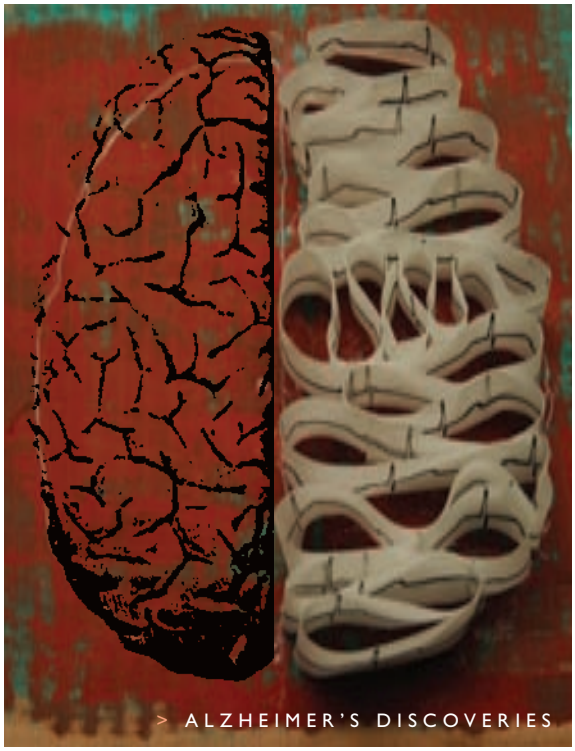
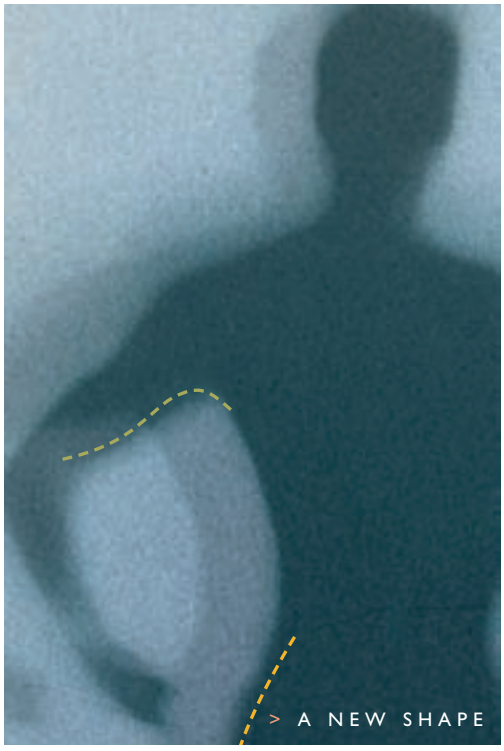
2005 Annual Review

SOUTHWESTERN MEDICINE



> ALZHEIMER'S DISCOVERIES



> A NEW SHAPE

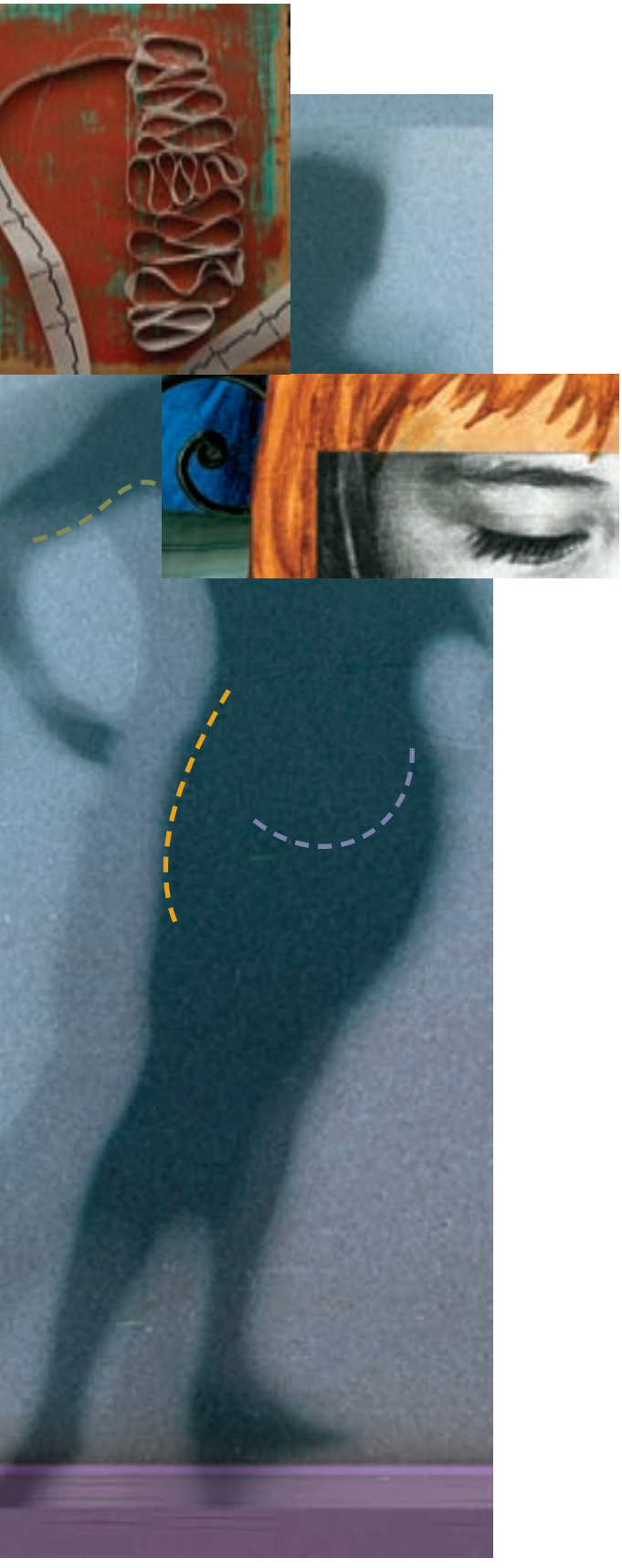
> THE DREAM OF UNDERSTANDING SLEEP

> LOOKING INSIDE THE BODY

ALSO INSIDE: > CANCER PREVENTION > CLINICAL FRONTIER

The Magazine of The University of Texas Southwestern Medical Center

C O N T E N T S



RESEARCHERS AND CLINICIANS OF UT SOUTHWESTERN MEDICAL CENTER'S ALZHEIMER'S DISEASE CENTER ARE STUDYING A FASCINATING LINK BETWEEN

heart and MIND

By Aline McKenzie

Watch your weight.

Lower your blood pressure.

Eat a healthful diet.

Reduce your "bad" cholesterol.

It's all sound advice for people who want to keep their bodies fit or stave off heart attacks and stroke.

But is it also a way to hold off the ravages of Alzheimer's disease?

Researchers and clinicians of UT Southwestern Medical Center's Alzheimer's Disease Center believe it is. The new paradigm is that if it's heart-healthy, it's brain-healthy.

At the National Institutes of Health-funded center, investigators are looking into that link: Could the villains of the cardiovascular system – obesity, high blood pressure and high cholesterol, which shrink blood-vessel diameter or cause inflammation – contribute to Alzheimer's destruction of the brain? And could there also be a genetic link?

These are only two of the newest lines of research undertaken at UT Southwestern against the brain-robbing disease.

For nearly two decades, scientists and physicians at the Alzheimer's Disease Center have been both treating patients with the insidious disease and studying its causes and treatments. More than 2,500 patients have been evaluated and cared for during that time. Since 1988, UT Southwestern has been one of the NIH's National Institute on Aging's Alzheimer's Disease Center sites. There are now 32 such centers in the United States, but UT Southwestern's remains the only one in the central part of the country.

It has recently been re-funded for $8 million over the next five years. These new dollars will underwrite research into two aspects of Alzheimer's that the center is taking up for the first time – the genetics of the disease and vascular risk factors behind it.

But despite work from some of the best minds worldwide, those looking for clues and cures have come away frustrated. Some drugs are available that can slow the development of symptoms, but there is nothing to stop the disease or reverse the damage.

"We really do not yet have very good therapy," said Dr. Ramon Diaz-Arrastia, associate professor of neurology and director of the center's clinical core.

Alzheimer's is universally fatal, he said.

At first, someone afflicted with Alzheimer's develops small problems, such as trouble thinking of words, or putting perishable food in the cabinet while storing clean dishes in the refrigerator. At the end, he or she needs help with every aspect of life.

"The best chance for slowing the disease is to identify it at the earliest stages and try to reverse it," said Dr. Roger Rosenberg, director of the center and holder of the Abe (Brunky), Morris and William Zale Distinguished Chair in Neurology. "Once the path - ology of Alzheimer's is entrenched, it is difficult to treat."

Charles Comfort, 73, a former management con - sultant from Sulphur Springs, is in the early stages of the disease. He is participating in several clinical studies – having spinal taps, magnetic resonance imaging, blood tests and other procedures. He's willing to help, and the researchers are grateful to be able to study someone in the earliest stage of the disease – a rarity.

He and his wife, Sunny, 62, began to notice the problem when he started having trouble speaking on stage in presentations that were essential to his job.

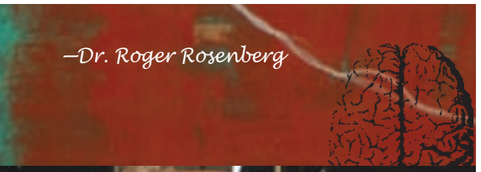
Once a jokester with a sharp sense of humor, he was losing his "edge," she said.

Now, when speaking, he often pauses while he searches for a word. When he manages to speak smoothly for a minute straight, he lights up with pleasure at his accomplish- ment. "I have a terrible time working words in," he said. "I forget terrifically."

Mrs. Comfort said, "It's a sad disease, but it's not any sadder than the things people face as they get older. We're committed Christians, and we believe that everyone has to sip from the cup of suffering."

But that suffering is what the center hopes to eliminate.

"THE BEST CHANCE FOR SLOWING THE DISEASE IS TO IDENTIFY IT AT THE EARLIEST STAGES AND TRY TO REVERSE IT."



A genetic link?

There is growing and compelling evidence of a genetic basis to the disease.

"Not to be funny, but pick your parents carefully," Dr. Rosenberg said.

A very small percentage of people have a form of the illness that is clearly passed on from a dominant gene. Familial Alzheimer's disease occurs before age 65 and affects less than 10 percent of Alzheimer's patients. Children of these patients have about a 50 percent chance of developing it.

Three proteins are involved: amyloid precursor protein, presenilin 1 and presenilin 2. A mutation in any one of the genes coding for these proteins causes early-onset Alzheimer's, which can strike people in their 40s and 50s.

At the cellular level, the beta-amyloid protein, which is produced from amyloid precursor protein that's been cut by enzymes, causes plaques and tangles in the brain, easily seen under a microscope.

While most people consider amyloid a villain, the early-onset cases of Alzheimer's help show how important it is in normal function. The body makes and removes amyloid at a certain rate for memory to function properly. Research has shown that this is true for species all the way down to fruit flies – even they lose their memory without amyloid.

Still, the vast majority of people with Alzheimer's are hit later in life, and the chance of getting it rises steadily with age. So the center is looking at late- onset Alzheimer's as well, which has more compli- cated genetics.

The only risk factor gene identified so far for late- onset Alzheimer's is a gene that makes the choles- terol-carrying molecule called apolipoprotein. Everyone has ApoE, but only 15 percent have the form that increases risk for the disease.

There are 10 to 20 other genes that also show intriguing variations. They may not only need to be present, but also to be exposed to some triggering risk factor to contribute to Alzheimer's, said Dr. Rosenberg. The result may be that the system that normally removes amyloid breaks down, so the substance begins to build up in the distinctive plaques that mar the brains of Alzheimer's victims.

For its work, the center is seeking about 1,000 families "enriched" in Alzheimer's – for instance, those who have siblings with the disease – to sequence their DNA and look for patterns. Dr. Rosenberg said he expects this to take about five years, but it could provide a "powerful answer."

Meanwhile, the researchers are looking for ways to fight the disease in those who have developed it. They have injected the gene for the beta-amyloid protein into mice, and the results have been encouraging: The mice have made antibodies to the protein without toxic side effects. Dr. Rosenberg and his colleagues hope to try this in humans soon.

A vascular link?

Another aspect of the center's work is an examination of vascular risk factors and their possible link to Alzheimer's – conditions such as hypertension, obesity, adult-onset diabetes, high cholesterol and high blood levels of homocysteine, an amino acid that is one of the building blocks of proteins.

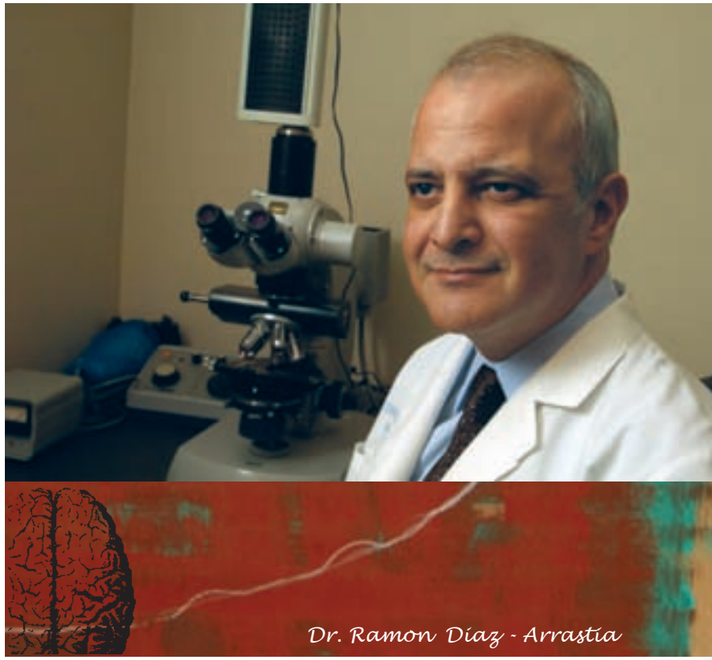
"We want to know if vascular risk factors cause an increase in the symptoms of memory and cognitive loss and which are the most important ones," Dr. Rosenberg said.

For instance, he asks, do these various factors increase the risk simply by damaging the circulatory system - for example, narrowing arteries in the brain, thereby shrinking or atrophying brain tissue? Or do they actually have to increase the number of plaques in the brain to sever the connections between nerves or to create strokes?

If a link is found, then there is hope, he said.

Dr. Bonnie Miller, assistant professor of internal medicine, is looking into a possible link between Alzheimer's and diabetes. An enzyme called insulysin, which degrades insulin, also seems to break up amyloid. In mice lacking the gene for insulysin, the level of amyloid-beta peptide in the brain is increased. Even a partial loss of insulysin activity raises the level of amyloid-beta peptide.

In humans, Dr. Miller is measuring insulin and glucose levels, as well as insulysin type, to see if there is a correlation between the presence and severity of diabetes and the presence and severity of Alzheimer's disease. They suspect there is.



Dr. Diaz-Arrastia is measuring cholesterol, lipo- proteins and other substances in blood and cerebro- spinal fluid in people with Alzheimer's and people without it.

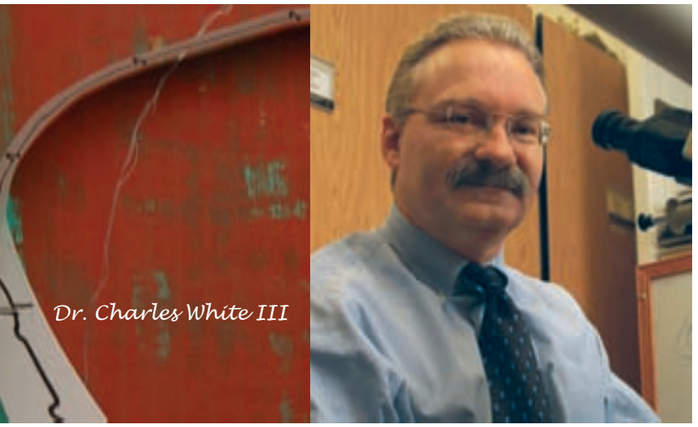
"That's often a very good way to start, although there's inherent difficulties in case-controlled studies," he said.

He is also using MRI to examine patients, looking for small, bright spots that indicate microvascular diseases.

"The significance of these images has been a little unclear," Dr. Diaz-Arrastia said.

The final clinical investigation occurs after the patient has died. Technically, Alzheimer's can be positively diagnosed only by autopsy, but many researchers are developing highly accurate means of identifying the disease in living patients, such as measuring blood flow in certain parts of the brain. The density and distribution of the amyloid plaques seen in the brain at autopsy still set the standard, however.

HAS BEEN USING MRI TO EXAMINE PATIENTS, LOOKING FOR SMALL, BRIGHT SPOTS THAT INDICATE MICROVASCULAR DISEASES.



Dr. Charles White III

"It's not a black-or-white, or yes-or-no, quite like it is with cancer."

amyloid plaques are distributed along a bell curve, so the distribution between normal and abnormal is not clear-cut.

"It's not a black-or-white or yes-or-no, quite like it is with cancer," said Dr. Charles White III, professor of pathology, head of the center's neuropathology core, director of the Winspear Family Special Center for Research on the Neuropathology of Alzheimer's Disease and holder of the John H. Childers, M.D., Professorship in Pathology.

In postmortem examinations, researchers tease out vascular problems, examining blood vessels and tissue for any abnormalities, such as amyloid deposits.

The scientists also look at the hippocampus, a structure in the brain involved in memory, to see whether it is shrunken or shows other changes.

"You can't store and retrieve new data without a hippocampus," Dr. Rosenberg said.

Finally, there's the ultimate step that everything depends on – reading and analyzing the information.

"You can spend a lot of money, time and effort on research, but if the data you collect aren't clean, accurate and complete, all the rest has been wasted," said Dr. Joan Reisch, professor in the Center for Biostatistics and Clinical Science and of family and community medicine and director of the Alzheimer's Disease Center's data management core.

Part of the new funding for all 32 centers is to standardize how data is collected and stored, allowing more accurate comparisons. Participants in studies will now complete extensive forms, providing about 1,500 pieces of data for the researchers.

"We do a lot of searching for relationships," Dr. Reisch said. "We're looking at new territory."

Of all the country's statisticians, she was one of three chosen for the national steering committee that oversees all Alzheimer's centers as they develop standardized data management procedures.

Reaching out

The center doesn't simply do research and traditional clinical work. There are several outreach programs, particularly aimed at blacks and American Indians, both of whom are more likely than whites to develop Alzheimer's. The education core staff, for example, has conducted programs at a predominantly black church about how to make sure Alzheimer's is diagnosed correctly.

Native Americans, in particular, pose an interesting puzzle, Dr. Rosenberg said.

The researchers have found that some tribes are genetically protected from Alzheimer's, but the influence of a Western high-fat diet and its resulting obesity and diabetes tip the balance against this group.

A study conducted nearly 10 years ago by Dr. Rosenberg found that Cherokees have genetic protection against Alzheimer's. The higher the percentage of one's tribal "blood," the lower the risk of Alzheimer's, Dr. Rosenberg said. Choctaw tribal members seem to be similarly protected, but only if they are "cardiovascularly healthy."

In 2004 UT Southwestern received a grant from the National Alzheimer's Association to look at cardiac risk factors affecting Alzheimer's disease in the Native American community. It is the only center in the country studying the clinical and scientific aspects of dementia in American Indians.

But no matter the direction their research takes them, UT Southwestern investigators can't answer all the questions about Alzheimer's soon enough. As baby boomers age, the number of people with the disease is predicted to snowball from 4 million today to 14 million by 2050.

"Many of our caregivers are family members, and they want to know how to protect themselves against this," said Margaret Higgins, assistant professor of health care sciences and the center's education core director.

"The cruel thing is there's no real answer to that question yet."⌘

For more information about the Alzheimer's Disease Center, please call 214-648-9376.

molecules and MIND

By Aline McKenzie

The struggle to understand and fight Alzheimer's disease is being waged on more than one front at UT Southwestern. In the Center for Basic Neuroscience, researchers are studying mice to tease apart the mechanisms behind the disease, both at the cellular and molecular levels.

