# SOUTHWESTERN MEDICINE

## *at the* PEAK *of* DISCOVERY

ALSO INSIDE: PEDIATRIC DEPRESSION ^ WEIGHING THE FAT FACTS ^ MICROBIOLOGY ^ RADIATION ONCOLOGY

THE MAGAZINE OF THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER

# C O N T E N T S



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university clinics

university hospitals

patient care

UT Southwestern Medical Center

Combining medical forces to create **one powerful institution** makes UT Southwestern Medical Center – a **top-tier** academic medical center –

# a nucleus for care

A pivotal moment in the history of The University of Texas Southwestern Medical Center at Dallas arrived with the 2005 New Year when Zale Lipshy and St. Paul University Hospitals consolidated under the banner and ownership of UT Southwestern. > It's an investment whose return will begin immediately, medical center administrators say, securing UT Southwestern's place among the nation's top-tier academic medical centers – like Johns Hopkins, Duke and the University of California, Los Angeles – all of which operate their own hospitals. > "This is a critical step in becoming a national and international medical destination for people seeking top-quality, specialized care," said Dr. Kern Wildenthal, UT Southwestern president. "It allows us to deliver seamless care and service to all our patients by directly supervising their medical experience whether they are in our outpatient clinics or hospitals."

By Michael Blackman

"We intend to achieve national prominence in clinical medicine. We want it to be recognized. We want to be as renowned for our patient care as we are for our research and education."

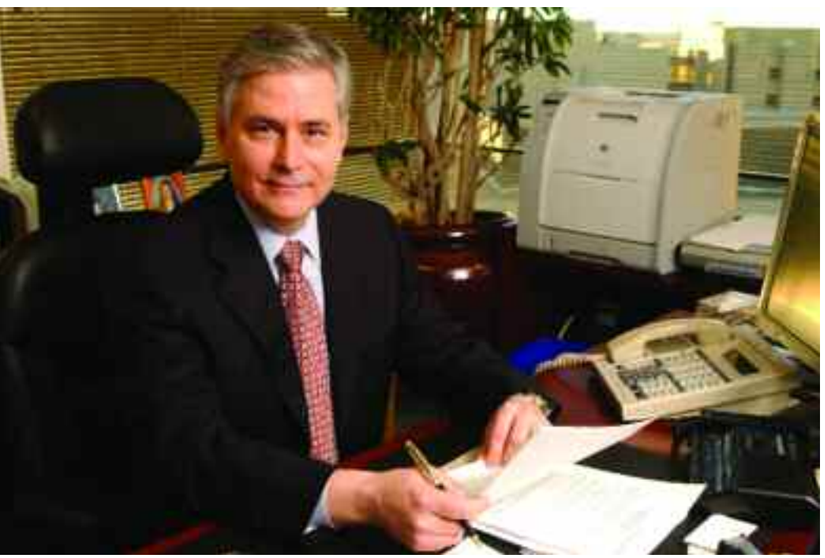
JOHN MCCONNELL, M.D.

**Dr. John McConnell,** executive vice president for health system affairs and chief executive officer of the health system including the university hospitals, said, "We intend to achieve national prominence in clinical medicine. Our clinical care is as good as you'll find, but it's not as comprehensive in all areas as it could be. We want it to be recognized. We want to be as renowned for our patient care as we are for our research and education. We want to be thought of like a Mayo Clinic or Johns Hopkins Hospital in the quality of our inpatient and outpatient care."

"I think this is as important in the history of the medical center as when we opened Zale Lipshy in 1989," said Paul Bass, chairman of Southwestern Medical Foundation and former chair of the Zale Lipshy board. "Before then, we were the only medical school in the country without our own private referral hospital.

"This merger will enhance the entire North Texas area – in patient care, medical education and research. Physicians will be able to deliver the best care and provide access to the most advanced clinical trials and innovations because the center will basically be one operation."

Improved quality of clinical care will lead to an overall strengthening of UT Southwestern, administrators say. Education, research and patient care all work together, complementing one another.



Developing renowned clinical care, for example, will help in recruiting top physician scientists, obtaining federal and private foundation grants, and broadening the scope of clinical trials.

"UT Southwestern has entered the hospital arena with both feet," said John Gavras, president of the Dallas-Fort Worth Hospital Council, a nonprofit trade association of regional hospitals. "This can be good. We're very fortunate to have the medical school; they do a great job. I think this consolidation can be a great asset."

Dr. McConnell said he believes the school's early operational moves already are providing positive results. Those moves included consolidating the hospitals' information-technology systems, which saved $1.8 million, as well as streamlining other services and the work force at the two hospitals.

Perhaps most important, he said, he has full confidence in the leadership UT Southwestern has put in place to run the new hospital entity, which will operate under the name UT Southwestern Medical Center.

"We have a great management team," Dr. McConnell said. "If you want to be world-class, you have to have world-class management. We spent a lot of time recruiting the individuals in place, who came from some of the leading health-care institutions in America."

Sharon Riley was recently hired as UT Southwestern's vice president for hospital operations and CEO, University Hospitals. She was formerly chief operating officer of Anne Arundel Medical Center in Annapolis, Md., and before that was chief operating officer of the University of Nebraska Medical Center and vice president of Nebraska Health System.

Ms. Riley, speaking of what attracted her to UT Southwestern, refers to the prominence of the medical school and its renowned teaching, research and clinical expertise.

"When the same visionaries say they want to build a world-class hospital, I want to be a part of it," she said. "I want to help build a hospital environment where the medical staff can practice their world-class skills – to bring their advances and discoveries into the inpatient setting.

"When that happens, the patients, the community and the state all benefit."

The decision to consolidate involved a long and thoughtful process.

In the beginning, there was the Clinical Services Initiative. It was the catalyst. It is UT Southwestern's $100 million investment to make the center's patient-centered service a model for American medicine.

In 2002, as part of that initiative, UT Southwestern faculty leadership, hospital boards and community supporters "encouraged the school to study and investigate what would be required to bring UT Southwestern's patient service programs up to the highest standard," Dr. McConnell said.

That suggestion led to groups of UT Southwestern officials visiting leading academic medical centers around the country in summer 2002, including Duke University Medical Center, Northwestern University, Johns Hopkins, Massachusetts General Hospital and Stanford University Medical Center. In addition, they did a detailed study of a consultant's report on Mayo Clinic. From those investigations, Dr. McConnell said, "a white paper was developed that really outlined a series of initiatives that would close the gap, to achieve that same overall quality and service at UT Southwestern.

"What we found was that we are structured much differently than other nationally leading medical centers. They were much more integrated in their inpatient-outpatient operations, under consolidated management."

That's when UT Southwestern leaders began thinking in earnest about a consolidation of all clinical services under UT Southwestern. The school utilized Zale Lipshy and owned St. Paul's buildings, but because of corporate and legal strictures UT Southwestern could not combine their operations or merge them with the school's outpatient clinics, which only served to hamper financial flexibility and inhibit the services of each entity.

The 152-bed Zale Lipshy opened in 1989 as a private referral and teaching hospital for UT Southwestern. The school purchased the 300-bed St. Paul in 2000. Both were operating under the nonprofit holding company University Medical Center (UMC) Inc. before their transfer to UT Southwestern at the beginning of 2005.

"We were landlocked at Zale Lipshy," said David Quinn, UMC's chairman of the board. "We knew if we were to develop new facilities we had to look to the St. Paul campus."

"I want to help build a hospital environment where the medical staff can practice their world-class skills – to bring their advances and discoveries into the inpatient setting. When that happens, the patients, the community and the state all benefit."

SHARON RILEY

The idea of integrating the hospitals into UT Southwestern was given impetus by recommendations of two independent parties – the external advisory committee for UT Southwestern's Clinical Services Initiative and the Hunter Group hospital consultants.

Both parties said the same thing: Merge the hospitals; make them a part of a larger system including UT Southwestern's outpatient services.

"I would say that both recommendations helped crystallize our thinking," Dr. McConnell said.

The first of those recommendations, from the school's external advisory committee, particularly resonated with UT Southwestern officials and community supporters, Dr. McConnell said. Dr. Eugene Braunwald, Hershey Distinguished Professor of Medicine at Harvard Medical School and faculty dean for academic programs, chairs this committee.

*Continued on page 40*

*Continued from page 5*


"I think hearing the views of Eugene Braunwald, who is one of the most respected academic physicians in America and a guardian of the academic enterprise – hearing this from him and his team – that was a pivotal, watershed moment," Dr. McConnell said.

Then another crystallizing realization: Operating two separate, small hospitals in today's medical marketplace is detrimental to the bottom line, administrators said. The hospitals together lost several million dollars in 2002 and 2003 while being operated as separate private entities. Under UT Southwestern's management, the hospitals improved their financial performance dramatically in 2004 and are projected to break even after the consolidation in 2005.

In August 2004, the UT System Board of Regents approved the acquisition and consolidation of the hospitals, which would bring 2,132 new employees into the official UT Southwestern family.

