATISTICS AND COMPUTATIONAL BIOLOGY, MEDICAL IMAGING, AND BIOTECHNOLOGY. With data from the Human Genome Project, UT Southwestern researchers are poised to make major breakthroughs in molecular research and biotechnology. To bring order to the ever-expanding data from research and clinical trials, researchers will rely on biostatistics and computational biology, burgeoning fields that merge computer science, mathematics and biomedicine. Both research and clinical diagnosis are being transformed by amazing advances in the ability to make computer-assisted images of the body's organs, tissues, cells and molecules. Many of the discoveries that will shape our future will be made in concert with private biotech companies to ensure that our discoveries are translated as rapidly as possible into effective and useful products.

FACILITIES AND EQUIPMENT. Without modern facilities and equipment, even the best scientists cannot apply their full intellectual resources to conquering the diseases we are targeting. Funds are being sought for the largest research building ever constructed at a Texas university or medical center, for a state-of-the-art medical imaging facility, for advanced technical research equipment, and for major clinical enhancements at St. Paul University Hospital, Zale Lipshy University Hospital and UT Southwestern's outpatient facilities.

ENDOWED CHAIRS AND SCHOLARS. Our future depends on our ability to assemble teams of the finest doctors and scientists available, retain them and allow them to flourish. Endowed chairs for outstanding senior faculty members will allow us to recruit and retain those who have already achieved great distinction in medical science and clinical care. Simultaneously, our acclaimed program for Endowed Scholars will be expanded, enabling us to attract tomorrow's superstars and launch their careers under the guidance of Nobel-caliber mentors.

ENDOWED CENTERS, CLINICAL PROGRAMS AND RESEARCH FUNDS. Support for targeted areas of medicine will bring together laboratory researchers and clinicians to work collaboratively on the most important and challenging problems of the future. UT Southwestern's tradition of utilizing multidisciplinary teams of the best basic scientists and doctors to bring the full force of modern science to bear on the major problems of medicine will be enhanced and extended, and our clinical services will be second-to-none.

CLINICAL TRIALS OF NEW THERAPIES. Although UT Southwestern has long been a leader in providing access to the latest drugs and therapies under development, our clinical trials program must be expanded so that no one from our region need go elsewhere in search of the latest medical hope. Added funding will allow us to enlarge and improve the existing structure of clinical trial programs and attract faculty and research nurses with extensive expertise in this area. This will ensure that the very latest cutting-edge medicine will always be available to patients in North Texas.

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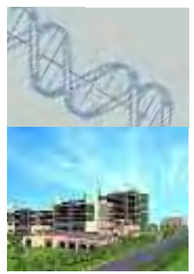
WILLIAM T. SOLOMON AND DR. KERN WILDENTHAL



Innovations in Medicine

Continued from page 5

Enhanced clinical services. Year by year, as UT Southwestern's reputation as an international center of medical excellence has grown, demands for our clinical services have multiplied. Once centered at Parkland Memorial Hospital, Children's Medical Center of Dallas and the Dallas Veterans Affairs Medical Center, our physician practice now also serves hundreds of thousands of patients at Zale Lipshy and St. Paul University Hospitals as well as at UT Southwestern's multiple outpatient clinics. All this has stressed the existing systems and created the need for a transformation of our patient services programs to ensure that each of our patients will be treated efficiently, graciously, expeditiously, and with all the care and attention they deserve. Additional support will enable us to update telephone, record-keeping and billing systems; establish electronic medical record systems; enhance communications with referring physicians; and provide optimal training for all staff who interact with patients — in sum, to provide a quality of care and service that is second-to-none. ✣

William T. Solomon

Leadership Council Chairman William T. Solomon leads the committee of prominent civic and business leaders who have volunteered to help UT Southwestern achieve its $450 million goal.

Solomon is chairman of Austin Industries. A Dallas native, he is a graduate of Southern Methodist University and the Harvard Graduate School of Business.

Solomon is a member of the boards of Belo, Hoblitzelle Foundation and Southwestern Medical Foundation. He previously has served as chairman of the Dallas Citizens Council; Greater Dallas Chamber; and Dallas Together Forum, which he co-founded in 1991.

He received the J. Erik Jonsson Ethics Award from the Cary M. Maguire Center for Ethics and Public Responsibility at SMU in 2000, and the Annette Strauss Dallas Together Forum Award in 1999. Solomon was named to the Texas Business Hall of Fame in 1996.

Leadership Council

Ebby Halliday Acers
Pedro Aguirre
Susan Albritton
Ruth Altshuler
Barry G. Andrews
Kim J. Askew
Marilyn Augur
George S. Bayoud, Jr.
Louis A. Beecherl
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Gene H. Bishop
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Norman Brinker
Denny Carreker
Don Carty
Al Casey
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Sarinder Chhabra
J. H. Cullum Clark
Mrs. William P. Clements, Jr.
Ray Clymer
Michael J. Collins
J. Jan Collmer
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Cece Smith
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Theodore H. Strauss
John Stuart
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Gifford Touchstone
Tim Wallace
Tom Walter
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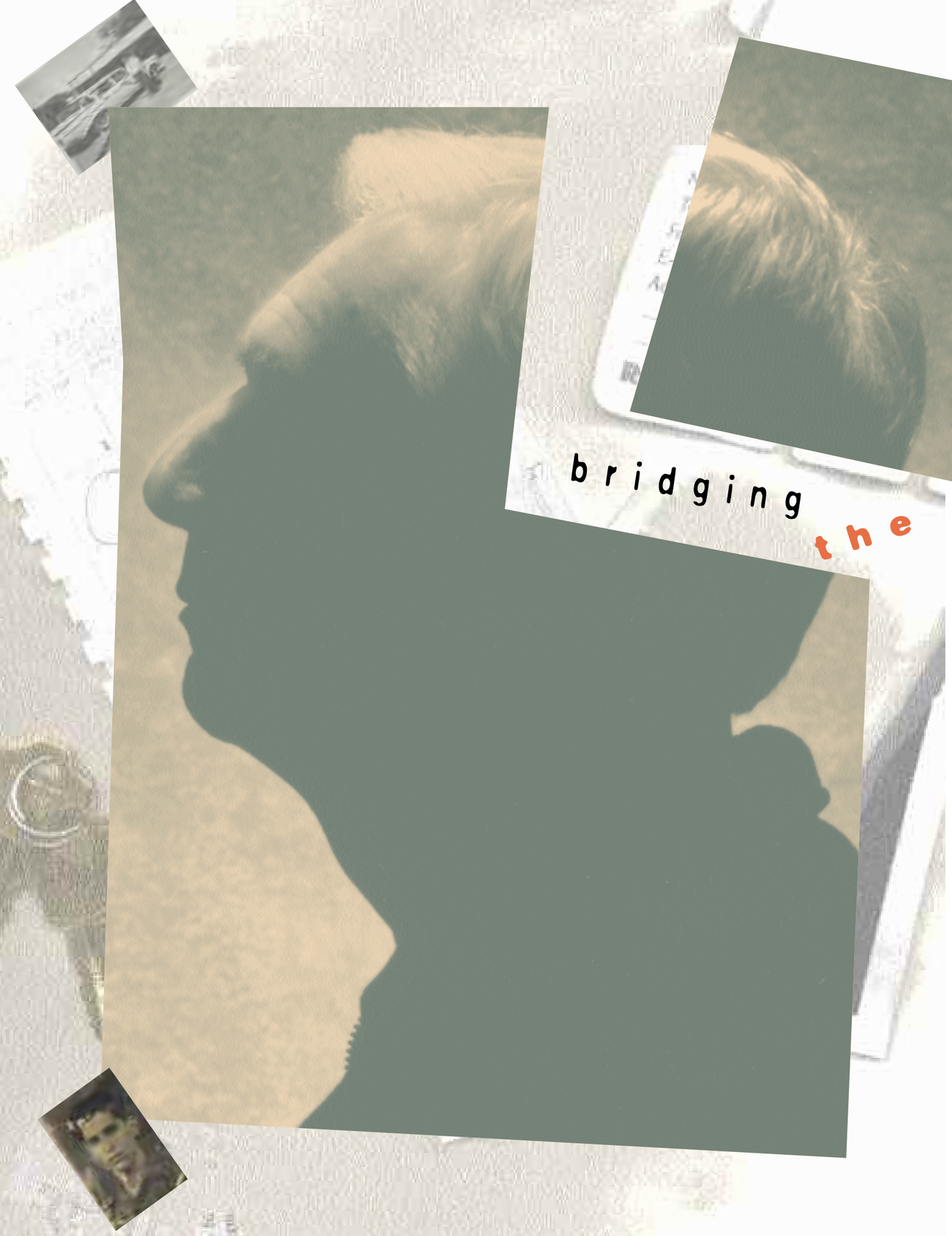


bridging the

Memory gap

By Mindy Baxter

Hold a piece of ice in your hand, and your brain is working feverishly. The sensory traits of the ice travel up nerve endings to your brain, where the feeling is registered.

Cold. Wet. Slippery. Hard.

But you knew how it would feel before you even touched the ice. You knew from experience. The first time you touched ice, the sensation traveled up nerve endings to your brain, where it was processed and stored. It became part of your permanent memory.

And this happens millions of times.

Memory — how it's processed and how it's stored and retrieved — is just one of many intricacies of the brain scientists and physicians are studying at The University of Texas Southwestern Medical Center at Dallas.

The Center of the Brain

A MEMORY ENTERS YOUR BRAIN not as a picture or sound or word or feeling, but rather as tiny electrical impulses traveling at warp speed on a superhighway of neurons. The impulses careen along nerve pathways in just milliseconds from your finger or ear or mouth to the center of the brain, the hippocampus. There, your brain evaluates the impulses. Is this something to keep or trash? Is it a visual image or an auditory sensation? Is it a piece of information needed again soon or something that might not be processed again for years?

Then, your brain files the information away, like another piece of paper on your desk. Sounds head toward your temporal lobes, portions of the brain located near your ears. Visuals are directed toward the occipital lobes at the back of the head. Touch is sent to the parietal lobe, which extends from your ears to the top of your head.

Of course, like most simple explanations, it's not so simple.

Dr. Munro Cullum, acting chairman of psychology and professor of neurology at UT Southwestern, says memory is a complex set of abilities and is not a unitary phenomenon.

"Memory is multifactorial. There are different types of memory and all have a different role," he said.

Can you remember your elementary school and first-grade teacher's name? What about the name of the first president of the United States? Odds are you can name those, Cullum said. Long-term or remote memories have already been firmly stored, making them less susceptible to diseases or injuries to the brain.

In contrast, the ability to form new memories is more vulnerable. Your brain doesn't place the same importance on what you had for dinner as it does your mother's name.

Memory often works like a contagion, with one memory triggering the next. Memories can be trig - gered by various stimuli, including things we see, feel, touch, smell and imagine.

After age 20, our brain and memory begin a slow decline. That decline doesn't usually become noticeable until our later years.

ALZHEIMER'S PATIENTS HAVE TROUBLE WITH ENCOD- ING, WHICH INVOLVES STORING A MEMORY, AND RETRIEVAL, WHICH INVOLVES THE BRAIN FINDING AND BRINGING FORWARD A MEMORY.

Alzheimer's Disease

MEMORY LOSS both intrigues— and scares — us.

Diseases — from Alzheimer's to depression and addiction, to post-traumatic stress disorder and multiple sclerosis — can all drain memory.

In most, the hippocampus is one of the affected areas. Levels of oxygenation, medications, steroids, disease and head injury can all influence the hippocampus' effectiveness as the brain's traffic director. And without a properly functioning hippocampus, memory communication throughout the brain can break down.

"As we age, we all experience some memory loss," said Dr. Myron Weiner, professor of psychiatry and neurology, who trained in geriatrics and now specializes in Alzheimer's disease. "In general, people find if they don't force it, the information will pop up. Most people can cue themselves. Things may take a little longer to process, but it's still there.

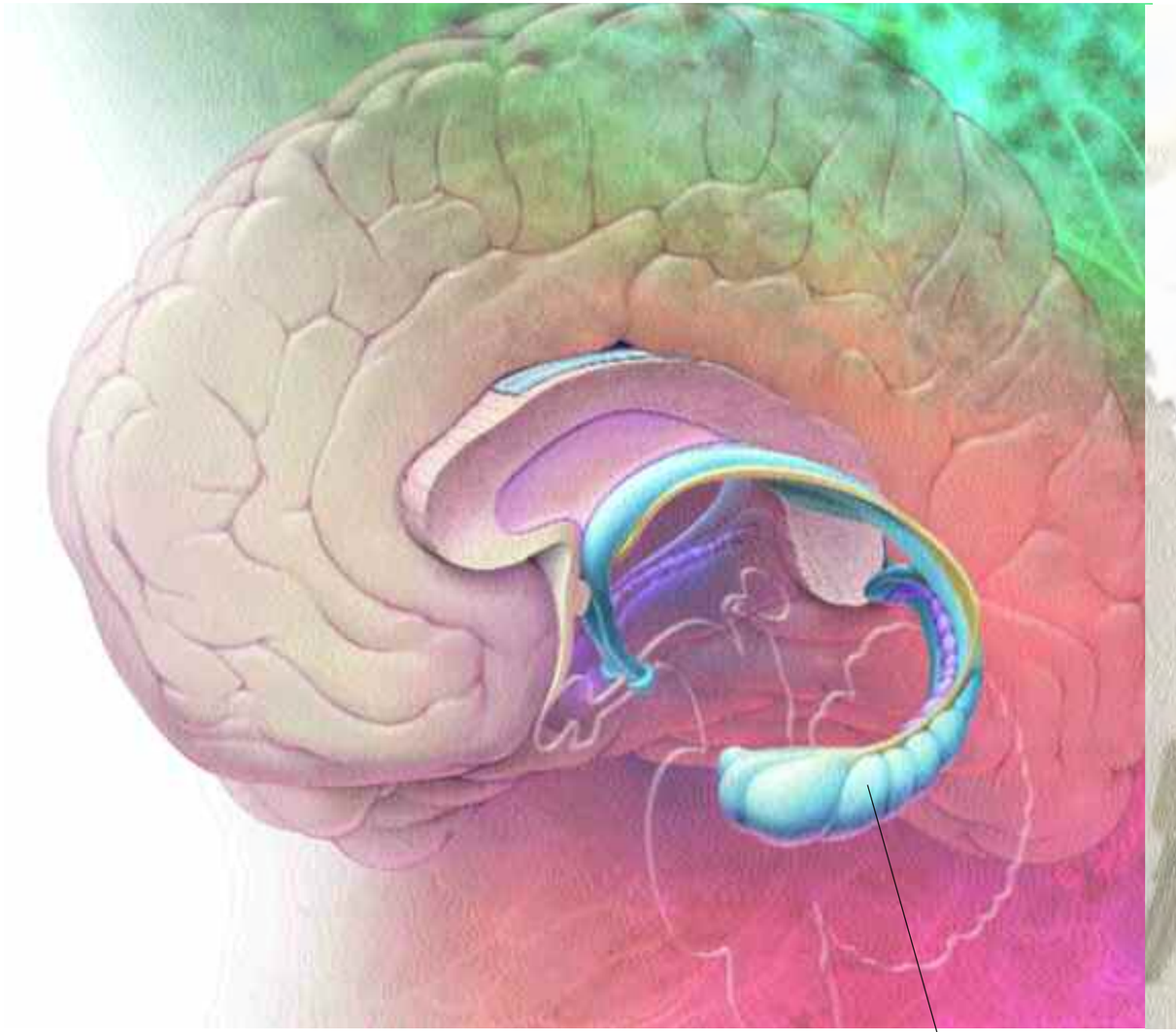
"But pronounced memory loss is not normal. It's really a matter of degree. You reach a certain threshold. It's like heart disease. Lots of us have cholesterol in our vessels, but we don't all have diagnosed heart disease. It's only at a certain point that heart disease is diagnosed. The same is true for Alzheimer's disease and memory loss."

Holder of the Ardine S. Ard Chair in Brain Science and the Dorothy L. and John P. Harbin Chair in Alzheimer's Disease Research, Weiner sees patients in UT Southwestern's Alzheimer's Disease Center, one of 29 funded by the National Institute on Aging. He estimates that more than half of his patients come to him not because they recognize they are experiencing loss, but because their families do.

"We used to see most Alzheimer's patients about four years after the onset of disease," he said. "But it's closer to three years now. More people are knowledgeable."

Alzheimer's patients have trouble with encoding, which involves storing a memory, and retrieval, which involves the brain finding and bringing forward a memory.

Patients with Alzheimer's, after being told a story about a boy in a rowboat fishing on a lake, might retell the story with plausible but incorrect or unrelated tangents, according to Cullum. Suddenly, the boat might be an ocean liner in the Gulf of Mexico.



THE HIPPOCAMPUS, WHERE EMOTION AND MEMORY ARE REGULATED.

"In Alzheimer's the information has trouble getting in and may become distorted, and this is compounded by deficits in retrieval," he said.

Four percent of people at age 75 have Alzheimer's disease, but by age 85 the average has climbed to 50 percent — and even higher if there is a family history. With each passing year the risk rises. And with life spans increasing in the United States, Weiner said specialized facilities like the Alzheimer's Disease Center at UT Southwestern play a key role in identifying and managing a growing public-health problem.

"Simply put, the country cannot afford institutional care for all of these patients," he said. "We would bankrupt the health system. With family support groups and other assistance, many families can maintain their loved ones at home."

Weiner finds that many patients are happier at home, as well.

"Certainly, caring for an Alzheimer's patient is stressful and difficult," he said. "It's not rewarding like caring for an infant, where advances are made every day. You're always giving more because the patient is always losing more."

Other Diseases of the Brain

ALZHEIMER'S MAY BE the best known of the memory thieves, but there are other diseases that rob memory as well.

People with Parkinson's disease often experience memory problems.

"In Parkinson's patients, the information is getting in, but they have trouble getting it out," Cullum said.

Brain scans of multiple sclerosis patients show lesions that can lead to memory loss. MS patients also can have memory problems as the side-effect of medications or of fatigue or depression. Sometimes antidepressants or drugs that stimulate the brain can help.

In MS patients, as in Parkinson's patients, memory retrieval is affected rather than encoding, said Dr. Elliot Frohman, associate professor of neurology and ophthalmology and head of UT Southwestern's MS program.

"Memory is central to much of what we do, but especially to learning," Frohman said. "Without the ability to learn, we lose the ability to be productive. If we had to take the time to reassemble every task we do every day in our minds, we'd be in quicksand."

"In Alzheimer's the information has trouble getting in and may become distorted, and this is compounded by deficits in retrieval."

—Dr. Munro Cullum

Neurons and Signaling

THE BRAIN IS composed of trillions of nerve cells. These brain neurons communicate constantly with each other through electrical activity and chemical signals. Even while we sleep, our neurons are firing away, telling each other and our bodies what to do with thousands of messages each second.

But a neuron won't act when it has received a message from only one neuron. It must receive messages from several different neurons before it reacts. If one neuron dies, communication does not stop; only as more and more neurons become injured or diseased does communication stall.

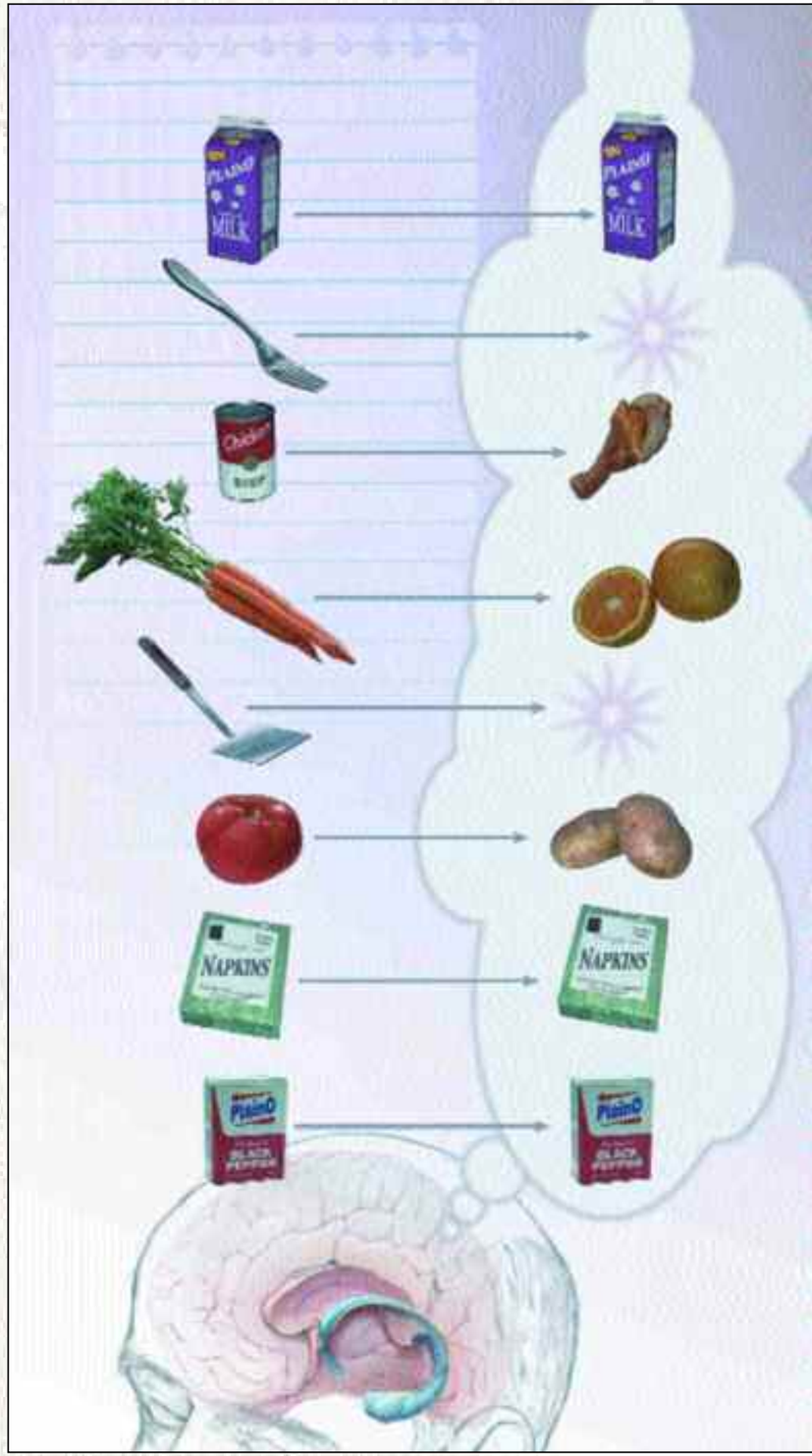
Memory lives in the nerve cells, where it grows infinitely more complex and difficult to understand.

Dr. Thomas Südhof, director of the Center for Basic Neuroscience and an investigator in the Howard Hughes Medical Institute at UT Southwestern, has spent his career exploring the communication between neurons and how they release chemical signals to each other. A remodeling of the neurons and the connections between them seems to be related to the process of memory, Südhof said.