The results are clear: There's much overlap with another neurodegenerative disease, Parkinson's, said Dr. Thomas Südhof, director of the center and holder of the Gill Distinguished Chair in Neuroscience Research and the Loyd B. Sands Distinguished Chair in Neuroscience. He also directs the Gill Center for Research on Brain Cell Communication and the C. Vincent Prothro Center for Research in Basic Neuroscience.

"Parkinson's disease can lead to severe cognitive losses as well as problems with movement, and Alzheimer's disease can lead to movement disorders in addition to mental problems," he said.

His research team is focusing on a few molecules and their actions. One is amyloid precursor protein (APP), which breaks down into beta-amyloid, a protein that causes plaques and tangles in the brains of Alzheimer's patients. It breaks down in healthy people, too, but sometimes too much is broken down, and it accumulates.

Mutations in the gene that controls the creation of APP are known to cause Alzheimer's disease.

Among the crucial questions that this research raises: What is the normal role of APP in healthy people? And how does an excess of beta-amyloid break down the connections between nerve cells?

"I have no idea," admitted Dr. Südhof.

Almost all scientists agree that excess beta-amyloid is a cause of Alzheimer's, he said, but it is not the only one.

One major finding of his, recently published in the journal *Cell*, showed how a large protein called nicastrin binds to APP and guides it to the enzyme that clips it into beta-amyloid. This discovery gives hope that by blocking that simple mechanism, the production of beta-amyloid can be slowed.

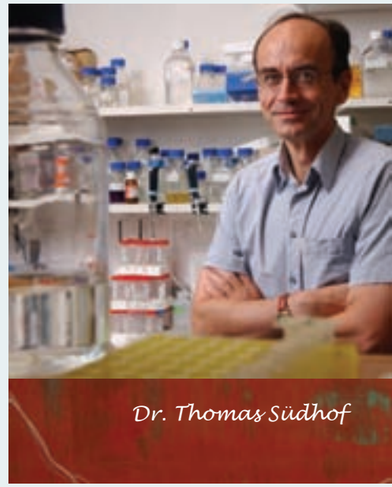
Another study focuses on a protein called synuclein, which seems to protect the junction between nerve cells. Normally, a short protein called cysteine string protein, or CSP, is involved in the process by which one nerve cell sends a signal to another. CSP is a co-chaperone, which helps other proteins fold into their normal shapes. If this function is disrupted, the nerve terminal dies. By breeding mice with or without synuclein or CSP, scientists found that synuclein seems to be able to repair damage within this process.

That was surprising, because the two proteins have entirely different structures, so synuclein is not simply filling in CPS' role, Dr. Südhof said.

And just as beta-amyloid clumps in the brains of people with Alzheimer's, synuclein makes clusters, called Lewy bodies, in the brain cells of people with Parkinson's disease. There is a link between the two diseases there, as well. Lewy bodies show up in 100 percent of Parkinson's cases and more than 30 percent of Alzheimer's cases.

With researchers finally finding a role for synuclein, they can now home in on exactly how it protects the nerve endings.

"This line of research, I think, is probably the most important we have done in the last couple of years, because it really changes the field," Dr. Südhof said.



Dr. Thomas Südhof

There's also molecular overlap between Alzheimer's disease and atherosclerosis, said Dr. Joachim Herz, professor of molecular genetics and holder of the Thomas O. Hicks Family Distinguished Chair in Alzheimer's Disease Research. Together, the diseases afflict more than half the Western world's population.

He and his team have identified several molecular mechanisms that play a role in both diseases. Their common factor is a set of cell-surface molecules, known as the low-density lipoprotein receptor gene family, which binds to LDL, the "bad" cholesterol. These molecules are involved in many cell functions: sending signals from one nerve cell to another, controlling cell propagation, metabolizing vitamins and many other tasks.

These molecules also bind ApoE, a risk factor in late-onset Alzheimer's. So which of them, if not all, is involved in the development of the disease?

"Our goal now is to dissect out the molecular interaction," Dr. Herz said. "We test predictions of specific mutations in the mouse by making target (genetic) deletions."

For instance, they've found that a receptor for ApoE, called ApoER2, plays a critical role in the synapse – the junction between nerve cells, where one sends packets of chemicals to the other to convey signals.

"This is a very plausible place in which ApoE receptors are likely to play a decisive role. It could explain how ApoE brings about the disastrous losses of synapses in Alzheimer's disease, the process that is directly responsible for the dementia," he said. ⌘

"This line of research ... is probably the most important we have done in the last couple of years, because it really changes the field."

A Look Inside

By Katherine Morales

At UT Southwestern Medical Center, a new state-of-the-art imaging facility will help researchers peer inside the human body and increase their understanding of its functions.

More than 100 years ago, a German physicist took a photo of his wife's hand that was destined to revolutionize every aspect of human existence.

The picture showed a large mass on her third finger – her wedding ring. But it also did the unthinkable: It revealed what lay beneath the skin – her bones.

That photo was the first X-ray and the beginning of modern radiology.

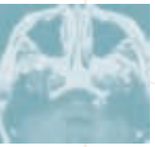
In the ensuing century since that image was taken, new technology has unfurled unprecedented diagnostic power, giving scientists the ability to detect early cancers, see aneurysms, and differentiate between dead and living tissue – all without breaking the skin.

Today, scientists and physicians can noninvasively peer inside the human body to view conditions as simple as broken bones and processes as complex as how the brain recognizes facial expressions.

At UT Southwestern Medical Center, new state-of-the-art imaging facilities and equipment will help researchers increase their understanding of the human body and its functions. In spring 2006, the Advanced Imaging Research Center, featuring the latest imaging equipment, will open on three floors of the new 150,000-square-foot, six-story Biomedical Research and Advanced Imaging Building.

The new building – the latest addition to the UT Southwestern North Campus – will also house the Mary Nell and Ralph B. Rogers Magnetic Resonance Center, established in 1991 to provide comprehensive magnetic resonance imaging tests for UT Southwestern patients. Two floors of the building will remain undeveloped for future expansion.

"The basic science and clinical impact of advanced imaging is widely agreed to be a critical element of new approaches to patient care."
—Dr. Craig Malloy



Research at the Advanced Imaging Research Center (AIRC) will help answer questions such as:

- What happens to our brain chemistry when we become depressed?
- What happens when our bodies gain weight?
- How can we improve the very technology that allows us to see inside our bodies?

"The basic science and clinical impact of advanced imaging is widely agreed to be a critical element of new approaches to patient care," said Dr. Craig Malloy, professor of radiology and medical director of the AIRC. "The new center represents a dramatic expansion of the infrastructure of research in imaging at UT Southwestern."

In addition, he said, it will foster collaboration among scientists and physicians. New faculty will be recruited across a broad range of disciplines to further the science of prevention, diagnosis and treatment of debilitating diseases in patients, as well as to improve current imaging technology.

For 15 years, UT Southwestern has used state-of-the-art diagnostic MRI equipment for patients in the Rogers Center. The addition of the AIRC provides researchers with access to even more powerful tools, such as functional magnetic resonance imaging, or fMRI, one of the most powerful new research instruments for studying structure and function simultaneously. fMRI allows the monitoring of regions of brain activation during different kinds of sensory stimulation or activity, such as sounds, sights or while performing simple manual tasks.

Researchers believe findings uncovered using this equipment will have tremendous implications in the clinical setting.

"The new center will allow the consolidation of investigators who are interested in a broad range of magnetic resonance applications into one site," said Dr. Malloy, holder of the Richard A. Lange Chair in Cardiology.

Eight new rooms, or bays, of the center will be dedicated to the latest diagnostic, research and clinical equipment, including one of the nation's first 7-Tesla MRIs, which use the most powerful magnets available for human studies.

Made available to UT Southwestern through a special federal appropriation, championed by Sen. Kay Bailey Hutchison, the 7-Tesla magnet is roughly 140,000 times more powerful than the Earth's magnetic field and is capable of the highest-resolution imaging currently available. MR images at 7T allow investigators to observe exquisitely small anatomical structures never before seen in the human brain.

In another part of the new building, basic scientists will be determining the three-dimensional structures of proteins and examining protein-to-protein interactions in solution.

They also will be able to examine structural biology, for instance, by putting proteins into solutions and then scanning them in a research magnet. And they will be able to use this technology, called magnetic resonance spectroscopy, to track disease progression in patients.

Dr. Carol Tamminga, professor of psychiatry and holder of the Communities Foundation of Texas Chair in Brain Science, said the promise of so much research capability in one place attracted her to UT Southwestern two years ago.

"One of the reasons I came here was to be able to work in this center. A facility with new research as well as clinical magnets is a big draw," she said. "Scientists will use the data they collect to ask questions about brain function, cancer, metabolism and cardiology."

Dr. Tamminga's research focuses on the brain.

"This will be a big step for clinical brain research on this campus."
—Dr. Carol Tamminga

"We're interested in seeing events in the human body as they occur."
—Dr. A. Dean Sherry

With such powerful tools available, she and her colleagues believe there will be no better place in the country to study devastating brain diseases such as depression, schizophrenia and autism.

"This will be a big step for clinical brain research on this campus," she said. "The facility will attract physicists, engineers, computer scientists, basic researchers and clinicians to work together in ways that have never before been possible."

Dr. A. Dean Sherry was recently named director of the Advanced Imaging Research Center. He anticipates new applications for imaging and a dramatic collaborative effort not only among researchers at UT Southwestern, but also between scientists at several other North Texas institutions, including UT Arlington and UT Dallas, where Dr. Sherry has a joint appointment as professor of chemistry.

"There are a number of faculty here and at UT Dallas involved in brain and behavioral science, so those faculty members will be involved in the center's research as well," Dr. Sherry said.

Gaining better insight into the function of body metabolism will be a key research focus at the new center.

Dr. Sherry uses magnetic imaging to study human metabolism. With the research capabilities of the equipment, he said, it will be much easier to translate research into clinical uses.

"We're interested in seeing events in the human body as they occur," Dr. Sherry said. "For instance, if a patient is overproducing glucose, we can put them in a magnet to gain some understanding of mechanisms involved in this abnormal process."

Dr. Michael Devous, associate director of the Nuclear Medicine Center, agrees that the new equipment in the AIRC will generate endless research possibilities. His work focuses on psychiatric disorders, substance abuse, the progression of diseases, such as dementia and Parkinson's, and speech and communication disorders.

"When I found out we were building this facility, I was overwhelmed," said Dr. Devous. "I've been doing functional brain imaging for most of the 25 years I've been at UT Southwestern and to see the university make such an enormous expansion in this area is incredible.

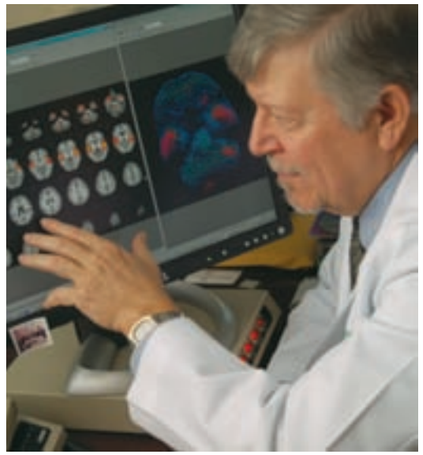
"These scanners will give us a level of detail that we've never had before."

Besides fMRI, a host of other new tools in the center will help UT Southwestern researchers and physicians better understand the body. One of these is high-resolution positron emission tomography.

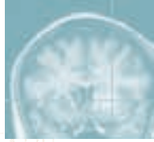
PET scanning is a medical imaging technique that produces a three-dimensional image, or map, of functional processes in the body. It allows researchers to put markers on certain medicines. When the medicines enter the human body, radiologists can see exactly where they are going and what areas of the body are affected by various diseases.

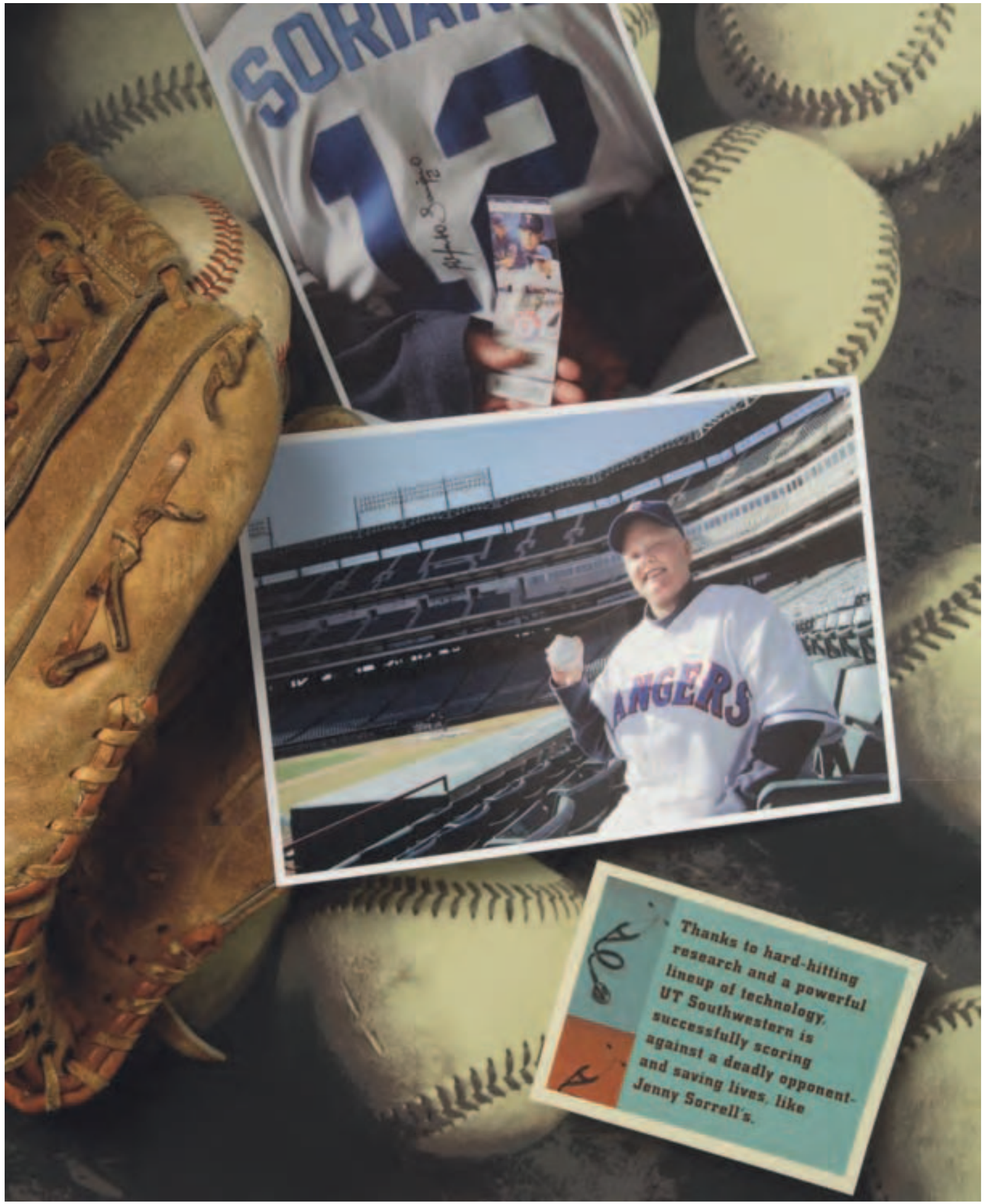
For the treatment of depression, for instance, doctors may be able to determine why some medicines work on some patients and not others. Dr. Devous said researchers also will focus on discovering new ways to diagnose mental disease earlier in patients. Powerful scanners, too, mean researchers may be able to test treatments for substance abuse by seeing which areas of the brain are affected.

"Access to state-of-the-art equipment of multiple types is available at very few centers in the United States and the world. Having this center on our campus will give us the ability to do research we couldn't do before," Dr. Devous said. "This will enhance current work here at UT Southwestern and at many other institutions, from which researchers will come for collaborative studies. It will allow us to do even more elegant and cutting-edge research." ⌘



"These scanners will give us a level of detail that we've never had before."
—Dr. Michael Devous





Catching the Cancer Curve Ball

Jenny Sorrell's life was saved by her favorite baseball player.

It was not with a Heimlich maneuver at a restaurant or cardiopulmonary resuscitation at the scene of a traffic accident. Ms. Sorrell's rescue arrived in the form of a blistering foul ball that struck her smack in the stomach and knocked the wind out of her.

It was May 7, a Saturday night at Ameriquest Field in Arlington, the second game of a three-game series with the Cleveland Indians, when Texas Rangers second baseman Alfonso Soriano stepped up to the plate in the bottom of the seventh inning. Ms. Sorrell was seated in the seventh row between third base and home plate. Thousands of spectators erupted in a collective, *"oooh,"* as the ball struck her.

"It felt like a line drive through my stomach," said Ms. Sorrell, a manager for a home mortgage company.

Paramedics at the stadium recommended that she go to a hospital emergency room. She waited a day until her sisters, concerned about swelling around her stomach, took her to a Fort Worth hospital.

An ER doctor ordered a computed tomography scan to check for a ruptured spleen or damaged kidneys.

She'll never forget the doctor's words when the test came back. "He told me, 'The good news is your spleen is not ruptured and your kidneys are not damaged. But you have cancer.'"

Further tests showed that she had an aggressive form of ovarian cancer that had spread to her stomach. She would need a top ovarian cancer specialist. A friend pointed her to Dr. John Schorge, a gynecologic oncologist and associate professor of obstetrics and gynecology at UT Southwestern Medical Center.

At 44, Ms. Sorrell felt perfectly healthy. She had no warning signs that one of the 15 tumors removed by Dr. Schorge had wrapped around her stomach and weighed 10 pounds. The doctor also removed her spleen and appendix and performed a hysterectomy.

"It was a life-or-death situation," she said about her cancer. "I could not have picked a better doctor or a better place to have chemotherapy."

Resting at her Grand Prairie home, Ms. Sorrell wrote a letter to Mr. Soriano recounting her miraculous encounter with the foul ball. She now is the proud owner of a baseball and a Rangers cap signed by her favorite slugger, who has since been traded to the Washington Nationals.

Far too often, cancer is diagnosed by chance or too late. Patients like Ms. Sorrell and doctors and scientists at UT Southwestern share the hope that steady progress in cancer research and clinical care will help prevent deadly types of cancer or catch the disease early enough to intervene and beat it.

Researchers look toward sensitive diagnostic tests and genetic screening in patients with a family history of cancer and molecular profiling of tumors to develop safer, targeted chemotherapy drugs that will zero in on the cancer cells without damaging healthy cells.

At UT Southwestern, these efforts are coordinated under the umbrella of the Harold C. Simmons Comprehensive Cancer Center.

By Toni Heinzl

At the Simmons Comprehensive Cancer Center, efforts at understanding, detecting and, ideally, preventing cancer reflect the forward-looking vision of its director, Dr. James Willson, associate dean for cancer programs.

Dr. Willson, a colon cancer expert, is working to prepare UT Southwestern's cancer center to join the nation's elite cancer centers, those certified as "comprehensive" by the National Cancer Institute. And a recent $50 million gift to UT Southwestern from Annette and Harold C. Simmons has given him the capital to reach that goal more quickly.

Currently, there are 39 NCI-designated "Comprehensive Cancer Centers." Dr. Willson, holder of the Lisa K. Simmons Distinguished Chair in Comprehensive Oncology, intends for the 40th to be here.

"UT Southwestern's long-standing strengths are in the scientific discovery area," Dr. Willson said. "Our next steps are to apply this scientific discovery engine to advance the treatment and prevention of cancer and provide exemplary care for cancer patients from North Texas and other regions."

Steady progress in cancer research at UT Southwestern is evident by the expansion of research and clinical facilities on the medical center's North Campus. More than 60,000 square feet of laboratory and office space in the Simmons Biomedical Research Building, the Seay Biomedical Building and the new Biomedical Research Tower are meant to inspire a multidisciplinary synergy between researchers and clinicians in the various subspecialties of oncology.

Dr. James Willson

Director of the Harold C. Simmons Comprehensive Cancer Center

Dr. John Schorge

Associate professor of obstetrics and gynecology

Ovarian cancer

Dr. Schorge's work is in one of these subspecialty areas. He is seeking to uncover the mysteries surrounding ovarian cancer, which kills more than 16,000 women in the United States annually and is diagnosed in 22,000 more each year.