Mr. Quinn extols the benefits: "the tremendous economies involved, the opportunity to bring together shared talent, elimination of redundancies, a stronger position to improve managed-care contracts and access to capital."

More importantly, he said, for the patient, "UT Southwestern can now be the provider of one-stop, seamless care delivery."

Said Dr. McConnell: "From day one in 2005 it allows us to begin developing strategic plans for each of our major patient-care service lines that take advantage of an integrated structure. To have an environment where hospitals and physicians can do joint planning is the key to success."

In addition, he said, consolidation will help eliminate patient confusion and marketing obstacles brought on by a lack of brand identity. "This is one of the things that has really inhibited our local, regional and national reputation. People were always confused about who we really are."

Over the years, he said, both hospitals enjoyed a reputation for exemplary patient care in selected areas despite their relatively small size. But their connection to UT Southwestern was often blurred if not obscured for lack of a clear and consistent identity.

The benefit of merged clinical operations also extends readily to recruiting key talent, which only strengthens UT Southwestern's clinical programs, said Dr. McConnell.

"A good example is the recent recruitment of the new director of the Harold C. Simmons Comprehensive Cancer Center, Dr. James Willson," he said. "He is one of the top oncologists in the country. With the consolidation, he'll have a better platform for the cancer center's patients and an opportunity to develop the Simmons program into a National Cancer Institute-designated center." Dr. Willson is the former director of the National Cancer Institute-designated Case Comprehensive Cancer Center in Cleveland and a pioneer in colon and rectal cancer research and treatment. He joined UT Southwestern in September 2004.

> "The tremendous economies involved, the opportunity to bring together shared talent, elimination of redundancies, a stronger position to improve managed-care contracts, and access to capital. UT Southwestern can now be the provider of one-stop, seamless care delivery."
>
> DAVID QUINN

His top priority in Dallas is to win Comprehensive Cancer Center designation from the NCI, its highest level of recognition. Dr. McConnell said achieving that recognition could not be done without consolidation of clinical services to provide a sufficient volume of patients with cancer in all stages.

Many players contributed visionary roles in the consolidation of clinical services at UT Southwestern, and many decisions were made over the past two years that proved crucial to the eventual merger.

Messrs. Bass and Quinn believe one such decision came in December 2002 when Dr. Wildenthal appointed Dr. McConnell to assume management responsibility for the two hospitals. Both men are generous with praise for the 51-year-old Dr. McConnell, the former chairman of urology. A Kansas native who came to UT Southwestern as an intern in 1978, Dr. McConnell joined the school's administrative team in the late 1990s.

"When Dr. McConnell became operationally involved in hospital management, he recognized the need for a more seamless program," Mr. Bass said. Mr. Quinn referred to Dr. McConnell's appointment to hospital leadership as "a turning point."

Dr. McConnell, with characteristic Midwest reserve, deflects attention.

"It was," he said, "probably less that they were convinced that I knew anything about running hospitals than it was they trusted I would get the people in there to do it."

Dr. McConnell, who is proud of balancing his career as a physician, an academic and researcher, says of his last two years: "I've probably never learned so much in such a short period of time, since my time as a first-year research fellow, and it has been an incredible experience."

As UT Southwestern continues to recruit top talent, strengthen clinical programs and provide the best patient care possible, these achievements will build on each other, suggests Dr. McConnell, and UT Southwestern will march steadily toward yet another pivotal moment in its history: national prominence in clinical medicine. ❄

BIOMEDICAL RESEARCH TOWER

# *at the* PEAK *of* DISCOVERY

## 14 FLOORS *of* SCIENTIFIC PARADISE

"RESEARCH IS FORMALIZED CURIOSITY. IT IS POKING AND PRYING WITH A PURPOSE. IT IS A SEEKING THAT HE WHO WISHES MAY KNOW THE COSMIC SECRETS OF THE WORLD AND THEY THAT DWELL THEREIN."

— Zora Neale Hurston, *Dust Tracks on a Road* (1942)

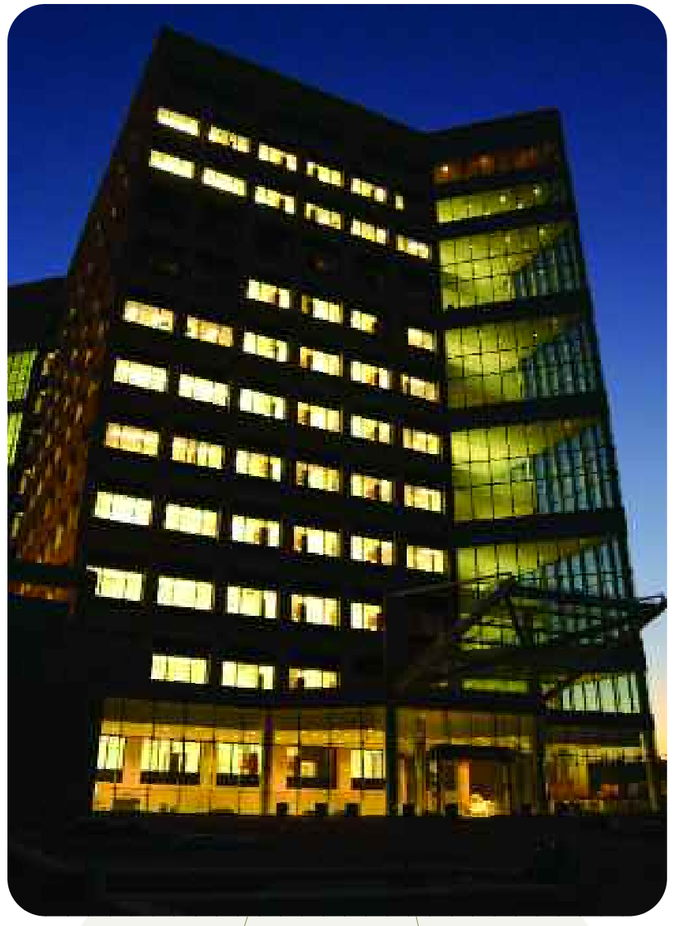
Scientists who poke at cells and pry secrets from the human genome have found a new home in the largest research building ever built at a Texas university.

Imagination, innovation and interaction fill the halls, offices and labs within the most recent addition to The University of Texas Southwestern Medical Center at Dallas skyline. Located on the burgeoning North Campus near three sister research buildings, the new medical research tower was built with the 21st-century investigator in mind. Between a three-story parking garage at its base and a conference and dining facility on its 14th floor are a massive complex of carefully planned laboratories and offices to provide an environment for inquisitive minds to pursue discovery across multiple scientific fields.

*By Amanda Siegfried*

# OCCUPYING THE NEW SPACE

are researchers from the departments of Neurology, Pharmacology, Biochemistry and Physiology; hematologists, oncologists and cardiologists from the department of Internal Medicine; and members of the Harold C. Simmons Comprehensive Cancer Center, the Center for Developmental Biology, the Alliance for Cellular Signaling, the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational and Systems Biology, and the Howard Hughes Medical Institute (HHMI).



"This new facility does a number of things," said Dr. James Stull, chairman of physiology, whose 19 faculty members will occupy nearly all of the 12th and 13th floors. "It provides new laboratory space custom-designed for modern research. It enables everyone in our department to be together, yet the layout also provides for close contact with collaborators in other departments.

The space in the new Biomedical Research Tower, whose views toward the south take in the Dallas skyline, also provides benefits for some researchers who may never reside in it. Those relocating to the new tower leave behind much-needed room for the expansion of several clinical departments on the South Campus. The Department of Pediatrics, for example, will expand into floors of the Philip R. Jonsson Basic Science Research Building and the Harry S. Moss Clinical Science Building that adjoins its current space. Internal medicine receives more than 40,000 square feet of contiguous new expansion space.

> THIS *building is* DIFFERENT, *said* Dr. James Griffin, chairman of the building committee. The designers have incorporated an open laboratory concept, featuring long uninterrupted series of benches with offices on each end for faculty.



# "THE CAMPUS

is growing," said Dr. Alfred Gilman, interim dean of Southwestern Medical School and chairman of pharmacology. "Basic science and clinical departments have the opportunity to expand their operations and recruit bright young people to do both laboratory and clinically oriented research. That's a big plus."

The new research tower is part of UT Southwestern's long-range building plan, which will ultimately include nine interconnected research buildings on the North Campus.

The $200 million tower is being funded from a combination of state, federal and philanthropic sources. Included in the total is $20 million from HHMI, which supports a number of the faculty who are moving into the facility.

A select committee of UT Southwestern researchers provided input on the design of the laboratories, with valuable assistance from HHMI, which has considerable experience in planning state-of-the-art research labs. Together they mapped out an optimal arrangement of lab and support areas for the 30,000 square feet of space on each floor.