How we remember

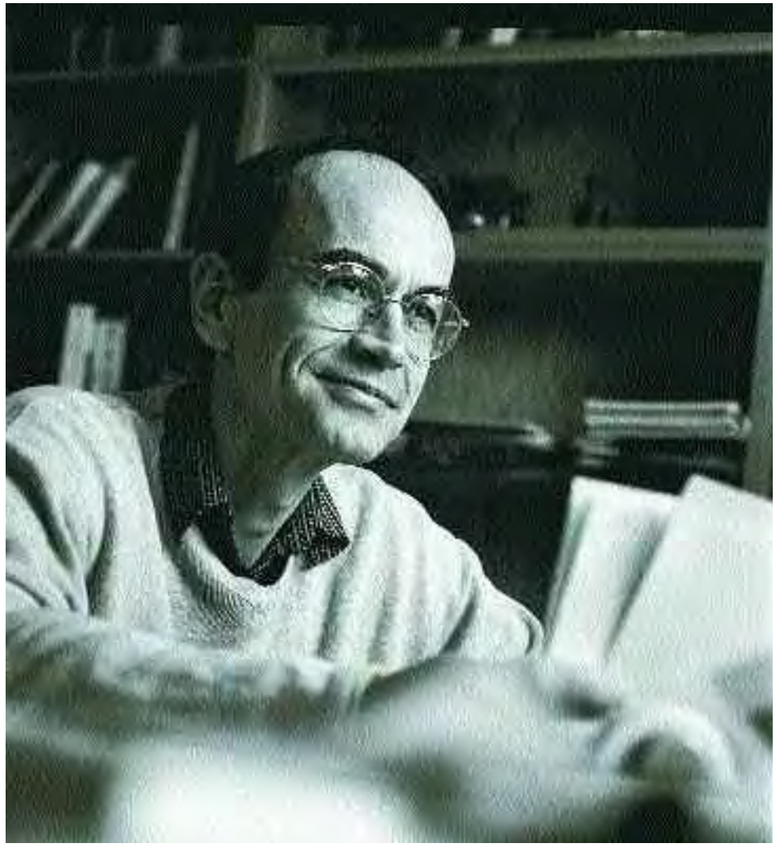
In this example of a memory task, a shopping list of items is presented for encoding and memorization. Some items are recalled with good accuracy (milk, napkins, pepper). Sometimes we may "draw a blank" and forget things completely (fork, spatula). Other responses may reflect faulty recollections or "near-misses" that bear some relationship to the target items (chicken soup – chicken leg) or belong to the same general category (carrots – oranges) or specific category (tomato - potatoes).

Neuroanatomically, the process of encoding and retrieving such recently presented information is dependent upon memory systems in the temporal lobes of the brain, primarily involving the hippocampus.



"It is amazing that you can remember things that happened decades ago. Fundamentally, everything that happens in the brain happens because cells communicate with each other, but that is only the beginning."

—Dr. Thomas Südhof



"In many ways, memory is a tremendous challenge," Südhof said. "The nature of memory storage is unclear. It is amazing that you can remember things that happened decades ago. Fundamentally, everything that happens in the brain happens because cells communicate with each other, but that is only the beginning."

Cell communication is complex, since one neuron may constantly talk to 1,000 or 10,000 other neurons.

"Memories are not like something you write down on paper," said Südhof, who holds the Loyd B. Sands Distinguished Chair in Neuroscience and the Gill Distinguished Chair in Neuroscience Research. "The brain is constantly losing neurons, but memories are not lost when this happens. Ensembles of neurons, almost like a circuit, hold the memories."

One advantage in the study of memory is that it is relatively easy to measure, Südhof said. Show 10 different people 10 different things; ask them to recall them 10 minutes later; and you've measured memory.

But with synapses — or connections between nerve cells — millions of times more numerous than the number of genes in the human genome, the web of brain function remains an enormous challenge for researchers, Südhof said.

Much of the ongoing work at UT Southwestern concerns the nature of cell communication and what role it plays in memory. For example, Dr. Joachim Herz does research on the biochemistry of cellular receptors that are involved in the transport of cholesterol and other molecules in the brain. His work has shown how disturbances in cholesterol can play a role in diseases like Alzheimer's. In the brain, cholesterol interacts with proteins, altering the chemical communication between neurons. For instance, the creation of the "Ab" protein, which plays a pivotal role in the development of Alzheimer's disease and gives rise to amyloid plaques in Alzheimer's-affected brains, is reduced under low-cholesterol conditions and increased when cholesterol is high.

"As medicine has gotten more advanced and people are living longer and longer, research into how the brain works has grown more important," said Herz, professor of molecular genetics. "We've extended the life span, but that's no good if your brain gives out."

Herz's continued research focuses on how these key chemical pathways work and what happens to them when cellular communication breaks down. With a clearer understanding of this process, Herz, holder of the Thomas O. Hicks Family Distinguished Chair in Alzheimer's Disease Research, hopes to uncover Alzheimer's disease treatments that attack the disease process at the most fundamental level.

He believes Alzheimer's disease will be conquered in the next two decades.

"What goes wrong within a cell?" he asks. "What does it mean? Exactly what are the proteins in cells doing? We have a lot of exciting scientific work ahead of us." ✣

Memory and Emotion

How emotions work

on the brain's memory is a complex question of integrated circuitry, cell communication and structural changes in the neurons of the brain.

"We still don't understand what makes long-term memory, and I'll defy anyone who says the opposite," said Dr. Eric Nestler. "It's something like a pinball machine, with protein X bouncing off of protein Y and hitting protein Z. But it's a biochemical cascade of these interactions infinitely more complex than a pinball machine."

Nestler should know. His 30-year career has focused primarily on the biochemical mechanisms of addiction. While scientists may not yet understand how memories are made, the chairman of psychiatry says it's obvious memory affects addiction.

"Cocaine addicts used to tell people that those old antidrug billboards with the mirror, white powder and razor blade were one of the most potent triggers for them," said Nestler, holder of the Lou and Ellen McGinley Distinguished Chair in Psychiatric Research. "They would avoid driving on highways just to avoid seeing the billboards and bringing back a powerful wave of craving.

"For a former addict, their most powerful memories are of highs and lows. Their memories are as intense as for a person suffering from post-traumatic stress disorder after war or a rape victim reliving the rape again and again. The memory of the high is just that powerful and all-consuming."

Visual and emotional cues are part of what makes memory so complicated. The way we remember multiplication tables is different than how we remember the way we felt on our first date. The way we remember not to do something is different than how we remember to do something. As our knowledge of the brain grows more sophisticated, researchers are beginning to see that emotions help channel and organize our memories, Nestler said.

"We will always remember what day the airplanes crashed into the World Trade Center," he said. "We have a strong emotional trigger for that day."

What is it about memory that makes us so afraid to lose it? The answer, doctors say, is really quite simple.

We are our memories.

"Memory is us," Nestler said. "If you don't have memory, you don't have yourself. You're a different person if you have different memories." ✣

UT Southwestern researchers are reaching out to the community in unique ways to study and prevent heart disease.

Community HEARTBEAT

By Barbara Bedrick

Since 1963, Carl Simon has managed Graham's Barbershop while handing out plenty of advice to his patrons. Snipping and shearing, Simon now also talks about cutting their blood pressure.

In the past six months, almost 2,000 clients have had their blood pressures measured in Graham's and two other Fair Park-neighborhood barbershops, and hundreds of African-American men with uncontrolled high blood pressure have been identified.

This neighborhood-based intervention study is an offshoot of the landmark Dallas Heart Disease Prevention Project — also known as the Dallas Heart Study — at The University of Texas Southwestern Medical Center at Dallas.

Heart disease, in particular high blood pressure, is highly prevalent in blacks, according to the Centers for Disease Control and Prevention.

"Despite impressive declines in the rate of heart disease among all Americans over the past 25 years, it is still the No. 1 killer of Americans, and African-Americans shoulder a greater burden than any other ethnic group," said Dr. Ronald Victor, chief of hypertension at UT Southwestern.

"Despite impressive declines in the rate of heart disease among all Americans over the past 25 years, it is still the No. 1 killer of Americans, and African-Americans shoulder a greater burden than any other ethnic group." — *Dr. Ronald Victor*

Heart disease kills more people every year in Dallas County than cancer, AIDS, motor vehicle accidents and violent crime combined, state health officials report.

Heart disease claims Dallas County residents at a higher rate than the nation's. On average, 14 people a day die of heart disease in Dallas County. To reduce that toll, researchers at UT Southwestern are forming collaborations between clinicians and basic scientists, with researchers nationwide and with Dallas community leaders, in a battle against cardiovascular disease.

Innovative clinical research

In 1998 the American Heart Association announced that the Donald W. Reynolds Foundation sought to establish a series of centers of excellence around the country to move toward cures for atherosclerotic heart disease, the most common cause of heart disease that leads to heart attacks. The foundation wished to fund cardiology centers to coordinate basic laboratory research with clinical studies involving patients with heart disease.

After an intense nationwide competition, the first Donald W. Reynolds Cardiovascular Clinical Research Center was established at UT Southwestern in October 1999 with a $24 million grant, the largest single grant to one medical center for heart-disease research.

Dr. Helen Hobbs, director of the Eugene McDermott Center for Human Growth and Development at UT Southwestern, directs the Reynolds Center.

"What captured the imagination of the review group was that we proposed bringing together the best of population science and laboratory science to focus on disparities in heart health," said Victor, principal researcher for the Dallas Heart Study and for center projects studying high blood pressure.

Hobbs and Dr. Scott Grundy, director of the Center for Human Nutrition at UT Southwestern, are the principal researchers for the projects studying cholesterol.

"Most heart-disease studies are multicenter studies and include populations from different regions of the country," Hobbs said. "We designed the Dallas Heart Study to be performed solely in the community in which we work and provide health care.

"In the first phase of the study we will learn a great deal about heart disease in Dallas County, including its geographic and demographic distribution. We will learn about the risk-factor profile of our own population. If the participants in the study agree by signing a consent form, we can recontact them to take part in future studies, which may include more detailed testing to probe the underlying mechanisms that cause heart disease. We can also perform family studies to explore the genetic underpinning of the disease.

"In the second phase of the study, we will take what we have learned about heart disease in our own community to design educational and therapeutic interventions with the goal of reducing heart disease in Dallas County."

Dr. Eric Olson, chairman of molecular biology at UT Southwestern, also is a principal researcher in the Reynolds Center. His focus is on defining the pathways involved in enlargement of the heart and the use of stem cells to potentially repair a damaged heart.

To ensure success, a team of individuals with diverse talents was required. Dr. Ronald Peshock, assistant dean for informatics at UT Southwestern, oversees the heart imaging studies performed at the Mary Nell and Ralph B. Rogers Magnetic Resonance Center. Drs. DuWayne Willett, associate professor of internal medicine, and Patrice Vaeth, assistant professor of internal medicine, are the project managers for the Dallas Heart Study. Dr. Ivor Benjamin, professor of internal medicine, leads the education of cardiology trainees and junior faculty in patient-oriented research.

The four goals of the Reynolds Center are to:

- Enhance the prevention of atherosclerotic heart disease;
- Reduce premature death and disability from heart disease throughout Dallas County;
- Close the ethnic gap in heart disease in Dallas County;
- Create a large group of study participants from the community to participate in future studies of heart disease.

"Our goal is to learn why more people are not being treated to avoid the development of heart disease," said Hobbs, holder of the Eugene McDermott Distinguished Chair for the Study of Human Growth and Development and the Dallas Heart Ball Chair in Cardiology Research. "What are the barriers to treatment in our community? We are hoping to use this information we gather to design intervention studies that will be tailored to the particular problems of the people we serve as physicians."

Building a community partnership

Nine months before recruitment began in the Dallas Heart Study, the research team formed a community advisory board, led by the Rev. Zan Holmes, Rodger Meier and Liz Flores-Velasquez, and recruited Myra Hollins as director of community outreach.

"We have excellent relationships with the community due to the hard work of our Community Advisory Board," Hobbs said. "We are learning a tremendous amount about our community, its neighborhoods, its attitudes and the distribution of disease."

The Dallas Heart Study randomly surveyed about 15,000 Dallas County residents of all social classes and geographical locations. By design, half of the study participants are female and half are minorities, to ensure adequate representation of heart disease in women and ethnic groups.

"We exceeded our study goals, recruiting more than 6,000 Dallas County residents, ranging in age from 18 to 65, to participate in the Dallas Heart Study," Victor said. "Because participants could not volunteer but were selected at random, each one represents hundreds of people like themselves with the same socio-demographic background and the same characteristics. This gives us a more accurate view of heart disease and its risk factors throughout Dallas County."

Three phases made up the Dallas Heart Study's initial project. The first phase included a 60-minute in-home questionnaire surveying not only medical and family history of heart disease but also personal knowledge, attitudes, and beliefs about its prevention and treatment. In Phase 2, blood and urine specimens were collected; these will be used to discover new early markers of heart disease, including genetic profiles. In Phase 3, participants came to the Rogers Center to obtain electrocardiograms to chart the heart's electrical activity as well as a series of imaging studies of the heart and body.

The imaging tests included electron-beam computed tomography to measure calcium deposits in the heart and magnetic resonance imaging to produce three-dimensional images of the heart. Doctors, using a DEXA scan, also measured fat distribution throughout each participant's body. Blood pressure was taken at all three visits.

"Entering our fourth year of the Dallas Heart Study, we had more than 1 million MRI images to evaluate and review," said Willett.

Kevin Burns, an African-American participant who coaches youth softball in DeSoto, expressed relief after hearing his test results. "I didn't have a family history, but I worried I had high blood pressure or an even bigger problem," he said.

But for many, the Dallas Heart Study was an urgent wake-up call.

"Already, the study has helped save many lives in Dallas County," Victor said. "We have identified more than 500 people with high blood pressure who did not know they had it until they participated in the Dallas Heart Study. We urged each of them to go to community-based or Parkland Memorial Hospital physicians to get it under control."

"We are learning a tremendous amount about our community, its neighborhoods, its attitudes and the distribution of disease."

— *Dr. Helen Hobbs*

"We exceeded our study goals, recruiting more than 6,000 Dallas County residents, ranging in age from 18 to 65, to participate in the Dallas Heart Study."

— *Dr. Ronald Victor*

High blood pressure, or hypertension, which affects 50 million Americans, is often referred to as the silent killer because its symptoms often go unnoticed until complications occur.

Many in the Dallas Heart Study learned they had high levels of glucose, including diabetes, or had high cholesterol. Diabetes affects more than 16 million Americans and, like high cholesterol, is a risk factor for coronary heart disease.

"The tremendous community participation in this study is important," Victor said. "Most of what we know about risk factors for heart disease was derived from the Framingham Heart Study, in which 99 percent of the participants were Caucasian. The Dallas population is much more representative of the entire United States."

What Hobbs, Victor and their colleagues discover may help determine how doctors treat heart disease in women and minority groups, including blacks and Hispanics, where health problems have historically received less focus than they have in white men. Understanding behaviors and beliefs, Hobbs said, may be key to assembling a comprehensive health-care strategy that employs the most effective courses of action in medications, treatments and therapies to improve the control rates and reduce deaths from heart disease in men and women of all races.

"We are learning that there are significant differences in the attitudes and beliefs about heart disease in different ethnic communities," Hobbs said. "We cannot use the same messages and approaches when we design interventions to increase the awareness and treatment of heart disease."

While unraveling the mysteries of heart disease and intervention, UT Southwestern researchers also face a shift in the nation's "stroke belt." The Southeastern seaboard, once considered to hold that dubious title because of its high rates of strokes, hypertension and heart disease, has nearly surrendered the distinction to the Southwest.

"The 'stroke belt' is moving to Texas, and the rates of heart disease and stroke are becoming higher in Texas than in many other states," Victor said. "Whether it's lifestyle or diet, we're not certain."

Genetics of the heart

After more than three years of research, Hobbs can appreciate how far the study has come, and how much remains to be done. The DNA of each participant has been banked for genotyping.

"We will be analyzing more than 1,000 sequence variations in the human genome and determining how they relate to heart disease or to risk factors for the development of heart disease," Hobbs said.

Study researchers will define genetic factors contributing to hypercholesterolemia, an inherited inability to metabolize cholesterol, and will study the genetic determinants that control plasma levels of cholesterol-rich lipoproteins, which in high concentrations are associated with coronary atherosclerosis.

Another team of scientists led by Olson, director of the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer and the Nearburg Family Center for Basic Research in Pediatric Oncology, is working to solve the puzzle of cardiovascular disease at the genetic level.

"My lab is working at the most fundamental level to understand how the heart works, and we're continually discovering new genes and new mechanisms for how the heart functions," Olson said. "Understanding the heart is like putting together a jigsaw puzzle. You can't put the puzzle together until you have all the pieces."

Olson's team has identified a new gene, called *HOP,* which regulates the number of heart muscle cells during development. The findings were published in the September 2002 issue of *Cell.*

"The HOP protein could be a really important piece of the puzzle for how the heart forms," said Olson, holder of the Robert A. Welch Distinguished Chair in Science. "Heart cells lose their ability to divide after birth, and that's the biggest hurdle in cardiovascular medicine because that means when the adult heart gets injured from a heart attack, it has no way to repair itself. So if one could develop strategies that could induce heart cells to divide, it would have very important implications."

The DNA of Dallas Heart Study participants with congenital or acquired heart disease will be studied and also will be screened for mutations in the *HOP* gene.

The identification of another heart gene regulator, *HDAC9,* is another primary focus of Olson's heart study projects. In a study published in the August 2002 issue of *Cell,* Olson described the mechanism by which *HDAC9* regulates cardiac hypertrophy, or enlarged hearts.

"Our goal at the Dallas Heart Study is to be able to explain heart failure in the context of a pathway from A to Z – all the steps involved," Olson said. "Once you know all the steps, then you can develop drugs or at least rationally think about how to develop drugs to target various steps in the pathway."

Olson's second study project involves angiogenesis, the development of new blood vessels, and gene transfer research. There are two approaches, each with different hurdles, but Olson believes both are possible.

From left to right: Graham's Barbershop; Carl Simon at work; and Felton Stevens Jr., research assistant, takes Chester Smith's blood pressure.

Barbershops are ideal settings for one-on-one education in a familiar environment, providing a unique opportunity to see if the control of hypertension in black men can be improved. "Getting one's blood pressure measured in the barber's chair could become as ingrained as getting one's hair cut." — *Dr. Ronald Victor*

One approach is to convert nonheart cells into heart cells by transferring in the master genes for heart formation — using either any nonheart cell or a stem cell. The other approach, Olson said, is to find the undiscovered signal that enables heart muscle cells to divide.

"I think it's going to be possible to regenerate the heart. I really do," said Olson. "I think there is going to be a way to unlock the ability in the heart to repair itself, and that's going to be a revolutionary therapy. No one yet has done effective gene therapy in humans.

"The heart has a very precise electrical activity that sustains its rhythmic contractions one time per second. If you disturb the architecture of the heart, it can mean electrical disturbances that can cause sudden death."

To restore function to the damaged heart, some very precise remodeling will be required.

"What is so unique about the Dallas Heart Study is that there are so many people across the country studying just one facet of heart disease, either just basic science or just epidemiology," Olson said. "There are few, if any, other examples where the entire research effort is brought together under one umbrella in an interlocking way so that the ideas and the technologies freely flow between the groups, and I believe that has made this a very special project."

Snipping a deadly disease

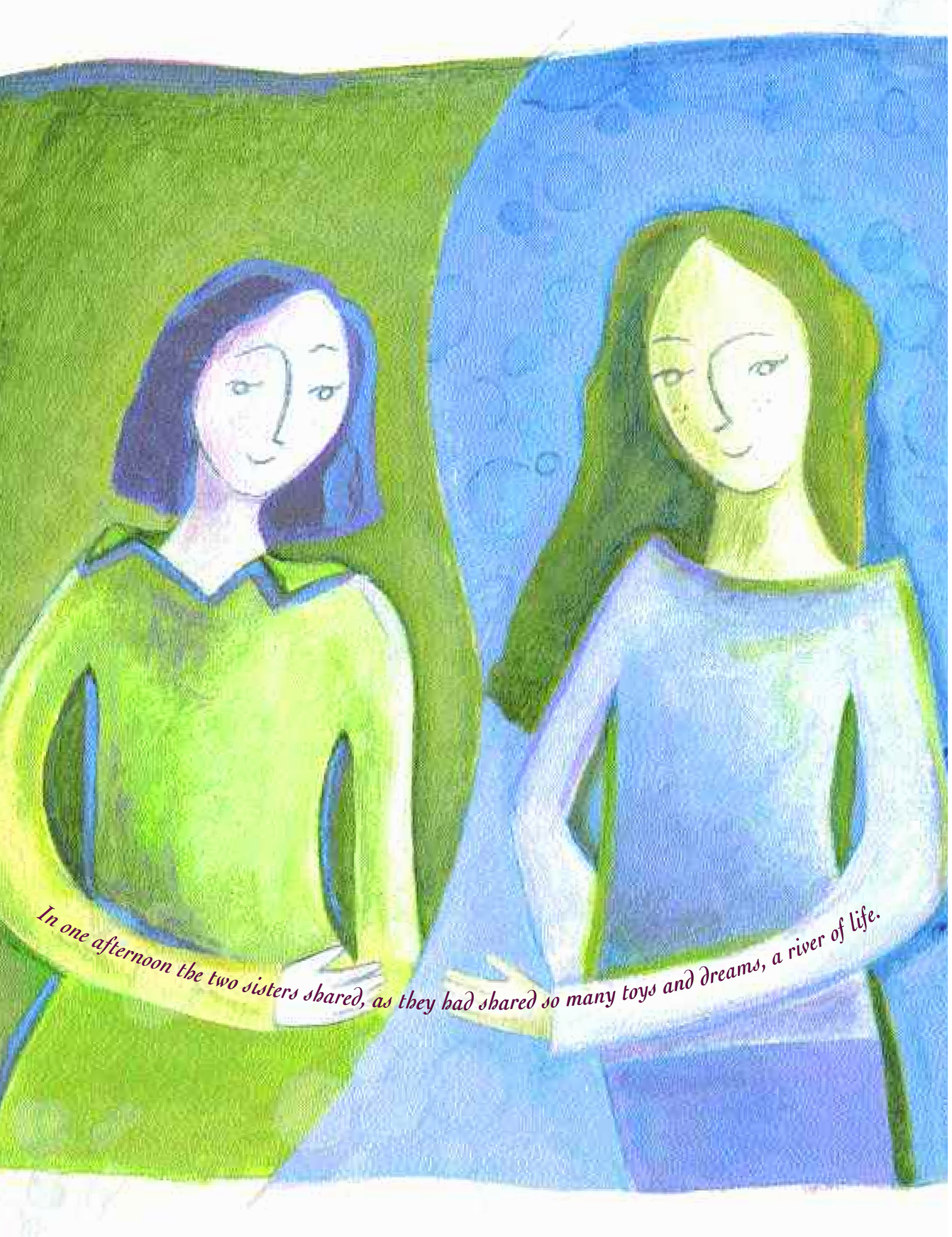
UT Southwestern researchers are beginning to use the wealth of information about heart disease in Dallas County to devise and test new interventional programs to improve early detection and prevention of heart disease and its risk factors.