"It has a very high mortality rate," said Dr. Schorge, holder of the Patricia Duniven Fletcher Distinguished Professorship in Gynecological Oncology. There are no standard screening tests for it, like the colonoscopy for colon cancer, the mammogram for breast cancer or the prostate-specific antigen test for prostate cancer. There often are no symptoms. In 75 percent of women with ovarian cancer, at the time of diagnosis, tumors have already spread to the abdomen.

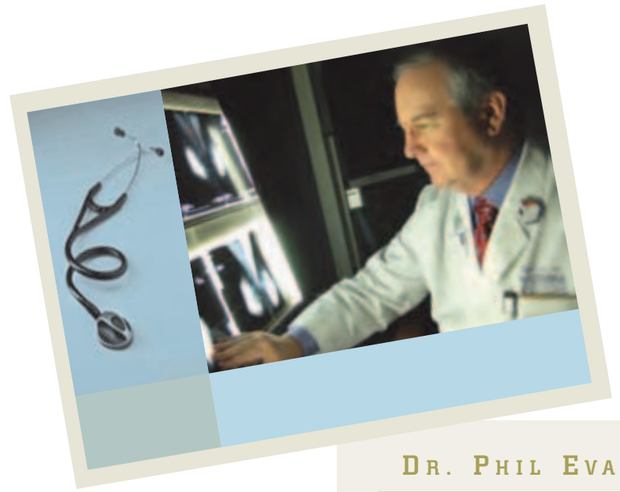
Ovarian cancer patients at UT Southwestern benefit from cutting-edge treatments thanks to a number of clinical trials conducted in conjunction with the nationwide Gynecologic Oncology Group, Dr. Schorge said. One ongoing trial involves the drug OvaRex, an immunotherapy drug that raises the body's defenses against the cancer cells.

OvaRex acts as an antibody to the ovarian tumor marker CA125, proteins produced by growing cancer cells. The antibody attaches to the CA125 found on the surface of ovarian cancer cells and triggers an immune response to kill the cancer cells.

Another strategy against this deadly cancer involves calculating a woman's risk based on her family history and, in high-risk patients, removing the ovaries with minimally invasive laparoscopic surgery as a preventive measure.

"This genetic screening has focused on 5 percent to 10 percent of patients who have a strong family history of breast or ovarian cancer, patients who have a least two relatives with breast or ovarian cancer," Dr. Schorge said. "Those are the ones we identify as high-risk."

In those cases, blood tests are performed to determine whether the patient carries an abnormal *BRCA1* or *BRCA2* gene, which sharply increases a woman's risk of developing breast cancer. Women with these mutations also are at greater risk of getting ovarian cancer: 55 percent for women with *BRCA1* and 25 percent for those with *BRCA2*.



Dr. Phil Evans

Director of the UT Southwestern Center for Breast Care

Breast cancer

At the UT Southwestern Center for Breast Care, a multidisciplinary team of experts is tackling the No. 2 killer of women in the United States from many angles.

Breast cancer will be diagnosed in about 211,000 U.S. women and kill more than 40,000 this year.

Yet, thanks to advances in screening and treatment, the five-year survival rate is up to 98 percent if the cancer is limited to one breast and has not spread to the lymph nodes. Early detection is the key to success in treating the disease.

Studies have shown that the mortality rate from breast cancer for women who start getting annual mammograms at age 40 can be reduced by as much as 50 percent, said Dr. Phil Evans, director of the Center for Breast Care.

"For women who are at extremely high-risk, those who carry the *BRCA1* and *BRCA2* genes, we offer screening with magnetic resonance imaging as well as mammography," said Dr. Evans, holder of the George and Carol Poston Professorship in Breast Cancer Research.

MRIs provide a more detailed image of breast tissue, but are 10 times more expensive than mammograms. It would not be cost-effective to use MRI in every case, he said.

In addition to MRI, advances are occurring in X-ray mammograms, with the use of digital images as well as standard film. UT Southwestern was one of 33 academic medical centers in the United States participating in a landmark study of nearly 50,000 women that concluded in 2005. Each participant was given a digital and a film mammogram to compare the effectiveness of those screening tests in detecting breast cancer.

Digital mammograms are studied on high-resolution computer monitors, allowing doctors to magnify images, zoom in or change the contrast. In addition, digital images are much easier to store and, as computer files, can be shared with other doctors easily.

The results of the study showed that digital mammograms are 15 percent to 28 percent more effective than those using film at detecting breast tumors in women under 50, in those with dense breast tissue and in women entering menopause, but not in women without these characteristics.

The study was conducted by the American College of Radiology Imaging Network and published in the *New England Journal of Medicine*. UT Southwestern had more than 1,700 women enrolled in the study.

Dr. David Euhus

Associate director of clinical care at the Harold C. Simmons Comprehensive Cancer Center

"In the future, we hope to be able to use our research in molecular profiling to predict a patient's risk for recurrence and develop new drugs to control the cancer in the individual patient."

– Dr. Debasish "Debu" Tripathy

Although they are 50 percent more expensive than film mammograms, digital mammograms' life-saving benefits justify the costs for the groups of women identified in the study, Dr. Evans said.

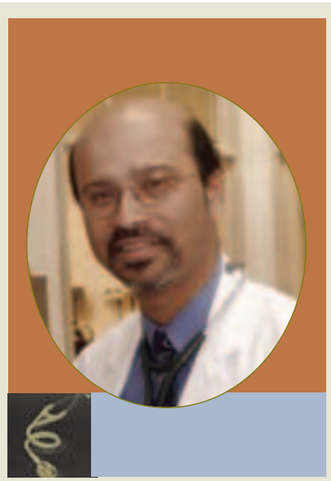
Conventional mammography missed about a third of the tumors detected digitally among women under age 50 and a quarter of the tumors among women with dense breasts. Most dramatically, among women who were premenopausal or perimenopausal, film mammography missed up to 40 percent of the tumors.

"These three subsets of women were found to receive a significant benefit from digital mammography," Dr. Evans said.

A researcher and surgeon at UT Southwestern is going beyond early detection to actually predict who may develop breast cancer, through the development of a novel computer program designed to do just that.

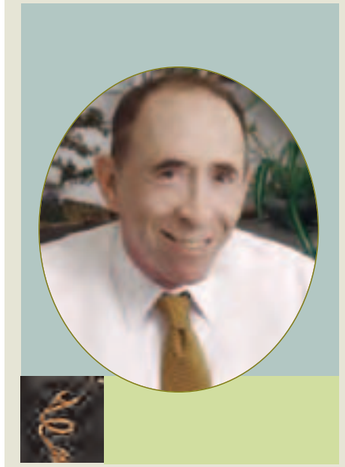
CancerGene, the invention of Dr. David Euhus, associate director of clinical care at the Simmons Comprehensive Cancer Center and co-director of the Mary L. Brown Breast Cancer Genetics and Risk Assessment Program, is used at almost 2,000 medical centers around the world. He also devised an interface for his *CancerGene* software, enabling medical centers to link it to their own databases for cancer patients.

"It is a way to collect and analyze family history information to determine the chance that an individual carries a mutation in a gene that predisposes her to cancer, and to estimate the chance that the individual will develop breast or ovarian cancer in the future," said Dr. Euhus, holder of the Marilyn R. Corrigan Distinguished Chair in Breast Cancer Surgery.



Dr. Debu Tripathy

Director of the Komen/UT Southwestern Breast Cancer Research Program



Dr. Jonathan Uhr

Professor of microbiology and internal medicine

Dr. Euhus is involved in several ongoing studies. In one, he is looking at molecular mutations that indicate breast cancer risk. For treatment, he's exploring ways to use dietary agents or chemotherapy drugs that will turn on tumor suppressor genes.

Dr. Debasish "Debu" Tripathy, director of the Komen/UT Southwestern Breast Cancer Research Program, focuses on developing medical treatments with chemo- and hormonal therapy as well as newer biological therapies to prevent the return or spread of breast cancer. His work seeks to profile the particular mutations in a patient's tumor, find out why certain tumors become resistant to standard chemotherapy drugs and devise new ways to attack the cancer target.

"We've always known that every patient is different," said Dr. Tripathy, holder of the Annette Simmons Distinguished Chair in Breast Cancer Research. "In the future, we hope to be able to use our research in molecular profiling to predict a patient's risk for recurrence and develop new drugs to control the cancer in the individual patient."

His colleague, Dr. Jonathan Uhr, professor of microbiology and internal medicine, discovered that certain breast-cancer survivors have innate mechanisms to keep the cancer from returning.

Dr. Uhr found that circulating tumor cells, which typically indicate a higher risk of cancer recurrence if identified shortly after a mastectomy, can be present up to 20 years after surgery in patients who are at little risk for recurrence. These tumor cells only last one hour in the blood and are constantly replenished by replicating tumor cells in the tissues. In these dormancy patients, there is a precise balance between replication and tumor cell death.

If researchers are able to pinpoint the mechanisms responsible for this balance, it could lead to the development of new drug therapies, said Dr. Uhr, holder of the Raymond Willie and Ellen Willie Distinguished Chair in Cancer Research, in Honor of Laverne and Raymond Willie Sr.

Working with other researchers at UT Southwestern, Dr. Uhr also has developed a blood test that detects acquisition of genetic changes in breast-cancer patients, such as developing too many copies of the *HER-2* gene on the surface of breast-cancer cells. *HER-2* overexpression gives the patient a poor prognosis. Although the overexpression of the gene is thought only to occur early in the disease (20 percent to 25 percent of patients have over-expression in their primary tumor), these researchers have found that an equal number of patients acquire the gene amplification in their circulating tumor cells after recurrence.

"Cancer is a moving target, and you have to know what bullet to put in your gun."

– Dr. Jonathan Uhr

Dr. John Minna

Director of the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research

Director of the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics

"Cancer is a moving target, and you have to know what bullet to put in your gun," Dr. Uhr said. "Our blood test pinpoints the unwanted genetic change at a particular point in time so that the oncologist will know which particular targeting agent should be given. We want to develop the test as a real-time noninvasive biopsy."

Lung cancer

Like breast cancer, lung cancer can sometimes be traced to hereditary patterns. While smoking is the strongest known risk factor for lung cancer, the causes go deeper, said Dr. John Minna, director of the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research and the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics.

Dr. Minna's life's work has been aimed at finding cures for this deadly cancer, which kills an estimated 164,000 people in the United States annually. It claims more lives than breast, colon and prostate cancer combined. The overall five-year survival rate is only 15 percent.

Dr. Minna led a team of researchers at UT South - western that identified a mutation on a region of chromosome 6 responsible for increasing a person's risk of developing lung cancer. This discovery could lead scientists to devise a standardized blood test to screen people who may be at a high genetic risk before they develop lung cancer.

"People with this genetic mutation can get lung cancer even if they smoke only small amounts of tobacco."

- Dr. John Minna

"If you carry the gene, and if you are a heavy smoker – typically a pack a day for 20 to 30 years – your risk of getting lung cancer goes way up," said Dr. Minna, holder of the Sarah M. and Charles E. Seay Distinguished Chair in Cancer Research and the Max L. Thomas Distinguished Chair in Molecular Pulmonary Oncology. "Eight percent to 12 percent of heavy cigarette smokers will come down with lung cancer during their lives. We also know that there is an inherited predisposition to develop lung cancer. If we can identify kids who carry these genes, we could enroll them in educational programs aimed at smoking prevention. People with this genetic mutation can get lung cancer even if they smoke only small amounts of tobacco."

Dr. Minna and his longtime collaborator, Dr. Adi Gazdar, professor of pathology and holder of the W. Ray Wallace Distinguished Chair in Molecular Oncology Research, are now working to identify the exact genes and mechanisms in chromosome region 6Q23 that are involved in tumor suppression and cell growth.

Dr. Minna leads one of the seven premier lung-cancer research programs funded by the National Cancer Institute called Specialized Programs of Research Excellence, or SPOREs.

Drs. Minna and Gazdar have blazed a trail in the study of the mutations in the epidermal growth factor receptor (EGFR), which are seen in lung adenocarcinoma, the most common form of lung cancer found in people who have never smoked. Their findings will help researchers better understand why certain lung-cancer patients respond to a particular chemotherapy drug and others do not.

Dr. Adi Gazdar

Professor of pathology

"If we can identify biomarkers for cancer risk, we could recommend lifestyle changes or intervention in the form of chemotherapy."

- Dr. Adi Gazdar

Another mystery is why it sometimes takes 20 years or longer for people to develop lung cancer after they quit smoking. And why are women who have never smoked more than twice as likely to get lung cancer as male non-smokers? UT Southwestern researchers believe they are on the right track to find the key molecular pieces of the cancer puzzle.

The first goal was to identify molecular evidence when cancer has occurred, Dr. Gazdar said. "The question developed: Can we determine the molecular basis, or biomarkers, for cancer before a person has cancer?

"This lengthy precancerous process offers opportunities for risk assessment and intervention. If we can identify biomarkers for cancer risk, we could recommend lifestyle changes or intervention in the form of chemotherapy."

Cervical cancer

Taking a page from the work of Drs. Minna and Gazdar in lung cancer, gynecologic oncologist Dr. Jayanthi Lea is trying to uncover the molecular signature of subtypes of the human papillomavirus (HPV), which is responsible for cervical cancer.

HPV is a common infection, which at least 75 percent of sexually active women contract in their lifetime. But most of them will never develop cervical cancer.

Dr. Jayanthi Lea

Assistant professor of obstetrics and gynecology

Cervical cancer is caused by only some of the more than 90 known HPV subtypes. The cancer kills an estimated 3,900 women and is diagnosed in more than 10,000 women annually in the United States.

Though highly treatable if detected early, cervical cancer can turn deadly. An NCI report found that patterns of high cervical cancer mortality exist in geographic locations and populations with limited access to health care. Women at the greatest risk, according to the study, include black women in the South, Hispanic women along the Texas-Mexico border, white women in Appalachia, American Indian women of the Northern Plains, Vietnamese American women and Alaska Native women.

Early detection is particular crucial in young and pregnant women or women who want to preserve their ability to have children, said Dr. Lea, assistant professor of obstetrics and gynecology.

"If we have a molecular signature indicating cervical cancer progression, then we'll be able to identify patients within their reproductive age who can undergo fertility-sparing treatment," she said.

"If we have a molecular signature indicating cervical cancer progression, then we'll be able to identify patients within their reproductive age who can undergo fertility-sparing treatment." - *Dr. Jayanthi Lea*

Colon cancer

Early detection also makes a big difference in outcomes for colorectal cancers, which kill an estimated 30,000 men and 27,500 women in the United States every year – accounting for about 10 percent of the cancer deaths for both men and women.

Yet experts say it is one of the most curable cancers. Up to 10 percent of all colorectal cancers are hereditary. And since doctors know that family history increases a person's risk significantly, they recommend that those with a known family history of colorectal cancers or polyps start getting screened at age 40 or younger. For the average person, annual screening should start at age 50.

The most reliable screening tool is a colonoscopy, which uses a tiny fiberoptic camera connected to a scope. The camera allows doctors to view close-up, detailed images of the colon on a video monitor and gives them the ability to capture images of any suspected abnormalities.

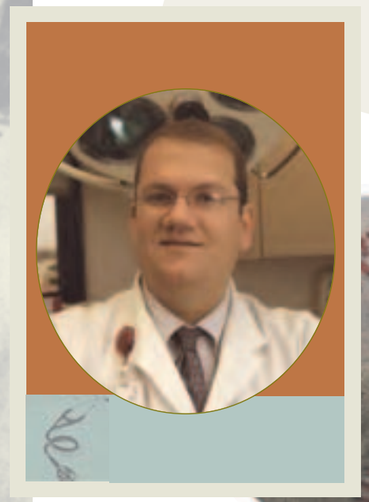
"When diagnosed early, the five-year survival rate for colon cancer is more than 90 percent," said Dr. Harry Papaconstantinou, assistant professor of surgery. "If the cancer has spread beyond the colon wall, but still remains in that region, the survival rate drops to 60 percent. And if the cancer has advanced with distant metastases in the liver or lung, the five-year survival rate is only 5 percent to 10 percent. That's why it's important to catch it early."

If the colonoscopy reveals polyps, which might be precancerous lesions, doctors can remove them before they turn cancerous.

"That's unique to our field," said Dr. Papaconstantinou, an expert in minimally invasive laparoscopic colorectal surgery, a camera-guided technique that requires only small incisions and allows patients to recuperate faster than with conventional open surgery.

Dr. Harry Papaconstantinou

Assistant professor of surgery



Preventing cancer

Researchers estimate that at least 5 percent of all cancers are due to a specific inherited genetic syndrome. By reviewing a person's family history of cancer, including cases in siblings, parents and grandparents, and through genetic screening for cancer biomarkers, doctors at UT Southwestern are trying to help patients at high risk prevent it.

A key player in these efforts is Dr. Gail Tomlinson, director of clinical cancer genetics at the Simmons Comprehensive Cancer Center and co-director of the Mary L. Brown Breast Cancer Genetics and Risk Assessment Program.

"Armed with the genetic information, we can individualize a patient's risk and recommend who will need more screening and who will need less," said Dr. Tomlinson, holder of the Children's Cancer Fund Distinguished Professorship in Pediatric Oncology Research.

Working on another front to combat cancer, Dr. Yvonne Coyle, associate professor of internal medicine, is developing models of successful cancer prevention. She has studied the impact of environmental risk factors on the development of breast cancer and has begun to make plans to enroll hundreds of women for a study of how physical exercise helps avert breast cancer. Earlier research indicated that physical activity reduces breast cancer risk by 20 percent to 30 percent.

Similarly, Dr. Coyle is investigating the effect of the environment on the development of lung cancer in smokers and nonsmokers. She also is laying the groundwork for future studies to determine the effectiveness of lifestyle changes, such as exercise, for reducing lung-cancer risk.

Dr. Gail Tomlinson

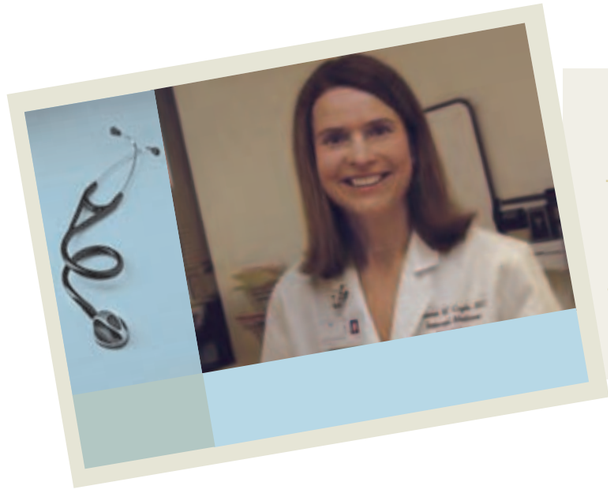
Director of clinical cancer genetics at the Harold C. Simmons Comprehensive Cancer Center

"The science and practice of cancer prevention challenge our traditional definition of the disease," Dr. Coyle said. "We have to view this disease as a set of defined risk factors that can be treated preventively over sustained periods of time."

Back at her home in Grand Prairie, UT Southwestern cancer patient Jenny Sorrell realizes that although her cancer may not have been caught early, there is a good chance it was found before it was too late.

"Of all the thousands of people in the path of that ball, the ball hit me," Ms. Sorrell said. "And instead of my head, it struck me in the stomach, where my cancer was. It helped doctors catch it before stage IV. It was like divine intervention – it happened for a reason."

For more information about the Harold C. Simmons Comprehensive Cancer Center, please call 214-648-4190. ⌘



Dr. Yvonne Coyle

Associate professor of internal medicine

UT Southwestern Medical Center clinicians and researchers are on a tireless pursuit of understanding normal sleep-wake behavior in order to find new treatments for sleep disorders.

1, 2, 3 ...

The *Dream of* Understanding Sleep

AFTER A LONG DAY spent evaluating, diagnosing and treating weary patients, an expert in sleep medicine, now at home, sets his alarm for 10 p.m. so he knows when to start winding down for the night.