Dynamic research calls for changing technologies, so flexibility and adaptability reign in the new space. Laboratory areas can be moved and reassigned without major reconstruction, and additional floor space can be made available for changing equipment and personnel needs.

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>
> — *Dr. James Stull*

"THIS BUILDING IS DIFFERENT from our previous buildings, which have a large number of smaller, individual labs," said Dr. James Griffin, associate dean for academic planning and chairman of the building committee.

"In the new space, designers incorporated an open laboratory concept, featuring long uninterrupted series of benches with offices on each end for faculty."

## RESEARCH GROUNDED IN INFORMATION

The second floor of the Biomedical Research Tower will be home to the new North Campus Library and Information Center, including a computer commons with space for 30 workstations and access to the full complement of electronic resources of the South Campus' Fred F. Florence Bioinformation Center.

Also on the second floor, and part of the third floor, are additional offices and research space for the Simmons Comprehensive Cancer Center.

"The opportunity to expand to the Biomedical Research Tower is very exciting," said Dr. James Willson, who joined UT Southwestern as director of the center in September 2004. He is also the associate dean for oncology at UT Southwestern and holder of the Lisa K. Simmons Distinguished Chair in Comprehensive Oncology.

The physician-scientists affiliated with the cancer center span multiple disciplines, promoting new initiatives in cancer investigation and coordinating cancer patient care at UT Southwestern and its affiliated hospitals and clinics. Researchers specializing in many fields – biochemistry, cancer genetics, epidemiology, physiology, pharmacology, surgery – work in tandem to deliver bench-to-bedside innovations in cancer prevention, diagnosis and treatment. Such integration of basic science and clinical activities facilitates "translational research," the crossover from laboratory discoveries to state-of-the-art clinical medicine.

"SHARING *the* THIRD FLOOR with internal medicine *will allow us* to integrate with its medical-oncology components ... allowing for the vital 'cross talk' that cancer centers aspire to achieve."

— *Dr. James Willson*

Faculty members from internal medicine's division of hematology/oncology also are to be among the third-floor tenants. In addition, contiguous space with the cancer center clinic area on the adjacent floor of the Seay Biomedical Building will enhance translational research programs at the center.

"Sharing the third floor with internal medicine will allow us to integrate with its medical-oncology components," said Dr. Willson. "Programs in developmental biology, pharmacology and structural biology also are in proximity, allowing for the vital 'cross talk' that cancer centers aspire to achieve."

## THE FOURTH FLOOR

will house faculty members from the expanding Department of Neurology, including Dr. Stephen Cannon, chairman and holder of the Linda and Mitch Hart Distinguished Chair in Neurology.

Dr. Cannon's investigations are directed toward understanding how defects in the electrical activity within nerve cells can lead to human disease. His research focuses on ion channels, which form pores in a cell's membrane to allow electrical current to pass in and out of the cell. Mutations of ion channel genes are responsible for several inherited diseases, such as episodic paralysis, migraine, fatal cardiac arrhythmias and some forms of epilepsy.

UT Southwestern researchers to occupy this floor are tackling some of the most devastating neurological and neurodegenerative disorders. They are studying mutations in the gene *SOD1*, which are the only proven cause of amyotrophic lateral sclerosis, or Lou Gehrig's disease. Others are investigating possible ways to improve recovery after stroke or traumatic brain injury.

DR. *Stephen Cannon's* INVESTIGATIONS are directed toward understanding how defects in the electrical activity within nerve cells can lead to human disease.

## ELBOW ROOM

The Center for Developmental Biology will expand across buildings, into the fifth floor of the Biomedical Research Tower from its home on the adjacent floor of the Simmons Biomedical Research Building. Dr. Luis Parada, director of the center and holder of the Diana K. and Richard C. Strauss Distinguished Chair in Developmental Biology and the Southwestern Ball Distinguished Chair in Nerve Regeneration Research, said the new space will allow elbow room for a number of new recruits. Although the overarching theme of the center's research is developmental biology, there is a new emphasis on two areas of high interest for which there are new initiatives on campus – stem-cell and cancer biology. Dr. Parada also directs the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration.

DR. *Luis Parada said the* NEW SPACE will allow elbow room for a number of new recruits.

## THE NEW SPACE

and proximity to researchers in the Simmons Comprehensive Cancer Center affords an opportunity for Dr. Parada's group to link cancer and developmental biology studies in exciting, new multidisciplinary ways. Core facilities on the fifth floor will provide specialized equipment that will be a focal point for stem-cell researchers across campus.

Investigators are pursuing work on human adult stem cells, which normally differentiate into specific tissue types. When there's a mix-up in the chemical signals that tell a stem cell how to become a nerve cell, for example, those cells can become tumorous.

> "DRUG DISCOVERY *will* become both faster and less expensive. But first, we need a model of the cell's signaling network."
>
> — *Dr. Alfred Gilman*

Dr. Michael Kyba, an assistant professor in the center and the Virginia Murchison Linthicum Scholar in Medical Research, is one of the first new center recruits on the fifth floor of the building. Dr. Kyba's research explores the basic biology of stem cells and aims at understanding the regulatory circuits that determine what type of cell stem cells are destined to become, as well as their therapeutic potential.

Studies of the intricate life of cells and the methods cells use to communicate continue to play out one floor above, on six. Here will be the new home of the Dallas-based Alliance for Cellular Signaling, an international consortium of researchers who pool their efforts to study how cells interact with, or signal, each other. The Alliance, directed by Dr. Gilman, includes several UT Southwestern researchers and core support facilities.

One of the long-term goals of the Alliance is to acquire precise knowledge about how the molecules and structures within a cell interact to permit efficient communication among cells. Alliance scientists are seeking enough information to develop a quantitative computer model of cellular signaling. Armed with the investigative power of such a "virtual cell," scientists will be able to obtain new types of information on therapies, diseases and drugs.

"Drug discovery will become both faster and less expensive," Dr. Gilman said. "But first, we need a model of the cell's signaling network."

## OCCUPYING THE

seventh floor and part of the eighth and ninth will be the Department of Pharmacology, also led by Dr. Gilman, who won the Nobel Prize in physiology or medicine in 1994 for his discovery of G proteins, research that has fostered a more complete understanding of how cells receive signals and respond to them. He holds the Nadine and Tom Craddick Distinguished Chair in Medical Science; the Raymond Willie and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, in Honor of Harold B. Crasilneck, Ph.D.; and the Atticus James Gill, M.D., Chair in Medical Science.

## *A* TOUR *of* SCIENTIFIC PARADISE

FLOOR

14 *Conference Rooms and Dining*

13 *Physiology*

12 *Physiology & Cardiology*

11 *Green Center for Reproductive Biology Sciences & Howard Hughes Medical Institute*

10 *Biochemistry (Structural Biology) & Howard Hughes Medical Institute*

9 *Green Comprehensive Center for Molecular, Computational and Systems Biology (Structural Biology) & Howard Hughes Medical Institute*

8 *Biochemistry (Structural Biology) & Pharmacology*

7 *Pharmacology*

6 *Alliance for Cellular Signaling & Microarray Core & Protein Technology Center*

5 *Center for Developmental Biology*

4 *Neurology*

3 *Simmons Comprehensive Cancer Center & Hematology/Oncology*

2 *North Campus Library & Simmons Comprehensive Cancer Center*

1 *Parking*

DR. GILMAN also directs the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational and Systems Biology, established in 2003, which is devoted to linking basic research on molecules and cells with analysis of how entire biological systems function, both in health and in sickness.

The Green Comprehensive Center's division of systems biology is to be located on the ninth floor and is directed by Dr. Rama Ranganathan, associate professor of pharmacology and an HHMI investigator. Systems biology researchers aim to understand how all the "parts" of cells – genes, proteins and many other molecules – work together to create complex living organisms.

ANOTHER *Nobel laureate,* DR. JOHANN DEISENHOFER, *and a* number of other structural biologists *from the* Department of Biochemistry will share the eighth floor with pharmacology and will also be located on the 10th floor.

Pharmacology researchers are engaged in a wide variety of projects, concentrating primarily on molecular processes and how drugs can alter them in a variety of diseases.

For example, Dr. David Mangelsdorf, professor of pharmacology and biochemistry, holder of the Doris and Bryan Wildenthal Distinguished Chair in Medical Science and an HHMI investigator, is studying proteins called receptors that are found on a cell's nucleus. One group of such proteins serves as sensors in protecting human cells against unusually high and possibly toxic levels of lipids, such as cholesterol and fatty acid. Dr. Mangelsdorf's analysis of these proteins has uncovered clues to the connection between high-fat diets and increased colon-cancer risk, suggesting possible avenues for new drug development against the third most-common type of cancer.

Another Nobel laureate, Dr. Johann Deisenhofer, and a number of other structural biologists from the Department of Biochemistry will share the eighth floor with pharmacology and will also be located on the 10th floor. All UT Southwestern structural biologists, regardless of departmental affiliation, will be together in the new building.