The pilot study spin-off involving Graham's and the other barbershops is called "Cut Your Pressure." The goal of the project is to determine if barbershops are effective places to improve the early detection and treatment of high blood pressure in black men, the group identified by the Dallas Heart Study as having the highest rates of untreated high blood pressure.

"We chose the neighborhood barbershop because it casts a wide net," Victor said. "Our pilot data indicated that African-American men are loyal customers of their chosen barbershop and average several haircut visits per month."

Barbershops are ideal settings for one-on-one education in a familiar environment, providing a unique opportunity to see if the control of hypertension in black men can be improved, Victor said.

"Getting one's blood pressure measured in the barber's chair," Victor said, "could become as ingrained as getting one's hair cut." ✣



Shelby Marshall gave her sister a magnificent gift on a cold January day in 2000. What was simply to Shelby bone marrow meant survival for Grace.

River of Life

Grace Marshall's days are measured in homework, gymnastic classes and schoolyard friendships, but the 9-year-old's life is measured by the love of her family and an extraordinary gift from her 12-year-old sister.

Grace's mother can't pinpoint the day that the Marshall family's lives began to unravel, but sometime in 1997 unexplained bruises began to appear on her youngest daughter's body. The once-animated 4-year-old had lost much of her energy, and the Marshalls feared the worst.

The devastating diagnosis that Grace had acute lymphocytic leukemia sent the family careening through a two-and-a-half-year cycle of grave illness and recovery, until they thought the disease had finally been conquered. But after a brief remission, the leukemia returned and specialists at The University of Texas Southwestern Medical Center at Dallas counseled the Marshalls that Grace's best — if not only — chance for long-term survival was a bone marrow transplant.

Once the family decided to go forward with the procedure, Grace's physicians had to find a suitable donor, which, say experts, can be akin to finding a needle in a haystack. For Grace, the process was made simpler by the fact that she had three siblings, one of whom had tissue that carried the genetic match necessary for a successful bone marrow transplant.

Shelby Marshall gave her sister a magnificent gift on a cold January day in 2000. What was simply to Shelby bone marrow meant survival for Grace. In one afternoon the two sisters shared, as they had shared so many toys and dreams, a river of life.

Bone Marrow Transplants

When the blood is affected by disorders such as Hodgkin disease, leukemia and other blood-borne cancers, bone marrow transplant (also referred to as stem-cell transplant) often is the patient's best treatment option.

"The implication of stem-cell transplant — what we know now and what we will discover in the very near future — is tremendously exciting," said Dr. Robert Collins Jr., director of the UT Southwestern Hematopoietic Cell Transplant Program. "It is immensely gratifying to see how many people's lives have been saved through a procedure that relies so heavily on the generosity of others."

BY RACHEL SKEI DONIHOO

Grace Marshall (front) received a bone marrow transplant from her sister Shelby.

When the blood is affected by disorders such as Hodgkin disease, leukemia and other blood-borne cancers, bone marrow transplant (also referred to as stem-cell transplant) often is the patient's best treatment option.

Bone marrow — the soft, sponge-like material found inside bone — contains immature cells called stem cells. Stem cells are responsible for producing white blood cells (which fight infection), red blood cells (which carry oxygen to and remove carbon dioxide from organs and tissues) and platelets (which enable the blood to clot).

Blood stem cells can be garnered from one of three sources for transplant: marrow, circulating blood and umbilical cord blood. Regardless of their source, they accomplish much the same thing — the ability to help a patient heal himself.

There are three types of blood stem-cell transplants: autologous, which uses the patient's own blood stem cells; allogenic, which requires the blood stem cells of a donor; and the less common, syn - geneic, in which patients receive stem cells from their identical twin.

Hunting for a Match

For children and adults with leukemia and blood-related cancers and diseases, healthy stem cells from a donor are needed. For these allogenic transplants, the donor can be either related (usually a sibling, as in Grace Marshall's case) or unrelated to the patient. If no tissue-type match can be found within a patient's family, UT Southwestern doctors turn to the National Marrow Donor Program's registry of more than 4.5 million potential donors for a match.

To increase the likelihood of successful transplantation and to minimize potential complications, it is crucial that the transplanted marrow match the patient's own marrow as closely as possible.

People are equipped with different sets of proteins, called human leukocyte-associated (HLA) antigens, on the surface of their cells. The success of allogenic transplantation depends largely on how well the HLA antigens of the donor's marrow match those of the recipient's marrow. Close relatives, especially brothers or sisters, are more likely than unrelated people to have HLA-matched bone marrow; however, only 30 percent to 40 percent of patients have an HLA-matched sibling or parent, and the chance of obtaining HLA-matched marrow from an unrelated donor is small.

"The uncertainty of finding a match is one of the most frustrating elements for patients to deal with," said Dr. Preet Chaudhary, associate professor of internal medicine and molecular biology. "Many do, fortunately, but the disappointment of those few who can't is very difficult for everyone. The more educated people become about the importance of donating bone marrow, the greater the number of patients who can beat the odds."

Patients with disorders that have not affected the bone marrow are often "transplanted" with their own stem cells, which are collected from their marrow and frozen. After the patient has received high-dose chemotherapy and/or radiation therapy to kill the affected cells, the stem cells are introduced back into the patient's body to begin their job of repopulating the bone marrow.

Although the science behind the inner life of stem cells is infinitely complex, the transplant itself is a relatively straightforward concept. Much like a heart or lung transplant, the diseased "organ" (in this case, bone marrow) is removed, providing a clean slate on which new stem cells can begin their work. Stem-cell transplants are surprisingly simple procedures.

"The transplant itself is almost anticlimatic, but what the body then is required to do with the new cells is elegant," said Dr. Robert Ilaria Jr., assistant professor of internal medicine and molecular biology.

The Procedure

Much of the process at UT Southwestern takes place in the outpatient clinic at the Harold C. Simmons Comprehensive Cancer Center, where more than 60 stem-cell transplantations are performed each year. Hospitalization in the bone marrow transplant unit at Zale Lipshy University Hospital or Children's Medical Center of Dallas is often required for the typical six- to eight-week recovery period.

Prior to the transplant, the donor's stem cells are collected either from the bone marrow in a simple surgical procedure requiring anesthesia or from veins in the arm or under the collarbone through a relatively painless procedure called apheresis. Pediatric patients (who require much smaller quantities of stem cells) also can receive transplants from umbilical cord blood. For several days before the transplant, the patient is treated with high doses of chemotherapy, with or without radiation, in order to destroy the "sick" bone marrow cells.

Stem cells then are infused intravenously in a process much like a blood transfusion. Within two to four weeks, the transplanted stem cells begin to engraft, or produce healthy marrow cells (white blood cells, platelets and red blood cells).

Thanks to ongoing research, cancers that were once considered invariably fatal can often be vanquished. Before a new double-transplant technique was developed, cancers such as neuroblastoma — a deadly cancer that affects the nervous system — were considered incurable. Dr. Victor Aquino, assistant professor of pediatrics and the first to conduct a tandem stem-cell transplant for neuroblastoma in North Texas, is conducting a clinical trial of this new treatment, which is repeated in back-to-back treatments.

While this kind of stem-cell transplant and chemotherapy is the only hope for a cure, it's still a risky proposition. Two out of every three neuroblastoma patients ultimately die from a recurrence of the cancer. For those who survive, however, the procedure is a lifeline.

"We treat diseases that for decades have been dismissed as incurable, so I think it's all the more important to stay focused on what we can do now, while looking to the future for even better treatment options," said Aquino, who performs about 20 transplants each year at Children's Medical Center. "Despite the unavoidable risks, transplant is a chance for life when otherwise there would be none."

A Sibling's Gift

Much like Grace Mashall, Dr. Alphonso Jones turned to an older sister after receiving an unsettling diagnosis.

As a Fort Worth family physician, Jones had seen the devastation of serious illness first-hand, but until a leukemia diagnosis last year forced him into a personal battle, his experience with illness had been strictly professional.

When Jones noticed a lump near his collarbone, the 55-year-old's intuition told him there might be something seriously wrong. Once the diagnosis of acute myelogenous leukemia was confirmed, Jones was referred to specialists at UT Southwestern, who recommended a stem-cell transplant.

"I was told soon after my diagnosis that the curability rate for my leukemia was low without the option of transplant," said Jones. "I tried to stay away from detailed medical literature about my disease — which can often be pessimistic and anxiety-provoking — because it was a frightening thing to know that my life was hinging on one procedure. I also knew that my chances for a successful transplant would depend largely on finding a well-matched donor."

As luck would have it, Jones' 65-year-old sister proved a suitable tissue match.

Jones has now been cancer-free for a year. "I really do feel that my sister is a blessing, and I will be eternally grateful for her gift," he said.

Graft-Versus-Host Disease

Despite the success rate of stem-cell transplants, they are not without significant risk. One of the most dangerous complications for allogenic transplant recipients is graft-versus-host disease (GVHD). In this condition the recipient's new immune system — created by the stem cells provided by the donor — attacks the patient's body, treating it as a foreign invader. Symptoms of GVHD, which range from cosmetic (skin rash) to life-threatening (intestinal problems and liver dysfunction), can arise immediately after transplant or develop slowly and linger for months or years.

"The transplant itself is almost anticlimatic, but what the body then is required to do with the new cells is elegant."

—Dr. Robert Ilaria Jr.

Dr. Victor Aquino was the first to conduct a tandem stem-cell transplant for neuroblastoma in North Texas.

Dr. Robert Collins Jr. (left), directs the UT Southwestern Hematopoietic Cell Transplant Program.

Patient Dr. Alphonso Jones received bone marrow from his sister in a transplant performed by Collins.

"It's time to find a gentler, highly targeted way of performing transplants. We are heading in that direction, but we still have a long, promising way to go."

—Dr. Robert Collins Jr.

"Graft-versus-host disease is one of the chief subjects of transplant research," said Collins, who holds the Sydney and J.L. Huffines Distinguished Chair in Cancer Research, in Honor of Eugene Frenkel, M.D., and the H. Lloyd and Willye V. Skaggs Professorship in Medical Research. "We still have a lot of work to do, but we are hopeful that current research will help us navigate a better path toward broader applications of stem-cell transplants and more effective ways of turning GVHD around. If we can determine why some patients are more susceptible to the disease, we will be another step forward in making bone marrow transplant an ideal treatment for a multitude of disorders."

One researcher who is doing just that is Dr. Ellen Vitetta, director of the Cancer Immunobiology Center and holder of the Scheryle Simmons Patigian Distinguished Chair in Cancer Immunobiology.

"Our goal is to find a way to harness the more desirable graft-versus-tumor effect [which occurs when donor cells recognize and attack cancer cells] in the absence of GVHD," she said. "Through the use of immunotoxins, which kill T-cells that mediate GVHD but spare the T-cells that attack the cancer, we hope to greatly improve the outcome of these transplants. Experiments in the laboratory already have demonstrated that this approach works *ex vivo*. We soon will launch a clinical trial to determine if this works in patients. If it does, it will be a major step forward."

In the meantime, a new blood transfusion treatment, called photopheresis, is offering hope and new possibilities to patients battling GVHD.

During photopheresis, the patient is connected to a machine that withdraws a quantity of blood in a manner similar to kidney dialysis. The machine separates the blood into red blood cells, white blood cells and plasma. The white blood cells are collected in a bag, and the red cells and plasma are returned to the patient.

"Many of the patients we see have been dealing with GVHD for many years, and their lifestyles have become greatly diminished because of its side effects," said Dr. Ravindra Sarode, associate professor of pathology and director of the transfusion medicine and coagulation laboratory. "One of modern medicine's great ironies is that even though something as deadly as leukemia can be defeated through bone marrow transplant, the life-giving cells can turn so violently on their new 'host.' Photopheresis can help reverse that effect by giving cells a new way to approach healthy tissue."

Minitransplants

Led by Collins, researchers at the medical center are evaluating a new "minitransplant" for the treatment of several types of cancer, including leukemia, lymphoma, multiple myeloma, melanoma and kidney cancer.

A minitransplant uses lower, less toxic doses of chemotherapy and/or total body radiation therapy to prepare the patient for an allogenic transplant. This approach eliminates some, but not all, of the patient's bone marrow (as opposed to traditional chemotherapy and radiation treatments, which destroy it completely). Minitransplants also reduce the number of cancer cells and suppress the patient's immune system to prevent transplant rejection.

"The idea of a low-toxicity transplant is immensely important on many different fronts," said Collins. "When bone marrow transplant was developed 35 years ago, there was only one way of doing things. It proved to be salvation for many patients, but the process was, and still is, highly toxic and risky. It's time to move away from that framework and find a gentler, highly targeted way of performing transplants. We are heading in that direction, but we still have a long, promising way to go." ✣

For more information on UT Southwestern's Bone Marrow Transplant Program, please call 214-648-7070 or go to www2.swmed.edu/bmt.

For more information on becoming a donor, contact Carter BloodCare, Dallas: 800-DONATE-4, ext. 8150; www.nmdpdallas.org.

The Future of Bone Marrow Stem-Cell Transplantation

Researchers at UT Southwestern, who have long been committed to finding new ways to combat complications of organ and bone marrow transplantation, continue to uncover the complexities behind the human immune system.

Dr. Michael Bennett, professor of pathology and pediatrics and holder of the A.J. Gill Professorship in Pathology, has spent the past four decades studying natural killer (NK) cells and their behavior in bone marrow transplants.

In healthy people, NK cells target tumor cells and protect the body against a wide variety of infections by targeting "invaders" and delivering a lethal burst of chemicals, killing their targets on contact. Although the NK cell is a biological necessity, its aggressiveness can backfire in transplant patients. Because NK cells recognize donor cells as foreign, they do not hesitate to wage war — often wiping out the trespassers.

T-cells, which are crucial to the body's immune defense, are responsible for keeping NK cells in check. Functioning in a kind of "yin-yang" partnership, they fight tumors and infection together, explained Bennett. In the absence of T-cells, which are intentionally destroyed before allogenic bone marrow transplants to reduce the risk of graft-versus-host disease (GVHD), the NK cells' natural instincts take over — leaving the door open for transplant rejection.

"The natural killer cell is a force to be reckoned with," said Bennett. "It would be impossible for our bodies to fight off infection without it, but its resistance to radiation and other foreign properties poses problems for transplant recipients. I believe, however, these cells can be an extremely powerful tool in achieving the desirable graft-versus-tumor effect, without the threat of GVHD. Once we can learn how to fine-tune the NK cells' response to foreign cells, we will be well on our way to changing the outlook and reducing the complications for transplant patients."

Dr. Robert Ilaria Jr., assistant professor of internal medicine and molecular biology, also has made a career of studying the molecular and cellular culprits in leukemia and solid tumors. His work on the molecular pathophysiology of Bcr/Abl, a protein responsible for a spectrum of leukemic illnesses, has made widely recognized strides in the testing and discovery of antileukemia drugs. Ilaria's recent research on gleevec, a popular cancer medication, has paved the way for further studies in gleevec-resistant patients with myelogenous leukemia.

"We know that one of the most dangerous causes of relapse in transplant patients is their resistance to drugs that inhibit Bcr/Abl," said Ilaria. "If we can figure out how and why certain patients randomly mutate the gene, we will take a major step forward in treating patients with diseases like myelogenous leukemia, which is notoriously difficult to control."

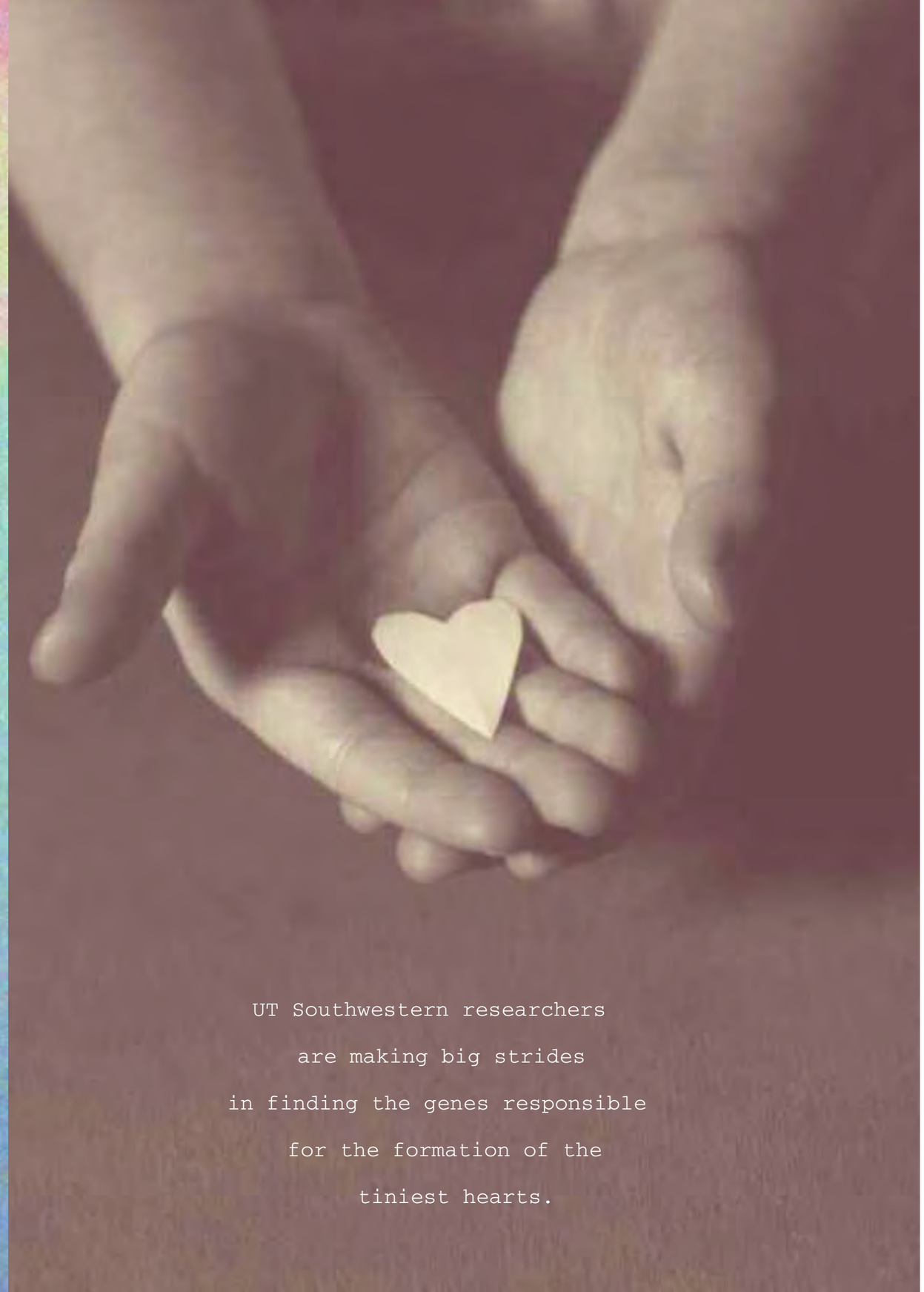
There also is much to suggest that bone marrow stem-cell transplantation may one day reach far beyond the treatment of cancer and blood disorders. Recent published reports on the ability of stem cells to give rise to new human tissue (pluripotency), have brought biomedical research to the edge of a new frontier.

Stem cells have the ability to divide for indefinite periods and "grow" specialized cells, explained Dr. J. Victor Garcia-Martinez, professor of internal medicine and microbiology. For example, blood stem cells can give rise to red blood cells, white blood cells and platelets, and liver stem cells can give rise to the various types of other liver cells.

"What all this means is that there is an amazing amount of untapped potential," he said. "There is a very real possibility that we one day may find a way to repair organs damaged by disease, such as the heart or liver, by streamlining the stem cell's un - paralleled ability to create." ✣

"There is a very real possibility that we one day may find a way to repair organs damaged by disease, by streamlining the stem cell's unparalleled ability to create."

—Dr. J. Victor Garcia-Martinez



UT Southwestern researchers
are making big strides
in finding the genes responsible
for the formation of the
tiniest hearts.

BiG Goals for SmaLL HeartS

By Amy Shields

Antonia Velazquez has one wish as her seventh birthday approaches. The Irving resident and youngest of three siblings wants something that money can't buy — to score a goal in soccer.

What may seem to be an attainable goal for many is nearly impossible for little Antonia. She was born without a right ventricle — one of the most lethal forms of congenital heart defects (CHD).

Born March 25, 1996, Antonia weighed a healthy 7 pounds, 4 ounces. Her parents, Maricela and Michael Velazquez, took their brown-eyed baby home from the hospital with a good prognosis from doctors. The pediatrician noticed a problem, however, when Antonia and her mother came in for the baby's 2-month checkup.

"The doctor said that my baby looked sick," Velazquez said. "I had noticed that her breathing didn't seem right and that she was not eating a lot, but I thought that would eventually pass."

The pediatrician diagnosed Antonia with a heart problem and advised her mother to seek care at Children's Medical Center of Dallas, affiliated with The University of Texas Southwestern Medical Center at Dallas.

After several tests, Velazquez was told her daughter's heart had never developed.

"It was a shock; it was terrible," said Velazquez. "I couldn't believe it. All of my other children were normal. My first thought was, 'Is she going to die?'

"She was born without any complications, and there was no sign of a health problem. Neither of her siblings were born with heart problems, and no one in the family that I knew of had any type of heart problems."

Scientists have yet to uncover all the causes of CHD, but researchers at UT Southwestern are searching for the genes involved in heart formation to devise ways to prevent defects by understanding the underlying molecular problems.

Leading research in this area are Dr. Eric Olson, chairman of molecular biology, and Dr. Deepak Srivastava, associate professor of pediatrics and molecular biology at UT Southwestern. Srivastava was Antonia's cardiologist at Children's as well.

"We're seeking the folic-acid equivalent for heart defects," said Srivastava, holder of the Pogue Distinguished Chair in Research in Cardiac Birth Defects and the Joel B. Steinberg, M.D., Chair in Pediatrics. Supplementing folic acid in expectant mothers' diets leads to a major reduction in spinal-cord defects, Srivastava explained.

Taking a folic-acid supplement intervenes in a series of steps that causes the neural tube to close," he said. "So just by increasing the amount of folic acid one can decrease spina bifida. Ultimately I think the solution for CHD will be that simple, but getting to that point won't be that easy."

Srivastava and Olson, however, are making significant discoveries about the genes involved in the formation of the heart.

"THERE HAS BEEN LITTLE OR NOTHING known about the genes involved in the formation of the heart until recently," said Olson, director of the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer and the Nearburg Family Center for Basic Research in Pediatric Oncology.