In a laboratory across town, a research scientist watches as his genetically engineered mice fall asleep when they should be awake. Another researcher studying biological clocks keeps tubes of fungus in a darkened lab.

From helping patients exhibiting abnormal sleep behavior to picking apart the anatomy of the brain or hunting for the genes that regulate the daily rhythms of life, UT Southwestern Medical Center clinicians and researchers alike go to great lengths in their tireless pursuit of the dream of understanding sleep.

On first sight of her favorite food – a plate of pancakes – a little girl becomes so excited that she falls asleep. Later, as the child runs after a friend at play, she falls suddenly in a heap, asleep, in mid-stride.

"One parent told me that she put her child in a shopping cart at a department store, and when they went down the aisle with the toys, the boy would stand up, excitedly point to the toys and then fall asleep," said Dr. John Herman, associate professor of psychiatry at UT Southwestern.

Such is the often paradoxical behavior of people afflicted with a sleep disorder called narcolepsy, a rare disease in which individuals uncontrollably fall asleep, have excessive daytime sleepiness and often experience sudden muscle weakness called cataplexy.

Narcolepsy is one of many sleep abnormalities Dr. Herman encounters in his patients at Children's Medical Center Dallas.

Dr. Herman treats young patients not only with narcolepsy but also with a range of problems, from simply not getting enough sleep to sleep apnea, sleep terrors and sleepwalking.

By Amanda Siegfried

A SELF-ADMITTED NIGHT OWL who sets an alarm to remind himself when it's about time for bed, Dr. Herman said sleep medicine is different from any other aspect of medicine. While only some people have a specific disease or disorder, everyone sleeps, and nearly everyone has some story about themselves or a family member that involves sleep weirdness. In addition, sleep medicine combines many different specialties, including psychiatry, neurology, pulmonary and internal medicine, otolaryngology and pediatrics.

"When these specialists get together, it's like the fabled blind men touching an elephant," he said. "Each touches a different part – the trunk, an ear, the tail – and collectively they can put together the elephant better than any one of them could. That's sleep medicine – a convergence of specialties, no one of which is sufficient to totally encompass the field."

"FIVE YEARS AGO WE DIDN'T REALLY KNOW WHAT CAUSED SLEEPWALKING OR NIGHT TERRORS, BUT NOW WE CAN EXPLAIN HALF OF THEM, WHICH IS PROGRESS."

—DR. JOHN HERMAN

Emotions, breathing patterns, the heart, even the immune system are different during sleep than during waking hours, so it's no surprise that sleep-medicine specialists have to be knowledgeable in several areas to diagnose the 100 or so known sleep disorders. Clinicians in such a specialized field require specialized training, such as that provided in the yearlong sleep medicine fellowship program, which Dr. Herman directs at UT Southwestern.

Launched in 2001, the program allows trainees in various specialties to work with sleep disorder patients at Children's, Dallas Veterans Affairs Medical Center and Presbyterian Hospital of Dallas, where they get an integrated view of sleep medicine. Including this year's class of five, which will finish in June 2006, 11 individuals have participated.

One of this year's trainees is Dr. Hilary Baldwin, who completed her pediatrics residency at UT Southwestern in 2001. She became interested in pediatric sleep medicine when she was chief resident at Children's and had occasion to order sleep studies for her patients.

Dr. Baldwin soon discovered that the burgeoning field of sleep medicine combined her interests in technology, child development and early learning.

"I am very interested in how sleep impacts children at the elementary-school age," she said. "As more research is being done in this area, we're discovering how sleep is important for kids to learn properly."

THE BALM OF HURT MINDS

Sleep typically occurs in successive stages that physiologically are very distinct. The first part of a night's sleep cycle is spent in a state called non-REM (rapid eye movement) sleep, followed by REM sleep. The cycle repeats throughout the night.

It's during REM sleep that dreams occur and muscles are paralyzed, a condition called atonia. Some individuals with a sleep disorder called REM sleep without atonia exhibit motor behavior during REM sleep – thrashing about and getting out of bed to act out their dreams. (This is a much different condition from sleepwalking, which occurs during non-REM sleep, when a person is not dreaming but muscles are working.)

Another disorder, called night terrors, also is associated with non-REM sleep and occurs when a person skips from non-REM directly into wakefulness, bypassing REM sleep altogether. After overshooting REM, the person awakens, often sweaty with heart racing, in a panic.

"What we have found in the past few years in children is that approximately one-half of all sleepwalking and night-terror episodes are secondary to breathing problems," Dr. Herman said. "Something interrupts their breathing, triggering an arousal and catapulting them into wakefulness and terror.

"Five years ago we didn't really know what caused sleepwalking or night terrors, but now we can explain half of them, which is progress."

The most common sleep disorder in adults is obstructive sleep apnea, in which the muscles holding the upper airway open during the day don't work as well when those affected get drowsy or fall asleep. The deeper the sleep, the less efficiently the muscles work, so the airway becomes blocked. Not only is the brain deprived of oxygen, but the person may also wake up as often as once a minute to breathe, resulting in an unrestful sleep and daytime sluggishness.

"This is the same airway that's there during the day, and it's not being blocked then. Obviously something different is going on while people are asleep, so we are trying to understand control of the upper airway," Dr. Herman said.

Most medical conditions also affect sleep, and sleep impacts most medical problems. Psychiatric disorders, for example, can be exacerbated by sleep disorders.

"If you take any adult or child and sleep-deprive them, you will bring out the worst psychiatrically in them," Dr. Herman said. "If you take someone who has a propensity toward a psychiatric disorder and meddle with their sleep – getting them up too early or letting them sleep too long – you will amplify the psychiatric disorder."

One of the most underdiagnosed sleep problems in children, but perhaps the easiest to treat, is insufficient sleep syndrome. Sleepwalking, excessive daytime sleepiness, falling asleep in school and poor school performance all can be symptoms of simply not getting enough quality sleep. Sleep-deprived children also are more likely to suffer from night terrors. Dr. Herman said children who come into his clinic with these symptoms often turn out to be over-scheduled, to stay up too late, or to start school too early.

"A lot of time in children, all that's necessary to get a handle on their problems is to improve their sleep," he said.

In Dr. Herman's laboratory, which is accredited by the American Academy of Sleep Medicine, clinicians and technical staff provide comprehensive evaluation, diagnosis and treatment of sleep disorders. To help reach a diagnosis, they use a technique known as polysomnography to measure changes in brain-wave activity, respiration, heart rate, blood oxygen levels, air flow and acid in the stomach, among other things. The catch for the patient: trying to sleep with so many wires and gadgets connected to one's head and body.

ALL IN THE FAMILY

As Dr. Herman and the physicians he trains help provide rest to the sleepless, laboratory scientists at UT Southwestern often burn the midnight oil conducting experiments that are beginning to shed light on just why and how we sleep, and what goes wrong when our rest is disturbed.

As was the case with the pancake-loving patient, narcolepsy can be triggered by laughter or strong emotions. While the condition can be treated to some degree with medications that help the patient stay awake, the cause of narcolepsy has not been clear.

Dr. Masashi Yanagisawa, professor of molecular genetics, is investigating the possibility that narcolepsy is a neurodegenerative disease and has discovered a potentially new avenue for treating the condition. He and his research group were the first to genetically engineer mice to lack brain cells that produce a chemical called orexin. Without these neurons, the mice do not wake up to feed as normal mice do; they fall asleep abruptly in the middle of their normal nocturnal routines; and they experience cataplectic episodes. In human patients, a lack of or deficiency in orexin causes narcolepsy.

"Current consensus is that narcolepsy is a neurodegenerative disorder, the specific loss of orexin-producing neurons," Dr. Yanagisawa said. "Essentially, it's orexin-deficiency syndrome, in the same sense that type 1 diabetes (insulin-dependent diabetes) is insulin-deficiency syndrome due to the death of certain pancreatic cells."

Dr. Yanagisawa and his colleagues recently found that artificially reintroducing orexin into mice that lack the ability to produce the chemical on their own rids the mice of their narcolepsy symptoms.

"Assuming that narcoleptic humans are like these mice, which is very plausible, our experiments provide a strong proof of concept that introducing into the brain a molecule that mimics the effect of orexin will be the fundamental cure for human narcolepsy," said Dr. Yanagisawa, a Howard Hughes Medical Institute investigator at UT Southwestern and holder of the Patrick E. Haggerty Distinguished Chair in Basic Biomedical Science.

Meanwhile, Drs. Yanagisawa and Herman have begun a collaboration in which they will perform genetic profiling of patients with sleep disorders. The goal is to identify new sleep-related genes.

A key aspect of their work is to identify different sleep tendencies. For example, "short sleepers" may sleep only four to five hours a night, while "long sleepers" need 10 to 12 hours a night to feel refreshed.

"We are looking at patients with very odd sleep patterns and their relatives who share the pattern, and we will compare their genetic information with normal relatives," Dr. Herman said.

I THINK, THEREFORE I SLEEP

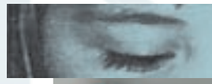
Because it's the brain that ultimately produces sleep, to understand the mechanisms of sleeping and waking is really to understand how the brain works, said Dr. Gerald Marks, associate professor of psychiatry at UT Southwestern who has been researching sleep for 30 years.

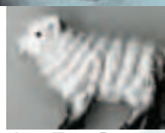
"Sleep behavior is interesting because humans spend about one-third of their lives doing it, and yet even today it's not clear how it's produced or for what purpose," he said.

Originally it was thought that sleep was a shutting down of the brain, but now scientists know that there are regions of the brain that are at their most active during sleep. In fact, the electrical activity of the brain during REM sleep, measured with an electroencephalogram, looks similar to the activity produced by a wakeful brain.

THAT WE ARE NOT MUCH SICKER AND MUCH MADDER THAN WE ARE IS DUE EXCLUSIVELY TO THAT MOST BLESSED AND BLESSING OF ALL NATURAL GRACES, SLEEP.

—ALDOUS HUXLEY (1894-1963)





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DR. MARKS CHARACTERIZES SLEEP

mechanisms as "distributed and interconnected systems" in the brain that change the way they interact from waking to sleep. Part of the complexity stems from the fact that many of the systems involved are not dedicated to just producing sleep.

"Sleep and wakefulness are malleable and subject to modulation by a tremendous number of variables, yet every system controlling sleep is not central to its production," Dr. Marks said. "How do you decide what is a sleep mechanism? You could say that the auditory system is a sleep mechanism. When I bang cymbals together I can keep somebody from sleeping. Yet the auditory system is not *necessary* for the production of sleep."

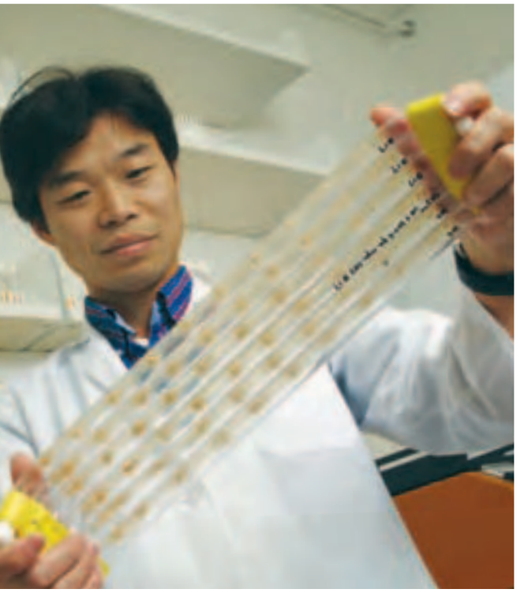
Dr. Marks is studying the anatomy of the brain and how different regions respond to brain chemicals involved in sleep and wakefulness. One of the chemicals he focuses on, GABA, is a neurotransmitter, which sends signals between neurons. Dr. Marks and his colleagues are studying why, in animals, GABA produces sleep when it's increased in some areas of the brain and wakefulness when it's introduced in other regions. Dr. Marks hypothesizes that GABA may actually change the relationship of brain cells within neural networks.

"Wouldn't it be something if GABA were able to alter the interconnectivity of cells and how they communicate with one another?" he said. "It's my guess that this is one way a single system can have multiple functions."

Another brain chemical, adenosine, may keep track of how long someone has been awake.

"THE FUNGUS CLOCK IS LIKE A VERY CHEAP PLASTIC WATCH, WHILE THE HUMAN CLOCK IS MORE LIKE AN EXPENSIVE ROLEX. THEY MAY APPEAR TO BE QUITE DIFFERENT, BUT WHAT IS BEHIND THE COVER OF THE WATCH IS, MECHANISTICALLY, VERY SIMILAR."

—*DR. YI LIU*



Dr. Robert Greene, professor of psychiatry, and his colleagues recently found that prolonged activity in neurons in the brain's arousal centers triggers them to release adenosine. When enough adenosine has built up, the chemical acts to slow down neural activity in the arousal centers. Because those centers facilitate arousal activity throughout the brain, the inhibition of the arousal process expands outward and causes neuron activity to slow down everywhere, resulting in sleep.

"What we have shown is that it's this prolonged neural activity of being awake that causes adenosine levels to go up, which in turn makes a person feel drowsy. It's the brain's way of achieving a proper balance between the neural activity of waking and the need for sleep. If something goes wrong with this adenosine system, a person may have a greater tendency toward insomnia," said Dr. Greene, who holds the Sherry Knopf Crasilneck Distinguished Chair in Psychiatry, in Honor of Albert Knopf.

OF MICE AND FUNGUS

Sleep is just one facet of the circadian clock, the internal biological clock fundamental to living organisms. For Earth-bound life, this central clock is set to about 24 hours, and it persists even in the absence of external time cues such as light and dark. The rhythmic ups and downs of this clock – its so-called homeostatic nature – influence many aspects of physiology, such as body temperature, hormone release, metabolism and gene expression, along with sleep and wakefulness.

"Sleep is just one of the oscillations the clock controls," said Dr. Yi Liu, associate professor of physiology and a Louise W. Kahn Scholar in Medical Research. "Our goal is to figure out what the molecular makeup of this circadian oscillator is and how the genes associated with it work together to generate an accurate 24-hour rhythmic pattern."

To understand these basic mechanisms, Dr. Liu focuses on a fungus, *Neurospora crassa*, one of the best-studied model organisms for circadian clocks. Fungi don't sleep, but one of their physiological processes, asexual spore reproduction, is controlled by the clock. In its natural habitat, *N crassa* produces spores only at a certain time each day.

To examine how the environment and genes affect internal clocks, Dr. Liu puts the organisms – along with some fungus food – in glass growth tubes, exposes them to light, then transfers the tubes into complete darkness, away from any cues that might indicate the time of day. Even in darkness, the fungi produce spores periodically, a little less than every 24 hours.

Dr. Liu has found that fungi with certain genetic mutations don't have this normal rhythmic pattern. Instead, they release spores all the time or at the wrong time.

Although human and fungi physiology may seem to have little in common, at the molecular level their biological clocks are quite similar, Dr. Liu said.

"The fungus clock is like a very cheap plastic watch, while the human clock is more like an expensive Rolex," he said. "They may appear to be quite different, but what is behind the cover of the watch is, mechanistically, very similar."

Recently, Dr. Liu and his colleagues identified a protein complex found in yeast and in humans that is crucial for the basic clock to maintain the proper oscillations. The same protein complex may be a factor in a human disease called Smith-Magenis syndrome, a genetic disorder characterized by a specific pattern of physical, behavioral and developmental problems, including sleep deficiencies. Individuals diagnosed with the syndrome are missing several genes, and they don't sleep or wake normally.

One of these missing genes affects production of the protein Dr. Liu identified.

"The partial deficiency in this critical protein may cause the sleep and circadian rhythm problems in these patients," Dr. Liu said. "Our findings raise some interesting possibilities that can be tested."

Many different molecules and proteins are involved in the complex chemical interactions controlling biological clocks. Dr. Steven McKnight, chairman of biochemistry, is studying mutations in some of the genes responsible for production of those proteins.

For example, he and his research group discovered a gene called *NPAS2*, which is the blueprint for a protein in a specific region of the brain.

"We have found that mice with mutations in the *NPAS2* gene fail to take a daily nap, as normal mice do," said Dr. McKnight, holder of the Sam G. Winstead and F. Andrew Bell Distinguished Chair in Biochemistry and the Distinguished Chair in Basic Biomedical Research.

The tendency for mice to nap in the middle of their active period, which occurs at night, is analogous to humans getting sleepy in the middle of the day, Dr. McKnight said.

"What this suggests is that the tendency for us to get tired and want a nap at midday may be genetically programmed," he said.

Dr. McKnight hypothesizes that the biological clock controlling all circadian rhythms, including sleep, is tied to metabolism. The metabolic properties of cells – how they use energy, when they use it, when they stop being active – change in a periodic, predictable fashion over the course of the 24-hour circadian cycle.

"The metabolic cycle is very homeostatic, and this could be the basis of sleep homeostasis," he said. "You get tired at the end of the day because your neurons are metabolically running out of gas; they're getting tired. Biochemically, the circadian cycle controls metabolism, but we also think that metabolism controls the circadian cycle – that they are coupled together. It's intriguing to think that metabolism can influence your wakefulness."

Not only is sleep tied to circadian rhythms, but evidence suggests mental illness may be linked to them as well. Over the past several years, Dr. McKnight and Dr. John Rush, professor of psychiatry, have pursued human genetic studies that may aid the understanding of mood disorders, including major depression. Dr. Rush holds the Betty Jo Hay Distinguished Chair in Mental Health and the Rosewood Corporation Chair in Biomedical Science.

They started with the hypothesis that mutations in human biological clock genes might cause patients to be susceptible to depression. With the help of many associates, and coupled with financial support from the David Nathan Meyerson Memorial Fund for Medical Research, the researchers collected DNA samples from more than 1,000 patients suffering from various forms of depressive illness.

When they examined the DNA sequences of 10 genes known to be vital to establishing and maintaining circadian rhythms, they found that one gene, called *Period 3*, contained mutations that inactivated the gene in an unexpectedly high proportion of patients.

"Although it is possible that these mutations in the *Period 3* gene cause patients to be susceptible to depressive illness, much work needs to be done to rigorously test this hypothesis," Dr. McKnight said.

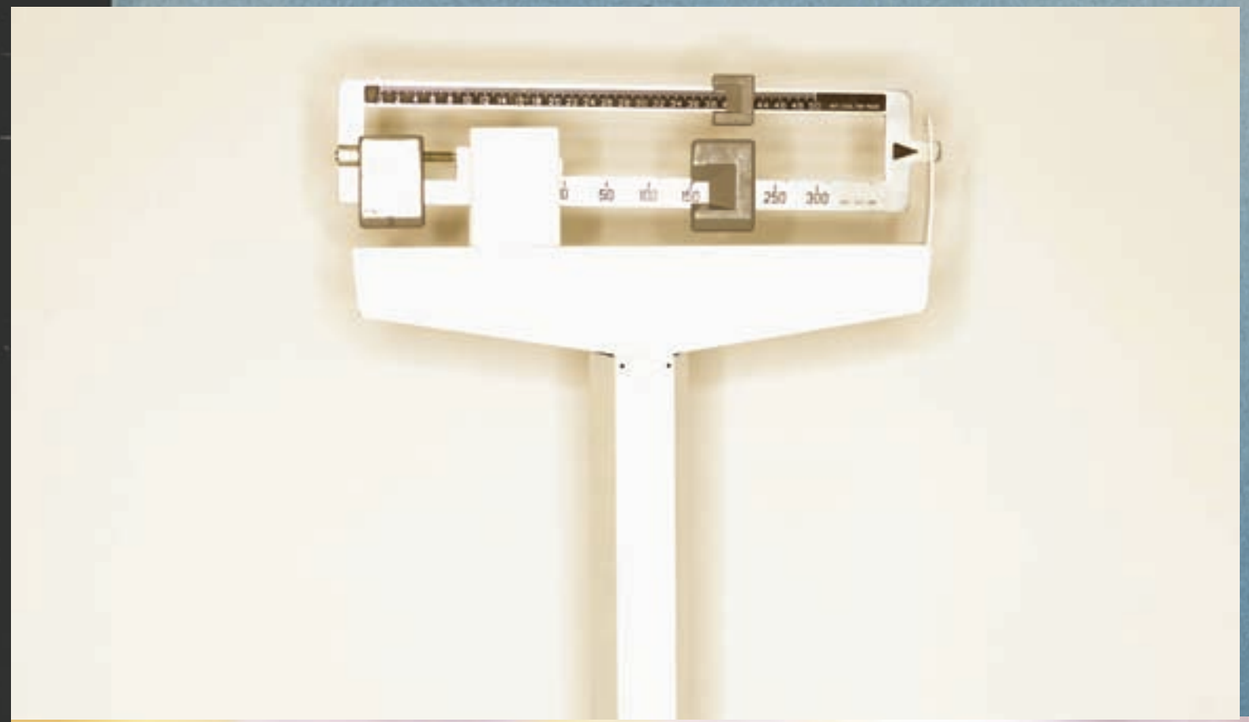
At UT Southwestern, laboratory studies of simple organisms such as mice and fungus are yielding new insights into the biology of human sleep and guiding the development of promising new treatments in the clinic.