STRUCTURAL biologists use techniques like nuclear magnetic resonance and X-ray crystallography to study the structure and function of proteins. Such information is key to understanding how they work and can lead to better drugs and treatments for disease.

Dr. Deisenhofer, an HHMI investigator, won the 1988 Nobel Prize in chemistry for using X-ray crystallography to reveal the three-dimensional structure of an important protein found in the membrane of cells. He is a professor of biochemistry and holder of the Virginia and Edward Linthicum Distinguished Chair in Biomolecular Science.

The 11th floor is to house the Cecil H. and Ida Green Center for Reproductive Biology Sciences, directed by Dr. David Garbers, an HHMI investigator and holder of the Cecil H. and Ida Green Distinguished Chair in Reproductive Biology Sciences.

Green Center researchers are working to uncover the intricacies of sperm maturation, fertilization, egg reprogramming and stem-cell biology – knowledge that may lead to new approaches for treating infertility, the development of contraceptives, and replacing lost cells or damaged tissues.

"Our new space is more effectively designed, and the connected lab space certainly will promote the exchange of ideas between different laboratories," Dr. Garbers said. "We're also an integral part of a stem-cell initiative that includes the Department of Molecular Biology and the Center for Developmental Biology. This move puts us in close proximity to those groups and will enhance the joint recruitment of faculty in the stem-cell area."

The 12th and 13th floors will be occupied by the Department of Physiology, where one of the newest faculty members is Dr. Youxing Jiang, an assistant professor and the W.W. Caruth Jr. Scholar in Biomedical Research. He's another structural biologist who will benefit from proximity to researchers from other departments.

Dr. Jiang focuses on the biochemistry of membrane proteins and electrophysiology. Like Dr. Cannon in neurology, his specialty is ion channels found in membranes, particularly voltage-dependent potassium channels. These tiny pores are crucial for the generation of electrical impulses in nerve and muscle cells, and their functions underlie all movement, sensation and thought. His work provides crucial insight into understanding how these channels work to excite nerve and muscle cells, studies that are vital elements in the fight against neuromuscular diseases.

*Continued on page 41*

"OUR NEW SPACE *is* more effectively designed, *and the* connected lab space certainly will promote the exchange of ideas between different laboratories."

— *Dr. David Garbers*

### At the Peak of Discovery

*Continued from page 15*

ROOM WITH A VIEW

FINALLY, ON the 14th floor, are a number of large and small conference rooms, a faculty dining area and space for special university functions.

The top floor provides an impressive vantage point from which faculty, staff, students and guests can take in a 360-degree panoramic view of downtown Dallas, the Trinity River and the medical center complex.

From such a place of quiet reflection, the view offers a humbling perspective on the scientific landscape of UT Southwestern, now enhanced by a major new addition to house the curious clinicians and laboratory scientists who poke and pry – and speed the delivery of biomedical discoveries to the world. ❋

## *A* NEW PLACE *for* CONTINUED LEARNING

NESTLED centrally between the new Biomedical Research Tower and the Simmons, Seay, Moncrief and Hamon Buildings is the new Medical Education Conference Center, a 200,000-square-foot facility designed to serve as the focus of the major educational programs on the North Campus.

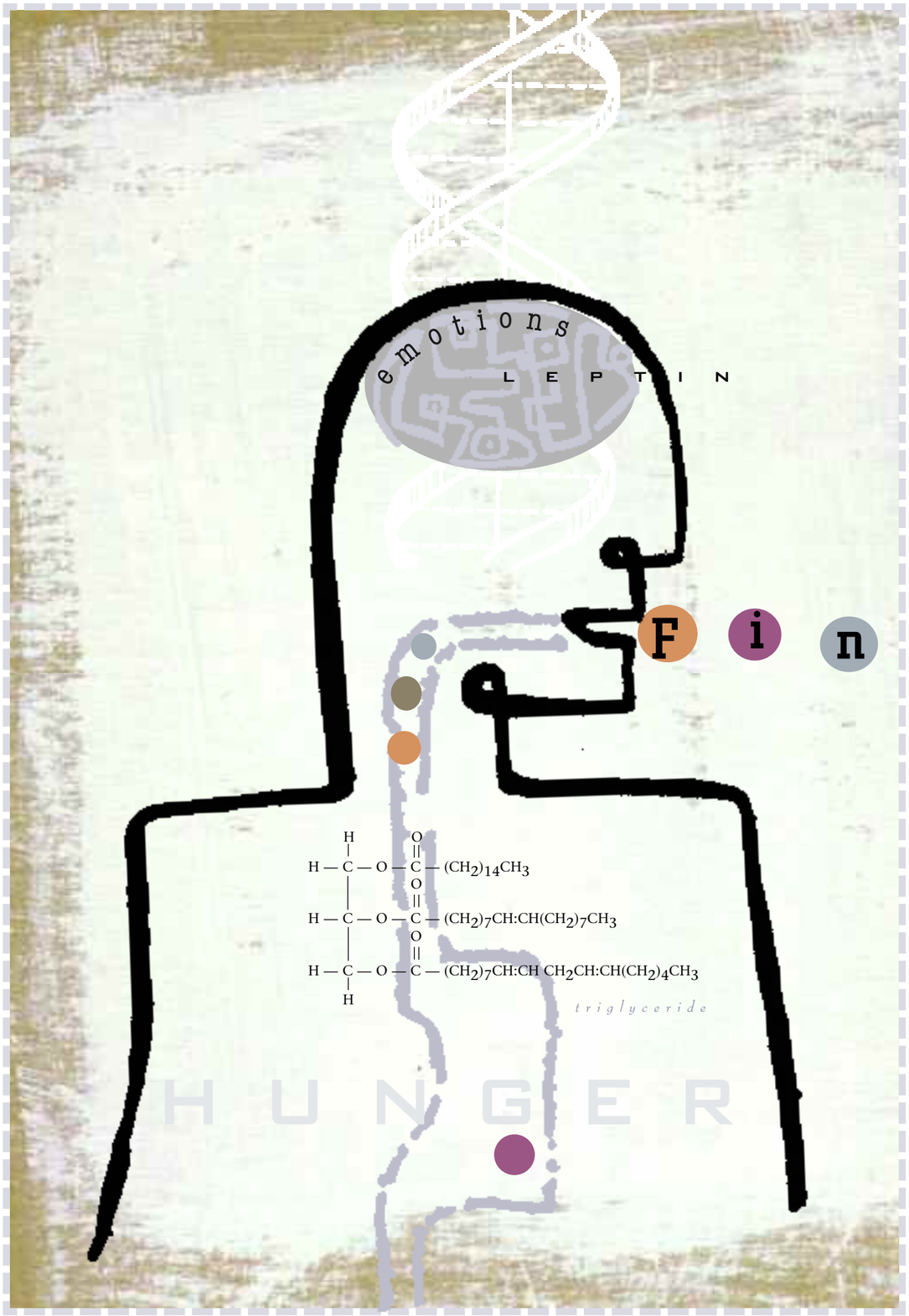
UT Southwestern's Office of Continuing Medical Education, which provides lifelong learning opportunities for health professionals, is a primary user of the facility. Underground parking, a large lecture hall and conference rooms for small-group sessions are included in the building.

The 170-seat Medical Lecture Hall and teaching areas in the center are scheduled for use throughout the day for student instruction, continuing medical education courses for physicians from around the country and for major public forums for Dallas citizens.

The teaching areas are equipped with the latest audiovisual, computer and Internet accessories, said Dr. Susan Cox, associate dean for professional education and professor of obstetrics and gynecology.

"We have held our programs as much as possible on the campus, but many times we've had to look off campus for venues due to limited parking and conference space here during the week," said Dr. Cox, holder of the Gillette Professorship in Obstetrics and Gynecology. "Those programs formerly held off-site are now able to come back to campus, thanks to this wonderful new facility."

The building also will be home to a university store and a food court similar to those found on the South Campus. Atop the facility are landscaped gardens and an open-air dining plaza. ❋




Is a raging global

epidemic in our genes?

Our biology?

Our body chemistry?

Our emotions?

# Finding the Fat Trigger

**The statistics are alarming.**

The National Institutes of Health reports that two-thirds of Americans are overweight. Even more staggering are the medical costs: Nearly $93 billion was spent in 2002 on obesity-related health care in the United States alone.

Americans, however, are not the only ones at risk. Throughout the world, the numbers of overweight and obese people are rising, both in developed and developing nations. Excessive fat has quickly become a global epidemic, and with it comes unprecedented numbers of people who are at risk for developing diabetes and heart disease.

"Around the globe, more people suffer from obesity than from starvation," said Dr. Jon Graff, assistant professor in the Center for Developmental Biology and of molecular biology. "Understanding and undoing obesity could help prevent an enormous amount of morbidity and mortality."