"We're discovering a growing set of genes involved in regulating the growth and contractility of the heart. Our goal is to understand how the proteins they encode work," added Olson, who holds the Robert A. Welch Distinguished Chair in Science. "Our long-term goal is to have a genetic road map to understand the genes and to understand how one gene affects another gene when mutated. Our aim is to have a prenatal screen to identify gene mutations that can cause congenital heart defects and ultimately to diagnose and correct cardiac malformations."

The heart is the first organ to form in humans, and the fetal heart's development takes on several distinct appearances before reaching its final shape and structure. During the first few weeks after conception the fetal heart has a tube-like structure, much like that of a fish heart. In the next phase, two atria connected to one ventricle are formed. The ventricle separates completely around the seventh week, and the heart fully develops with four chambers.

Researchers began their studies about seven years ago with a data collection phase, which involved gathering information about the genes that play a critical role in the formation of the heart.

"We have been focused on this for several years," said Srivastava, who worked with Olson at UT M.D. Anderson Cancer Center before both researchers joined the UT Southwestern faculty.

They are now in the second phase of the study, which involves determining the genes that actually play a role in human congenital heart defects. To date, most studies have been done in animal model systems, Srivastava said.

"The real breakthrough in this field came some years ago when we realized that we have almost the same sets of genes that control the heart as fruit flies," he said. "That realization allowed us to study many different model organisms and extrapolate to what might be happening in humans."

The third phase, Srivastava said, is to identify which genes are actually involved in human heart disease.

"We have also started to do that on a large scale here. We are analyzing about 100 genes and looking for mutations or alterations in a large number of patients with congenital heart disease," Srivastava said.

"In another 10 years

we will have an idea of most if not all of the genes involved in heart formation, but we will ultimately need to know how the proteins they encode work."

— Dr. Eric Olson

"We predict that we may find one, two or three mutations in different genes, and when they are present together an individual may develop congenital heart disease.

"By piecing that information together we hope to understand what the steps are that contribute to certain types of heart defects. That information should lead us to understand the nitty-gritty of how these events occur and how we can intervene, possibly with medication or in a dietary fashion in a pregnant or pre-pregnant mother who may be predisposed to the defect."

Scientists have only recently come to the realization that congenital heart disease is a genetic condition, Srivastava said.

"It is probably an inherited genetic disease, but it has a low penetrance; there may be one or more inherited mutations, but they may not always cause disease," he said. "It's something like cancer, where we know that malignancy runs in families, but not everyone in that family necessarily develops cancer."

UT Southwestern researchers and others have already identified almost 100 genes essential for heart development, including the *Bop* gene and the *Hand 1* and *Hand 2* genes.

In the May 1, 2002, issue of the journal *Nature Genetics,* Srivastava and his collaborators reported that the *Bop* gene controls the formation of the heart's ventricles. The *Hand 1* and *Hand 2* genes, previously discovered by Olson's group, regulate the formation of the right ventricle and left ventricle, respectively.

The genes discovered by UT Southwestern researchers, Olson said, are key control genes in cardiac development.

"We are among the leaders in the field," he said. "In another 10 years we will have an idea of most if not all of the genes involved in heart formation, but we will ultimately need to know how the proteins they encode work. It's like trying to draw the blueprints to a house. Once you find the gene you have to figure out how it connects to another gene. There are many details to fill in."

In a study in the journal *Cell* in 2001, Olson reported that the protein myocardin, which is expressed in cardiac muscle cells and turns on cardiac genes, controls the development of the heart in frog embryos. Without this protein, the heart did not form.

"This protein specifically turns on cardiac genes that are expressed from the embryonic stage throughout the life of the organism," Olson said. "This protein appears to be essential for heart formation in the embryo."

WHILE SCIENTISTS HOME IN ON THE ANSWERS, children like Antonia still need to be treated.

"In most heart defects, the blood is not flowing in the proper direction or the heart is not hooked up to certain vessels that take blood to the heart and away from the heart properly," Srivastava said. "Surgeons attempt to rearrange that plumbing so that it is functional. In many cases this works fairly well, and the kids are fine, and they have a normal life span. For some of the more severe types of heart defects, as in Antonia's case, there is a high mortality rate even with surgery.

"It's not a cure, and we expect as the children get older they are going to have problems again. We know that children born with only one ventricle would die without surgery, but even with our best current efforts, only half of them survive. Those who do survive often start to have all sorts of problems when they get to 10 to 20 years of age. The ventricle begins to fail, and many of them have to have heart transplants or other interventions."

At four months, Antonia underwent the first of two complicated surgeries.

"The first year of life is the hardest for children born without a right or left ventricle," Srivastava said. "However, if they make it past the first two surgeries, they can actually have a pretty good life and be active children."

Antonia and her family lived through that physical and emotional roller coaster following her surgeries.

"After the first surgery Antonia had a very good recovery," her mother said. "She started eating right, walking and running.

"The second surgery was the total opposite. She had a month-long hospital stay because of fluid buildup in her lungs. She was about 18 months old, and I thought I was going to lose her, she was so delicate."

But Antonia bounced back. "People still can't believe that she's come all this way," her mother said.

As Antonia's health continued to improve, the active toddler began to express an interest in soccer. When she was 5, with Srivastava's approval, Antonia joined the Lady Cardinal soccer team in Irving.

"Antonia is very active. She may get a little tired sooner than the other children while playing, but the fact that she is able to play soccer is pretty remarkable," Srivastava said.

While Antonia may not directly benefit from Olson's and Srivastava's research findings, thousands of newborns in the next decade may be spared the complications of CHD. The researchers have begun a pilot study of 50 children, which has been so successful that it is being expanded to all UT Southwestern pediatric cardiology surgery patients. Collaborating with Dr. Jonathan Cohen, associate professor of internal medicine at UT Southwestern and a scholar in the Center for Human Nutrition, researchers are collecting DNA samples to establish the correlations between specific gene mutations and heart defects. Once the links are made, the research team will try to determine how to prevent or modify exposure of the fetus to the contributing factors of CHD.

Dr. Deepak Srivastava and Dr. Eric

"We already know

at least one-third of the critical genes involved in this process. The heart is very complex and a rather remarkable organ."

—Dr. Deepak Srivastava

"We're receiving the best treatment, and everything her doctors have done was for Antonia's well-being and best interest," she said. "If it wasn't for them, Antonia wouldn't be here." ✣

ThE BIologIcal arms racE

Sept. 11, 2001, demonstrated America's vulnerability to terrorist attacks. Later, the threat was driven home when anthrax-laced letters were mailed to unsuspecting victims.

Until now, the moral repugnance of biological warfare had deterred its widespread use. But a new breed of terrorist has the financial and technological capabilities to manufacture lethal agents, such as anthrax, botulism, ricin and smallpox, with which they can attack entire cities or countries.

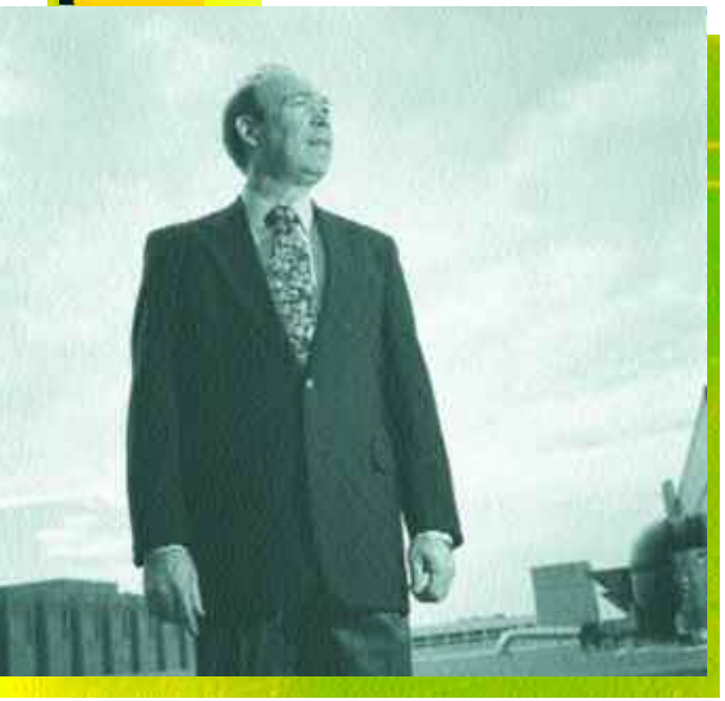
Dr. Robert Haley, chief of epidemiology at The University of Texas Southwestern Medical Center at Dallas, said that for the past 10 years the public-health community has tried to sound an alarm.

But by and large, the warning had fallen on deaf ears.

"Of the many things that changed after Sept. 11, we now realize that America is in a new biological arms race," said Haley, professor of internal medicine. "There is going to be a race for scientists to develop technology that will take these biological weapons off the table. This is going to be a long-term research priority. In fact, it may be indefinite."

The biological weapons revolution has created new defenders of freedom — scientists around the world and at UT Southwestern. Armed with advances in science and biotechnology, they are joining forces to develop high-tech diagnostic tools and effective treatments to stay ahead of terrorists' capabilities.

By Ione Echeverria



Dr. robert haley, chief of epidemiology

america's readiness will also depend on the first responders — practicing physicians in private clinics and emergency-department physicians. They will be the eyes and ears of the community. These individuals must recognize early signs and symptoms of biological exposure and apply treatments to prevent contamination, illness and death.

UT Southwestern has assembled a cadre of research scientists to prepare for any eventuality.

History of biological warfare

Incidents of germ warfare are rare. In the mid-1300s, the Tartars used catapults to hurl plague-infected bodies over the walls of besieged cities. In the 19th century, Indians are said to have been given deadly "gifts" of smallpox-contaminated blankets by settlers.

At one time or another, the United States, Japan, Germany, Soviet Union, Britain and other countries have engaged in biological weapons experiments. In World War I, the German army used plague, cholera and anthrax in limited attacks, mainly against horses. The British tested anthrax bombs on sheep on Gruinard Island off the northern coast of Scotland in 1942. The Cold War caused further development and stockpiling of these weapons.

The United States unilaterally ended biological warfare research in 1969 and signed the Biological Warfare Convention in 1972. Now, only defensive biological warfare research is allowed.

The public-health community's attention to the potential for biological and chemical warfare was heightened in 1991 during the Persian Gulf War, said Haley.

"Although the Iraqis did not use biological weapons, their frightening capabilities served as a warning that we must prepare to defend against biological warfare agents in the future," said Haley, holder of the U.S. Armed Forces Veterans Distinguished Chair for Medical Research, Honoring America's Gulf War Veterans. "We also became aware of the detrimental effects of chemical weapons when Gulf War veterans started to exhibit mysterious symptoms."

With funding from the Perot Foundation, Haley and colleagues traced Gulf War veterans' chronic sleep problems, neurological problems, and muscle and joint aches to combinations of environmental exposures on toxic battlefields, though he has not yet directly linked it to the use of chemical or biological weapons.

In a groundbreaking paper in the January 1997 issue of *The Journal of the American Medical Association,* Haley identified three distinct syndromes, each related to various Gulf War chemical exposures, including pesticides, insect repellants and pyridostigmine bromide tablets soldiers took to combat the effects of nerve gas.

Haley said the attraction of biological warfare is its capability to cause large numbers of casualties with relatively minimal cost, technological expertise and logistical requirements.

"In one of the most recent studies available, the cost of producing 50 percent casualties per square kilometer was $2,000 for conventional weapons, $800 for nuclear devices, $600 for chemical agents and $1 for biological weapons," he said. "Technology is a double-edged sword. Technology can protect us from threats, but it can also be used by terrorists to manufacture bioweapons."

"Technology is a double-edged sword. Technology can protect us from threats, but it can also be used by terrorists to manufacture bioweapons." —Dr. robert haley

The "A" list

Bioterrorist agents can be bacteria, viruses or chemical toxins naturally produced by bacteria. The Centers for Disease Control and Prevention ranks anthrax and smallpox on its "A" list — the immediate-threat category — of biowarfare or bioterrorist agents.

In early October 2001, a tabloid photo editor from Florida was diagnosed with the first confirmed case of inhalation anthrax in the United States in more than 25 years. Subsequently, several anthrax-laced letters were mailed to different people across the United States, resulting in 22 confirmed or suspected cases of anthrax infection.

"The first confirmed case of inhalation anthrax was a rare and notable event," Haley said. "Throughout the entire 20th century, only 18 known cases of inhalation anthrax were identified in the United States, and almost all were traced to occupational exposures, to infected animals or contaminated animal products."

Anthrax is an acute infectious disease caused by the spore-forming *Bacillus anthracis*. The disease typically occurs in plant-eating animals, which are infected after ingesting spores from the soil.

Anthrax comes from the Greek word for burning coal, *anthrakis,* because of the black skin lesions it causes. In humans, anthrax produces three syndromes: cutaneous, inhalation and gastrointestinal. Early symptoms of inhalation anthrax include fever, malaise and cough; the late phase involves respiratory distress, shock and death.

Smallpox was eradicated worldwide as a health threat in 1977. Smallpox is caused by the variola virus and is spread mainly by infected respiratory droplets. Initial symptoms include high fever, fatigue, and head and back aches. A characteristic pustular rash develops on the face, arms and legs.

"These two agents have the best mix of all features that a terrorist would look for in a biowarfare agent, but the list of possible biological weapons is much longer and expanding," Haley said. "The challenge to researchers and physicians is to understand each agent separately because each one has a distinct diagnosis, treatment and public-health solution."

Disarming biological weapons

For the past 10 years, Dr. Stephen Johnston, director of the Center for Biomedical Inventions at UT Southwestern, has collaborated with the Defense Advanced Research Projects Agency (DARPA) to develop technology that will disarm terrorists' biological arsenals.

DARPA is the central research and development organization for the Department of Defense. Its work has been crucial to development of, among other things, the Internet, Stealth technology and microwave energy. Just last year the agency awarded $3 million to UT Southwestern and Johnston to determine if vaccine development can be accelerated and super vaccines protecting against multiple diseases can be created. Johnston and his collaborators are initially working on vaccines against anthrax, plague and an infectious disease called tularemia.

Johnston was the first to demonstrate genetic immunization in 1992 following the development of a "gene gun," which shoots tens of thousands of microscopic "BBs" coated with gene segments into the cells of animals. This method of delivering antigen genes provokes an immune response. The gene gun is now being tested in clinical trials.

He later pioneered a revolutionary method of vaccine development called expression library immunization (ELI), in which vaccines for any animal or human pathogen can be discovered by shooting all the genomic bits of a pathogen into an organism.

"DARPA has a good reputation of being far-thinking and being able to bring those ideas into reality," said Johnson, holder of the Dr. Eugene Tragus Chair in Molecular Cardiology. "The three-year DARPA grant is intended to figure out if a speculative theory has legs or not. If it does, they want us to work as fast as we can to get it out commercially."

The technologies developed with the DARPA funds, spawned MacroGenics, a biotechnology company that will continue to develop vaccines for biothreat agents.

"In many ways, we can't lose," Johnston said. "Say we develop a better way to make vaccines, and we apply that to anthrax. That same technology could be used for conventional infectious diseases. All the technology that people are developing to counteract biological agents crosses over into standard biomedical practice. It's a win-win position."

Johnston said two new research projects that could reduce the impact of biological warfare are the development of fast-acting vaccines and diagnostic systems that diagnose an infection soon after an exposure.

"A smaller project we are working on is to develop technology that will allow us to clinically validate vaccines and diagnostic systems for biothreat agents," he said. "Since these pathogens are rare, it's more difficult to validate them. We are using biosignature-type approaches to see if we can create a shortcut for that challenge."

UT Southwestern researchers have also developed a vaccine for ricin, a toxin that terrorists have used as biological "ammunition" in many parts of the world. The vaccine seems to be effective in studies with mice.

"all the technology that people are developing to counteract biological agents crosses over into standard biomedical practice. It's a win-win position."

—Dr. stephen Johnston

"Primary-care physicians in clinics and emergency-department personnel will be the first responders to an attack."—Dr. Paul Pepe

Ricin is produced by a protein found in castor beans. A single molecule inside a cell shuts down protein synthesis, killing the cell. A group linked to the terrorist organization al-Qaeda has experimented with the poison as a weapon.

Dr. Ellen Vitetta, director of the Cancer Immu - nobiology Center at UT Southwestern and holder of the Scheryle Simmons Patigian Distinguished Chair in Cancer Immunobiology, reported her findings last year in the journal *Vaccine*.

Vitetta and her colleagues mutated the DNA encoding the active A chain of the toxin. They took out the site that inhibits protein synthesis, as well as the site responsible for inducing vascular leak. The new recombinant A chain induces a protective immune response in mice and protects them against very high doses of the toxin.

Dr. Paul Pepe, chairman of emergency medicine

Haley said Vitetta's research has found a unique solution to a potential threat.

"Ellen came up with a clever idea," Haley said. "Her discovery could provide immunity against one of the most potent toxins known to man. This type of research will make terrrorists' biological weapons ineffective."

Haley, Johnston and Dr. Michael Norgard, chairman of micro- biology, serve as board advisors for UT Southwestern's Regional Center of Excellence for Bioterrorism Research. On the board's agenda are plans to enlarge its biosafety level 3 laboratory — which incorporates special engineering features to allow researchers to handle hazardous material without endangering themselves, the community or the environment — to accommodate additional research projects.

Preparing for bioterrorism

Imagine that over the course of one week, 15 people visit an emergency department complaining of fever, physical discomfort and a cough.

Before Sept. 11, this scenario would not raise much concern. But in the post-9/11 era, nothing should be above suspicion, said Dr. Paul Pepe, chairman of emergency medicine at UT South- western.

"Doctors must maintain a high degree of suspi- cion for biological terrorism when numerous pa- tients present with similar, unexplained symptoms," said Pepe, who oversees the emergency medical services for Parkland Memorial Hospital. "Primary- care physicians in clinics and emergency-department personnel will be the first responders to an attack. They will experience an influx of patients and must have a viable plan to prevent illness and death."

Since the mid-1990s, the federal government has devoted funding, resources and equipment to pre- pare its 120 largest metropolitan areas — Dallas is eighth — for a terrorist event.

The Dallas Metropolitan Medical Response Team was developed to teach police, fire, and emergency and medical personnel how to minimize the impact of a terrorist attack, limit morbidity and, hopefully, prevent mortality.

Government agencies have recognized Parkland, the primary teaching hospital for UT Southwestern faculty physicians, as a model system.

According to the American Hospital Association, approximately 25 percent of hospitals are currently at some state of readiness for a chemical or biological incident. As the Dallas County hospital, Parkland's emergency-room personnel and physicians have been planning since 1998 for what most people used to believe was unthinkable.

The response team developed a disaster plan by running mock scenarios and functional chemical exercises. These drills are intended to identify both strengths and weakness in response-system plan- ning.

"One of the UT Southwestern/Parkland initiatives is to train first responders to administer smallpox vaccinations under expert supervision," said Pepe, holder of the Riggs Family Chair in Emergency Medicine and medical director of the response team. "Currently there are fewer than 100 people who are designated to administer smallpox vaccinations. Training other personnel, such as paramedics, on this technique will expedite the vaccination of large populations of people in case of a disaster."

Many terrorist agents — anthrax, pneumonic plague and tularemia among them — mimic symp- toms of other naturally occurring diseases, said Dr. Kathy Rinnert, assistant professor of surgery at UT Southwestern and on-scene medical team leader of the response team.

"It's vital for doctors and medical personnel to differentiate between symptoms of a garden-variety flu and those associated with a biological exposure," she said. "Diseases of the past are coming back, and rare diagnoses could become mainstream. Physicians must be taught that weapons of destruction are a reality and their practice could end up in the war zone."

To fulfill this educational need, the department is developing a national "all hazards" disaster-medicine training course to instruct first responders on the most likely weapon — explosive, chemical or bio- logical — that a foreign or domestic terrorist may deploy.

Biological agents are the weapons of choice for terrorists because they disrupt civil order and infra- structure, overwhelm emergency response systems, and create panic, confusion and fear.

The Dallas County Biotel system links Parkland with other area trauma center hospitals and emer- gency medical services so they can share day-to-day information on patient loads and types of cases being admitted. In case of an attack, the system can help to disperse patients to appropriate hospitals.

"In case of an emergency, the Biotel system can be used to triage patients to surrounding hospitals so that one particular hospital is not overwhelmed and to detect trends in suspicious patient loads, county- wide, long before any individual facility can," Pepe said.

Delving into a terrorist's mind

The attacks on the World Trade Center and the Pentagon left the nation in a state of shock. People struggled to comprehend terrorists' actions and their disregard for human life.

Dr. Jaye Crowder, associate professor of psychi- atry at UT Southwestern, has insight into criminal thinking and behavior from his work as a forensic and threat-assessment consultant and profiler.

"Terrorists come to identify with a particular ideology and wish to see that agenda enacted in the world," said Crowder, head of forensic psychology at UT Southwestern.

Crowder said terrorism is facilitated by the injunction of a transcendent authority — like the self-proclaimed religious leader Osama bin Laden, head of the fundamentalist terrorist group al-Qaeda and mastermind behind the Sept. 11 attacks — to remove the internal human imperative that one person not harm another.

"Physicians must be taught that weapons of destruction are a reality and their practice could end up in the war zone."

—Dr. Kathy rinnert

"It's really their own aggressive impulses that they project onto God," Crowder said. "They say, 'God wants me to kill you,' to avoid the responsibil- ity of abrogating the natural law that we all follow. This rationalization allows terrorists to act out their aggressive impulses and not feel guilty."

Fundamentalist terrorists perceive a threat to their group identity. The Muslim religion is facing a rapidly changing world that is encroaching on the traditional values of Islam.

"A small subset react to this infringement by striking out," Crowder said. "The subtext is, 'I feel impotent to preserve my sense of self in the midst of this cultural confusion, but I will feel powerful if I can do something dramatic and destructive to the more prosperous and influential United States. I feel out of control in my life, but I can regain mastery if I can hurt the great Satan which threatens our lives, lifestyle, religion and morality.'"