"Alternating periods of rest and activity appear in single-celled organisms and even plants," Dr. Marks said. "That says how adaptive and important it is to life to have a mechanism to regulate activity. If we can truly understand the mechanisms underlying normal sleep-wake behavior, then we could understand what happens when something goes wrong and come up with more rational treatments."

And maybe this will help a little girl finally enjoy her pancakes. ⌘

"WHAT THIS SUGGESTS IS THAT THE TENDENCY FOR US TO GET TIRED AND WANT A NAP AT MIDDAY MAY BE GENETICALLY PROGRAMMED."

—*DR. STEVEN MCKNIGHT*



a measure of success

UT Southwestern's Clinical Center for the Surgical Management of Obesity has quickly become the nation's leader in weight-loss surgeries.

When diets fail and exercise resolve turns to despair, the truly obese turn to surgeons at UT Southwestern Medical Center, which in a few short years has become a national leader in weight-loss surgeries. Doctors here were the first in the Southwest to perform laparoscopic gastric bypass surgery, and the first in North Texas to perform the laparoscopic Lap-Band surgery. The two procedures make up nearly all of the weight-loss, or bariatric, procedures performed today. Interest in bariatric procedures has surged in part because of the growing numbers of obese patients and the resulting difficulties they have, including high blood pressure, diabetes, sleep apnea, heart disease, joint and back pain, tumors and depression. Doctors more generally accept that diet alone often can't produce the desired weight loss needed to alleviate those problems in severely obese patients. "You often can make all of those things better or go away with one operation," said Dr. David Provost, director of UT Southwestern's Clinical Center for the Surgical Management of Obesity. Gastric bypass, the most popular surgery, shrinks the stomach and bypasses a portion of the small intestine, where nutrients are absorbed. The relatively new Lap-Band surgery places a band around the stomach to make the patient feel full and, therefore, eat less. These days, both are usually done laparoscopically – a few small incisions are made, rather than one large incision. Because they are complex, bariatric cases require a well-coordinated medical effort. UT Southwestern's clinic offers a comprehensive approach, including nutritional, psychological and rehabilitative care. It also sponsors bimonthly support groups for pre- and postoperative patients, trains other doctors, and conducts groundbreaking research in the field. By Russell Rian

Dr. Provost helped launch the center

in 2000, just a year after performing the Southwest region's first laparoscopic bypass surgery. Since then he has performed more than 1,000 such surgeries, and the center's doctors, including Dr. Edward Livingston, chairman of GI/endocrine surgery, have trained more than 100 surgeons nationwide in the Lap-Band and laparoscopic bypass procedures.

This year, 150,000 to 200,000 bariatric procedures will be performed, while as many as 10 million patients who qualify for the surgery wait, Dr. Provost said.

"We've got a lot of work to do to catch up," he said.

About one-third of Americans are now considered obese, and some 3 percent of them qualify for the surgery based on their body-mass index, a calculation of weight and height. Although someone with a body mass index over 30 is considered obese, the surgeries are aimed at those with BMIs over 40, or those whose BMI exceeds 35 and have complications such as diabetes or hypertension.

"Laparoscopic surgeries remain major operations that can be associated with significant complications and a real chance of death, but with experienced surgeons they can have better outcomes."

--Dr. David Provost

The center now performs more than 350 procedures annually at UT Southwestern University Hospitals and Parkland Memorial Hospital. Annual clinic visits total 1,500. The bariatric program attracts patients from Oklahoma, Tennessee, Louisiana and as far away as Australia, as well as from the Dallas-Fort Worth area.

To handle the growing caseload, new surgeons like Dr. Mark Watson, assistant professor of surgery, who focuses exclusively on Lap-Band procedures, have been recruited. Other new faculty include Dr. Nancy Puzziferri and Dr. Homero Rivas, both assistant professors of surgery.

The procedures are gaining acceptance by insurance companies, which enables more patients to have the operation, the physicians said.

Initially, insurers shied away from the Lap-Band procedure, considering it experimental. But as it proved effective and showed less morbidity than bypass procedures, insurance companies began paying for it, and patients have seized the advantage.

"The U.S. data now show that the Lap-Band is nearly as effective as the bypass, with a much lower morbidity and mortality rate," Dr. Watson said. It's also easily reversible, unlike the bypass.

"I would predict there will be a floodgate that will open up as even more insurance companies approve it," Dr. Watson said.

The ability to perform 90 percent of the operations laparoscopically has also been an advantage, translating to shorter hospital stays and less morbidity than with traditional open surgeries.

"Laparoscopic surgeries remain major operations that can be associated with significant complications and a real chance of death, but with experienced surgeons they can have better outcomes, Dr. Provost said.

Experience counts because laparoscopic surgeries require learning some 50 to 70 new surgical procedures, as well as learning to recognize and handle complications, Dr. Livingston said.

"An experienced team generally knows how to deal with complications," noted Dr. Livingston, who has performed thousands of such surgeries.

"I've looked at many cases," he said, "where bariatric surgeries have gone wrong, and the difference between living and dying is whether your surgeon knows how to deal with complications.

"That's something we do particularly well here, so our outcomes are quite good with complicated patients."

Such confidence is reflected in the center's patient population. Increasingly, bariatric patients with complex needs are being referred to UT Southwestern from other hospitals and practices.

"We get the more high-risk patients," said Dr. Livingston, adding that he doesn't mind the burden. "I think the community needs to recognize that's what we do. That's what a university medical center is for. That's our role."

And that is why it is vital to have skilled surgeons like Dr. Provost, he said.

"He's probably the best technical surgeon I've ever seen do these operations. The outcomes are outstanding, absolutely outstanding."

Also critical to the center's success is a comprehensive approach to address patients' financial, nutritional and emotional needs.

"The center is more than just a place. It's a team that has the structure available to pull those resources together and make successful outcomes for these patients," Dr. Livingston said.

Much of the groundbreaking research in the field now involves developing treatment criteria to improve outcomes.

Dr. Livingston, holder of the Dr. Lee Hudson - Robert R. Penn Chair in Surgery, is in charge of bariatric surgery for the Department of Veteran's Affairs national system and has been looking at its database to determine the efficacy of bariatric surgeries. The VA's database is considered the best available, with more than 1 million patients represented, 600 of whom have had bariatric surgeries.

His goal is to determine the mortality rate for such surgeries and who is the best candidate for which bariatric operation.

"There's an interest in knowing whether certain types of medical conditions would be better served by treatment with bariatric surgery versus medical therapy," Dr. Livingston said.

"The current criteria are based on pretty minimal data," Dr. Livingston noted.

Dr. Livingston conducted one of the early studies, now considered the standard in bariatric surgery morbidity reporting. He found a mortality rate of around 1.3 percent and a complication rate of around 5.8 percent.

That's higher than many other general elective surgery mortality rates, which hover around 0.3 percent to 0.5 percent.

Continued on page 36

"We get the more high-risk patients. I think the community needs to recognize that's what we do. That's what a university medical center is for. That's our role."

--Dr. Edward Livingston

"That's because you're dealing with high-risk people," Dr. Livingston said. Some surgeons may have lower mortality rates because they don't accept high-risk patients, he noted.

Ongoing studies have found that certain categories of patients have a higher risk for complications, such as people who smoke or individuals who are extremely large.

The most common complication is pneumonia, he said.

On the other hand, it is unusual to see heart attacks resulting from the surgeries, despite obesity's propensity to aggravate coronary problems, Dr. Livingston said.

He has also found, surprisingly, that if you take away factors such as diabetes and hypertension, there's very little mortality from the obesity itself.

It's not a finding that's been readily received by colleagues.

"The public has been inundated with the message that if you're fat you're going to die. But if someone is 70 years old, and they've been fat for 50 years, their fatness is not going to kill them," Dr. Livingston said.

So it may turn out that the reason for doing the surgery may not be the obesity itself, but to cut risks for factors like diabetes and hypertension, or because the patient has trouble getting around or difficulty sleeping.

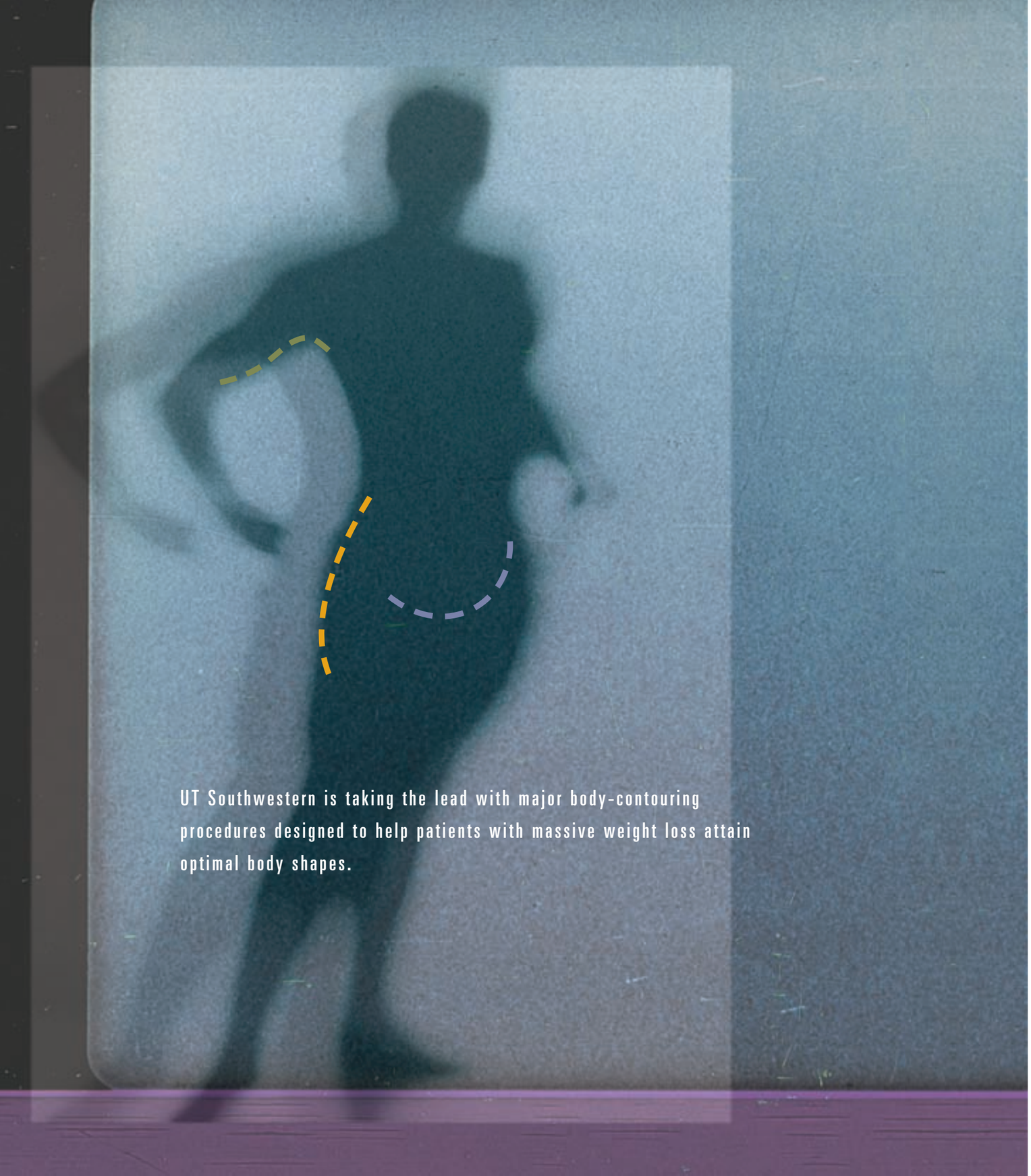
About 90 percent of patients with diabetes will have the condition cured after weight surgery, and about 75 percent of patients with hypertension will return to normal blood pressure, he said.

UT Southwestern research may also influence standards of care, specifically in determining when such surgeries are not likely to prove beneficial.

Bariatric surgery is not routinely covered by Medicare, but the government is re-examining its coverage of the procedure. That's important because other insurers watch for changes in Medicare coverage.

"Usually all the private insurers follow in lockstep after Medicare coverage becomes standard," said Dr. Livingston, whose research is being considered by Medicare officials as part of their review.

"So everyone's looking toward Medicare right now to make a statement about bariatric surgery," he said. "The stakes for it are really high." ⌘

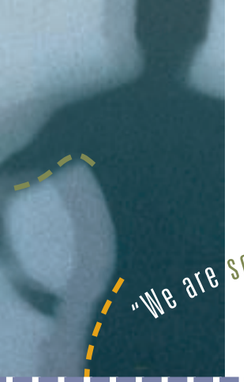


UT Southwestern is taking the lead with major body-contouring procedures designed to help patients with massive weight loss attain optimal body shapes.

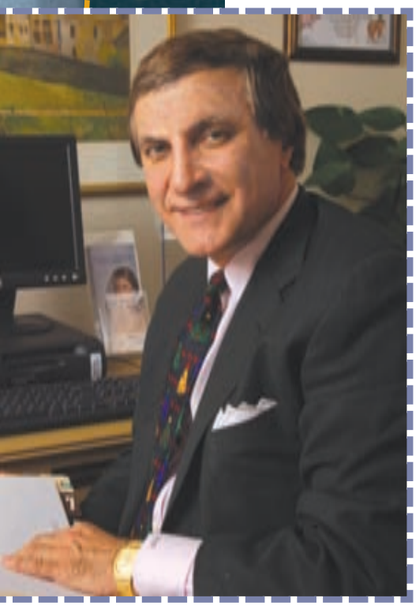
new contours

Sonya Sartain still felt fat—even after losing 150 pounds. The year before, at age 35 and weighing 315 pounds, she had joined the growing ranks of overweight Americans opting for bariatric surgery to radically rid them of extra body mass. And it had worked. The problem, however, was that while half her weight was gone, the excess skin wasn't, although she was working out with a personal trainer, running several miles a day and carefully watching her diet. Ms. Sartain recalls lying on her back, lifting her body up on her hands, and watching rolls of loose skin from her abdomen sag beneath her. "I had thought that if I could just lose 150 pounds, I would be fine," she said. "But I wasn't. "When I would run, I would wear bicycle shorts and another pair of shorts on top of that, and at least two sports bras and another shirt over them. "It was really frustrating, and I was physically exhausted," Ms. Sartain said. "And then this epiphany hit: It wasn't the weight I needed to lose. It was the baggy skin." Four years later, Ms. Sartain, who now wears a size 8 or 10, is trying to adjust not only to clothes that actually hug her skin, but also to skin that hugs her body – thanks to several relatively new surgical procedures that reduce sagging fat and skin and better proportion the body. Three surgeries at UT Southwestern Medical Center last January and August made the difference.

by Donna Steph Hansard



"We are seeing more and more patients who have gone to great lengths to make themselves healthier through losing excessive weight, often through bariatric procedures," said Dr. Jeffrey Kenkel, vice chairman of plastic surgery and holder of the Rod J. Rohrich, M.D., Distinguished Professorship in Wound Healing and Plastic Surgery.



"But the main problem is that while they've lost sometimes between 100 to 200 pounds, they look in the mirror, and they still see someone who looks heavy and overweight. They're frustrated with that image," he said.

UT Southwestern takes the lead

Plastic surgeons at UT South - western have developed several major body-contouring procedures designed to help patients attain optimal weights and body shapes after massive weight loss.

"Traditional body-contouring procedures that have been done and taught in the past don't really work in this patient group," Dr. Kenkel said. "We've had to learn different ways to approach these prob - lems in these patients and develop new metho- dologies and techniques."

Dr. Kenkel is one of fewer than a dozen plastic surgeons in the country who are at the forefront of this body-contouring revolution. Body-lift surgeries have gone from comprising about one-third of his practice a few years ago to almost 70 percent today.

And like Ms. Sartain, who lives in Atlanta and located Dr. Kenkel through a consultant who specializes in plastic surgery, many patients are coming from outside the area to take advantage of his expertise.

"UT Southwestern has been the innovation epicenter in plastic surgery for more than a decade with advances in plastic surgery techniques, such as ultrasound liposuction, rhinoplasty, burn reconstruc- tion and breast reconstructive procedures," said Dr. Rod Rohrich, chairman of plastic surgery.

"UT Southwestern has been the innovation epicenter in plastic surgery for more than a decade with advances in plastic surgery techniques."

--Dr. Rod Rohrich

"With these new body-lift surgeries becoming more in demand, we are continuing to take a cutting-edge approach to management of this new subspecialty of bariatric surgery in a multidisciplinary manner with our colleagues in UT Southwestern's Clinical Center for the Surgical Management of Obesity," said Dr. Rohrich, holder of the Crystal Charity Ball Distinguished Chair in Plastic Surgery and the Betty and Warren Woodward Chair in Plastic and Reconstructive Surgery.

While president of the American Society of Plastic Surgeons in 2004, Dr. Rohrich created a task force on post-bariatric procedures, of which Dr. Kenkel is chairman. The task force was designed not only to educate plastic surgeons about the procedures, but also to teach the public about safety issues, selecting the right doctor and what to expect after massive body surgery.

As a result of that task force, UT Southwestern hosted the first educational seminar dedicated to management of massive weight-loss patients last April, attracting about 250 physicians from across the country.

Number of surgeries growing

The number of body-contouring procedures performed in the United States is still relatively small but is expected to increase rapidly. Last year, about 56,000 such surgeries were done.

At UT Southwestern, the number of body-lift surgeries doubled from 2003 to 2004. As more people continue to choose bariatric surgery for weight loss, the number will continue to rise, Dr. Kenkel said.

In addition, television shows such as "Extreme Makeover" have focused public attention on plastic surgery.

"The reality shows have been somewhat mislead- ing in making people think that an individual can go through such a major ordeal and bounce back so quickly," Dr. Kenkel said. "What television doesn't show is all the therapy and things that are done behind the scenes to get patients to full recovery."

Body-lift surgery involves major invasive procedures and should be viewed accordingly, he said. Patients should be healthy going into surgery, have maintained the same weight for a minimum of three months, understand that the process typically requires two to four separate operations, and be aware that, as with any major surgery, there are potential risks and complications.

"You have to educate patients," Dr. Kenkel said. "They need to realize what the potential problems could be and that the scars from the surgeries will be very visible. They also need to realize that the entire process – from the first bariatric surgery to the last plastic surgery – can take up to four to five years."

Body-contouring procedures

Body-contouring surgery after massive weight loss focuses on several key areas where skin and tissues often lack elasticity and cannot conform to a patient's reduced body size.

Each patient at UT Southwestern is evaluated on an individual basis and offered recommendations based on specific needs and goals. Typical plastic surgery procedures can include:

- Facelift to reduce sagging of the mid-face, jowls and neck;
- Breast lift to correct sagging, flattened breasts;
- Tummy tuck to correct the apron of excess skin hanging over the abdomen;
- Lower body lifts to correct sagging of the abdomen, buttocks, groin and outer thighs;
- Medial thigh lift to correct sagging of the inner, outer and mid-thighs; and
- Brachioplasty to correct sagging of the upper arms.

Because the surgeries are major, Dr. Kenkel emphasized that they should be performed only by a board-certified plastic surgeon and in an accredited facility.

Beforehand, doctors discuss the different stages of surgery – including how many procedures it will take to meet their objectives – with their patients. Patients also have photographs made and view computer-enhanced images of likely results, as well as undergo thorough health screenings and blood analyses.