As a nation, we are armed with reams of information on how to lose weight, and we know that in general, diet and exercise play an important role. What we still do not know, however, are the specifics: how fat cells are made; how they are stored in the body; and how they are burned to make energy. With this kind of information, preventive measures could be established, stemming the tide of obesity and obesity-related illnesses.

Researchers at The University of Texas Southwestern Medical Center at Dallas are at the forefront of this battle, attacking the epidemic from many angles and asking important questions: Which molecules help us store fat? Which help us burn fat? And literally, with recent discoveries in the behavioral sciences, how are our brains working and what are we *thinking* when we eat?

By Megha Satyanarayana

**These researchers** are making breakthroughs that may change the course of medicine and science, uniting behavior and genetics in this most complex of diseases.

## How Fat Cells Accumulate

The process of fat-cell formation is called adipogenesis, and the cells that store fat are called adipocytes.

Fat formation is a multistep process. The early steps involve rapid division of a stem cell, followed by its conversion to an adipocyte, which is identified based on the presence of fat droplets.

At each of these steps, numerous changes occur in the cell, and gene expression changes dramatically. Studies have determined a few of the major molecules involved in this conversion, and the appearance and disappearance of these molecules allow researchers to track the different stages of fat-cell formation. In the complicated progression of fat development, however, these discoveries are just the tip of the iceberg. Most of our understanding of fat development is still a black box.

## The Hunt for "Fat" Genes

Dr. Graff is a geneticist on a mission. He is hunting for genes involved in the formation of fat cells. Using the microscopic worm *Caenorhabditis elegans*, and the common fruit fly, *Drosophila melanogaster*, his laboratory has uncovered more than 700 genes associated with fat development. Half of these genes have never been described before.

**"In trying to understand the creation of fat cells, our real goal is to help people get healthy and stay healthy."**

*— Dr. Jon Graff*

Simple organisms such as flies and worms offer multiple advantages for researchers in terms of lifespan, number of offspring, and recently, the complete sequencing of their genomes.

By observing tens of thousands of these organisms, researchers in the Graff lab have quickly identified several that have defects in fat formation. Some may have too little fat. Some may have too much. Where a defect is noted, a search is begun for the gene that is responsible.

Commonly, a gene from a worm or a fly has a relative in the mouse. So, the corresponding genes in mice are now being studied, using complex genetic engineering techniques.

One of these techniques, called gene knockout, allows researchers to study the function of a gene in a particular tissue. By knocking out genes only in fat, Dr. Graff can analyze precisely how that gene affects fat formation. These findings can then be translated to humans. By learning how fat develops in lower animals, Dr. Graff's research could lead to insights into human obesity and, potentially, new approaches to prevention.

"Our lab started out on a completely different mission, but I'm an endocrinologist by training, and obesity really caught my attention," said Dr. Graff. "Obesity dramatically increases the risk for such devastating illnesses as diabetes, some cancers, heart failure, arthritis and much more. In trying to understand the creation of fat cells, our real goal is to help people get healthy and stay healthy."

## The Link Between Genetics and Behavior

A decade ago, genetic studies of obese mice led to the discovery of a small molecule that mediated food intake. This molecule, leptin, is a hormone released by fat cells and is thought to indicate fullness, or satiety, in the brain.

At UT Southwestern, leptin has grabbed the attention of prominent researchers. From single cells to whole organisms, these researchers are delving into leptin and asking what it does to us physically and how it controls feeding behavior.

## Turning Fat-Storers Into Fat-Burners

"Fat cells were essential to the salvation of mammals because they allowed us to survive famine," said Dr. Roger Unger, director of the Touchstone Center for Diabetes Research and holder of the Touchstone/West Distinguished Chair in Diabetes Research. "By storing energy, humans can go long periods of time without eating. Nowadays, with plenty of food available and no famine, we eat more than we can burn and store the excess as excess fat."

**Recent work** in Dr. Unger's laboratory has focused on the role of leptin in fat storage and fat utilization. One experimental model is the Zucker diabetic fatty rat, an animal that cannot respond to leptin. Like its human counterparts, it eats uncontrollably and rapidly becomes obese, eventually developing type 2 diabetes (non-insulin dependent diabetes).

"It's like they're eating junk food three times a day," said Dr. Unger.

The Zucker diabetic fatty rat also has fat deposits in tissues where fat normally does not belong, like the liver, heart and pancreas. Fat in the liver is a hallmark of chronic diabetes, and fat in the heart can cause severe damage.

At the opposite end of the spectrum are normal rats that have been given large doses of leptin. Unlike the fatty rats, these normal animals respond very well to the hormone. What Dr. Unger observed was that the rats started eating less and rapidly began to lose weight. Large doses of leptin seemingly controlled their appetites.

They also found that the fat cells of mice treated with large doses of leptin had been transformed into an entirely different kind of cell. Cells that would have normally contained fat droplets now lacked them and instead contained large numbers of structures often found in cells that are high consumers of energy, like muscle. These fat cells, which normally release their stores for other tissues to burn, had reacted to large amounts of leptin by transforming into cells that could burn their own fat.

The transformation of fat-storage cells to fat-burning cells led Dr. Unger to an idea: One of the roles of leptin may be to signal tissues that should not be storing fat to burn it. As body fat increases, so do leptin levels. But once fat vanishes, so do the high levels of leptin. "Why?" he wondered.

Dr. Unger and his colleagues are currently testing the hypothesis that leptin may act as a watchdog, making sure that fat stays in fat cells, while keeping it out of tissues like the heart and liver. Uncovering how leptin controls where fat is deposited would have an enormous impact on understanding how obesity leads to diabetes.

## Leptin Receptors in the Brain

"In the same way that diabetics are insulin resistant, obese patients can become leptin resistant," said Dr. Cai Li, assistant professor of physiology and internal medicine. "We are studying the activity of the leptin receptor in order to learn how leptin works."

*Dr. Roger Unger*

Receptors are molecules that are commonly found on the surface of cells. When a specific molecule floats by a cell, it attaches to the receptor on the cell wall, like a boat docking in a harbor. The docking event often leads to signals being sent into the cell. These signals lead to a multitude of events inside the cell, including turning specific genes on or off. Under certain circumstances, the signals cause proteins to move from one place in the cell to another. When a receptor is missing there can be devastating outcomes, as in the Zucker diabetic fatty rat.

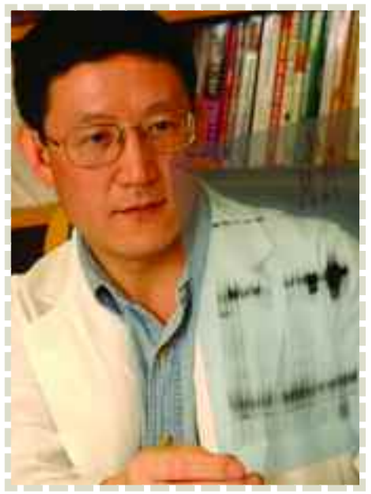
The leptin receptor is expressed in many cell types, including neurons in the brain. When leptin is released from fat cells and travels to the brain, it encounters its receptor on certain brain cells. What happens inside those cells after the initial encounter remains unclear.

Dr. Li and colleagues are testing three different paths that the signal from the leptin receptor can follow. In one of these paths, the signal given when leptin meets its receptor activates a molecule called SOCS3, which blocks the ability of the leptin receptor to function properly. This blocks future signals and eventually leads to hunger. Researchers believe this occurs when a person is eating normally.

*Continued on page 42*

**The transformation of fat-storage cells to fat-burning cells led Dr. Unger to an idea: One of the roles of leptin may be to signal tissues that should not be storing fat to burn it.**

*Continued from page 19*



**"Some studies have shown that leptin may actually affect the way the brain develops. Perhaps these early developmental changes play a role in how a person interacts with food throughout life."**

*— Dr. Cai Li*

They also suspect that leptin resistance may occur with increased eating. Constant eating leads to the creation of more leptin, which travels through the bloodstream to the brain. Large amounts of leptin soon have no place to dock. So the normal pathway that signals fullness becomes overloaded and shuts down.

Scientists have also found that mice missing a protein called STAT3 in the pancreas and in the brain become obese, much like the fatty rats. One of their most interesting discoveries is that in specific neurons of the brain, both STAT3 and the leptin receptor are present at the same time. Dr. Li and colleagues believe that leptin, the leptin receptor and STAT3 work together to regulate eating.

"Obesity is a complex social problem," said Dr. Li. "There are strong hereditary and environmental inputs into weight gain. Leptin is fascinating because it is a metabolic regulator. At the same time, because leptin receptors are found in the brain, leptin has a profound effect on eating behavior as well. Some studies have shown that leptin may actually affect the way the brain develops. Perhaps these early developmental changes play a role in how a person interacts with food throughout life."

## A Mind Game

Another research group at UT Southwestern has pioneered a technology that will allow researchers to examine genes in specific cells of the brain.

Since eating makes people happy, psychiatry researchers have been exploring whether there is an addiction/reward pathway that would explain overeating.