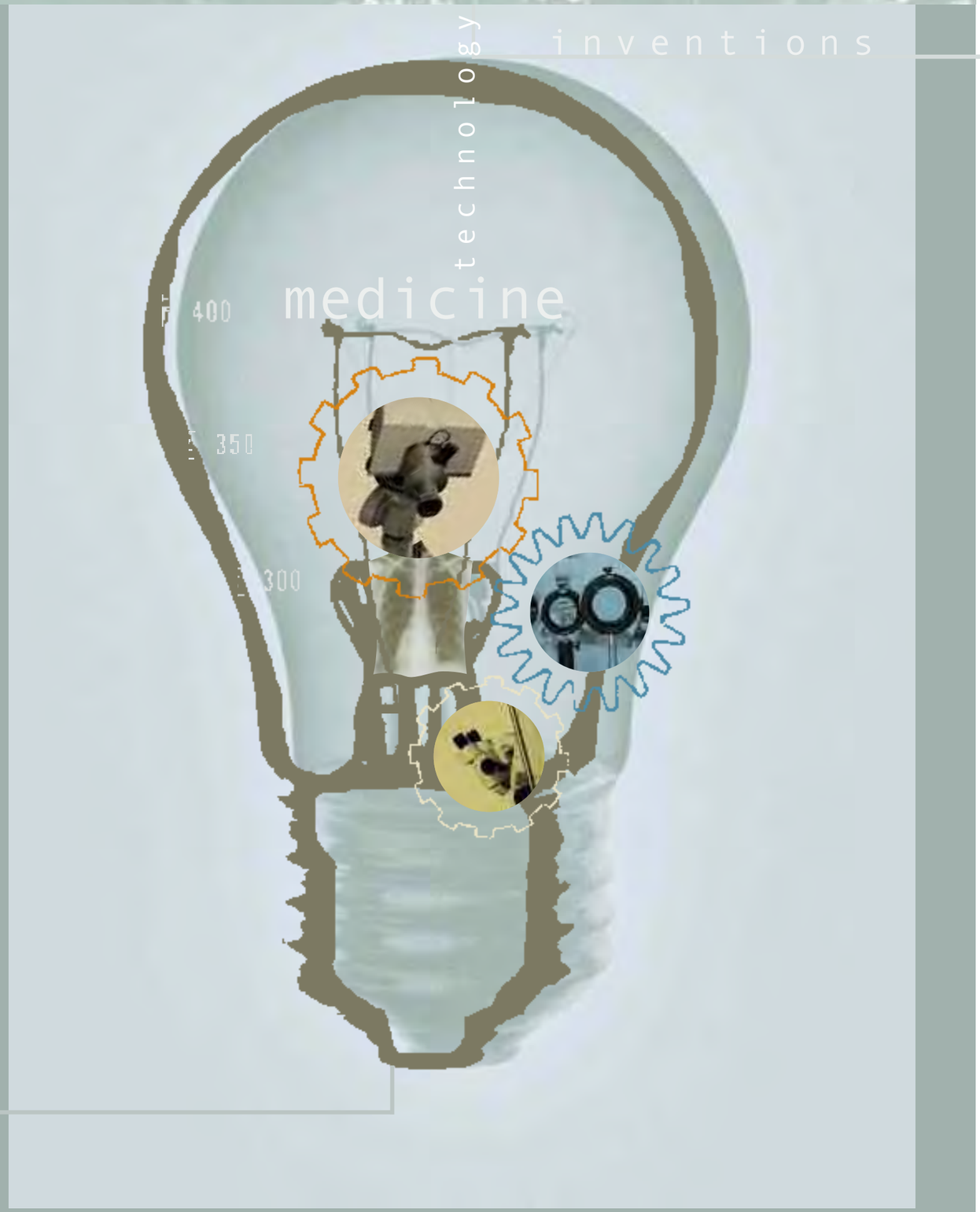
Aside from the physical damage, biological war- fare can also inflict psychological damage. Americans are adapting to a new way of life that includes na- tional security alerts from the Department of Home- land Security. For some people, the threat of terror- ism consumes their lives.

"Concerns about loved ones who travel, especial- ly overseas, are normal and appropriate," Crowder said. "However, some people project the problems and fears in their lives onto the threat of terrorism. They displace the fear and pain of the troublesome issues they deal with on a daily basis onto a dread terrorism will devastate who and what they cherish the most. Rumination about the terrorist threat sub- stitutes for other problems, which seem paradoxical- ly more difficult to solve.

"So instead of worrying about your son who is in prison, or that your daughter is marrying the wrong man, or losing your job, you direct your repressed anxieties towards the threat of terrorism."

While it is impossible to avoid much of the danger because of the random nature of attacks, people shouldn't let terrorism disrupt their lives.

"Statistically speaking, we all face more serious dangers on a daily basis," he said. "You can lose your physical life to a terrorist, but too many people lose their psychological lives by worrying about terrorism and restricting their activities."



WHETHER COMPLEX OR STRAIGHTFORWARD, LEADING-EDGE TECHNOLOGY AND NEW APPLICATIONS OF TRADITIONAL TECHNOLOGY ARE EMBRACED DAILY AT UT SOUTHWESTERN.

INCREDIBLE MEDICAL MACHINES

The tools of technology. *At The University of Texas Southwestern Medical Center at Dallas, they're all around. Many may be stunningly high-tech; others less so; and some so deceptively simple one may muse, "Why didn't we think of this before?" Traditional technology often begets promising new uses, therapies and techniques.*

But whether complex or straightforward, there remains a singular purpose to these tools. In skilled hands, they can discover and can heal.

Leading-edge technology and, or in some cases, new applications of traditional technology, are embraced daily at UT Southwestern.

BY MICHAEL BLACKMAN

On the left, Dr. Cole Giller and the Accuray. Right, Dr. Masahide Kikkawa.

for infants with brain tumors, a new chance at life

They were all very young, these children; one 3 years old, the other two less than a year. They all suffered from devastating and highly aggressive forms of brain cancer. Their prognosis was bleak.

Only rarely, said Dr. Cole Giller, associate professor of neurological surgery, does anyone with such cancers survive "more than two or three years."

But Giller and other doctors at the medical center are pioneering a therapy in which they use high-beam radiation via Accuray CyberKnife technology to treat young children with brain tumors.

"With every treatment we have a better feel for doses and plans," Giller said. "We are encouraged with the results; some but not all of the results have been superb."

Until now infants have not been able to undergo traditional radiation treatment because of the dam - age it causes their fragile brains. But the Accuray technology at Zale Lipshy University Hospital is able to precisely target cancerous cells, leaving healthy tissue unharmed.

The Accuray, installed at Zale Lipshy in 1997, moves robot-like around the patient, delivering its high-beam radiation from various angles. Because this treatment had previously only been used on older children and adults, radiation technicians had to design a special bed for their three smallest patients.

What also makes Accuray appropriate for treating infants is that, unlike the older "gamma knife" technology, it requires no frame bolted onto the child's head. "Their skulls are too pliant, are still developing, and that's too much for them," said Giller, who expects the Accuray therapy for infant brain tumors to become more widely used in the near future.

Giller credits the success of this groundbreaking therapy to UT Southwestern doctors throughout the medical center. "It's very much been a multidisciplinary effort."

THE ACCURAY, INSTALLED AT ZALE LIPSHY IN 1997, MOVES ROBOT-LIKE AROUND THE PATIENT, DELIVERING ITS HIGH-BEAM RADIATION FROM VARIOUS ANGLES.

The million-dollar microscope, and then some

Very few people can clearly see structures a mere one-billionth of a meter or less in size.

UT Southwestern scientists can.

That's because in fall 2002 UT Southwestern's new $1.6 million cryo-electron microscope — after nearly a year of undergoing custom design and construction — went into action.

Acquisition of the cryo-electron microscope is expected to elevate UT Southwestern's cell-research capabilities significantly, said Dr. Richard Anderson, chairman of cell biology. Only a handful of other universities utilize cryo-electron technology, he explained.

The new microscope is expected to lead to research breakthroughs in such areas as Alzheimer's disease, nerve regeneration, spinal-cord injuries, cell biology, cellular aging and death, cancer, diabetes, and cholesterol.

Already, UT Southwestern is reaping dividends with the acquisition, having recruited internationally prominent scientist Dr. Masahide Kikkawa from the University of Tokyo's Graduate School of Medicine. The new UT Southwestern assistant professor of cell biology is widely known for his use of cryo-EM technology.

The state-of-the-art microscope allows scientists to view, analyze and computer-simulate individual molecules, clusters of molecules and other sub-cell structures, Anderson explained. That resolution, he said, is more than three times the whole-cell magnification now possible with standard electron microscopes, which typically focus down to about three nanometers — three-billionths of a meter — and typically cost $200,000 to $400,000.

"It's a great leap forward to be able to use cell biology, genetics, biochemistry and other disciplines to reveal how the genes, proteins and other functional components interact," Anderson said. "But it's another major stride to be able to see the actual sub-nanometer-size structures and the functional organization of these structures at sites in the cell where these processes take place. That's the beauty of this cryo-electron microscope and related technology."

Cryo-EM uses an ultra-fast freezing technique coupled with high-powered energy filtration and a special prism and other computer enhancements to provide three-dimensional views of cell components with a resolution unequaled by standard electron microscopes.

These are promising days for all members of cell biology.

With the new microscope and the arrival of Kikkawa, "we'll have the instrumentation; we'll have the talent; and we'll attract and develop more talent," said Anderson, who holds the Cecil H. Green Distinguished Chair in Cellular and Molecular Biology.

A guru of gadgetry

As Skip Garner will tell you, "I do gadgets."

Does he ever. Wander through his melange of gadget-laden labs, all 5,000-square feet of leading-edge clutter galore, and one recognizes that Dr. Harold "Skip" Garner and his colleagues tinker their day away with considerable industry.

And with admirable success. But, then, no less is expected from the coterie of creative minds serving in the labs of the Eugene McDermott Center for Human Growth and Development and in the Center for Biomedical Inventions. That's because the professor of biochemistry and internal medicine and his 30 research colleagues create hardware and software as well as new methodology in their quest to exploit the massive amount of emerging sequence from the Human Genome Project and the Cancer Genome Anatomy Project, among others.

"These new technologies are then applied to problems in biomedicine to validate their efficacy and to develop new knowledge in human genetics as well as all areas of biomedical research," said Garner, who holds the Philip O'Bryan Montgomery Jr., M.D., Distinguished Chair in Developmental Biology.

From idea to design and building, testing, and deploying, Garner and his team nurture their "gadgets" to maximum potential. Some will debut in the marketplace at other medical centers and research labs across the country. Sometimes an invention may even serve as a catalyst for a startup company.

Garner is no stranger to achievement. The 48-year-old scientist chose his career in the sixth grade, when, inspired by two engineer uncles, he built his first nuclear reactor — "out of cardboard." Garner holds 15 patents and has another dozen pending. His team's projects have been instrumental in helping bring more than $50 million in research grants to UT Southwestern.

Currently, Garner and his colleagues have more than 50 projects under way. Among the most prominent is a second-generation Digital Optical Chemistry program, a system developed with Texas Instruments and Affymetrix that analyzes gene components through custom DNA microarrays. It is, said Garner, a process considerably faster, more efficient and less expensive than others, and one that can significantly aid research in such areas as cancer, cardiac disease and "even bio-threat/infectious agents." A related area of exploration for Garner's lab is computational biology/informatics — in effect, making further sense and good use of the massive information gathered from gene study: sequence annotation/visualization, microarray analysis and text-data mining, for example. Garner and his researchers have created programs that facilitate the use of this information.

Continued on page 54

"THESE NEW TECHNOLOGIES ARE THEN APPLIED TO PROBLEMS IN BIOMEDICINE TO VALIDATE THEIR EFFICACY AND TO DEVELOP NEW KNOWLEDGE IN HUMAN GENETICS AS WELL AS ALL AREAS OF BIOMEDICAL RESEARCH."

— DR. HAROLD "SKIP" GARNER

Dr. Harold "Skip" Garner, reflected on a section of the holographic 3-D image projection system, one of his latest inventions.

Continued from page 39

"*In computational biology*, there is now more raw and processed data available for biomedical researchers than they can ever comprehend," said Garner. "So we have developed tools that enable researchers to exploit all this data for their own purpose. Computational biology — you don't know what you've missed until you experience what it can do for you."

HDTV that's easy on the brain

At Zale Lipshy University Hospital, there's a new way of looking at television, and it doesn't have a thing to do with channel-surfing. The little screen's gone big in a high-definition, state-of-the-art way in one of the Zale Lipshy neurological surgery operating rooms.

What it means is an up-close and uncommonly detailed view of brain surgery, allowing everyone in the room to see the same clear view surgeons see through their microscope when, for instance, they're looking at the brain's tiny vascular structures, where aneurysms occur.

Same clear view. Only larger. Much larger — a plasma screen 50 inches wide hanging on the wall. So significant is the HDTV's impact, surgeons say, that it's affecting their surgical technique.

"This system is primarily for the benefit of staff involved with the specific operation," said Dr. Thomas Kopitnik, professor of neurological surgery and holder of the Birsner Family Professorship in Neurological Surgery. "Now the entire operating room can see the minute details of the surgery and follow closely along."

The system, installed in 2002, was the first of its kind in the Southwest and is getting such good reviews that additional HDTVs are planned for two more neurological-surgery operating rooms at Zale Lipshy, an adult referral hospital for UT Southwestern physicians.

Dr. Thomas Kopitnik with the HDTV.

PET-CT scanner, a two-for-one bargain

UT Southwestern is among the leaders in acquiring another technological system. It's called the PET-CT scanner, a $2 million medical-imaging machine that allows physicians to simultaneously perform a positron emission tomography (PET) scan and computerized tomography (CT) scan.

Dr. Dana Mathews with the PET-CT scanner.

PET scanners and CT scanners are not new, but performing them dually is. And that ability enables doctors to locate tumors and other abnormalities with greater precision.

The advantage of accurately comparing the two images, said Dr. Dana Mathews, associate professor of radiology and medical director of the PET facility at UT Southwestern, is that it could possibly prevent having to do more invasive and potentially painful procedures.

It also means faster diagnoses for patients.

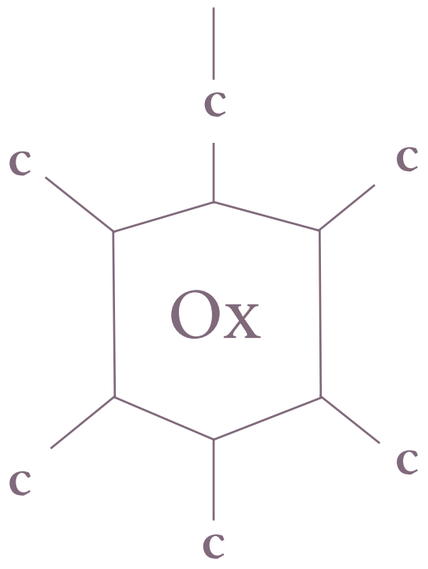
"A PET scan analyzes metabolic changes in the body, while a CT scan shows anatomic detail," she explained. "When we have to do the scans at different times, the patient can move or be in a slightly different position and make the results harder to compare."

PET scans are traditionally used to diagnose or monitor cancer, cardiovascular disease, epilepsy and Alzheimer's disease, among other afflictions.

Tools of Technology

But for the imagination of the mind, nothing else so engages or accelerates scientific discovery and all that flows from it. Ask the parents of the babies treated by Cyberknife technology. Listen to the excitement in the voice of the scientist talking about his lab's discoveries, how they may aid in fighting cancer and heart disease. Think of the sheer marvel of a machine that under the eye of a master can break down the nanometer mysteries of matter.

These tools, be they fixtures of lab, clinic or surgical suite, may in some cases be as high-dollar as they are high-tech. But their return on investment is undeniable in their contribution to UT Southwestern's mission and the relentless pursuit of medical research, new clinical therapies and the education of young physicians and scientists — those who, with the tools of their own generation's technology, will not just embrace but extend the quest of medical science. To discover and heal. ✣



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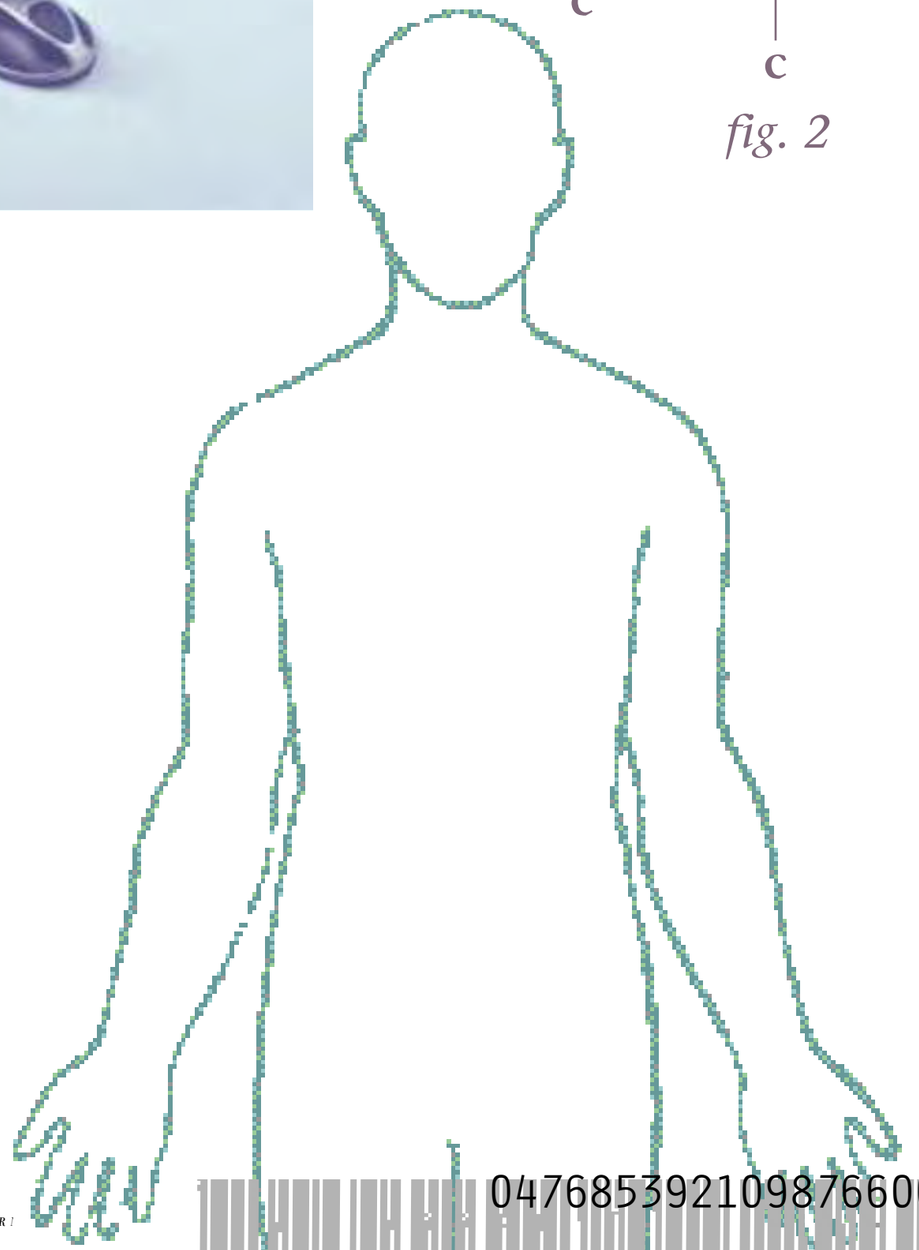


02

UT Southwestern's efforts in patenting new discoveries and licensing them to private entities is creating a firm foundation to launch and support biotechnology companies.

License to HEAL

Dr. Dennis Stone operates at the center of a whirlwind of researchers, venture capitalists, entrepreneurs and economic-development professionals. His job as vice president for technology development at The University of Texas Southwestern Medical Center at Dallas requires him to have a hand in every facet of technology licensing —identifying potentially marketable research, dealing with individuals who can finance and manage new companies, and working to make biotechnology a bigger part of the local economy by enlisting local support and recruiting experienced executives to the area.

A medical doctor and researcher who joined the UT Southwestern faculty in 1984, Stone now has responsibility for the medical center's efforts in patenting new discoveries and licensing or selling them to private entities that want to translate laboratory progress into marketable products and services.

"We are dedicating a lot of work to creating an infrastructure in Dallas to launch and support biotechnology companies," Stone said.

By Wayne Carter

02

Dennis Stone, M.D.

There was a time

when the high ideals of academic research and the bottom-line sensibilities of business were considered incompatible, if not mutually exclusive.

The Bayh-Dole Act, signed into law in 1980, changed all that. The legislation made it legal for academic institutions and their researchers to retain patent rights to technological and scientific breakthroughs achieved in government-funded labs. The law allows institutions and researchers to benefit from licensing or selling those developments to private entities that could mold them into marketable products and services.

In the 22 years since Bayh-Dole, technology licensing has become a major operation for many academic institutions. The Association of University Technology Managers (AUTM) annual licensing survey for fiscal 2000 drew 142 responses, with licensing revenue of more than $1 billion from those reporting institutions.

UT Southwestern's history of licensing new technology predates Bayh-Dole. The medical center has been patenting and licensing breakthroughs for more than 25 years and, in the late 1980s, was at the center of a venture that foreshadowed the current boom in transferring technology from public labs to private businesses.

Dallas Biomedical Corp. was founded in 1986 to create companies that would commercialize UT Southwestern research. With backing from local investors — including Dallas Semiconductor Corp. founder C. Vin Prothro, a longtime UT Southwestern supporter who died in 2001 — Dallas Biomedical achieved success as a technology incubator long before the term became a 1990s venture capital buzzword.

GeneScreen Inc., founded in 1988 as Dallas Biomedical's first venture, still is in business. The company, bought by Princeton, N.J.-based Orchid Biosciences early in 2002, provides paternity, forensic and bone-marrow testing services out of facilities in Dallas; Sacramento, Calif.; and Dayton, Ohio.

"GeneScreen was a clear success, and Dallas Biomedical was something that was clearly ahead of its time," Stone said.

Regardless of its early success, UT Southwestern officials weren't satisfied that the medical center was making the most of licensing opportunities. Annual licensing revenue never broke the $1 million mark until 1992. Until 1998, the moderate annual growth trend continued, with licensing revenue reaching $4 million that year. The licensing mechanism also was retooled in 1998 with the establishment of the Office of Technology Development and the naming of Stone as vice president.

By 2001 UT Southwestern was receiving more than $10 million per year in licensing income.

"The revenue provided by technology licensing has become very substantial, and the Office of Technology Development has grown from six people at the start to 15 people now," said Stone, who holds the NCH Corporation Chair in Molecular Transport.

The opportunities are increasingly understood and appreciated by UT Southwestern researchers.

"Over the past three years, there has been a dramatic change in the emphasis on technology licensing and how things are conducted," said Dr. Stephen Johnston, director of UT Southwestern's Center for Biomedical Inventions. "We have focused on taking developments and translating them into useful, clinically viable stuff."

The Center for Biomedical Inventions (CBI) itself is a product of UT Southwestern's recognition of the importance of advancing science and doing so with an eye toward the practical application of new developments.

Johnston is one of four members of the CBI, established in 1997 to conduct research that would have immediate possibilities for commercial development. CBI work includes Johnston's development of a gene gun that delivers genetic vaccines by driving tiny gold pellets coated with DNA through the skin. Rather than conditioning immune-system responses to certain pathogens, the genetic vaccines are designed to alter cells at the molecular level. Those changes program the body to be able to respond appropriately to certain pathogens.

Johnston, holder of the Dr. Eugene Tragus Chair in Molecular Cardi-ology, is conducting research to develop genetic vaccines for biothreat agents such as anthrax and smallpox. That work has received ongoing funding from the Defense Advanced Research Projects Administration, and early developments already are in the hands of a private company.