"There is a direct correlation with the size of the patient and his or her outcome and risk factors," Dr. Kenkel said. "Patients who are above 35 BMI (body mass index) are at a higher risk for developing complications.

"Candidates for these procedures also must be aware that they're trading scars for contour shape. An arm scar typically goes down to the elbow, and a leg scar down to the knee. And while scars will get better over time, it takes about two to three years for them to fully mature."

Is it worth it?

Marcia Conner thinks so. A nurse practitioner in the UT Southwestern Center for Breast Care, she understood the ramifications of major surgery probably better than most.

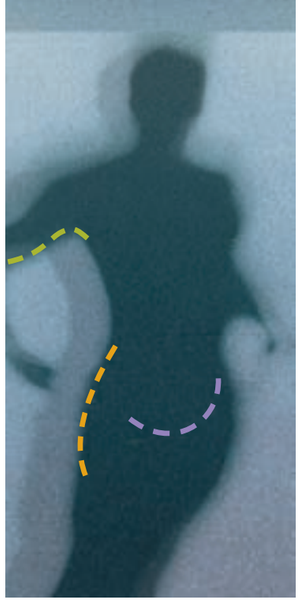
"It's not as easy as they make it look on TV, but it really wasn't that bad either," she said. "I think much of it is mental. You have to be mentally ready and have the right attitude. I was determined I was going to do well."

Ms. Conner underwent gastric bypass surgery in January 2003, then lower body and breast lifts last April and a thigh lift in May. Dr. David Provost, director of the Clinical Center for the Surgical Management of Obesity, performed the bypass surgery, and Dr. Kenkel did the body-contouring procedures.

She has lost 120 pounds and dropped eight clothing sizes.

Marcia Conner with Dr. Jeffrey Kenkel

"I was carrying around a whole extra person. I now am much healthier and have a lot more self-confidence *and* a whole new wardrobe. I like to say of my experience: Dr. Provost *saved* my life, and Dr. Kenkel *improved* my life." --Marcia Conner



"After going through all this, I've come to the conclusion that plastic surgery is an art as well as a science."

--Sonya Sartain

"It was no secret I was fat," Ms. Conner said. "I was carrying around a whole extra person. I now am much healthier and have a lot more self-confidence *and* a whole new wardrobe.

"I like to say of my experience: Dr. Provost *saved* my life, and Dr. Kenkel *improved* my life."

Ms. Sartain, back in Atlanta, cautions that the surgeries may make a dramatic difference, but they are not a cure-all. Even though 13 additional pounds of skin were removed from her abdomen area, five pounds from her thighs and still more from her buttocks, she still has to work at maintaining her new weight and shape, including running every day, eating healthier and consuming fewer calories.

"Some people think the surgery is the easy way out and that once you've had the surgery, it's all done," she said. "They don't realize that you have to continue to do a lot of work. I'm going to have to get up and exercise almost every day for the rest of my life."

Changing behaviors

Ms. Sartain also has had to adjust her mind-set.

"It's not just your body you have to work at," she said. "There's a lot more to it. Most people who are morbidly obese do not eat just because they're hungry. They're eating for other reasons.

"The behaviors that got me over 300 pounds are still in me," Ms. Sartain said. "What I have to learn to do is understand those behaviors and thought processes, and then change them."

While it's been a grueling emotional, physical and financial ordeal and has consumed four years of her life, Ms. Sartain said she made the right decisions.

"I would not change having the surgery. And I would not change using Dr. Kenkel. I think finding the right doctor is everything," she said.

"I talked to numerous doctors, one of whom was going to do the lower body work, my arms, my breasts and my legs all in one surgery in his outpatient clinic, and then let me go home the next day," she said. "Dr. Kenkel, on the other hand, was very conservative in his approach and didn't promise me the world. I felt very comfortable with him.

"After going through all this, I've come to the conclusion that plastic surgery is an art as well as a science." ⌘

Smile, you're on PillCam

By Russell Rian

Back in 1966, a Hollywood science-fiction film offered something new to viewers – a "Fantastic Voyage" through the inner workings of the human body with a team of shrunken doctors.

These days, fantasy is becoming closer to reality.

There is no shrunken medical team, but Dr. Charles Ulrich has taken the trip through the inner workings of his patients some 50 times now via the PillCam. The camera is an inch-long capsule that snaps thousands of images as it makes its way down the throat and into the stomach and bowels.

The special effects are dramatic: The inner workings of the digestive system can reveal inflammation, ulcers, abnormal blood vessels, polyps, tumors and other problems.

"It is very cool technology, and it's very patient-friendly," said Dr. Ulrich, associate professor of internal medicine at UT Southwestern Medical Center. "The patients love it, and it's painless."

The traditional route is far less appealing for many – a long, thin tube called an endoscope goes into the mouth and down the throat. It requires patients to take a day off work, refrain from eating, be sedated during the procedure and have someone drive them home – none of which is required for the PillCam.

"The PillCam has the potential to get a lot more people to come in for a screening examination of the esophagus because they get to swallow a pill instead of a scope," Dr. Ulrich noted. Not all patients are willing to have the endoscope.

"But I haven't had anybody say no to the pill," Dr. Ulrich said.

There are now two versions of the PillCam – one that reveals problems in the esophagus, and another that travels deep into the small bowel to areas only poorly visualized by barium X-rays and computed tomography.

The esophageal PillCam has cameras at both ends and takes about 14 shots per second as it travels downward. The battery life is about 20 minutes, and a transmitter worn on the patient's belt tells the doctor when it's finished. It has proved useful in detecting Barrett esophagus and dilated veins, known as varices. Barrett esophagus is a precancerous condition generally attributed to long-standing acid reflux. Esophageal varices are typically due to cirrhosis or other conditions that increase pressure in the veins draining into the liver.

The small-bowel PillCam has a camera on only one end taking shots at four frames per second, but working about eight hours, enough time to travel through the small bowel and into the colon. Its images can help doctors detect inflammation, including ulcers, sources of gastrointestinal bleeding, polyps, tumors, blockages and conditions in which the immune system attacks the lining of the small intestine, causing an inability to absorb nutrients. Such findings cannot be seen in most cases by other noninvasive methods.

While the PillCam doesn't allow doctors to steer it or stop it at a specific place, it does provide a useful look around, and the resulting images are of high quality.

"If you considered endoscopy the 100 percent gold standard, this test is about 95 percent, so it's very, very good," Dr. Ulrich said.

The PillCam, however, doesn't signal the end of endoscopes.

For one thing, it is not appropriate for those who have difficulty swallowing or have suspected stomach ailments.

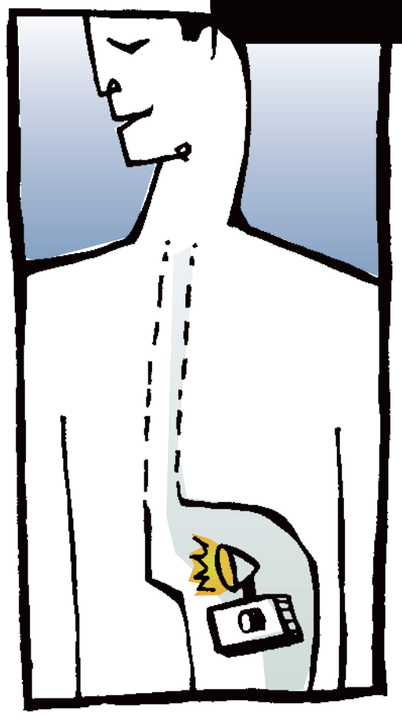
Also, endoscopes allow physicians to cleanse and expand the stomach and colon with air, so they can see areas that might otherwise be hidden during a PillCam study.

"With a scope you can always take another look, blow things up. With this you get what you get," Dr. Ulrich said. "While you can't see everything, the view is generally excellent, and even in areas where retained food obscures a complete view, it's a whole lot better than nothing.

"It's certainly technology worth using."⌘

For more information on the PillCam, please call 214-648-5400.

> "It is very cool technology, and it's very patient-friendly."
>
> *– Dr. Charles Ulrich*



Targeted Therapy

By Toni Heinzl

Catherine Padilla will never forget the phone call from her physician the day she arrived in Dallas for her 2003 Christmas vacation. He said he had concerns about her recent mammogram and wanted her to schedule a biopsy.

Ms. Padilla felt her heart sink. Cervical cancer had taken her mother from her; stomach cancer had killed her grandfather. She was only 46 years old. The accountant, who lives on a golf course in Maui, Hawaii, did not want to become another statistic in the grim annual reports of breast cancer deaths, which total about 40,000 in the United States each year.

"I'm so grateful ...

I had no side effects, and I can run for half an hour on the beach."

—Catherine Padilla

Ms. Padilla decided not to wait for her return to Hawaii to schedule the biopsy, so she contacted the UT Southwestern Center for Breast Care after a friend told her about the state-of-the-art screening technology and the team approach involving top-notch radiologists, cancer specialists and surgeons there.

Her biopsy was performed by the center's director, Dr. Phil Evans, holder of the George and Carol Poston Professorship in Breast Cancer Research. The results came back two days later: It was a benign growth.

The quality of care and the professionalism of the staff she witnessed at UT Southwestern Medical Center persuaded her to return a year later for her annual mammogram. This time she was found to have early-stage breast cancer. It was three days after Christmas. Instead of returning home, Ms. Padilla chose to continue her cancer treatment in Dallas.

The day after her diagnosis, she met with her surgeon, Dr. David Euhus, associate director of clinical care for the Harold C. Simmons Comprehensive Cancer Center, co-director of the Mary L. Brown Breast Cancer Genetics and Risk Assessment Program, and holder of the Marilyn R. Corrigan Distinguished Chair in Breast Cancer Surgery.

After removing the small, localized tumor and two lymph nodes, Dr. Euhus had good news for Ms. Padilla.

"I didn't have to undergo chemotherapy," she recalled. "And he said I'd be a good candidate for this brand-new radiation therapy called MammoSite."

MammoSite is a revolutionary type of internal breast irradiation focused on a small area of tissue. The procedure is significantly shorter than conventional radiation, in which patients have the entire breast treated five days a week for up to seven weeks. MammoSite takes only five days, with two short treatments a day.

In the MammoSite procedure, a balloon catheter is inserted into the cavity where the tumor was, and the catheter is inflated. A radiation oncologist delivers the treatment using a seed of the radioisotope iridium-192. Actual treatment time is about six to nine minutes.

"We use it for tumors of less than 2 centimeters, which are less aggressive and have sufficient healthy tissue around them," Dr. Euhus said.

Launched in August 2004, the MammoSite procedure was used on a dozen patients in its first 12 months. Patients typically have to be older than 45 because younger patients tend to have more aggressive types of cancer.

"MammoSite has been a major development in the past year," said Dr. Marilyn Leitch, professor of surgical oncology and medical director of the Center for Breast Care.

And the success rate is comparable to conventional whole-breast radiation, with a recurrence rate in less than 4 percent of patients, said Dr. Leitch, holder of the S.T. Harris Family Distinguished Chair in Breast Surgery.

Ms. Padilla today enjoys jogging and long walks on the shores of Hawaii more than ever.

"I'm so grateful," she said about her treatment. "I had no side effects, and I can run for half an hour on the beach."⌘

For more information on MammoSite treatment, please call 214-645-8525.

Cutting recovery time

By Toni Heinzl

It was by word of mouth from two Fort Worth doctors that John Rutherford first heard about a young surgeon at UT Southwestern Medical Center who uses an innovative approach to removing cancerous prostate glands.

Mr. Rutherford, a retired maintenance supervisor for an oil-field pump manufacturer, was relieved that he found Dr. Jeffrey Cadeddu, associate professor of urology and an expert on minimally invasive urologic cancer treatment.

Dr. Cadeddu, holder of the Ralph C. Smith, M.D. Distinguished Chair in Urological Surgery, is one of only two Dallas-area doctors who use laparoscopic surgery for radical prostatectomy. His patients come from across North Texas and as far as Louisiana, New Mexico, Oklahoma and Arkansas. He also uses laparoscopic surgery to remove kidney tumors.

"The doctor did his work Friday night, and I came home Sunday morning," Mr. Rutherford said, pleased about his quick recovery. "I was up walking three blocks Sunday afternoon."

Dr. Cadeddu, who has performed about 250 prostatectomies using laparoscopic surgery, said the procedure takes about three to four hours – longer than the conventional, open surgery (which takes about 2 1/2 hours). But there are significant benefits for the patients.

Compared with conventional surgery, hospitalization is reduced by a day or two, and patients recuperate twice as fast.

"They are back to normal in two to three weeks after laparoscopic surgery, compared with four to six weeks after open surgery," Dr. Cadeddu said.

In laparoscopic surgery, a tiny video camera is inserted through a small incision. The camera provides up-close images on a video monitor of the area targeted for surgery. While one doctor guides the camera, the surgeon uses special instruments inserted through other small incisions. Guided by the video images, the surgeon removes the prostate through additional small incisions.

Thanks to advances in screening and treatment, prostate cancer – which affects as many as one in six men older than 40 – has become a disease that can often be cured.

However, it still was expected to kill an estimated 30,000 men in the United States in 2005, accounting for almost 10 percent of all cancer deaths among men, and it is the second deadliest cancer for men after lung cancer.

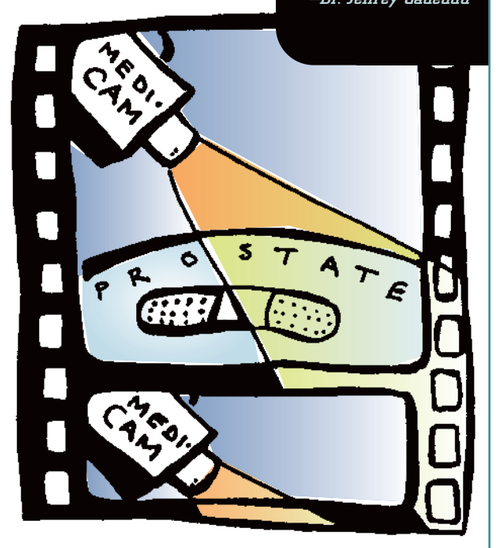
Early detection through screening for prostate-specific antigen, or PSA, is the key to curbing these statistics, said Dr. Claus Roehrborn, chairman of urology and holder of the E.E. Fogelson and Greer Garson Fogelson Distinguished Chair in Urology.

"We aim for a cure with surgery," Dr. Roehrborn said. "But one out of five patients will need other therapies as well. These patients will require radiation and hormone therapy to stop the cancer from growing and chemotherapy if everything else fails."

Detecting and curing aggressive cancer that cannot be held in check by prostatectomy is a major challenge. Researchers at UT Southwestern are trying to identify a biomarker that will discern this aggressive type of prostate cancer earlier, Dr. Roehrborn said. In high amounts in the blood serum, biomarkers indicate tumor activity.

"They are back to normal in two to three weeks after laparoscopic surgery, compared with four to six weeks after open surgery."

—Dr. Jeffrey Cadeddu



Dr. Yair Lotan, assistant professor of urology, is working to build a large serum bank to help identify such biomarkers. The effort, however, will require a significant amount of time to initiate, first by enrolling patients who are at high risk for aggressive prostate cancer and then by collecting and evaluating multiple samples.⌘

For more information on laparoscopic surgery for radical prostatectomy, please call 214-645-8765.

Pain, pain go away

By Kara Lindsley

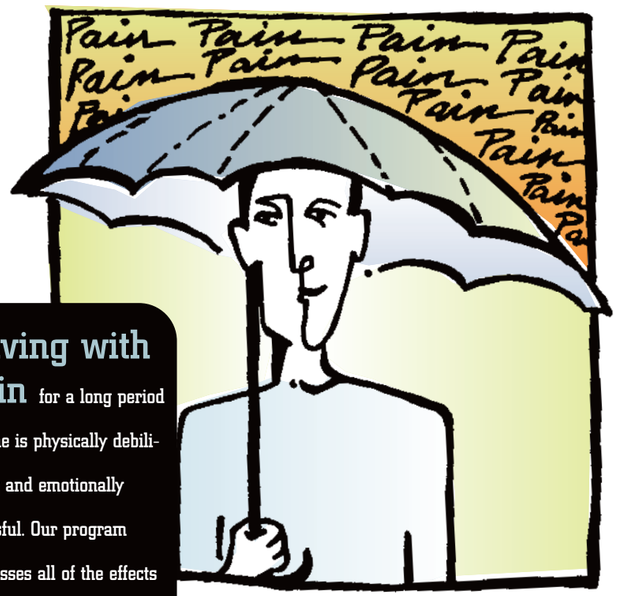
Fifty million Americans live with chronic pain. Clifton Bise was one of them. An inoperable tumor in his spine, along with bull-riding injuries from his college days, had left him with chronic pain in his back.

"I was in so much pain that I had no life. I would just lie on the couch all day. I didn't have any motivation to get better because so many doctors had told me that they couldn't do anything for me. I was really pessimistic," he said.

A referral to the Eugene McDermott Center for Pain Management at UT Southwestern Medical Center eventually brought him relief. Dr. Joysree Subramanian, assistant professor of anesthesiology and pain management, performed a minimally invasive procedure called caudal lysis of adhesion.

"We removed scar tissue from his back to alleviate the pain," Dr. Subramanian said.

Two days after the procedure, Mr. Bise said he felt good for the first time in four years. But his treatment didn't end there.



"Living with pain for a long period of time is physically debilitating and emotionally stressful. Our program addresses all of the effects that chronic pain can have on a person's life."

–Dr. Leland Lou

"Living with pain for a long period of time is physically debilitating and emotionally stressful. Our program addresses all of the effects that chronic pain can have on a person's life – physical discomfort, reduction in activity and emotional symptoms," said Dr. Leland Lou, associate professor of anesthesiology and pain management.

The McDermott Center employs a team of pain specialists who combine state-of-the-art medical, psychological and rehabilitative therapy with the latest advances in laboratory science. The mission is to reduce patients' suffering and disability, eliminate excessive reliance on medication and return them to a normal life.

With a referral from a primary-care physician, the pain management specialists, behavioral medicine specialists and physical therapists evaluate the patient and design a treatment plan based on the patient's specific needs.

"All of our doctors and professionals work under one roof as a team. This makes a difference to patients because they don't have to travel from doctor to doctor to continue their treatment," Dr. Lou said.

Behavioral medicine and physical therapy are vital components of the plan.

"Pain can cause significant changes in relationships with family, friends and co-workers. Patients can develop depression, anxiety and trouble sleeping. Our behavioral medicine experts teach stress management and relaxation techniques," Dr. Lou said.

Mr. Bise said he didn't realize how much his personality had changed because of his chronic pain. "Counseling really showed me what I needed to do to get back to normal."

Physical therapy provides patients with the tools to increase their range of motion, muscle strength, endurance and coordination and teaches them how to reduce tension.

Mr. Bise said physical therapy stretched him to his limits, but he's a better person for it.

He no longer needs medication for his back. He's back at work, enjoys riding his motorcycle, and goes hunting and fishing.

"I'm tickled to death with the McDermott Center. Can't thank my doctors enough," he said.⌘

For more information on treatments for chronic pain, please call 214-645-8450.

2005

ANNUAL REVIEW

HIGHLIGHTS
of the year

FALL 2004

REYNOLDS GRANT CONTINUES TASK OF DALLAS HEART STUDY

A $12 million grant from the Donald W. Reynolds Foundation to UT Southwestern has enabled researchers to continue the Dallas Heart Study, a groundbreaking investigation of cardiovascular disease involving thousands of Dallas County residents.

The foundation's two-year grant to the Donald W. Reynolds Cardiovascular Clinical Research Center at UT Southwestern supplements previous foundation grants it awarded to the medical center totaling $30 million, bringing total Reynolds Foundation support for UT Southwestern to $42 million.

The grant continues research into the prevention and treatment of heart disease caused by atherosclerosis and by heart enlargement. Reynolds Center researchers are using molecular and clinical research techniques to examine a large multi-ethnic group of individuals from Dallas County, to develop new biotechnology and to establish a novel training program for scientists-physicians.