The brain, which is made up of several different kinds of cells, has often been difficult to study on a gene-by-gene basis, because the same gene can have different functions in different cells within the brain.

One technique takes advantage of the fact that when a gene is turned on, it creates a copy of ribonucleic acid, or RNA. The cell then converts RNA to protein. Proteins do much of the work in a cell. By targeting the RNA instead of the gene, researchers can study the gene without removing it from the animal. This practice, called RNA interference, is well-established in cell lines and in lower organisms. UT Southwestern researchers are the first to use this technique in the brain of a higher organism.

In practice, the gene to be studied is identified. An artificial, man-made RNA is introduced into specific cells of the brain. The artificial copy interferes with the processing of the real RNA from the gene in the cell, and both RNAs are destroyed, leaving the cell with no means to make protein. The technique is specific: Only the cells that contain the artificial RNA are affected, and the rest of the brain is unaltered.

The UT Southwestern research group's next target is the leptin receptor.

"We know that the receptor is expressed in several areas of the brain, but the most interesting thing is that it's expressed in the same cells that express dopamine," said Dr. Eric Nestler, chairman of psychiatry and holder of the Lou and Ellen McGinley Distinguished Chair in Psychiatric Research.

Dopamine is a small molecule made in the brain that is associated with eating, movement and addiction. It has been implicated in reward pathways in the brain, where an action, such as eating, leads to dopamine production and a feeling of well-being. The continuous quest for that feeling of well-being may be the basis of overeating.

By using RNA interference to knock out the leptin receptor, the researchers want to find out if removing the leptin receptor from neurons that make dopamine will affect the function of dopamine-containing neurons and, thus, the reward pathway. They wonder if animals will feed more because they do not get the feeling of well-being anymore. Can they turn these animals from "live to eat" to "eat to live?"

Dr. Nestler is optimistic.

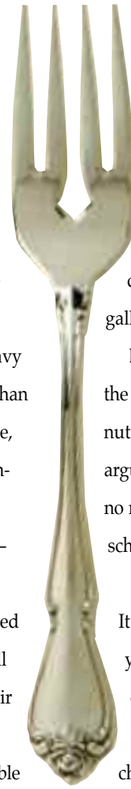
"An imbalance between leptin and its receptor may affect brain chemistry. This might lead to overeating or an addiction to food," said Dr. Nestler. "By finding out which elements in the brain control feeding, we can develop novel drugs to control eating. Leptin is somehow involved in both behavior and metabolism. It's very interesting because drugs that affect the metabolic aspect of eating could affect behavior, too."

Dr. Li concurs, adding that it's not just a case of willpower. The obesity associated with leptin deficiencies offers great insight into genetic regulation of body weight.

"Fifty years ago," he said, "10 percent of Americans were overweight. Now it's two-thirds. Something has to be done." ❊

# FACING THE FACTS ABOUT DIETING

## CALORIES STILL COUNT



In a society fueled by convenience and endless abundance, we live and die by the proverbial 24-hour drive-through and panic when we can't find the television remote – lest we have to leave the couch to change the channel. But many Americans are paying a heavy price for this life of plenty. More than 64 percent are overweight or obese, and – despite a surplus of get-thin-quick schemes and the thrust of a multibillion-dollar diet industry – the numbers continue to climb.

We have, by all accounts, created a national epidemic – one that will cost more than 300,000 people their lives this year alone (second only to cigarette smoking as a preventable cause of death).

Combating this alarming rise in obesity is the mission of nutrition experts at The University of Texas Southwestern Medical Center at Dallas, who are confronted daily by the nation's growing girth. Not only are patients getting heavier, they are battling a growing list of obesity-related illnesses – from diabetes and heart disease to gallstones and incontinence.

Despite the grim statistics and the complexity of obesity risk factors, nutritionists at the medical center argue that the key to weight loss is no more complicated than grade-school math.

"Simply put, it's all about calories. It comes down to burning more than you consume," said Dr. Scott Grundy, director of UT Southwestern's Center for Human Nutrition and chairman of clinical nutrition at the Southwestern Allied Health Sciences School. "For most people, weight gain can be attributed to an imbalance in calories – and not always a big one.

BY RACHEL SKEI DONIHOO

# A Healthy Balance

*Grilled chicken breast, brushed with Italian vinaigrette dressing, served with a side of pasta seasoned with olive oil, and steamed yellow squash and zucchini slices is an example of a low-cal, low-fat meal.*

"Eating an extra 300 a day – the equivalent of a small piece of chocolate cake – translates into a 30-pound per year weight gain. And the same works in reverse. When people cut back on calories – or burn them through exercise – pounds are lost."

But if weight loss is really so simple, why are so many Americans so fat? For many reasons, say experts – not the least of which is a knee-jerk reaction to the availability of inexpensive, calorie-rich foods.

"They're *everywhere*, at any time, in any place," said Dr. Jo Ann Carson, associate professor of clinical nutrition. "When it comes to food, Americans are faced with endless choices. Unfortunately, many of us don't always make good ones. When you combine a fast-food, sedentary lifestyle with the growing social norm of obesity, it's easy to see how our society's collective weight is spiraling out of control."

This spiral is a familiar one to patients like 40-year-old Zina Cunningham, whose steady diet of processed foods and extra desserts had propelled her to almost 200 pounds. Concerned about her weight and long history of yo-yo dieting, Ms. Cunningham's doctor referred her in 2002 to a UT Southwestern dietitian, who analyzed her eating patterns and developed a long-term weight-loss strategy.

Now 50 pounds lighter – and light-years more energetic – the Dallas native attributes her success to hard work, good choices and the simple caloric equation of "burning" what she eats.

"I realized very early in this process that I was going to have to readjust my way of thinking," she explained. "I had always equated weight loss with dieting and deprivation, which, in the past, had always set me up for failure. I was used to eating in extremes: One day I'd eat whatever I wanted, without any thought to how it was affecting my health; and then the next day I'd start on a stringent, ultra-low-calorie diet. There was no balance. Once I was forced to take an honest look at my bad habits, I could see that it was time to take on a new way of life."

Gone are the second helpings and the processed foods, sweets and fried-anythings that Ms. Cunningham says were once her staples. Also gone are the diet supplements and low-carbohydrate fad diets that she used to offset her creeping weight. Sensible portions of lean meats, fresh fruits and vegetables, and whole grains are the foods that now fill her refrigerator, and her once-sedentary lifestyle has been transformed into one in which she remains in "perpetual motion."

"One of the keys to my success has been exercise because it has changed the way I think about my body and my health," said the single mother, who exercises daily by running on her home treadmill or walking during her lunch hour.

"I feel like I accomplish something everyday – something beyond fitting into a size 8. I'm finally living a life in which I feel good about myself."

Getting to that point, however, can be rife with challenges.

"Patients come into my office, often overweight and confused by whatever fad diet they happen to be on. They're desperate to lose weight, and they're frustrated that their diet-of-the-week is so limiting or hasn't yielded better results," said Leigh Ann Kowalsky, clinical instructor of clinical nutrition at UT Southwestern. "They want immediate results, and many of them are willing to try just about anything – from grapefruit diets to gastric bypass surgery – to get them. But I tell patients that if what they want is weight loss that lasts a lifetime, they have to make a lifetime commitment to reaching their goals."

The word "diet" evokes negative feelings for many Americans – and with good reason. Deprivation, hunger and failed attempts too often eclipse any permanent success, resulting in a familiar pattern of rapid weight loss and even more rapid weight gain.

Restricting calories – or burning them through exercise – is the only way to lose unwanted pounds. But the way in which we do this often means the difference between weight-loss success and failure. Though would-be dieters search book stores, the Internet, doctor's offices and drugstore shelves for a "quick fix," weight-loss experts caution that – for permanent weight loss – there is no such thing.

"It takes years to develop poor eating habits, and it often takes years to undo the damage. Unfortunately, that's not what people want to hear," explained Lona Sandon, assistant professor of clinical nutrition at UT Southwestern. "The explosive popularity of fads like the Atkins Diet is a testament to our desperation. And the bottom line is this: They don't work – for long, anyway. These kinds of diets are so restrictive, impractical, nutritionally imbalanced and expensive, that they are impossible to maintain for any great length of time."

Dr. Grundy, who holds the Distinguished Chair in Human Nutrition, added, "It just doesn't make sense to go on a diet that you can't maintain for the rest of your life. People who jump on the next fad bandwagon almost always gain back what they've lost and then some. Good health isn't a gimmick, but many popular diets approach it this way."

There are other problems with quick-fix diets as well. Research points to the fact that the faster the weight loss, the quicker the rebound gain.

Continued on page 43

## When the Equation Doesn't Work

By Staishy Bostick Siem

WEIGHT LOSS should be simple arithmetic: Calories gained from food minus calories burned by exercise equals a smaller waistline. But for those who are severely obese and those with a family history of obesity, shedding extra weight is more like struggling with advanced calculus than breezing through basic subtraction.