MacroGenics Inc., based in Rockville, Md., and Seattle, is working to develop viable vaccines based on Johnston's work. The company has a development facility in Dallas as a result of its 2002 acquisition of Eliance Biotechnology Inc., a Dallas-based company that was founded specifically to translate Johnston's lab work to the commercial market.

Dr. Eric Olson, chairman of molecular biology at UT Southwestern, said the administrative infrastructure that supports technology transfer is vital to the process.

"Academic institutions and researchers are generally not familiar with individuals in private sector biotech business," Olson said. "It's hard to know how to get started; it's hard at first to see the complete financial picture, to know the difference between purely academic and commercial ideas."

Those comments are telling, coming from someone who has co-founded a company.

Olson helped put together Myogen Inc., a Denver-based company that specializes in developing and marketing cardiac drugs. Olson and colleagues founded the company shortly after his arrival at UT Southwestern in 1996. Myogen has licensed some of Olson's discoveries and provides some funding for his ongoing research. But even as a co-founder, Olson prefers to work at arm's length. The organizational separation gives a bit of breathing room between scientists working on new developments and business experts looking for new opportunities, said Olson, who directs the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer and the Nearburg Family Center for Basic Research in Pediatic Oncology and holds the Robert A. Welch Distinguished Chair in Science.

Currently, the majority of biotech companies are located on the East and West coasts — which Stone and others in the Dallas area would like to change. Dallas is one of many municipalities nationwide working to siphon biotech talent and money away from centers like Boston; Washington, D.C.; and San Diego.

UT Southwestern has developed a strong partnership with StarTech Early Ventures, a small-business incubator based in Richardson, originally founded to support startups in that city's telecom corridor. StarTech, which invests in early-stage companies and provides expert counseling and executive talent, was an investor in Eliance and now holds a stake in MacroGenics.

But beyond StarTech, it's hard to find local capital and leadership for the kinds of companies that would buy UT Southwestern technology.

"There's a lack of biotech venture capital, whether it's seed funding or firms capable of doing large-round investments," Stone said. "And we don't yet have a pool of entrepreneurs with the credibility and exposure to attract East Coast and West Coast venture firms."

Dr. Harold "Skip" Garner, chairman of biomedical engineering and also a founding CBI member, agreed. He has found fertile ground for cultivating new scientific developments at UT Southwestern, but he admits missing his old stomping grounds when it comes to turning ideas over to the private sector.

"I came here from San Diego, where if you have a commercially viable idea, you can walk down the street and round up venture capital and a chief executive officer and a chief financial officer," said Garner, holder of the Philip O'Bryan Montgomery Jr., M.D., Distinguished Chair in Developmental Biology. "There are people working hard to change this, but Dallas has little history in biotech. Entrepreneurs and venture capitalists in Dallas traditionally have been focused on telecommunications and semiconductors."

Stone and others believe they are up to the challenge. Stone says he'd rather see companies starting up and staying in Dallas, but that trying to force the issue at the expense of getting deals done would be counterproductive. Rather than viewing Eliance's acquisition by an out-of-state company as a blow to the Dallas biotech scene, Stone points to the fact that the former Eliance operation still is fully intact in Dallas and has greater opportunity for growth through MacroGenics and its investors.

Continued on page 56

"We are dedicating a lot of work to creating an infrastructure in Dallas to launch and support biotechnology companies."

—*Dr. Dennis Stone*

02

Stephen Johnston, Ph.D., with his gene gun

License to Heal

Continued from page 43

The most important thing is to do what's best for the company," Stone said. "I do believe that both would have thrived with corporate headquarters in Dallas, and hopefully the next company will stay here in its entirety."

That desire is important enough for Stone to make it a priority to try to help Dallas create a firm foundation for biotech. Thanks to the Office of Technology Development, UT Southwestern is active with the Greater Dallas Chamber of Commerce and the Dallas Plan's biotechnology initiative. The Dallas Plan is an independent, nonprofit group working with business and community leaders to plot the city's course in several strategic areas, one of which is real-estate development.

"There's a lack of laboratory space," Garner said. "You can find all kinds of space that's tailored for electronics or telecommunications but not for bio - medical space."

The next company already is on the drawing board.

Stone said his office is close to finalizing a deal that would create a company to develop technology created by Dr. Jon Graff, associate professor in the Center for Developmental Biology and of molecular biology. Graff has developed a way to rapidly characterize cell-surface proteins that act as gateways to the cell for outside elements. Understanding those proteins and how they work will allow development of drugs to attack diseases like cancer, in which rogue cells proliferate.

But Stone and his colleagues have much more on their plates than just start-up companies. More than 70 technologies available for licensing are listed on the Office of Technology Development's World Wide Web site, and there are many more active licensing agreements that don't require the office's day-to-day attention.

Among those is a licensing agreement with San Antonio-based Mission Pharmacal Co., which manufactures an over-the-counter calcium supplement developed by Dr. Charles Pak, director of the Center for Mineral Metabolism and Clinical Research. Citrical is one of the most effective and widely recommended calcium supplements to halt the bone-ravaging effects of osteoporosis.

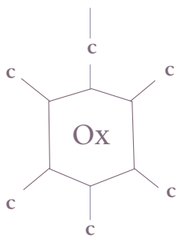
The list of available technologies constantly is in flux as new developments are patented and others fall behind due to lack of interest. It seems that fresh inventory is as important in the technology-licensing business as it is in the grocery business.

"We try to keep a viable portfolio," Stone said. "If we're unable to commercialize something, we will look at doing nonexclusive licensing or we will abandon the patent."

Perhaps the greatest challenge Stone and his staff now face is maintaining the momentum they have been able to generate in a very short time. New developments will continue to surface, and entrepreneurs and investors are always on the lookout for new opportunities. ✣

"We have focused on taking developments and translating them into useful, clinically viable stuff."

—Dr. Stephen Johnston



UT SOUTHWESTERN'S

Rising Stars

Dr. Kristen Lynch remembers exactly what she said the day her husband told her he'd been offered a job in Dallas.

"Over my dead body!"

Not that she was crazy about California, where the New England native and her scientist husband were living at the time. He was working at a biotech company, and she at the University of California, San Francisco, completing a postdoctoral fellowship. The clouds, the fog and the high cost of living seemed to stretch endlessly before them.

Fast forward to today.

Lynch, who vowed "never to set foot in Texas," is one of five young medical investigators — among the brightest and best in the world — recruited to The University of Texas Southwestern Medical Center at Dallas last year under its Endowed Scholars Program in Medical Science. Now an assistant professor of biochemistry, she is on a fast-track toward success, practicing leading-edge research alongside some of the most revered scientists in the world as the E.E. and Greer Garson Fogelson Scholar in Medical Research.

For Lynch, the Endowed Scholars Program was a primary factor in changing her mind about Texas in general and Dallas in particular.

Unique and highly competitive, the program is designed to launch the next generation's scientific leaders on their biomedical careers by providing seed money and start-up support for groundbreaking research projects. Five candidates with extraordinary credentials and potential are handpicked each year from top universities, institutions and laboratories and appointed as tenure-track assistant professors in various UT Southwestern departments.

By Donna Steph Hansard

Established in 1998, the Endowed Scholars Program in Medical Science was created by a $52 million fund-raising campaign, which included major gifts from a dozen individuals and foundations that met an anonymous donor's $25 million challenge. Income from the endowments provide exceptionally generous recruitment packages to attract some of the best young researchers in the world.

Thanks to the generosity of these forward-thinking supporters, UT Southwestern has brought to Dallas 25 of today's most brilliant young medical minds — hailing from as far away as Russia, Japan, China, Germany and Turkey — during the past five years.

Collectively, the Endowed Scholars in Medical Science represent UT Southwestern's "rising stars," destined to discover new ways to benefit science and mankind and assure UT Southwestern's continued international prominence.

"There is no more important goal than to continue to attract the finest young minds in the world to UT Southwestern," said Dr. Alfred Gilman, a Nobel laureate who is chairman of pharmacology. "These young people, who have just finished their training, are the source of incredible ideas and great creativity. They're full of fire and imagination and will be the great researchers and leaders of the future."

Once again living in a locale with trees and sun — even though it's not Boston — Lynch now is a staunch advocate of UT Southwestern and the nurturing environment it provides.

"One thing that says a lot about UT South–western is that I'm a New Englander, heart and soul, and I'd never planned to set foot in Texas," she said. "And I hadn't, until I interviewed here. I immediately fell in love with it — both UT Southwestern and my department. It went very quickly from me saying, 'No way I'm going to Dallas' to 'Absolutely, let's go!'

"I have to say now, after being here a year, that I still feel that same way. The energy and enthusiasm that were so appealing to me are real. They weren't just a show. Also, I've never had as much fun at a job as I have here."

Like Lynch, many of the Scholars had not fore - seen a career track involving Texas. But the unique characteristics of UT Southwestern's program and mentoring by experienced researchers were too inviting to pass up. Most turned down lucrative offers from other prestigious universities and institutions to come to UT Southwestern.

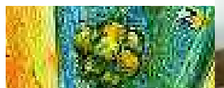
Dr. Kim Orth — one of the few Texas-trained scientists in the program, having earned an undergraduate degree from Texas A&M University and a Ph.D. from UT Southwestern — was wooed by four institutions, including Harvard Medical School, upon completion of her postdoctoral work at the University of Michigan. She and her husband, also a UT Southwestern alum, had not intended to return to their home state.

"I never envisioned it being a possibility that we would come back here," said Orth, assistant professor of molecular biology and a W.W. Caruth Jr. Scholar in Biomedical Research.

A visit to Dallas, during which they both lectured at UT Southwestern, however, started the momentum. The Endowed Scholars Program, an equally challenging position at UT Southwestern for her husband, Dr. Ron Taussig, as associate professor of pharmacology, and a way of life that met her children's needs won them over.

"One of the reasons I made the decision is because I really love the scientific environment at UT Southwestern," Orth said. "You have a great set of scientists who are ambitious and competitive, but who also work together to produce an extremely supportive environment.

"They make you feel a part of a community where people offer suggestions, collaborate, interact and are really happy," she said. "There are great scientists in Boston, too, but the offer from UT Southwestern provided an opportunity where neither excellence in science nor lifestyle for our family would be compromised. Practicing science is a stressful thing, but if you can do it in an environment that is positive and supportive, it makes a huge difference."



"Typically, young people are hired and not given much support. **This school has a different philosophy."**

—Dr. Hongtao Yu

A Michael L. Rosenberg Scholar in Medical Research, Dr. Hongtao Yu, was recruited in 1998 as an assistant professor of pharmacology after earning an undergraduate degree at China's Peking University and a doctorate in chemistry at Harvard, where he worked for several years in a cell biology lab.

"Part of the reason I came here is because this school is known for its strength in medical research — much of that related to the work done by senior scientists such as Dr. Gilman and Dr. (Joseph) Goldstein (chairman of molecular genetics and also a Nobel laureate)," he said. "They're known not only for their accomplishments, but also for their vision in bringing in the correct crowd of young scientists and supporting them from the very beginning.

"That is not always the case in other schools. Typically, young people are hired and not given much support. This school has a different philosophy."

More than 1,000 potential candidates annually apply for the Endowed Scholars Program in Medical Science. UT Southwestern recruits these individuals through advertisements in medical journals, its World Wide Web site, word-of-mouth and personal letters sent from various department leaders to colleagues and medical experts around the country. The process usually begins about a year out, with the heaviest recruiting in late summer and early fall.

Individual medical departments may propose their own candidates, each usually inviting five to six applicants for visits in October and November, following a rigorous pre-screening process. From these candidates, each department selects one or two of its strongest applicants to present to the Endowed Scholars executive committee, composed of six members, four of whom are Nobel Prize recipients. These include Drs. Michael Brown, director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease; Johann Deisenhofer, professor of biochemistry; Gilman; Goldstein; Helen Hobbs, director of the Eugene McDermott Center for Human Growth and Development and the Donald W. Reynolds Cardiovascular Clinical Research Center; and Thomas Südhof, director of the Center for Basic Neuroscience.

Program finalists are required to write a brief synopsis of their research accomplishments and future goals, bring three letters of recommendation, and show at least two to three published articles.

"One of the reasons I made the decision is because I really love the scientific environment at UT Southwestern. **You have a great set of scientists who are ambitious and competitive,** but who also work together to produce an extremely supportive environment."

—Dr. Kim Orth

"You tell people that we have this fabulous recruiting package and ask them to send us their best," said Gilman, who holds the Raymond Willie and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, in honor of Harold B. Crasilneck, Ph.D. "You gather a lot of applications, and then individual search committees screen through those and pick out about half a dozen, based on qualifications, record, accomplishments and statement of what they want to do when they 'grow up.'

"By the time the Endowed Scholars executive committee makes final selections, there are one dozen to two dozen people left, all of whom will receive offers from numerous places. They are superstars with great accomplishments and even greater ideas for the future. And, if they can convince us that they can do what they say they can, then they're asked to be a part of the program."

A program that gains more of a reputation each year.

Yu said he received phone calls from colleagues all over the country after they read in *The Dallas Morning News* that he was hired as a Scholar. "My friends said it was like UT Southwestern was signing its first-round draft picks. They complained that they never got that kind of publicity."

Said Lynch: "The program definitely has a reputation throughout the United States. Several of my peers, when they heard I was going to UT Southwestern, commented on the fact that I would be a part of that 'fabled, big-money start-up package.' The Endowed Scholars Program has done a good job of getting the UT Southwestern name out there."

That's because the Endowed Scholars Program gives young investigators the chance to take risks and the money to do so — along with nods of approval and knowledgeable mentoring from department chairs and other established scientists.

"I don't know of any other program that is quite as focused as this, specifically when it comes to recruiting junior faculty," Gilman said. "This is a commitment, with very substantial funds, that allows them to blossom in a secure environment, mentored by some of the greatest senior scientists in the world."

In addition to full salary support, each Scholar receives $600,000 to support his or her research projects for four years, covering initial expenses related to start-up costs. Scholars also are provided competitive salaries and sophisticated labs stocked with state-of-the-art equipment.

Typically, in the medical industry, researchers must demonstrate proven successes before they are given capital to further expand their work. That is particularly true in procuring federal grants.

"I immediately fell in love with it — **both UT Southwestern and my department.** It went very quickly from me saying, 'No way I'm going to Dallas' to 'Absolutely, let's go!'"

—Dr. Kristen Lynch

"It gives you a lot of freedom to concentrate on research in your early years. **And, that's really at the heart of why all of us are here.** We love doing research, and we're good at doing research."

—Dr. Kevin Gardner

At UT Southwestern, grand ideas are rewarded with upfront dollars.

"When I started here, I changed the kind of research I was doing as a postdoc," said Dr. Kevin Gardner, a W.W. Caruth Jr. Scholar in Medical Research and assistant professor of biochemistry and pharmacology. "That's not usually practical when it comes to obtaining funding. When you try to get funding, especially from the National Institutes of Health, they want to see preliminary data and a lot of feasibility studies before they give you research money.

"Having access to funds — like those in the Endowed Scholars Program — that are unrestricted and available in significant amounts as I was just getting started was exactly what I needed to 'prime the pump' for the research in which my lab now is happily engaged.

"It gives you a lot of freedom to concentrate on research in your early years. And, that's really at the heart of why all of us are here. We love doing research, and we're good at doing research," said Gardner, who did his undergraduate work at the University of California, Davis before earning a Ph.D. at Yale. Gardner's postdoctoral work was completed at the University of Toronto.

Obtaining funding is critical for new researchers, Gilman said.

"The money is incredibly important. People have to have money to get going. If there's adequate money to get your lab set up and rolling, you can be more innovative. You can take risks," he said. "The NIH grant-writing process almost discriminates against risk takers. They want preliminary data before they put money into a project.

"But how do you get preliminary data without money? That's what this program allows you to do — to take chances. People don't want to do mundane things; they want to press the limits of their imagination. And they need money to do that."

Dr. Stephen Hammes, also a W.W. Caruth Jr. Scholar in Medical Research and assistant professor of internal medicine, earned both M.D. and Ph.D. degrees from Duke University and finished an internship, residency and fellowship at UC, San Francisco, where he also did three years of postdoctoral research. When he was hired at UT Southwestern, his research focus took a 180-degree turn.

"I wanted to do something completely different than what I was doing as a postdoc," he said. "It was an unusual thing to try and do, and when I was looking for jobs, most places didn't want me coming and doing that. But when I visited UT Southwestern, people were excited about my idea because they thought it was unusual and different and would be worthwhile.

"The nice thing about the Endowed Scholars Program is that it gives you some security for four years, so you can pursue something that is interesting and even off-the-wall. No other places are willing to have such an open mind. That's what really attracted me — even more than the amount of money offered."

Most Scholars agree it's the advice and over-the-shoulder presence of UT Southwestern's senior faculty that are the greatest key to success.

"In addition to the money, there's a whole lot of moral support given here," Lynch said. "There are other places and universities where new researchers are like little fish swimming with sharks. Here, it's different. The young people feel that the senior faculty is really looking out for them and trying to help them."

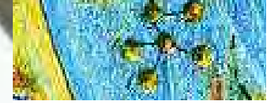
Said Dr. Scott Cameron, the Children's Cancer Fund Scholar in Medical Research and assistant professor of molecular biology and pediatrics: "The support provided here is first-class. By support, I don't mean only physical resources, although that is certainly part of it. What is more important is the support we get from a group of world-class scientists who are easily available and ready to assist us."

Having access to a network of young researchers on similar tracks also helps, said Cameron, who did graduate work at Cold Spring Harbor Laboratory in New York before postdoctoral research at Harvard and Massachusetts Institute of Technology. "In coming here, I was introduced to a group of other new scientists who I knew were high-quality. When we get together and they tell me things they are worried about, I find they are the same things I worry about — so I know I'm in good company."

Starting a lab from scratch can be mind-boggling, said Gardner, who was in the first group of Endowed Scholars. "When you're a postdoc, you usually work in a mature lab, which is a vibrant and exciting place full of people and things coming and going constantly. On your first day as an independent investigator, you're put in an office with a computer and no one around to give you orders, and you're faced with a totally new set of challenges you've never had before — such as managing your time over a much wider area, including research, teaching and clinical work.

"No other places are willing to have such an open mind. **That's what really attracted me** — even more than the amount of money offered."

—Dr. Stephen Hammes



"In addition to being able to get advice from some of the greatest senior scientists in the world, having the ability to touch base with other young faculty who are going through the same things at the same time makes a difference."

Besides informal peer review, internal as well as external advisory committees annually evaluate Scholars and the program's progress. Scholars also present seminars describing their works-in-progress for other faculty members.

"There's an external committee of simply fantastic researchers who come in once a year, and you present your work to them," Gardner said. "It's fun being able, as a young faculty member making your first steps, to get that kind of feedback. At times, I've been in a room with five Nobel Prize winners who took the time to share their thoughts regarding the strong or weak points of my research."

Dr. Stanley Prusiner, director of the Institute for Neurodegenerative Diseases and professor of neurology and biochemistry at UC, San Francisco, is a member of the Endowed Scholars Program's external advisory committee. In 1997 he won the Nobel Prize in physiology or medicine.

"I think the Endowed Scholars Program helps bring to UT Southwestern some of the most talented and imaginative young assistant professors in the entire world," Prusiner said.

Other members of the external advisory committee include: Dr. Bruce Alberts, president of the National Academy of Sciences; Dr. Richard Axel, Higgins Professor of Biochemistry and Molecular Physics and a Howard Hughes Medical Institute investigator at Columbia University; and Dr. Titia de Lange, Leon Hess Professor, Laboratory of Cell Biology and Genetics, Rockefeller University.

"**What is more important is the support we get** from a group of world-class scientists who are easily available and ready to assist us."

—Dr. Scott Cameron

Although the Endowed Scholars Program is still relatively young, the summer of 2002 marked its fourth anniversary — a milestone in that Scholars receive funding support for a total of four years. After that, they are expected to compete for capital from other outside sources.

"Many of us, during our first few years, have received grants from the NIH — which is an indicator of how the seed money has really helped us in developing our research to the point that we can attract other funding," Yu said. "One of the things that is a testament to the Scholars and the program is that most of us have gotten nationally competitive awards, which have supplemented our initial funding.

"It also says that we are competitive with the best schools anywhere."

As for the program itself, has it raised the bar and lifted UT Southwestern's rising stars to new plateaus?

Gilman believes it has.

"It's a little too early to say, but in general, the Scholars are doing well," he said. "By four years, they should be generating external grants and be self-sufficient. They're doing that. The real proof in the pudding will be when these individuals begin to go through the promotion and tenure committee. In about five to seven years, on average, they should be eligible for promotion."

Gardner believes being a Scholar has catapulted him to levels he might not have achieved as quickly elsewhere. He also has personally seen how it has broadened UT Southwestern's reputation.

"It is a fantastic way to get outstanding candidates to consider coming to UT Southwestern," he said. "And, once they're here, it gives them the tools they need to help ensure they get their research programs started successfully. Those include financial tools, ways to interact with other young faculty and ways to get feedback from experienced mentors.

"It also has helped make UT Southwestern even more competitive nationally. Many of us came from training at places on either coast, which is a very traditional pathway to take. Fortunately, I'd been lucky enough to learn about the research going on here through several routes."

For UT Southwestern, luring such rising superstars as those hired through the Endowed Scholars Program is a real coup. But does the attraction last?

"In general, people who do well stay here, despite the best efforts of other places to recruit them," Gilman said. "We do a good job of holding onto people because they really do like working here. Their accomplishments are noted and rewarded, and their research is supported."

Not only was the Endowed Scholars Program created to bring the best minds to Dallas and UT Southwestern, it also was born out of a desire to continue UT Southwestern's far-reaching inroads into changing the face of biomedicine and the future.

"Because of the remarkable foresight of the anonymous challenge donors who helped conceive the Endowed Scholars Program and craft its structure, and because of the enthusiasm of other supporters who embraced the idea of endowing the future through investing in the best young minds anywhere, Dallas will remain at the forefront of the medical world," said Dr. Kern Wildenthal, president of UT Southwestern.

A visit to the labs and discussions with any one of the 25 Scholars already appointed offer insights into greater things to come. First-year Scholar Yu is passionate about his research efforts delving into the division of cells from a structural, as well as biochemical, point of view.

"We are hoping that by studying how cells normally duplicate and split, we can eventually understand how cancer cells divide and discover a way to inhibit the cell division process of cancer," he said. "That is a very long-term goal of our research. If we can apply the knowledge we learn to human health, that becomes the ultimate pleasure of this business."

Finding new ways to treat, prevent and cure diseases ultimately is what the Endowed Scholars Program is all about.