EARLY DOSES OF STATINS SAVING HEART ATTACK PATIENTS

Treating heart-attack patients earlier with a more aggressive regimen of cholesterol-lowering medicines may help diminish their chances of sustaining more complications later or dying after their heart attack, UT Southwestern researchers found.

The findings, published in *The Journal of the American Medical Association,* showed benefits of

DR. JAMES DE LEMOS

treating patients who have recently suffered acute coronary syndromes with higher doses of the cholesterol-lowering drugs called statins soon after they experience heart-attack symptoms.

Dr. James de Lemos, associate professor of internal medicine, was lead author of the second of a two-part, collaborative international study called the Aggrastat to Zocor study, or A to Z study.

HOBBS, MCCONNELL INDUCTED INTO INSTITUTE OF MEDICINE

Two faculty members at UT Southwestern – one specializing in genetics and heart disease and the other in urology – were elected to the Institute of Medicine, a component of the prestigious National Academy of Sciences.

Dr. Helen Hobbs, director of the Eugene McDermott Center for Human Growth and Development and chief of clinical genetics, and Dr. John D. McConnell, executive vice president for health system affairs, were the only Texans among 65 new members elected in 2004 to the institute, which addresses national health issues.

Drs. Hobbs and McConnell bring the total number of current UT Southwestern faculty members who are institute members to 17, the largest representation in Texas and surrounding states.

DR. HELEN HOBBS

DR. JOHN D. MCCONNELL

UT SOUTHWESTERN GRADUATE WINS NOBEL PRIZE

Dr. Linda Buck, a UT Southwestern graduate, was awarded the 2004 Nobel Prize in physiology or medicine. She is the first alumnus of the Southwestern Graduate School of Biomedical Sciences to win the prize. She joined Dr. Joseph Goldstein, a graduate of UT Southwestern Medical School, now chairman of molecular genetics, as a UT Southwestern-trained Nobel laureate.

DR. ELLEN VITETTA (RIGHT) ATTENDED A RECEPTION FOR HER FORMER STUDENT, DR. LINDA BUCK, THE 2004 NOBEL PRIZE WINNER IN PHYSIOLOGY OR MEDICINE.

As a graduate student in microbiology, Dr. Buck worked under Dr. Ellen Vitetta, now director of the Cancer Immunobiology Center. She received her doctorate with an emphasis in immunology in 1980 and in 1995 received the Distinguished Alumnus award from UT Southwestern's graduate school.

Dr. Buck, a professor at the Fred Hutchinson Cancer Research Center in Seattle, shared the Nobel Prize with Dr. Richard Axel of Columbia University College of Physicians and Surgeons for their work in understanding the sense of smell.

MCKNIGHT RECEIVES NEW PIONEER AWARD

Dr. Steven McKnight, chairman of biochemistry, received a National Institutes of Health Director's Pioneer Award, a new initiative designed to support exceptionally creative investigators.

The award, $500,000 per year for five years, aims at encouraging investigators to take on creative, unexplored avenues of research that carry a relatively high potential for failure, but that also possess a greater chance for truly groundbreaking discoveries.

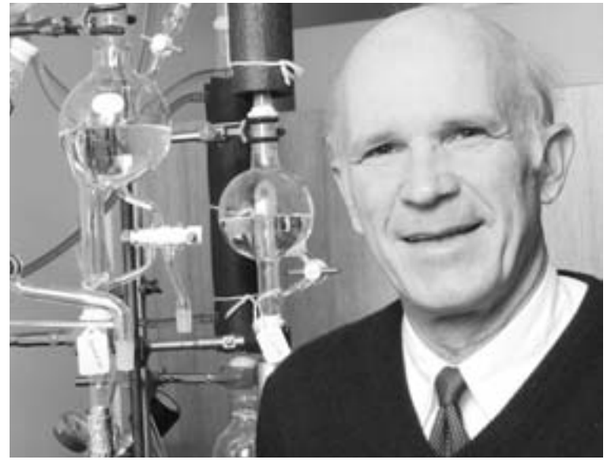
Dr. McKnight – the only winner from Texas – is one of nine U.S. researchers to receive the award. His research involves the regulation of transcription factors, the proteins that switch genes on and off.

GULF WAR SYNDROME DAMAGES VETERANS' NERVOUS SYSTEM

Researchers led by Dr. Robert Haley, chief of epidemiology, have uncovered damage in a specific portion of the nervous systems of veterans suffering from Gulf War syndrome.

The researchers reported in the *American Journal of Medicine* that damage to the parasympathetic nervous system may account for nearly half of the typical symptoms – including gallbladder disease, unrefreshing sleep, depression, joint pain, chronic diarrhea and sexual dysfunction – that afflict those with Gulf War syndrome.

Dr. Haley recently received the Congressional Medal of Honor Society's Patriot Award for his research into Gulf War syndrome. It is the highest honor bestowed by the society to people whose life work is dedicated to courage, sacrifice and patriotism.



DR. STEVEN MCKNIGHT, WINNER OF THE NIH DIRECTOR'S PIONEER AWARD.

WINTER 2004-2005

PROTEIN CONTROLLING BONE FORMATION DISCOVERED

Researchers led by Dr. Eric Olson, chairman of molecular biology at UT Southwestern, discovered a protein that controls an early and significant step in the exquisitely timed process of bone formation.

Dr. Olson and colleagues showed the protein HDAC4 to be essential for proper bone development, or osteogenesis. Their findings, reported in the journal *Cell*, may have widespread implications for understanding and preventing osteoporosis or other bone disorders.

Dr. Olson and colleagues studied mice lacking the *HDAC4* gene. At birth these animals had misshapen skulls and spines, and as they got older, failed to thrive. Retraining the bone-formation process, they discovered that the defect occurred in the earliest steps, where the cartilage foundation was being laid and filled with minerals.

DR. ERIC OLSON

DR. CLYDE YANCY

NEW MEDICATION HELPS BLACKS WITH HEART FAILURE

A new medication has dramatically reduced mortality among black patients suffering from heart disease, according to results of a study that included UT Southwestern researchers.

The results, published in *The New England Journal of Medicine*, were so favorable that investigators halted the multi-center trial so that all the 1,050 study participants suffering from advanced heart failure, including those on a placebo, could be given the combined drug treatment, said study author Dr. Clyde Yancy, director of the Congestive Heart Failure/Transplant Program at UT Southwestern.

A 43 percent decrease in the one-year mortality rates among blacks in the study receiving the combined treatment was observed by Dr. Yancy and his UT Southwestern colleagues, working in conjunction with University of Minnesota researchers. The African-American Heart Failure Trial used a combination of hydralazine and isosorbide dinitrate.

SCIENTISTS DETER CHOLESTEROL GALLSTONES

A promising experimental compound prevents cholesterol gallstone disease in mice by stimulating the biochemical pathway that controls the liver's bile acid secretion, according to studies by UT Southwestern researchers.

The findings suggest new approaches to developing drugs to prevent the disease, which afflicts some 20 million people a year. The studies also propose novel strategies for developing diagnostic tests to identify people with a genetically increased risk for developing gallstones.

A research team led by Dr. David Mangelsdorf, professor of pharmacology and biochemistry and a Howard Hughes Medical Institute investigator at UT Southwestern, published its findings in the journal *Nature Medicine*.

DR. DAVID MANGELSDORF

UT SOUTHWESTERN UNIVERSITY HOSPITALS

ZALE LIPSHY, ST. PAUL HOSPITALS MERGE UNDER MEDICAL CENTER

Zale Lipshy and St. Paul University Hospitals became a fully integrated part of UT Southwestern on New Year's Day.

The consolidation of the 150-bed Zale Lipshy and the 300-bed St. Paul facilities will help secure UT Southwestern's place among the nation's top-tier academic medical centers, almost all of which operate their own hospitals, administrators said.

Dr. Kern Wildenthal, UT Southwestern president, called the acquisition a critical step in becoming a national and international medical destination for people seeking top-quality, specialized care.

Dr. John McConnell, executive vice president for health system affairs, is chief executive officer of the health system including the university hospitals.

DOGS HELP UNCOVER THEORY OF RAPID EVOLUTION

UT Southwestern researchers used canine DNA to identify a genetic mutation mechanism they believe is responsible for rapid evolutionary changes in the physical appearance of many species.

The findings, based on data gathered from hundreds of museum specimens of dogs and from blood samples of volunteered live dogs, offer a new explanation for the sudden, rapid rise of new species found in the fossil record. Dr. Harold "Skip" Garner, professor of biochemistry and internal medicine and one of the authors of the study, said the findings, reported in the *Proceedings of the National Academy of Sciences*, also help explain the variability in appearance among individual members of a species, such as the length of the nose in different breeds of domestic dogs.

The scientists combined extensive genetic data from different dog breeds and data on the shapes of dog skulls with computer programs developed by study co-author Dr. John "Trey" Fondon, a UT Southwestern research fellow.

SPRING 2005

GENETIC MUTATIONS LINKED TO LOWER 'BAD' CHOLESTEROL

Researchers at UT Southwestern linked two genetic mutations to low levels of "bad" cholesterol, or low-density lipoproteins, in a number of black participants in the Dallas Heart Study, a discovery that could lead to more effective drugs for lowering LDL cholesterol in the blood.

Two percent of the blacks in the study had one or both mutations. On average, the study found that individuals with the mutation will have LDL levels 40 percent lower than if they did not have the mutation.

Dr. Helen Hobbs, director of the Eugene McDermott Center for Human Growth and Development and the Donald W. Reynolds Cardiovascular Clinical Research Center; Dr. Jonathan Cohen, associate professor of internal

medicine; and their colleagues discovered the genetic mutations caused deficiencies in an enzyme that affects how much cholesterol the liver removes from the blood. The investigators published their study in the journal *Nature Genetics*.

CHEN, ROSEN RECEIVE HHMI APPOINTMENTS

Two UT Southwestern scientists, Dr. Zhijian "James" Chen and Dr. Michael Rosen were named Howard Hughes Medical Institute investigators.

They were the only investigators from Texas out of 43 named nation - wide this year by the HHMI, a philanthropic organization that promotes biomedical research. Now, UT Southwestern has 12 current faculty members who are HHMI investigators.

Dr. Chen, associate professor of molecular biology, uses rigorous biochemical testing to unravel complex problems in the lab. His most substantial discovery has been uncovering an unanticipated second function of a small protein called ubiquitin. Known as the "Kiss of Death" for its role in targeting other proteins for destruction, ubiquitin was thought to have only one molecular function. Dr. Chen discovered that ubiquitin also plays a crucial role in activating certain proteins. The idea, initially contro - versial, is now widely accepted in the scientific community.

Dr. Chen recently received the 2005 Norman Hackerman Award in Chemical Research. The Robert A. Welch Foundation, one of the nation's oldest and largest sources of private funding for basic research in chemistry, presents the $100,000 award annually to honor up-and-coming scientists at Texas institutions who are 40 years old or less.

Dr. Rosen, professor of biochemistry and pharmacology, is interested in the smallest of skeletons, which are found inside every cell. The cytoskeleton is responsible for helping cells move, change shape and respond to various environmental cues. Dr. Rosen studies the basic building block of the cytoskeleton, a protein called actin, using highly sophisticated nuclear magnetic resonance techniques.

EXERCISING HELPS REDUCE SYMPTOMS OF DEPRESSION

Jumping on that treadmill or bike is not only good for one's health, but also can help significantly reduce depression, researchers at UT Southwestern found.

The first study to look at exercise alone in treating mild to moderate depression in adults aged 20 to 45 showed that depressive symptoms were reduced almost 50 percent in individuals who participated in 30-minute aerobic exercise sessions three to five times a week.

The results, published in the *American Journal of Preventive Medicine*, are comparable to results from studies in which patients with mild to moderate depression were treated with antidepressants or cognitive therapy, said Dr. Madhukar Trivedi, professor of psychiatry.

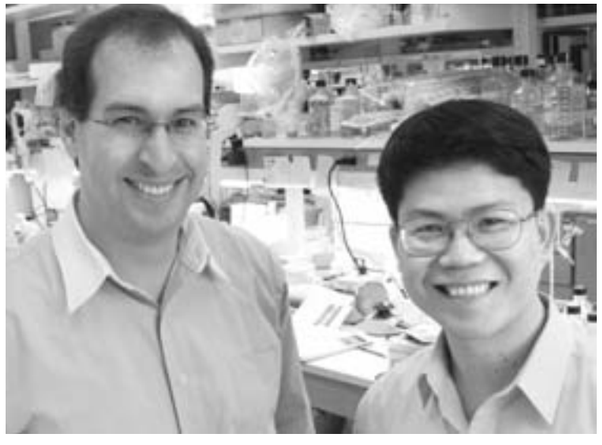
Using aerobic exercise alone in treating clinical depression is similar to what is found with antidepressant medications, said Dr. Trivedi, a study author. The key, he said, is the intensity of the exercise and continuing it for 30 to 35 minutes per day.

PROTEIN KEY TO INSECTS' SENSE OF 'SMELL' IDENTIFIED

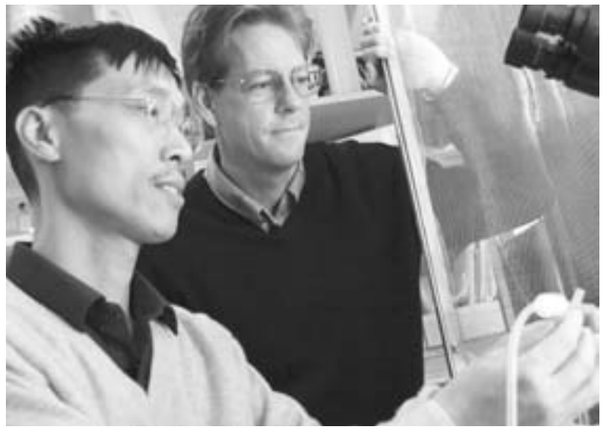
How do insects smell? Badly, according to a UT Southwestern study, if they lack a certain kind of protein critical to their ability to detect and interpret pheromones – the insect equivalent of "smelling."

Researchers discovered how a protein, called an olfactory binding protein, links incoming pheromone signals and specific nerve cells in an insect's brain, which in turn translate those signals. Pheromones are chemical signals given off by animals that, when detected by others of the same species, mediate a variety of behaviors, such as feeding, mating and colonizing.

The findings, which appeared in the journal *Neuron*, not only shed light on insect behavior, but also suggest that olfactory binding proteins may be new targets for synthetic chemicals that could trick insects like mosquitoes into traps or could function as repellents, said Dr. Dean Smith, associate professor of pharmacology and senior author on the study. Humans give off signals that attract mosquitoes, the insect responsible for spreading malaria, which kills up to 3 million people each year.



DRS. MICHAEL ROSEN (LEFT) AND ZHIJIAN "JAMES" CHEN WERE THE ONLY TEXANS AMONG THE 43 SCIENTISTS NAMED HOWARD HUGHES MEDICAL INSTITUTE INVESTIGATORS THIS YEAR.



DRS. PINGXI XU, A PHARMACOLOGY POSTDOCTORAL RESEARCHER, AND DEAN SMITH UNCOVERED AN OLFACTORY BINDING PROTEIN THAT ALLOWS INSECTS TO DETECT AND INTERPRET PHEROMONES, CHEMICAL SIGNALS GIVEN OFF BY ANIMALS.

SUMMER 2005

NOBEL LAUREATE NAMED DEAN OF MEDICAL SCHOOL

Dr. Alfred G. Gilman, Nobel laureate and chairman of pharmacology, was named dean of Southwestern Medical School on June 1.

Dr. Gilman will continue to lead the Alliance for Cellular Signaling, a $10 million-a-year, multi-institutional research effort aimed at advancing the understanding of how cells communicate with each other. He also continues oversight of the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational and Systems Biology and serves with other distinguished faculty members on the selection committee for the UT Southwestern Endowed Scholars Program in Medical Science.

DR. ALFRED GILMAN

Dr. Gilman was awarded the 1994 Nobel Prize in physiology or medicine for his work with G proteins, which serve as a crucial part of cell communication networks. He is a member of the National Academy of Sciences, the Institute of Medicine and the American Academy of Arts and Sciences. He earned an M.D. and Ph.D. in pharmacology from Case Western Reserve University.

PRC PRESENTS TWO DISTINGUISHED AWARDS

The President's Research Council presented its 2005 Distinguished Young Researcher Award to a pair of exceptional UT Southwestern investigators – one who is seeking ways to stop a deadly childhood cancer and another who is studying a bacterium that causes severe gastrointestinal disease.

The recipients – Dr. Rene Galindo, a pediatric pathologist, and Dr. David Hendrixson, a microbiologist – each received a $70,000 award.

Dr. Galindo, a second-year fellow in the Physician Scientist Training Program, is pursuing research aimed at unraveling the genetic basis of an aggressive cancer of muscle cells called alveolar rhabdomyosarcoma that attacks infants and children.

Dr. Hendrixson, assistant professor of microbiology, is conducting research aimed at ridding the world of one of the most common and severe forms of diarrheal disease in humans. His work on the bacterium *Campylobacter jejuni*, one of the major causes of food-borne diarrheal illness in humans, focuses in part on the bacterium's flagellum, a rotating appendage the organism uses for locomotion.

DRS. DAVID HENDRIXSON (LEFT) AND RENE GALINDO RECEIVED THE 2005 PRESIDENT'S RESEARCH COUNCIL DISTINGUISHED YOUNG RESEARCHER AWARD.

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

GENE CONTROLLING CIRCADIAN RHYTHMS LINKED TO ADDICTION

The gene that regulates the body's main biological clocks also may play a pivotal role in drug addiction, researchers at UT Southwestern found.

The *Clock* gene not only controls the body's circadian rhythms, including sleep and wakefulness, body temperature, hormone levels, blood pressure and heart activity, it may also be a key regulator of the brain's reward system.

UT Southwestern researchers showed that, in mice, the *Clock* gene regulates the reward response to cocaine, suggesting that similar actions take place in humans. Findings from the multi-center study appeared in the *Proceedings of the National Academy of Sciences*.

Dr. Eric Nestler, chairman of psychiatry at UT Southwestern and the study's senior author, said the results suggest there may be a link in disruption of circadian rhythms and the tendency to abuse drugs.

In 2005, Dr. Nestler was elected to the American Academy of Arts and Sciences, making him the 13th faculty member from UT Southwestern serving on the academy.

DR. ERIC NESTLER

HYPERTENSION MECHANISM DISCOVERED

An enzyme known to cause hypertension increases blood pressure by activating tiny pores, or channels, in kidney cells that allow increased levels of sodium to be reabsorbed into the blood, researchers at UT Southwestern found.

The findings shed light on the underlying mechanisms that cause hypertension and may also help explain why patients with hypertension linked to salt intake often need to take potassium supplements in order to keep their high blood pressure in check.

By studying animal and human cells in culture, UT Southwestern researchers, led by Dr. Chou-Long Huang, associate professor of internal medicine, and Dr. Melanie Cobb, dean of the UT Southwestern Graduate School of Biomedical Sciences, determined that the enzyme WNK1 – an enzyme known to cause a form of hypertension – interacts with another enzyme, SGK1, which is well-known to lead to the activation of sodium ion channels in kidney cells.

Published in *Proceedings of the National Academy of Sciences*, the research showed that the kidney plays a very important role in controlling high blood pressure by controlling how much sodium gets reabsorbed back into the kidney and the blood, Dr. Huang said.

MILLER RECEIVES FRIENDS OF ALZHEIMER'S DISEASE CENTER AWARD

The Friends of the Alzheimer's Disease Center awarded $50,000 to support the research of Dr. Bonnie Miller, assistant professor of internal medicine.

Dr. Miller and her colleagues found a link between an insulin-degrading enzyme called insulysin and Alzheimer's disease. When levels of the enzyme fell, the level of amyloid-beta peptide levels in the brain increased, possibly increasing the risk for Alzheimer's. This work suggested a link between diabetes and Alzheimer's, since insulysin also helps control the level of insulin in the body. She also has found evidence that some cells in the brain may secrete insulysin.

DR. BONNIE MILLER

Dr. Miller is now looking at mechanisms that may control how the enzyme is distributed inside and outside the cell, thus parsing out one of the many complex interactions of insulysin in the body.

384 EARN DEGREES FROM THREE SCHOOLS

Diplomas were awarded to 211 UT Southwestern Medical School students and 50 UT Southwestern Graduate School of Biomedical Sciences students at June 4 commencement ceremonies.