Just ask Sharon Burnside and her granddaughter Ashlee Kopp of Plano. The two, along with many others in their family, had always battled obesity. They had tried dieting – everything from Weight Watchers to Atkins – and sought help from personal trainers without success.

In August 2003, just before she entered high school, Ashlee decided surgery was her only hope for shedding more than 120 pounds in excess weight. Ms. Burnside made the same decision about her own weight and a week later also had surgery.

Their choice has become a common one among those who feel that diet and exercise – and perhaps even genetics – have failed them. It is estimated that more than 100,000 Americans have bariatric surgery each year and, as the country's waistline continues to grow, the demand for this surgery is increasing steadily.

At UT Southwestern, surgeons perform more than 400 such procedures each year, with family referrals becoming increasingly common.

"We have no other equally effective therapy for morbid obesity," said Dr. David Provost, director of the Clinical Center for the Surgical Management of Obesity at UT Southwestern and associate professor of surgery. "Attempts at dietary weight reduction are often futile for people who are morbidly obese. Although there are occasional successes, less than 2 percent of these people are able to maintain a weight loss of 50 pounds for a year.

"You frequently see obesity run in families. I have several families where I have performed bariatric surgery in three generations. Weight reduction can be especially hard when others in the household are not following similar eating and exercise plans."

The Clinical Center for the Surgical Management of Obesity at UT Southwestern is a regional and national referral center for bariatric surgery.

Continued on page 45

*Sharon Burnside and her granddaughter Ashlee Kopp now enjoy shopping for new clothes.*

## Facing the Facts About Dieting

*Continued from page 23*

"When you tackle weight issues you have to be prepared to address both cause and effect. In other words, all of us – heavy or thin – have a very personal way of dealing with food. We all have certain food preferences, certain 'triggers' that can cause us to overeat and certain feelings that we attribute to eating," Ms. Kowalsky explained.

"It's important in any successful weight-loss plan to be able to examine all these things and come up with long-term strategies for reaching your goal. Because 'quickie' fad diets don't give you the opportunity to take these important steps, failure is almost always inevitable," she continued.

There is also physiological backlash that occurs when calories are suddenly and significantly restricted. When calorie intake is dramatically reduced, which is often the case with many popular diet plans, the body's metabolism slows to protect itself from perceived starvation conditions.

Ms. Sandon explained that a sensible diet plan calls for a minimum of 1,200 calories for women and 1,500 a day for men. Anything below that is risky and often unsuccessful.

"Simply put, it's all about calories. It comes down to burning more than you consume."

*—Dr. Scott Grundy*

"A pound of body fat equals 3,500 calories, which means that cutting 500 calories a day will result in a 1 pound loss per week – a rate that most nutrition experts recommend. This equation, however, disappoints many patients looking for more dramatic results," Dr. Carson said.

"What people often fail to realize, is that a 75-pound weight loss is only as good as the amount of time it stays off. In other words, dieters don't always measure success the way it should be measured," she said. "A 20-pound loss over the course of a year is a tremendous accomplishment, provided the loss endures. And if the weight loss is slow and steady – and is coupled with positive lifestyle changes, like increased activity – the likelihood that it *will* last is high. On the flip side, dieters who sacrifice everything, including their health, to race to the finish line, often find themselves back at the starting gate several months down the line with even more to lose."

"A pound of body fat equals 3,500 calories, which means that cutting 500 calories a day will result in a 1 pound loss per week – a rate that most nutrition experts recommend." *—Dr. Jo Ann Carson*

From a physiological standpoint, weight loss is relatively straightforward, but there also are psychological and social forces at work, which make the battle more complicated. Our emotions often govern what, when and how much we eat, said Bernadette Latson, director of the Coordinated Program in Dietetics at the allied health school. And all too often, we are oblivious to the amount we're consuming.

"Many of our patients are surprisingly unaware of their own food habits. They greatly underestimate the amount of calories they're consuming in a day – often snacking mindlessly as they go about their routines," she said. "Many of our new patients are also – sometimes blissfully – unaware of how much they weigh. But, as with food, what you don't know really *can* hurt you."

Ms. Latson recommends that people weigh themselves at least once a month, whether they like the results or not. She also suggests that people – particularly if they're early in their weight-loss journey – keep a log of what they're eating.

"This level of accountability can be very effective in educating people about what role their own actions have played in their problems with weight," she explained.

"Many of our patients … greatly underestimate the amount of calories they're consuming in a day." *—Bernadette Latson*

Another major problem dieters face, said Ms. Sandon, is in sizing up their food choices. The vast majority of convenience-food items – from breakfast bars to French fries – are neither satisfying nor nutrient dense, she explained. These quick, easy picks often result in premature hunger, sluggishness, and eventually, a deficit of vital nutrients the body needs to operate properly.

"Learning to look for whole, natural and nutrient-dense foods is one of the most important steps toward maintaining a healthful diet," she said. "One of the wonderful things we have in our society is the power of choice, but we can make those decisions work for or against us. Learning to read labels while consciously making the decision to avoid fatty or 'low-value' foods is tremendously important in maintaining a sensible diet. And it is really the only way to achieve long-term weight loss without deprivation."

This is a lesson that it has taken 55-year-old Nancy Doerr years to learn. For several years the grandmother of four had ignored the tightening waistbands on her clothes, but when an annual checkup revealed a dangerously high cholesterol level, she knew it was time to take action. Her doctor referred her to a UT Southwestern dietitian, who forced her to take a hard look at her eating habits. Although she had made a "career" of trying different diets, Ms. Doerr said she had yet to find a lasting solution to the creeping pounds.

"I had always equated dieting with giving up the foods I loved and, through the years, felt like I was constantly fighting temptation (which often won)," said Ms. Doerr, whose cholesterol has dropped 24 points since she began UT Southwestern's dietitian-guided program six months ago. "I had to do a lot of soul-searching to figure out where I was going wrong, and I realized that I needed to find a whole new way of thinking, eating and living," she said.

With a fresh resolve to change her habits, the newly retired Ms. Doerr focuses on portion control and low-fat, low-cholesterol foods. She seeks out healthier alternatives to the sweet snacks she's always loved and has launched an exercise routine that includes water aerobics and walking.

These are the kinds of lifestyle changes that Ms. Latson said dietitians like to see in patients. "The old stand-bys – as cliché as they are – still apply. 'Everything in moderation' really is relevant. The principles behind healthful eating really are very straightforward. With a little education, patients can learn quite easily how to make better food choices. What separates people who succeed at weight loss from those who don't is the 'a-ha' moment, when they decide once and for all that they don't want to live the rest of their lives at risk."

This moment came for Zina Cunningham none too soon. Her erratic food habits and sedentary desk job had stressed her body and her mind. Her weight now under control, Ms. Cunningham meets with her UT Southwestern dietitian three times a year to "regroup."

"My health is my No. 1 priority, and there is always more to learn. Before I began this program, I obsessed about my weight. Now I concentrate on feeding my body well, and the natural consequence of that has been *this*," she said, pointing to her trim waistline.

And does she ever feel deprived now that she has traded in candy bars for fresh fruit?

"Never. Look what I've gained," she said. "And what I've *lost*." ❊

**"IT TAKES YEARS TO DEVELOP POOR EATING HABITS, AND IT OFTEN TAKES YEARS TO UNDO THE DAMAGE."**

*—Lona Sandon with patient Zina Cunningham, who has lost 50 pounds*

*Dr. David Provost*

## When the Equation Doesn't Work

*Continued from page 23*

It provides bariatric patients multidisciplinary clinical care, which includes nutritional, psychological and rehabilitative programs. The center also supports research into the causes and treatment of severe obesity.

Doctors and scientists, in conjunction with those at UT Southwestern's Center for Human Nutrition, are currently studying the effects of massive weight loss on the metabolic syndrome, how weight loss impacts insulin resistance and hyperlipidemia, and elevation of lipids in the bloodstream.

Researchers hope these efforts will help them improve weight loss results for those who are overweight and help them better understand the mechanisms behind non-insulin-dependent, or type 2, diabetes. Gastric bypass cures type 2 diabetes in more than 85 percent of those who undergo the operation, and the remaining patients experience improvement, Dr. Provost said.

The most common bariatric surgeries performed at the center are gastric bypass – where surgeons reduce the size of the stomach – and Lap-Band, in which an inflatable, saline-filled silicone band is fitted around the stomach to restrict intake.

Both surgeries work by greatly limiting the volume of food a person can eat at any one time – usually only about half a cup. Still, surgery is not an easy or uncomplicated route to weight loss, Dr. Provost said. Patients must avoid carbonated beverages and can't overeat without feeling discomfort. Foods that are high in sugar or fat may also make them sick.

The new lifestyle may sound restrictive but the surgery has actually been extremely liberating, Ms. Burnside said.