"In this century and those to come, there will be a constant influx of brilliant minds into our midst," Wildenthal said. "Of the Endowed Scholars who pass through the program, a few may not realize their full potential. But hundreds will have made major contributions to medical research; some will have become the Nobel laureates of the 21st century; and Dallas will have been the site of remarkable discoveries that will have transformed medicine forever." ✣

Endowed **Scholars**

and the institutions from which they came

★ ★ ★ ★ ★

Wade Bresnahan, Ph.D.
W.W. Caruth Jr. Scholar
in Biomedical Research
Princeton University

Richard Bruick. Ph.D.
Michael L. Rosenberg
Scholar
in Medical Research
UT Southwestern

Scott Cameron, M.D., Ph.D.
Children's Cancer Fund
Scholar
in Medical Research
Dana Farber Cancer Institute
at Harvard University

Yuh Min Chook, Ph.D.
Eugene McDermott Scholar
in Medical Research
Rockefeller University

Simon Daefler, M.D., Ph.D.
William P. Clements Jr.
Scholar
in Medical Research
Rockefeller University

Michael Gale Jr., Ph.D.
Nancy C. and Jeffrey A.
Marcus Scholar in Medical
Research,
in Honor of Dr. Bill S. Vowell
University of Washington

Kevin Gardner, Ph.D.
W.W. Caruth Jr. Scholar
in Biomedical Research
University of Toronto

Nick Grishin, Ph.D.
Virginia Murchison
Linthicum Scholar in
Medical Research
UT Southwestern

Stephen Hammes, M.D.
Ph.D.
W.W. Caruth Jr. Scholar
in Biomedical Research
University of California, San Francisco

Kimberly Huber, Ph.D.
Southwestern Medical
Foundation Scholar in
Biomedical Research
Brown University

Jin Jiang, Ph.D.
Eugene McDermott Scholar
in Medical Research
Howard Hughes Medical Institute
at Columbia University

Ege Taner Kavalali, Ph.D.
Cain Foundation Scholar
in Medical Research
Rutgers University

Makoto Kuro-o, M.D., Ph.D.
Southwestern Medical
Foundation Scholar in
Biomedical Research
National Institute of Neuroscience,
Japan

Wen-hong Li, Ph.D.
Southwestern Medical
Foundation Scholar in
Biomedical Research
California Institute of Technology

Yi Liu, Ph.D.
Louise W. Kahn Scholar in
Biomedical Research
Dartmouth University Medical School

Qing "Richard" Lu, Ph.D.
Southwestern Medical
Foundation Scholar in
Biomedical Research
Dana Farber Cancer Institute
at Harvard University

Kristen Lynch, Ph.D.
E.E. and Greer Garson
Fogelson Scholar in Medical
Research
University of California, San Francisco

Kim Orth, Ph.D.
W.W. Caruth Jr. Scholar
in Biomedical Research
University of Michigan

Duojia Pan, Ph.D.
Virginia Murchison
Linthicum Scholar in
Medical Research
University of California, Berkeley

Anne Satterthwaite, Ph.D.
Southwestern Medical
Foundation Scholar in
Biomedical Research
University of California, Los Angeles

Joachim Seemann, Ph.D.
Virginia Murchison
Linthicum
Scholar in Medical Research
Imperial Cancer Research Fund
in London

Keith Wharton Jr., M.D.,
Ph.D.
W.W. Caruth Jr. Scholar in
Biomedical Research
University of California, Los Angeles

Christoph Wülfing, Ph.D.
W.A. Moncrief Jr. Scholar
in Medical Research
Max-Planck Institute
of Biochemistry in Germany

Gang Yu, Ph.D.
Thomas O. Hicks Scholar
in Medical Research
University of Calgary

Hongtao Yu, Ph.D.
Michael L. Rosenberg
Scholar
in Medical Research
Harvard University

A picture is worth a thousand words

By Ione Echeverria

Like most parents, Tammy Stewart enjoyed taking candid photographs of her 9-week-old daughter, Alexis Diaz. But a particular set of pictures made Stewart uneasy.

"In some of the pictures, Alexis' right eye had a golden, iridescent reflection, like a cat's eye," said Stewart, a stay-at-home mom from Duncanville. "I showed the pictures to family and friends, but they all said I was overreacting."

Trusting her instincts, Stewart took her daughter in for another examination. Alexis' pediatrician used an ophthalmoscope — a lighted instrument used to examine the interior of the eye —to elicit a red reflex from her retina. In Alexis' left eye, the reflex was normal. But her right retina appeared white, a sign that there was an abnormality.

"Red-eye," which can be captured in a photo, is caused by a reflection off the blood in the retina. Leukocoria, or white pupil, is caused by something blocking the reflex. Absence of blood in the retina would have to be extreme to reduce the coloration.

Alexis was referred to Dr. Albert Edwards, assistant professor of ophthalmology at The University of Texas Southwestern Medical Center at Dallas. Tests revealed that the infant girl had retinoblastoma, a rare cancer of the retina.

Each year 350 American children are diagnosed with the disease, which can occur in unilateral (tumors in one eye) or bilateral (both eyes) form. UT Southwestern ophthalmologists treat a handful of these cases at the James W. Aston Ambulatory Care Center and at Children's Medical Center of Dallas.

"Retinoblastoma is a childhood disease that is typically diagnosed before age 5," said Dr. Nick Hogan, assistant professor of ophthalmology, neurology, neurological surgery and pathology. "Although the disease is rare, it is the third most common cancer and the No. 1 ocular cancer affecting children."

Retinoblastoma, however, can now be cured in 90 percent of cases because it can be detected early and treated aggressively.

Children with the hereditary form of retinoblastoma typically develop the disease at a younger age, have bilateral eye tumors and an increased chance of developing other cancers in later years.

When retinoblastoma was detected in Alexis' right eye, Edwards ordered a battery of eye scans and tests, including a systemic work-up to determine if cancer was present in other parts of her body and brain. Based on the results, her eye was removed in a procedure called enucleation.

"Conservative treatments, such as radiotherapy and chemotherapy, have decreased the frequency and necessity of enucleation, but it still is necessary in some cases," Hogan said.

Doctors and patients must weigh the pros and cons of different treatments, Edwards said.

"If the eye has large-sized tumors that fill up 50 percent of the back of the eye or is fragmented, the eye is typically removed because its survival is not likely after external beam radiation treatment," he said.

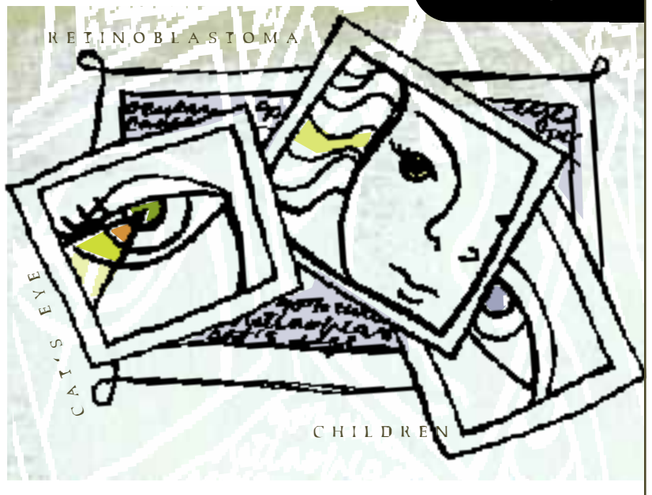
At the time of Alexis' surgery, an adult-size anchoring implant was placed in the eye orbit and muscles were reattached. Because the implant is made of a derivative of coral, it is porous enough to allow blood vessels to grow into it. The little girl was then fitted with a cosmetic prosthesis that matched the color of her other eye. The prosthesis will continue to be refitted as her healthy eye grows.

Looking at Alexis, who is now an active and happy 3-year-old, Stewart is grateful that her daughter's life and eyesight were spared.

"Alexis started pre-kindergarten this fall," Stewart said. "Despite all the poking and prodding she's had to endure in her young life, she has adjusted well to living with one eye."

And she's ready for her first school photograph.✣

> **"In some of the pictures, Alexis' right eye had a golden, iridescent reflection, like a cat's eye."**
>
> *—Tammy Stewart*



Setting the pace in a heartbeat

By Amy Shields

The heart pumps about 1 million barrels of blood during an average lifetime. But for the 5 million Americans suffering from congestive heart failure, the organ's ability to perform this monumental task is greatly diminished.

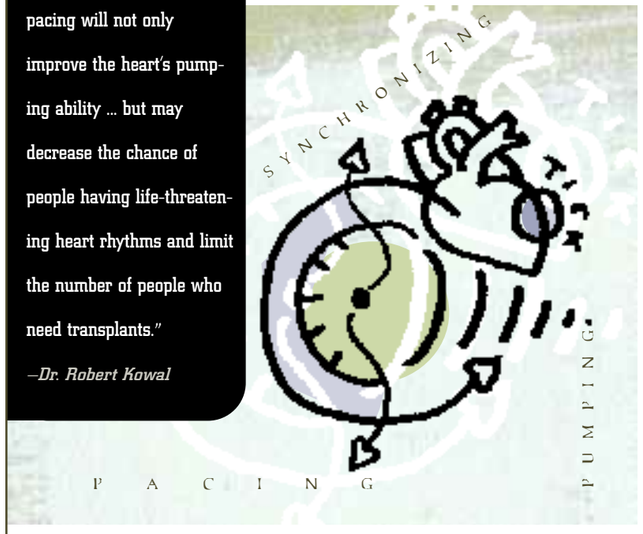
A new Food and Drug Administration-approved pacemaker, however, is offering new hope for these patients.

The University of Texas Southwestern Medical Center at Dallas is one of the first sites in Texas to offer the biventricular pacemaker. The device resynchronizes an uncoordinated beating heart with electrical abnormalities, allowing the heart to more efficiently pump the 31 million gallons of blood circulated during an average lifetime.

In about one-third of people diagnosed with congestive heart failure, the left ventricle — the heart's main pumping chamber — is no longer synchronized. As a result, the heart cannot push blood out to the rest of the body as efficiently. This leads to fatigue, complications of the respiratory system and, sometimes, death.

The new pacemaker significantly reduces the complications associated with congestive heart failure, improves a patient's mobility and cuts hospitalizations by almost half, according to a study published in the June 13 issue of *The New England Journal of Medicine*.

> "There are some reasons to suggest that this type of pacing will not only improve the heart's pumping ability ... but may decrease the chance of people having life-threatening heart rhythms and limit the number of people who need transplants."
>
> *—Dr. Robert Kowal*



"The biventricular pacemaker is designed for persons with severe congestive heart failure who are not responding to optimized medications and have electrical conduction delays in their hearts," said Dr. Robert Kowal, assistant professor of internal medicine who performs the implantation procedure. "It provides a non-pharmacologic method of improving heart function, making patients feel better and allowing them a greater exercise capacity. In the long term it may decrease mortality from congestive heart failure."

A standard pacemaker addresses rhythm disturbances. The biventricular pacemaker is designed to treat impaired blood flow by resynchronizing the ventricles of the heart. Implanted in a patient's chest during a minor surgery, the device simultaneously paces both the right and left ventricles.

"Preliminary studies have shown that biventricular pacing may decrease hospital admissions by up to 70 percent in these patients. I think that is incredibly promising," Kowal said.

Although the pacemaker improves quality of life, the device is not designed to replace drug therapy to treat the condition, said Dr. Clyde Yancy, medical director of the UT Southwestern/St. Paul Heart Transplant Program.

There are several causes of congestive heart failure, including coronary artery disease, heart valve disease and hypertension. General treatment includes salt restriction, diuretics to get rid of excess fluid, digoxin to strengthen the heart and other medications.

Kowal and other cardiologists in the electrophysiology lab at Parkland Memorial Hospital began implanting biventricular pacemakers in October 2001. Similar devices are being implanted at the Dallas Veterans Affairs Medical Center where Dr. Mohamed Hamdan, associate professor of internal medicine and holder of the Dallas Heart Ball Chair in Cardiac Arrhythmia Research, is leading research in this area.

"There are some reasons to suggest that this type of pacing will not only improve the heart's pumping ability and allow the heart to pump more efficiently, but may decrease the chance of people having life-threatening heart rhythms and limit the number of people who need transplants," Kowal said. "I think it's going to be a real breakthrough in treatment options for congestive heart failure."✣

Overtaking early ovarian cancer

By Ann Harrell

Sharon Hahs had no idea a tumor that appeared in her neck was a late sign of ovarian cancer.

"Three-quarters of women with ovarian cancer present with their disease at an advanced stage because they have no symptoms, and there's currently no accepted test to detect it early enough to prevent its development," said Dr. John Schorge, assistant professor of obstetrics and gynecology at The University of Texas Southwestern Medical Center at Dallas.

Currently, the disease is fatal for about 56 percent of the patients diagnosed with it, making it the most deadly of the gynecologic cancers. However, good news may be on the way.

Schorge and his team of specialists, along with medical scientists from Harvard Medical School and three other academic medical centers, last spring found a marker for ovarian cancer that utilizes osteopontin, one of the body's many proteins. Osteopontin, which may be revealed by a simple blood test, is found in bodily fluids such as blood plasma, urine, milk and bile. It is elevated in ovarian cancer patients, even those in the early stages of the disease, leading researchers to believe they are on the way to developing the first successful early-stage ovarian cancer test.

Most of the patient research was conducted at UT Southwestern under Schorge's supervision, and his findings were published in the April 3 issue of *The Journal of the American Medical Association*.

There is currently only one blood test associated with ovarian cancer, Schorge explained, but it's not effective as an early diagnostic tool. The test, called CA125, is used to follow women who already have been diagnosed with the disease to determine whether they are responding to treatment.

"We identified a specific protein, osteopontin, that is overproduced 184-fold in ovarian cancer cells. Then we wondered if that was measurable in the blood. So we tested it," said Schorge.

Preliminary results of the first stage of testing showed that osteopontin levels in blood plasma were significantly higher in 51 patients with epithelial ovarian cancer than in 199 other women, including 107 healthy controls, 45 patients with benign ovarian disease and 47 with other gynecological cancers. The researchers recommended further testing because of the early success with the biomarker.

"Every year 25,000 patients with ovarian cancer are diagnosed, and approximately 14,000 of these women die," said Schorge, who is a member of the Harold C. Simmons Comprehensive Cancer Center team at UT Southwestern. "That's why finding a biomarker that can be used at the beginning is so vital."

Schorge explained that most ovarian cancer is detected at Stages III or IV, the most advanced levels of the disease. Patients with Stage III or IV ovarian cancer have a five-year survival rate of less than 30 percent while patients detected during Stage I have a 95 percent survival rate. Medical scientists have investigated a number of markers for ovarian cancer, he said, but none so far have been successful in detecting early-stage disease.

"Our team is hoping that the osteopontin, which is present in the actual tissue of the cancer, will lead to the development of an early blood test for ovarian cancer that could affect the lives of all women," Schorge said.

The next step will be a clinical trial using a variety of early detection biomarkers, including osteopontin.

Within five years, Schorge said, there could be an economical blood screening test for ovarian cancer that might be used annually in conjunction with a Pap test for cervical cancer.

That's why Sharon Hahs volunteered to be part of the ongoing UT Southwestern study.

"If you know you have ovarian cancer already, but the doctors are working to catch it early, other women may have a better survival rate," Hahs said. "Anything I can do to help that research I'm willing to do. I want to be part of the solution."✣

> "Our team is hoping that the osteopontin, which is present in the actual tissue of the cancer, will lead to the development of an early blood test for ovarian cancer that could affect the lives of all women."
>
> *—Dr. John Schorge*

2002

ANNUAL REVIEW

HIGHLIGHTS
of the year

FALL 2001

RESEARCHERS UNCOVER HOW BRAIN, SPINAL CORD FORM CONNECTION

UT Southwestern researchers discovered a biochemical pathway that helps describe how neurons in the brain and spinal cord form their connections. Further study of the phenomenon, which was described in *Nature,* could lead to discoveries in nerve regrowth following spinal cord injury.

By learning how nerve fibers grow and form connections in the embryonic brain and spinal cord, researchers may eventually be able to determine how to coax nerves to regenerate, said Dr. Mark Henkemeyer, associate professor in the Center for Developmental Biology.

The research focuses on a specific group of receptors and ligands that are widely expressed in the developing nervous system. Normally, ligands produced by one cell bind to their corresponding receptor, which is expressed on target cells. This causes a change in the receptor, allowing it to transduce signals into the receiving cell.

TRANSPLANT SERVICES AIDS 9/11 BURN VICTIMS

Two UT Southwestern Transplant Services Center employees drove cross-country to take skin from the UT Southwestern tissue bank to aid victims of the Sept. 11, 2001, terrorist attack on the Pentagon.

The tissue was needed for burn victims being treated at the Washington Hospital Burn Center. The head of the burn center, Dr. Marion Jordan, requested assistance from UT Southwestern. Jordan had completed his fellowship under UT Southwestern burn specialists Dr. Charles Baxter and Dr. John Hunt, professor emeritus and chairman, respectively, of burn/trauma/critical care.

Because the Federal Aviation Administration had shut down the nation's air traffic, two transplant technicians volunteered to drive the 1,300 miles with 70 square feet of donor skin.

DR. JAMES DE LEMOS AND COLLEAGUES FOUND THAT A SINGLE MEASUREMENT OF A CARDIAC HORMONE CAN PREDICT HEART FAILURE, OR EVEN DEATH, IN A PATIENT.

CARDIAC HORMONE SERVES AS WARNING SIGN OF HEART FAILURE

Researchers at UT Southwestern found that elevated levels of a cardiac hormone are predictive of an increased risk of death or heart failure in patients with complications of coronary artery disease.

The findings, published in *The New England Journal of Medicine,* provide physicians with a new method of assessing adverse outcomes in patients with acute coronary syndromes, said Dr. James de Lemos, lead author of the study and assistant professor of internal medicine.

A single measurement of the hormone gives important information about how likely a patient is to die or develop heart failure, said de Lemos, who works in the Harry S. Moss Heart Center and the Donald W. Reynolds Cardiovascular Clinical Research Center.

Researchers also found that the level of the hormone, termed brain natriuretic peptide, or BNP, was better at predicting adverse outcomes compared to traditional ways of prognosticating after a heart attack, de Lemos said.

SUSTAINED-RELEASE SODIUM FLUORIDE DECREASES NUMBER OF SPINAL FRACTURES

UT Southwestern researchers found that using sustained-release sodium fluoride with calcium citrate and vitamin D safely reduces the risk for vertebral fractures while increasing spinal bone mass in older women with osteoporosis.

The 42-month study, published in the *Archives of Internal Medicine,* followed 85 women who were 65 years and older and had one or more nontraumatic vertebral fractures.

The efficacy of sodium fluoride therapy had been debated in a previous study, which promulgated the thought that fluoride only makes weaker bone.

This new study showed that this combination of therapy safely reduced the risk for vertebral fractures by stimulating new bone formation by fluoride-mediated increased osteoblastic (bone-forming cell) activity. In addition, the adequate provision of calcium and vitamin D reduces bone resorption.

INSTITUTE OF MEDICINE SELECTS GANT, OLSON

Two internationally recognized researchers at UT Southwestern were elected to the Institute of Medicine, a component of the National Academy of Sciences.

Drs. Norman F. Gant Jr., professor of obstetrics and gynecology, and Eric Olson, chairman of molecular biology, were named to the prestigious organization, charged with addressing national health issues.

Gant and Olson brought the total number of UT Southwestern faculty members inducted into the institute to 15. UT Southwestern has more IOM members currently on faculty than all other Texas medical institutions combined.

FOR NEARLY 10 YEARS, DR. H. DWIGHT CAVANAGH HAS BEEN STUDYING HOW THE ATTACHMENTS OF A BACTERIUM TO THE CORNEA CAN INCREASE CHANCES OF EYE INFECTIONS AMONG CONTACT-LENS WEARERS.

WINTER 2001-2002

NEW CONTACT-LENS MATERIALS REDUCE EYE INFECTIONS

UT Southwestern researchers reported that contact lenses, both rigid and soft, made from new hyper-oxygen transmissible materials will reduce the possibility of bacterial infection better than contact lenses currently on the market. Based in part on these findings, the Food and Drug Administration approved hyper-oxygen transmissible contact lenses for 30-day continuous wear.

The results of the study were published in the journal *Ophthalmology*.

Dr. H. Dwight Cavanagh, vice chairman of ophthalmology, associate dean for clinical services and senior author of the study, said the study strongly suggests that these new lenses will be a breakthrough in reducing risk for infection.

STUDY ADDS TO INSIGHT ABOUT BRAIN FUNCTION

Researchers at UT Southwestern are a step closer to defining the function of two proteins involved in neurotransmitter release, which initiates communication between neurons in the brain.

Findings from the two-part study, published in *Nature,* provide new insight in understanding how the brain functions, which ultimately has broad implications for the development of drug therapy to treat neurological diseases such as Alzheimer's and Parkinson's, as well as learning and memory disorders.

Dr. Thomas Südhof, senior author of the first part of the study and director of the Center for Basic Neuroscience, said it is essential for understanding various diseases of the nervous system. "The premise of our work is the understanding of neurotransmitter release, which is a necessity for understanding brain function and how the brain works."

UT SOUTHWESTERN OFFICIALS APPOINTED TO FEDERAL POSTS

Two senior UT Southwestern officials were appointed to federal positions.

President George W. Bush appointed Dr. Daniel W. Foster, chairman of internal medicine, to the newly created President's Council on Bioethics. The 18-member council, comprising doctors, lawyers and philosophers, examines ethical, legal and scientific issues.

U.S. Department of Health and Human Services Secretary Tommy G. Thompson named UT Southwestern President Dr. Kern Wildenthal to his Advisory Committee on Regulatory Reform. The 29-member committee, which includes consumers, doctors and other health-care professionals, is charged with helping Thompson identify and change health-care regulations that hinder patient care more than they improve its quality.

ADA EXPERT PANEL SETS NEW DIET FOR DIABETICS

Diabetics are no longer limited to a high-carbohydrate/low-fat diet, according to the latest guidelines issued by the American Diabetes Association (ADA). Dr. Abhimanyu Garg, professor of internal medicine, served on the 12-member expert panel convened by the ADA that formulated the new evidence-based guidelines, which emphasize individualized diets and a variety of food choices.

Garg's research showing the benefits of a high-monounsaturated fat diet was instrumental in leading to the change in guidelines.

In the past, a diet packed with carbohydrates and low in fats was recommended to all patients with diabetes, Garg explained. The panel found that a diet rich in monounsaturated fatty acids led to improvement in high-density lipoprotein cholesterol, triglycerides and most importantly, diabetes control, giving diabetics the option of a diet rich in carbohydrates or a diet rich in monounsaturated fats.

LEPTIN REPLACEMENT THERAPY TREATS RARE FAT DISORDERS

Leptin replacement therapy drastically reduces triglyceride levels and controls diabetes in patients with rare fat disorders known as lipodystrophies, according to researchers at UT Southwestern and the National Institute of Diabetes and Digestive and Kidney Diseases.