Ron W. Haddock, CEO of Prisma Energy International and chairman of the Board of Visitors of the UT Southwestern Health System, gave the commencement address.

The top award to a medical student, Southwestern Medical Foundation's Ho Din Award, was presented to Dr. Michael Herman.

Eileen Foy received the Nominata Award, given to the outstanding graduate school student.

UT Southwestern Allied Health Sciences School conferred degrees on 72 students during its summer commencement and awarded 51 in the winter.

PHYSICIAN ASSISTANT GRADUATE SALLY WILLIAMS RECEIVES HER DIPLOMA FROM THE ALLIED HEALTH SCIENCES SCHOOL.

CAMPAIGN CONTRIBUTIONS TOP $450 MILLION WITH $50 MILLION COMMITMENT FOR SIMMONS CENTER

Generous donor response to UT Southwestern's *Innovations in Medicine* capital campaign pushed the total raised by September 2005 to $450 million, including a $50 million pledge by Dallas entrepreneur Harold C. Simmons and his wife, Annette.

The Simmons pledge, along with a number of other gifts for cancer, will accelerate development of a nationally ranked cancer program at UT Southwestern. Dr. James Willson, director of the center and associate dean for oncology programs, said the funds will allow recruitment of more than 30 top cancer specialists and implement a broad range of supporting programs, enabling the Harold C. Simmons Comprehensive Cancer Center to achieve recognition as a National Cancer Institute-designated Comprehensive Cancer Center on an earlier timetable.

The $500 million *Innovations* campaign has now met 90 percent of its overall goal in less than four years, but major additional funds remain to be raised in many priority areas of the campaign, including Alzheimer's and other neurological disorders; heart disease and stroke; pediatric illnesses, birth defects and inherited disorders; infectious diseases, immunology and bioterrorism defense; basic molecular research, biostatistics and computational biology, medical imaging, and biotechnology; and enhancement of patient care and service at UT Southwestern's hospitals and clinics.

NEW APPOINTMENTS IN 2004-2005

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

- Dr. David A. Boothman, to the Robert B. and Virginia Payne Professorship in Oncology.
- Dr. Robert Bucholz, to the Dallas Rehabilitation Institute Distinguished Chair in Orthopaedic Rehabilitation.
- Dr. David J. Chen, to the David A. Pistenmaa, M.D., Ph.D., Distinguished Professorship in Radiation Oncology.
- Dr. Joaquin E. Cigarroa, to the Audre and Bernard Rapoport Distinguished Professorship in Cardiovascular Research.
- Dr. Susan Cox, to the Gillette Professorship in Obstetrics and Gynecology.
- Dr. Carol Croft, to the Baldridge Family Professorship in Internal Medicine and Preventive Care.
- Dr. Julio Pérez Fontán, to the Joel B. Steinberg, M.D., Chair in Pediatrics.
- Dr. Joseph Forbess, to the Pogue Distinguished Chair in Pediatric Cardiac Surgery Research.
- Dr. Alfred Gilman, to the Nadine and Tom Craddick Distinguished Chair in Medical Science.
- Dr. Joel Goodman, to the Jan and Bob Bullock Distinguished Chair for Science Education.
- Dr. Frank Gottschalk, to the R. Wofford Cain Distinguished Chair in Bone and Joint Disease Research.
- Dr. David Hemsell, to the Frank C. Erwin Jr. Professorship in Obstetrics and Gynecology.
- Dr. Donald Hilgemann, to the Roy and Christine Sturgis Chair in Biomedical Research.
- Dr. John Hunt, to the Golden Charity Guild Charles R. Baxter, M.D., Chair.
- Dr. Susan Iannaconne, to the Jimmy Elizabeth Westcott Distinguished Chair in Pediatric Neurology.
- Dr. Robin Jarrett, to the Elizabeth H. Penn Professorship in Clinical Psychology.
- Dr. R. Ellwood Jones, to the Paul T. Stoffel/Centex Professorship in Clinical Care.
- Dr. Lynne Kirk, to the Tim and Toni Hartman Professorship in Medicine.
- Dr. Thomas J. Kodadek, to the Julie and Louis Beecherl Jr. Chair in Medical Science.
- Dr. William Kovacs, to the Diana and Richard C. Strauss Professorship in Biomedical Research.
- Dr. Kenneth Leveno, to the Jack A. Pritchard, M.D., Chair in Obstetrics and Gynecology.
- Dr. Beth Levine, to the Jay P. Sanford Professorship in Infectious Diseases.
- Dr. Bradley Marple, to the T.C. Lupton Family Professorship in Patient Care, in Honor of Dr. John Dowling McConnell and Dr. David Andrew Pistenmaa.
- Dr. Chandra Mohan, to the Walter M. and Helen D. Bader Professorship in Arthritis and Autoimmune Disease Research.
- Dr. Jerry Niederkorn, to the J. Wayne Streilein, M.D., Professorship in Immunology.
- Dr. Nancy Olsen, to the McGee Foundation Chair in Arthritis Research.
- Dr. Eric Olson, to the Annie and Willie Nelson Professorship in Stem Cell Research.
- Dr. Milton Packer, to the Gayle and Paul Stoffel Distinguished Chair in Cardiology.
- Dr. Michael Racke, to the Lois C.A. and Darwin E. Smith Distinguished Chair in Neurological Mobility Research.
- Dr. Robert Reilly Jr., to the Fredric L. Coe Professorship in Nephrolithiasis Research in Mineral Metabolism.
- Dr. Charles M. Reinert, to the Hansjörg Wyss Distinguished Professorship in Orthopaedic Trauma.
- Dr. John Richmond, to the Stanley Gilbert, M.D., Professorship in Family Practice.
- Dr. Don C. Rockey, to the Dr. Carey G. King Jr. and Dr. Henry M. Winans Sr. Chair in Internal Medicine, and to serve as chief of the digestive and liver diseases division.
- Dr. David Self, to the Wesley Gilliland Professorship in Biomedical Research.
- Dr. Key H. Stage, to the Paul C. Peters Sr., M.D., Chair in Urology.
- Dr. Adam Starr, to the Aaron A. Hofmann, M.D., and Suzanne Hofmann Distinguished Chair in Orthopaedic Surgery, in Honor of Richard E. Jones, M.D.
- Dr. Louis Stool, to the Anesthesiology Alumni Professorship.
- Dr. R. Stan Taylor III, to the J.B. Howell Professorship in Melanoma Education and Detection.
- Dr. Robert D. Timmerman, to the Effie Marie Cain Distinguished Chair in Cancer Therapy Research.
- Dr. Robert Toto, to the Mary M. Conroy Professorship in Kidney Disease.
- Dr. Madhukar Trivedi, to the Lydia Bryant Test Professorship in Psychiatric Research.
- Dr. Belinda Vicioso, to the Jose Garcia, M.D., Professorship in Internal Medicine.
- Dr. Jonathan White, to the Birsner Family Professorship in Neurological Surgery.
- Dr. Gil Wolfe, to the Dr. Bob & Jean Smith Foundation Distinguished Chair in Neuromuscular Disease Research.
- Dr. Thomas Zellers, to the Kathryne and Gene Bishop Distinguished Chair in Pediatric Care at Children's Medical Center, and to serve as the chief medical officer at Children's.

MAJOR GIFTS IN 2004-2005

Philanthropists continued to demonstrate their commitment to UT Southwestern in 2004-2005 by providing support for a variety of clinical, educational and research programs.

Major new pledges and gifts received in the 2004-2005 fiscal year included:

- $50,000,000 from Annette and Harold C. Simmons, for the acceleration of research and promotion of exceptional clinical care and service in the Harold C. Simmons Comprehensive Cancer Center, plus an additional $500,000 in September 2005, to endow a chair in memory of Dr. Charles C. Sprague.
- $5,000,000 from an anonymous couple, to establish and endow a new program for creating outreach medical programs in underserved areas of Dallas.
- $4,300,000 from the Perot Foundation, for ongoing annual support of research programs and for the Medical Scientist Training Program for M.D./Ph.D. students.
- $2,786,000 from Mary Dees McDermott Hicks, through a bequest in support of medical research.
- $2,500,000 from the Cain Foundation, in addition to an earlier pledge of $2.5 million, to establish and endow the Cain/Denius Comprehensive Center for Research on Mobility Disorders.
- $2,000,000 from Boone Pickens, in honor of Dr. Eugene Frenkel, to support UT Southwestern's *Innovations in Medicine* campaign.
- $2,000,000 from the Hoblitzelle Foundation, for priorities within UT Southwestern's *Innovations in Medicine* campaign earmarked for construction and equipment.
- $1,688,000 from the Jameson Family Trust and the estate of Maurice L. Jameson, in support of medical research.
- $1,500,000 from Nancy B. Hamon, as a challenge grant to establish and endow the George N. Peters, M.D., Center for Breast Surgery.
- $1,266,000 for UT Southwestern's Clinical Services Initiative and for research on neurological diseases, from Once Upon a Time ...
- $1,016,000 from proceeds of the 2005 Sweetheart Ball, for heart research.
- $1,000,000 from Children's Cancer Fund Inc., added to the Fund's earlier gift of $1 million plus contributions by other donors, to endow the Children's Cancer Fund Comprehensive Center for Pediatric Oncology Research.
- $1,000,000 from Dallas friends and admirers of Texas Speaker of the House Tom Craddick and his wife, Nadine, to establish and endow the Nadine and Tom Craddick Distinguished Chair in Medical Science.
- $1,000,000 from the Hillcrest Foundation, founded by Mrs. W.W. Caruth Sr., for equipment in the new Heart, Lung and Vascular Clinical Center at UT Southwestern University Hospital - St. Paul.
- $1,000,000 from an advise and consent fund of Communities Foundation of Texas, to establish and endow the Nancy and Ray L. Hunt Chair in Crisis Psychiatry and to provide start-up funds for the chair holder.
- $1,000,000 from Mary Kay Inc., to establish and endow the Mary Kay Distinguished Chair in Dermatology Research.
- $1,000,000 from the Eugene McDermott Foundation, to supplement earlier gifts for completing and furnishing the top floor of UT Southwestern's new Biomedical Research Tower.
- $1,000,000 from Norma and James C. Smith, to establish and endow the Jim and Norma Smith Distinguished Chair in Interventional Cardiology.
- $1,000,000 from Jimmy and Carl H. Westcott, to establish and endow the Jimmy Elizabeth Westcott Distinguished Chair in Pediatric Neurology.
- $959,000 from Gladys S. Gahagan, through a bequest in support of medical research.
- $850,000 from an anonymous foundation, for support of research on infectious diseases and for early-stage high-risk/high-gain research projects.
- $550,000 from Jean Ann and Stephen W. Brock, for support of medical research within UT Southwestern's *Innovations in Medicine* campaign.
- $514,000 from Ruth and Robert C. Womack, for support of medical research within UT Southwestern's *Innovations in Medicine* campaign.
- $506,000 from the Dr. Bob and Jean Smith Foundation, for support of stem cell research.

■ $500,000 from colleagues, former students, friends and admirers of Dr. Daniel Foster, for the establishment of the Daniel W. Foster, M.D., Distinguished Chair in Internal Medicine.

■ $500,000 from Susan and Lawrence Hirsch, toward the endowment of the Laurence and Susan Hirsch/Centex Distinguished Chair in Heart Disease.

■ $400,000 from Texas Stampede, in support of pediatric programs at UT Southwestern, which are allied with Children's Medical Center Dallas.

■ $400,000 from the Ted Nash Long Life Foundation of Waco, Texas, for support of novel research programs on human aging.

■ $360,000 from NCH Corporation, as an in-kind contribution of materials used in UT Southwestern's research and clinical programs.

■ $350,000 from Elaine D. Sammons, to provide further support for cancer research under the direction of Dr. Eugene P. Frenkel.

■ $319,000 from proceeds of the Muscular Dystrophy Association's ALS Evening of Hope, for research on Lou Gehrig's disease.

■ $310,000 from the Kent Waldrep National Paralysis Foundation, to support clinical research on spinal cord injury.

■ $252,000 from colleagues, former students, and family of Dr. Jack Pritchard, to upgrade the Jack A. Pritchard Professorship in Obstetrics and Gynecology to a Chair.

■ $250,000 from Ebby Halliday Acers, as part of St. Paul Medical Foundation's commitment to support the new Heart, Lung and Vascular Clinical Center at UT Southwestern University Hospital - St. Paul.

■ $250,000 from Wilhelmina and Edward M. Ackerman, for additional support of medical research.

■ $250,000 from Dr. Kenneth and Ruth Sharp Altshuler, in honor of Dr. Eric Nestler, to enhance clinical programs in UT Southwestern's psychiatry department.

■ $250,000 from the Gaston Episcopal Hospital Foundation, toward the establishment of an endowed chair in medical research.

■ $250,000 in additional support from Giant Tiger Stores Limited, for research on muscle metabolic diseases.

■ $250,000 from the Hegi Family Foundation, to support programs in medical ethics in honor of Dr. Daniel W. Foster, and for the Clinical Services Initiative.

■ $250,000 from Drs. Willis C. and Ann Matt Maddrey, to establish and endow a distinguished professorship in liver disease.

■ $250,000 from the McGee Foundation, the Kenton McGee and Robert Lavie families, and Communities Foundation of Texas, to upgrade the McGee Foundation Professorship in Arthritis Research to a Chair.

■ $250,000 for stem cell research, from the proceeds of a benefit concert organized by Annie and Willie Nelson and his band, along with the Los Lonely Boys, all of whom donated their services.

■ $250,000 from David W. and Stephanie A. Quinn, for clinical enhancement at UT Southwestern University Hospitals, through the establishment of the John D. McConnell, M.D., Hospital Fund.

■ $250,000 from Laura and Jack Roach, to increase the endowment for the E.E. Fogelson and Greer Garson Fogelson Distinguished Chair in Urology, to help endow a new chair in radiation oncology in honor of David Pistenmaa, M.D., Ph.D., and to support UT Southwestern's clinical services.

■ $250,000 from the Thomas C. and Carolyn W. Walker Family Foundation, to help establish and endow the George N. Peters, M.D., Center for Breast Surgery.

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

■ An anonymous couple, for cancer research, in honor of Drs. Hak Choy, Michael DiMaio, Jonathan Dowell and David Pistenmaa.

■ An anonymous foundation, to support scholarships in memory of Frances B. Conroy.

■ An anonymous individual, to establish and endow the Judy Sinclair Radman Neuro-Oncology Research Fund.

■ Alzheimer's Association, for research on new therapies and diagnostic procedures.

■ Mary Kay Ash Charitable Foundation, for dermatology research.

■ Emy Lou and Jerald T. Baldridge, to establish and endow a professorship in internal medicine and preventative care.

■ Harry W. Bass, Jr. Foundation, to establish and endow a professorship in pediatric education.

■ Joan and George S. Bayoud Sr., M.D., to establish and endow a fund to support programs in general surgery.

■ Horace C. Cabe Foundation, for research in amyotrophic lateral sclerosis.

■ Amon G. Carter Foundation, for research on ovarian cancer.

■ Rita C. and William P. Clements Jr., for the *Innovations in Medicine* campaign.

■ Frances B. Conroy Living Trust, to endow a professorship and support research on kidney disease.

■ Lou Ann and Michael Corboy, through the St. Paul Medical Foundation, for the Heart, Lung and Vascular Clinical Center at UT Southwestern University Hospital - St. Paul.

■ David M. Crowley Foundation, for ophthalmologic research.

■ Alice M. Cunningham, through a bequest for medical research.

■ Dallas Eye Ball 2005 and Prevent Blindness Texas, to support ophthalmologic research.

■ Peggy and Wayne E. Dear, M.D., to establish a professorship and support research on macular degeneration.

■ UT Southwestern friends and admirers of Carolyn Bacon Dickson, to create the Carolyn R. Bacon Professorship in Medical Science and Education.

■ Friends and admirers of Carla Francis, to create the Carla Cocke Francis Professorship in Alzheimer's Research.

■ Jane and Mark D. Gibson, to establish and endow a professorship in cancer research.

■ Irma and Irwin J. Grossman, in support of diabetes research.

■ Nancy and James M. Hoak Jr., for medical research and to advance UT Southwestern's Clinical Services Initiative.

■ J.B. Howell, M.D., through a bequest for a professorship in mela - noma education.

■ M.R. and Evelyn Hudson Foundation, for radiology education and medical research.

■ Sydney and J.L. Huffines Jr., in honor of Dr. Gary Reed, for the Clinical Services Initiative.

■ Kathryn H. Jordan, for research on neuro-degenerative diseases.

■ Dorothy Faye Holt Kimsey, in honor of Dr. Barbara Haley, for cancer programs.

■ Lone Star Paralysis Foundation, to endow a fund for clinical research on spinal cord injury.

■ Gillson Longenbaugh Foundation, for biomedical research.

■ Lowe Foundation/Mary Ralph Lowe, to help endow the George N. Peters, M.D., Center for Breast Surgery.

■ Colleagues, former students, patients and admirers of Dr. John R. Lynn, to create the John R. Lynn, M.D., Lectureship in Ophthalmology.

■ Diana and S. Todd Maclin, to establish and endow a professorship in medical science.

■ Nasher Foundation, in honor of Dr. Eugene Frenkel, for cancer research.

■ Mary Nell Plumhoff, through a bequest to support Alzheimer's disease research.

■ Lillian and Thomas B. Rhodes Sr., to establish and endow a professorship in stem cell research.

■ Duke Rudman Personal Trust, in memory of Josephine D. Rudman, for Alzheimer's disease research.

■ C.B. Sacher Memorial Medical Library Foundation, to endow a fund for library support in honor of C.B. Sacher.

■ Hortense L. Sanger, to establish an endowed professorship, through a bequest and charitable remainder trust.

■ Diana and Richard C. Strauss, for the Clinical Services Initiative and medical research.

■ Former students, colleagues, and admirers of Dr. Wayne Streilein, to establish the J. Wayne Streilein, M.D., Professorship in Immunology.

■ Friends of Texas Ballet Theater, to support the *Innovations in Medicine* campaign.

■ Sands A. Tsai, M.D., and Michael B. Yuen, for scholarship support through the Yuen-Tsai Family Endowment Fund.

■ Viragh Family Foundation, to support multiple sclerosis research.

■ Jean and J. Thomas Walter, to help endow the George N. Peters, M.D., Center for Breast Surgery.

IN MEMORIAM

Dr. Charles Sprague, UT Southwestern's first president, remembered for visionary leadership

Dr. Charles Cameron Sprague, the first president of UT Southwestern Medical Center at Dallas and a visionary leader who initiated the medical center's rapid growth, died on Sept. 17 in Dallas, at the age of 88.

Dr. Sprague, whom friends described as an outstanding physician and teacher possessing unique qualities of leadership and personal warmth, guided Southwestern Medical School and UT Southwestern for nearly 19 years. Upon his retirement in 1986, he was named president emeritus of the medical center and joined Southwestern Medical Foundation, becoming chairman of the board and chief executive officer in 1988. In 1995 he was named chairman emeritus of the foundation.

Gregarious, with a booming baritone voice and an engaging smile, Dr. Sprague joined UT Southwestern as its top administrator, dean of Southwestern Medical School, in 1967. Five years later, upon the school's reorganization as a comprehensive academic medical center with three distinct schools (medical, graduate biomedical sciences and allied health sciences), the Dallas native became the institution's first president.

Under Dr. Sprague's leadership, UT Southwestern added $80 million in new building projects. Southwestern Medical School grew from a regional facility into a nationally renowned medical complex. The medical center began receiving international recognition for its strong research accomplishments and assemblage of awarding-winning faculty members.

"UT Southwestern and Dallas were extraordinarily fortunate that Charlie Sprague agreed to become the medical school's leader in 1967," said Dr. Kern Wildenthal, who served as dean under Dr. Sprague and was his successor as president of the medical center. "He had an instinctive vision of what was required to move the institution to greatness and an ability to persuade everyone he dealt with of the importance and value of his goals. He was the classic example of the right man for the right job at the right time.

"Dr. Sprague's integrity and trustworthiness were absolute. He inspired and enriched the lives of all of us who had the privilege of working with him and learning from him."