Leptin is a protein produced by fat cells and is nearly absent in patients with generalized lipodystrophies — disorders which result in extreme loss of body fat. Generalized lipodystrophies are associated with metabolic abnormalities such as diabetes, high blood cholesterol and an accumulation of fat in the liver. Current treatment consists of high-dose insulin plus triglyceride- or lipid-lowering medications.

Results of the study, published in *The New England Journal of Medicine,* indicated that leptin replacement therapy not only controlled severe insulin resistance and lowered triglyceride levels but also decreased fat accumulation in the liver, an abnormality for which there has been no effective therapy.

DR. ABHIMANYU GARG SERVED ON THE AMERICAN DIABETES ASSOCIATION PANEL THAT FORMULATED NEW DIETARY GUIDELINES FOR DIABETICS.

SPRING 2002

LYMPHOMA-VIRUS LINK MAY LEAD TO NEW WAYS TO PREVENT, TREAT NON-HODGKIN CANCERS

UT Southwestern researchers established a link between human non-Hodgkin lymphomas and a monkey virus carried by some people, possibly opening new avenues for detection, prevention and treatment.

In the study, published in the British medical journal *The Lancet,* researchers examined nearly 400 tumors and control tissues and found the viral footprint for simian virus 40 (SV40) in the tumors of 43 percent of non-Hodgkin lymphoma patients. The virus, predominantly of the B-cell type, was present in 9 percent of Hodgkin disease cases, a significantly lower rate. SV40-positive findings among healthy subjects and patients with other types of adult and pediatric cancers, other than bone tumors, were 0 percent to 6 percent. Approximately 287,000 new non-Hodgkin lymphoma cases are diagnosed annually worldwide.

SV40 was first transmitted to humans between 1955 and 1963 in contaminated batches of polio vaccine, administered to as many as 30 million people.

Dr. Adi Gazdar, professor of pathology and principal investigator on the study, said the findings confirm earlier research on hamsters that associated SV40 with brain and bone tumors, mesotheliomas — tumors in the lining of the lungs and other organs — and B-cell lymphomas.

COCAINE CAUSES CARDIAC EMERGENCIES BY RAISING HEART RATE, BLOOD PRESSURE

Researchers at UT Southwestern identified the underlying mechanism by which cocaine triggers hypertensive crisis, the most severe form of high blood pressure and one of the most common cocaine-related cardiovascular emergencies in the United States.

The findings, reported in *Circulation,* may lead to the development of new treatment strategies for cocaine-induced blood pressure elevation and related complications, including stroke and acute myocardial infarction.

The underlying mechanism of the blood-pressure-raising effect of cocaine use in humans had not been well-studied, said Dr. Wanpen Vongpatanasin, senior author of the study and assistant professor of internal medicine. Most researchers, she said, had believed that cocaine increases blood pressure mainly by causing constriction of blood vessels from excess levels of noradrenaline.

But it was discovered that this mechanism plays a very small role in humans. Instead, cocaine increases blood pressure by stimulation of the heart to cause rapid heartbeat and increased cardiac output. This elevation in blood pressure, if severe or persistent, can lead to damage of multiple vital organs such as the heart, brain and kidney.

JAPANESE CORP. AWARDS $15 MILLION GRANT TO RESEARCHER

UT Southwestern researcher Dr. Masashi Yanagisawa received a five-year, $15 million grant from Japan Science and Technology Corp. to expand his research on receptor genes and the roles they play in the body.

DR. MASASHI YANAGISAWA WILL CONTINUE HIS RESEARCH OF "ORPHAN" G-PROTEIN RECEPTORS WITH A $15 MILLION JAPANESE GRANT.

Japan Science and Technology, administered by the Japanese prime minister's office, conducts and promotes basic research, technology transfer and research cooperation in fields including biology, physics, chemistry and electronics. It annually awards Exploratory Research for Advanced Technology (ERATO) grants to four investigators.

Yanagisawa, professor of molecular genetics and an investigator in the Howard Hughes Medical Institute at UT Southwestern, will continue his research of "orphan" G-protein receptors — those whose function is unknown. His team of researchers discovered a hormone that is an important pathway in the regulation of hunger. During this research, the team also found that mice lacking the hormone orexin developed narcolepsy, a sleep disorder.

CALCIUM-SIGNALING PROTEIN CREATES FIT MUSCLES WITHOUT EXERCISE

A calcium-signaling protein transforms sedentary, easily fatigued muscles into energy-producing, fatigue-resistant muscles, UT Southwestern researchers reported in *Science*.

The researchers found that by genetically expressing the protein in skeletal muscles of laboratory mice, easily fatigued, or type II, muscle fibers were transformed into fatigue-resistant and mitochondria-rich, or energy-producing, type I muscle fibers, which resemble muscles that have been exercised.

This research could lead to novel measures to stimulate muscles in patients with chronic diseases such as congestive heart failure or respiratory insufficiency, or individuals confined to bed rest, said Dr. Rhonda Bassel-Duby, associate professor of internal medicine and co-author of the study.

SCIENTISTS PROVE GROUP OF PROTEINS TURNS GENES ON, OFF

Researchers at UT Southwestern proved that a group of proteins previously thought to have no role in turning genes on and off actually plays a part in that process, which is critical to both human development and understanding some diseases.

The work — conducted under the direction of Dr. Stephen Johnston, director of the Center for Biomedical Inventions, and Dr. Thomas Kodadek, professor of internal medicine and molecular biology who also works in the Center for Biomedical Inventions — was published in *Science*. The research focuses on the proteasome, a group of proteins present in all cells.

Conventional wisdom held that the proteasome serves one purpose: working as a unit to break down individual proteins that have done their work and are no longer needed in the cell, a process called proteolysis. The new research showed that certain proteins can break away from the proteasome to perform other functions and are involved in gene transcription, in which a gene's genetic sequence is copied into messenger RNA. Transcription is the first step in gene expression — when proteins that perform specialized functions are produced according to the gene's sequence.

SUMMER 2002

BIBB, KARANDIKAR WIN PRESIDENT'S RESEARCH COUNCIL AWARD

For the second year in a row, the President's Research Council at UT Southwestern gave two $60,000 awards to outstanding young scientists at the medical center.

The recipients of the 2002 Young Researchers Award were Dr. James Bibb, assistant professor of psychiatry who is studying how proteins affect the brain, and Dr. Nitin Karandikar, assistant professor of pathology and neurology who is investigating the role of the body's immune system in multiple sclerosis.

DR. NITIN KARANDIKAR (LEFT) AND DR. JAMES BIBB WERE EACH HONORED BY THE PRESIDENT'S RESEARCH COUNCIL. BIBB'S RESEARCH INVOLVES PROTEIN REGULATION IN THE BRAIN, AND KARANDIKAR IS INVESTIGATING THE CAUSE OF MULTIPLE SCLEROSIS.

Increased membership last year allowed the group to again present more than one award.

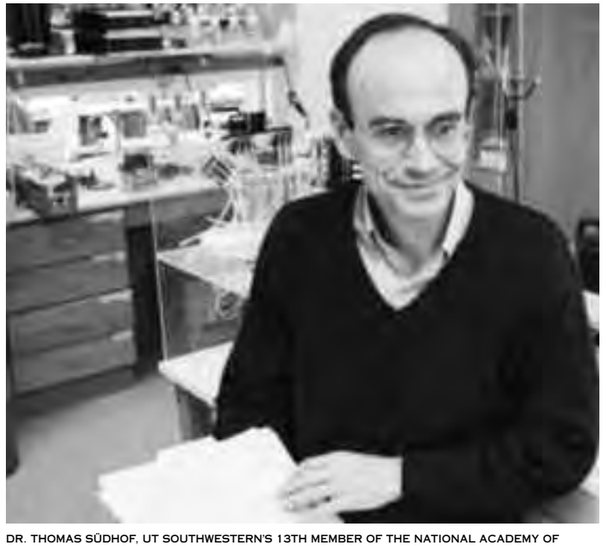
NATIONAL ACADEMY OF SCIENCES ELECTS SÜDHOF

Dr. Thomas Südhof, director of the Center for Basic Neuroscience at UT Southwestern, was elected to the National Academy of Sciences (NAS) — one of the highest honors bestowed on American scientists.

Südhof was the only Texan among the 72 new members, who were elected in recognition of their distinguished and continuing achievements in original scientific research.

Members of the NAS are elected from more than two dozen scientific disciplines ranging from astronomy to geology. In 1979 a UT Southwestern faculty member was the first medical scientist elected from Texas. In all, 13 of the current 16 NAS members at Texas medical institutions come from UT Southwestern.

Südhof's work into the mechanism by which neurons communicate in the brain and into the pathogenesis of Alzheimer's disease is internationally recognized. In 2001, Südhof made a breakthrough discovery about the role of a protein involved in the onset of Alzheimer's, a finding that may have a profound impact on how doctors treat the disease.



DR. THOMAS SÜDHOF, UT SOUTHWESTERN'S 13TH MEMBER OF THE NATIONAL ACADEMY OF SCIENCES, DIRECTS RESEARCH INTO THE PATHOGENESIS OF ALZHEIMER'S DISEASE.

MEDICAL, GRADUATE, ALLIED HEALTH STUDENTS EARN DEGREES

Dr. Kern Wildenthal, president of UT Southwestern, presided at the June 1 graduation of 200 students from Southwestern Medical School and 35 students from Southwestern Graduate School of Biomedical Sciences.

Southwestern Medical Foundation's Ho Din Award, the top award given to a graduating medical student, was presented to Dr. Christine Kulstad, who plans a career in emergency medicine. Jared Paul Rutter, whose research focuses on a protein that regulates energy in cells, received the Nominata Award, the highest honor bestowed by the graduate school.

Southwestern Allied Health Sciences School conferred degrees on 141 students during its Aug. 25 commencement exercises.

RESEARCHERS EXPLAIN DIET, CANCER-RISK LINK; UNCOVER NATURAL CHOLESTEROL REDUCER

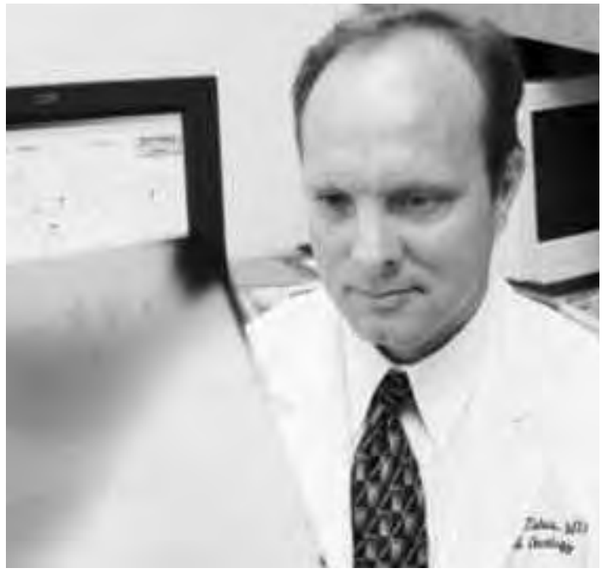
Researchers at UT Southwestern have uncovered what could be a key clue in tracing the connection between high-fat diets and increased colon-cancer risk.

The findings, published in *Science*, reveal that the body's natural mechanisms aren't built to handle lithocholic acid, a toxic by-product of dietary fat, in the volume generated by high-fat diets.

Dr. David Mangelsdorf, professor of pharmacology and an investigator in the Howard Hughes Medical Institute at UT Southwestern, said observational evidence established a strong association between high-fat diets and colorectal cancer, but scientists previously could not explain the biological and biochemical mechanisms that formed the link.

UT Southwestern researchers, led by Mangelsdorf, also helped prove that a naturally occurring compound used for centuries as a dietary supplement in India can help lower cholesterol levels.

The research, published in *Science* and completed in collabora-



WORK RECENTLY PUBLISHED BY DR. DAVID EUHUS SHOWED THAT COMPUTER MODELING USING FAMILY HISTORIES AND MICROSCOPIC EXAMINATION OF DNA IN BREAST CELLS ARE VIABLE TOOLS IN ASSESSING WOMEN'S RISK OF CARRYING CANCER-CAUSING GENETIC MUTATIONS.

tion with Baylor College of Medicine in Houston, shows that guggulsterone — made from the sap of *Commiphora mukul*, a tree commonly known in India as guggul — blocks the FXR receptor, which regulates cholesterol metabolism. Mangelsdorf and his colleagues previously had revealed FXR's role in the body's conversion of cholesterol to bile acids. When bile acids reach a certain level in the body, FXR is activated to interrupt the cholesterol-to-bile-acid process.

CELL MOLECULAR MAKEUP HELPS GAUGE RISK FOR BREAST CANCER

Researchers at UT Southwestern showed that examining the molecular makeup of breast cells can provide a better way to predict breast-cancer risk, and that computer-based risk-assessment tools can help identify women who would benefit from genetic testing.

The findings were published in separate papers in the *Journal of the National Cancer Institute*. Dr. David Euhus, associate professor of surgical oncology, was lead author on both papers.

Women participating in the cell-examination study were not cancer patients; however, their risk of developing breast cancer had been assigned as low, moderate or high using the Gail model, a computer model known to be an accurate predictor of breast cancer. Euhus found that the detection of small DNA deletions in breast cells from these women correlated with Gail-model risk and with precancerous changes in the cells diagnosed by routine microscopy.

NEW APPOINTMENTS FOR 2001-2002

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

■ Dr. Stephen Cannon was named chairman of neurology. He is the first holder of the Linda and Mitch Hart Distinguished Chair in Neurology and also holds the Lois C.A. and Darwin E. Smith Distinguished Chair in Neurological Mobility Research. Cannon formerly was a neurologist at Massachusetts General Hospital and neurobiologist at Harvard Medical School.

■ Dr. W.P. "Phil" Evans III was named director of breast imaging at the Southwestern Center for Breast Care and professor of radiology. He had been director of the breast center at Baylor University Medical Center.

■ Dr. Charles Ginsburg, former chairman of pediatrics, was named associate dean for faculty development. He holds the Marilyn R. Corrigan Distinguished Chair in Pediatric Research.

■ Dr. Joseph Hill was named chief of cardiology. He holds the James T. Willerson, M.D., Distinguished Chair in Cardiovascular Diseases and the Frank M. Ryburn Jr. Chair in Heart Research. Hill formerly was at the University of Iowa College of Medicine.

■ Dr. William E. Johnston was named chairman of anesthesiology and pain management. He holds the Margaret Milam McDermott Distinguished Chair in Anesthesiology and Pain Management. He was formerly chief of cardiothoracic anesthesiology at UT Medical Branch in Galveston.

■ Dr. Claus Roehrborn was named chairman of urology. He is also holder of the E.E. Fogelson and Greer Garson Fogelson Distinguished Chair in Urology and is chief of urology at the Dallas Veterans Affairs Medical Center.

■ Dr. Debasish "Debu" Tripathy was named director of the Komen/UT Southwestern Breast Cancer Research Program. He is the first holder of the Annette Simmons Distinguished Chair in Breast Cancer Research. Tripathy was at the University of California, San Francisco, School of Medicine.

MAJOR GIFTS 2001-2002

Philanthropists continued to demonstrate their commitment to UT Southwestern in 2001-2002, providing support for a variety of research and clinical programs.

New gifts and pledges that were received for UT Southwestern's *Innovations in Medicine* campaign during this fiscal year included:

■ $25 million from a trust established by Bulah "Lucy" MacAdams Luse to support medical research and treatment.

■ $20 million from the Howard Hughes Medical Institute toward the construction of the North Campus' new $240 million research tower.

■ $11.7 million from the Harry S. Moss Trust for the Prevention and Cure of Heart Disease to expand cardiovascular research in the Harry S. Moss Heart Center.

■ $7.5 million from Deborah and W.A. "Tex" Moncrief Jr. for a new 40,000-square-foot Radiation Oncology Center on the North Campus.

■ $5 million from the Vin and Caren Prothro Foundation and from Caren Prothro for a center for basic neuroscience research.

■ $3.5 million from Dr. Steven McKnight, chairman of biochemistry, and Jackie McKnight to create the Sara and Frank McKnight Fund for Biochemical Research.

■ $3 million from the Pogue Foundation to endow distinguished chairs in pediatric cardiac surgery and pediatric cardiology research.

■ $2 million from the Hoblitzelle Foundation toward construction of the new North Campus research tower, and an additional $1.5 million for the acquisition of patient-care equipment for use at St. Paul University Hospital.

■ $2 million from the Pauline Allen Gill Foundation to establish a special research center to study how brain cells communicate with one another.

■ $2 million from Anne Marie and Thomas B. Walker to endow centers for research on breast cancer and age-related macular degeneration.

■ $2 million from Margot and Bill Winspear to establish the Winspear Family Center for Research on the Neuropathology of Alzheimer's Disease.

■ $1.1 million from Grant Dove to support oncology research.

■ $1.1 million from the Hawn Foundation, $100,000 to be used for medical research and $1 million to support the campaign's goals.

■ $1 million from an anonymous donor to support clinical programs at Zale Lipshy University Hospital.

■ $1 million from 318 donors, including friends, colleagues and former residents of Dr. C. James Carrico, to establish the C. James Carrico, M.D., Distinguished Chair in Surgery for Trauma and Critical Care.

■ $1 million from Margaret and Trammell Crow to establish the Margaret and Trammell Crow Chair in Alzheimer's and Geriatric Research and to support ongoing research in the area.

■ $1 million from the ExxonMobil Foundation to support a new program in epidemiology and public health.

■ $1 million as a charitable remainder trust from Ute Schwarz Haberecht and Rolf R. Haberecht.

■ $1 million from the Eugene McDermott Foundation to establish the S.T. "Buddy" Harris Distinguished Chair in Cardiac Anesthesiology.

■ $1 million from friends and admirers of Dr. J. Denis McGarry, including $200,000 from the Lattner Foundation, to endow the John Denis McGarry, Ph.D., Distinguished Chair in Diabetes and Metabolic Research.

■ $1 million from the Pollock Foundation to establish the Lawrence S. Pollock Jr. Center for Intestinal Cancer Research.

■ $1 million from Gay and William T. Solomon for the support of clinical program enhancements.

■ $950,000 from the A.L. Chilton Foundation to establish the Mar Nell and F. Andrew Bell Distinguished Chair in Biochemistry as well as support for current programs.

■ $905,066 from the Children's Cancer Fund for the recruitment of a new faculty member in pediatric oncology and to support six ongoing research projects.

■ $600,000 from Mrs. Bea Haggerty for stroke research.

■ $550,000 from Diana and Jack Kettman, Ph.D., for acquisition of special equipment for microbiology research.

■ $500,000 from an anonymous donor for an endowed chair in psychiatric research.

■ $500,000 from Kathryne and Gene Bishop to upgrade an earlier endowment to a distinguished chair for the UT Southwestern faculty member who serves as the chief medical officer of Children's Medical Center of Dallas.

■ $500,000 from HBK Invest - ments to establish the HBK Invest- ments Fund for Medical Research.

■ $500,000 to endow the Nancy R. McCune Chair in Alzheimer's Disease Research.

■ $500,000 from the St. Paul Foundation to establish the Ernest Poulos, M.D., Distinguished Chair in Surgery.

■ $400,000 from Dr. Gerald A. Belkin to create an endowment to support four Belkin Scholars.

■ $285,000 from the Charles and Dana Nearburg Foundation to advance research on Ewing's sarcoma.

■ $261,000 from Suzy and Larry Gekiere to establish the Gekiere Family Program for Neuro-Oncol- ogy Support.

■ $250,000 from Wilhelmina and Edward Ackerman to support research in human nutrition.

■ $250,000 from Richard Ferguson for research on liver disease.

■ $250,000 from Paula and Jon Mosle to establish the Meredith Mosle Distinguished Professorship in Liver Disease, in Honor of Dr. William M. Lee.

■ $250,000 from the Nasher Foundation and the family of Mrs. Patsy Nasher for cancer research.

■ $250,000 from the Gayle and Paul Stoffel Foundation to support heart research.

■ $250,000 from Harriet L. and Jos. Irion Worsham, further endow- ing the Harriet L. Worsham Fund for Alzheimer's Disease Research.

■ $225,000 from Jackie and Charles M. Solomon to provide research and clinical support for breast-cancer research.

■ $210,000 from Once Upon a Time….

Contributions of $100,000 or more were received from a number of donors, including the following new commitments:

■ Bank of America to support pediatric clinical and research programs.

■ Lucy and Henry Billingsley to support the Margaret and Trammell Crow Chair in Alzheimer's and Geriatric Research

■ Jean Ann and Steve Brock for multiple sclerosis research.

■ Eunice and Leland Carter as an unrestricted contribution.

■ Dianne T. Cash for psychiatric treatment and research programs.

■ Bequest from Lillian B. Clark to establish the Lillian B. Clark Lecture Series in Mineral Metabo- lism.

■ Lou Ann and Michael Corboy to support oncology research.

■ Robert Fletcher, Wilma Duniven and Karen McCloskey to establish the Patricia Duniven Fletcher Professorship in Gyne- cologic Oncology.

■ Fredric King to establish the Fredric King Family Endowment for Liver Disease.

■ Gillson Longenbaugh Foundation to support cancer research.

■ William McGowan Charitable Fund to support research on cardiac birth defects.

■ Garry McKinney Auto Group to support multiple sclerosis research.

■ Patricia, William, Josh and Abby Miller to establish the Miller Family Professorship in Neuro- Oncology.

■ Dr. John S. Smale to support medical research through a charitable remainder trust.

■ Dr. Bob and Jean Smith Foundation to support neurological research.

■ Vanberg Family Foundation to support allergy research.

■ Viragh Family Foundation for research on multiple sclerosis.

■ Carolyn and Richard L. Walton to support medical research through a charitable remainder trust.

■ West Endowment for research on bone marrow transplantation in cancer therapy.

■ Funds from colleagues and friends, including lead gifts from the Cimarron Foundation and Dula Foundation, to establish the Warren A. Weinberg, M.D., Chair in Pediatric Neurology and Learning.

■ Funds from several founda- tions, including the William Wright Family Foundation and the K.H. Jordan Foundation, to establish the Mary Quincy Parsons and Kelsey Louise Wright Professorship in Mitochondrial Disease Research.

Several charitable events held in Dallas during the fiscal year 2001-2002 dedicated their proceeds to special programs at UT Southwest - ern and affiliated institutions.

■ $1,134,982 from the Crystal Charity Ball to establish the Crystal Charity Ball Collaborative Program for Pediatric Brain Injuries.

■ $700,000 from the Sweetheart Ball for research on heart disease.

■ $500,000 from the Avon Foun- dation walk to create the Avon Foundation Breast Cancer Program.

■ $250,000 from the Texas Stampede for pediatric research and clinical programs.

■ $210,000 from KidneyTexas Inc.'s fall style show and luncheon for a KidneyTexas Inc. Pediatric and Adult Research Laboratory.

■ $204,250 from the Eye Ball 2002 — A Night for Sight for re- search, clinical activities, education programs and screenings.

■ $140,000 from the 2001 Dallas Heart Ball to further pediatric car- diology research. ✣