"There are a lot of things we can eat," she said. "We don't get cravings. I think sometimes a lot of problems related to experiencing constant failure at weight loss come because you feel bad and want to 'pig out.' Now, instead of being sedentary, Ashlee and I are active, and we think positively."

The two work out before Ashlee goes to school and enjoy frequent shopping trips for new, smaller clothes. Ms. Burnside, who wore a size 22 more than a year ago, now peruses clothes racks looking for a size 12 or 14. Ashlee, who used to be a 24, now buys size 10 fashions.

The pair is also much healthier than before surgery. Ms. Burnside used to take 10 medications for obesity-related problems. Now she's down to two. Ashlee's blood pressure is back within normal range.

Dr. Provost said patients usually see improvement in their overall health after surgery. It can be a lifesaving choice for many people, despite the potential risks that come with any medical procedure.

"While bariatric surgery certainly carries a risk, there have been substantial improvements in the safety as well as the efficacy of the operations, especially at centers where many of these surgeries are performed and surgeons are highly experienced," he said.

While it certainly feels great to be healthier, Ms. Burnside said that perhaps the best part of surgery has been the effect it has had on the pair's self esteem, outlook on life and time together.

"Ashlee and I have always been really, really close but now it's on a happier note," she said. "Instead of hearing her lament and hearing how cruel the kids have been, we are talking about friendships and boys and cute clothes." ❊

*I visited Moncrief every day for several weeks, and each and every person I dealt with was in tune to what patients are going through." —Barbara Goltz*

UT Southwestern radiation oncologists orchestrate state-of-the-art treatment with state-of-the-heart care.

# In Tune

By Scott Maier

Already worn thin from chemotherapy and other cancer treatments, Barbara Goltz, a 47-year-old Web designer from Addison, expected to be "just another ID number" when she began radiation therapy for cancer of the lung, neck and brain.

But when she arrived at the new W.A. Monty & Tex Moncrief Radiation Oncology Building at The University of Texas Southwestern Medical Center at Dallas, she was pleasantly surprised.

"I was made to feel very welcome, and the staff was so nice and helpful," said Mrs. Goltz. "I visited Moncrief every day for several weeks, and each and every person I dealt with was in tune to what patients are going through."

What she was going through was dealing with a January 2004 diagnosis of lung cancer that by summer had spread to her neck and brain.

"Since I've been receiving treatment, the spot on my lung is gone; the tumor on my neck is about 90 percent gone; and I'm hopeful that the tiny tumors in my brain will be 'toast' soon, too," said the mother of a 20-year-old daughter and a wife for 25 years.

*W.A. Monty & Tex Moncrief Radiation Oncology Building*

Opened in September 2003, the three-story, 34,000-square-foot Moncrief facility on the medical center's North Campus joins the ranks of the best treatment centers in the nation.

And it was precisely what cancer patients in Dallas needed.

Complementing the UT Southwestern Moncrief Cancer Centers in Fort Worth and Weatherford – which serve patients from Tarrant County and areas to its west, south and north – the new $15 million facility in Dallas houses $9 million in the latest radiation therapy and research equipment. It adjoins the Seay Biomedical Building and the under-construction Biomedical Research and Advanced Imaging Building, which will house the Mary Nell and Ralph B. Rogers Magnetic Resonance Center as well as other clinical and research facilities.

"The Moncrief Radiation Oncology facility has cutting-edge technology and the manpower to do incredible things for our patients," said Dr. Hak Choy, chairman of radiation oncology and director of the facility. "We are now the second-largest radiation oncology department in Texas."

The center is named for W.A. "Monty" Moncrief – who, with his wife, Elizabeth, founded the Fort Worth facility in 1958 – and their son W.A. "Tex" Moncrief Jr., who along with his wife, Deborah, contributed $7.5 million to UT Southwestern's *Innovations in Medicine* campaign to help fund the Dallas facility.

"I'm truly excited and pleased to see the academic program we came to develop some years ago taking shape with tremendous energy and organization," said Dr. David Pistenmaa, professor of radiation oncology and former chairman of the department. "I am grateful to the administration and the Moncrief family for providing the resources to build and equip this facility. We've got a fantastic building with the latest equipment and top-notch staff."

The facility centralizes the radiation therapy outpatient services of the UT Southwestern University Hospitals and Parkland Memorial Hospital.

This therapy uses various forms of radiation to treat cancer by damaging the DNA in cancer cells and destroying their ability to reproduce. When these damaged cancer cells die, the body eliminates them.

The Dallas facility's sophisticated equipment includes three of the latest Varian linear accelerators with the capability for intensity-modulated radiation therapy (IMRT), which through computer targeting delivers a higher dose of radiation more precisely to a tumor, sparing the surrounding healthy tissue and organs.

It includes a suite for high-dose-rate brachytherapy – an outpatient procedure in which a high level of radiation is delivered quickly to a small, specific area. The facility also houses three state-of-the-art linear accelerators – the primary delivery devices for radiation therapy.

A dedicated computed tomography scanner is used for radiation treatment planning. Images imported into a computer aid in identifying a tumor and any nearby critical organs.

"The Moncriefs' generosity has enabled UT Southwestern to construct and operate an exceptionally functional and attractive radiation treatment facility with state-of-the-art technology," said Dr. Kern Wildenthal, president of UT Southwestern. "It will serve as a model for patient care throughout the country and, together with the Moncrief Cancer Centers in Tarrant County and Weatherford, it will provide a network for unsurpassed cancer care throughout the Dallas-Fort Worth area."

For about nine weeks, Mrs. Goltz received external-beam radiation treatments with the linear accelerators while having standard chemotherapy. She experienced little, if any, side effects during her therapy. For her, the Moncrief facility has been a lifesaver.

"I've really been impressed with the planning of my radiation treatment, as well as the doctors, nurses, staff and scheduling," said Mrs. Goltz. "The technicians were so helpful and answered each and every question I could raise about the radiation, no matter how silly it sounded."

Overseeing all of this is Dr. Choy, former vice chairman of radiation oncology at Vanderbilt University Medical Center and a national leader in treating brain, lung, and head and neck cancers. In September 2003, UT Southwestern recruited him to Dallas.

Holder of the Nancy B. and Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research, Dr. Choy has been involved in the development of new combined chemoradiation therapy for solid tumors. In addition, he is a leading authority in the clinical testing of novel radiation sensitizers and is pioneering studies in non-small cell lung cancers.

"Dr. Choy has tremendous energy and foresight, and it's just amazing what he's doing," said Dr. Pistenmaa, who holds the David Bruton Jr. Professorship in Clinical Cancer Research. "His experience and interest in clinical research has been beneficial in shaping the department, and his interest in the academic portion has strengthened the physics and radiation biology programs. He's also very experienced in combined modality treatments, especially chemotherapy and radiotherapy."

Since Dr. Choy's arrival, the radiation oncology faculty has more than doubled in size – from 11 faculty members to 25, all with special interests covering a full range of therapies.

A recent addition is Dr. Robert Timmerman, who joined UT Southwestern in September as vice chairman of radiation oncology. He is a national authority in image-guided stereotactic radiosurgery, a procedure whereby tumors are attacked with highly focused and precise radiation delivery techniques that markedly reduce normal tissue exposure.

"It's well-known that UT Southwestern has made a strong commitment to translating novel research into clinical practice," said Dr. Timmerman, former associate professor of radiation oncology at Indiana University Medical Center. "Dr. Choy has a vision that involves the integration of laboratory-based radiobiology research, state-of-the-art physics capabilities and a strong clinical team, all aimed at delivering new and better treatments for our patients' cancers. These efforts properly put the patients' needs as the focus."

*Continued on page 46*

"The Moncrief Radiation Oncology facility has cutting-edge technology and the manpower to do incredible things for our patients."

*—Dr. Hak Choy*

*Continued from page 27*

"It's well-known that UT Southwestern has made a strong commitment to translating novel research into clinical practice."

*—Dr. Robert Timmerman*

Another recent recruit is Dr. David Chen, professor of radiation oncology and a leading expert in DNA repair. A former senior staff scientist at the Ernest Orlando Lawrence Berkeley National Laboratory in California, he joined the medical center in October. His research expertise includes the effects of radiation on astronauts, the overall effects of low-dose radiation and radiation from bioterrorism events.

Four faculty members have also been recruited from UT M.D. Anderson Cancer Center.

"Until recently, the research being conducted here in radiation oncology was limited," said Dr. Choy. "We now have recruited outstanding faculty to the department, which ultimately will provide unique opportunities for patients that they otherwise would not have."

The Moncrief Radiation and Research Foundation, chaired by W.A. Tex Moncrief Jr., gave the Moncrief Radiation Center to the UT System in 1995. The cancer treatment and research facility was the first community radiation-therapy center in the Southwest. The Board of Regents entrusted the center to UT Southwestern in 1999.

A 7,000-square-foot diagnostic center was added to the Fort Worth facility in 2000, along with an adjacent breast-imaging center. Risk assessment and genetic counseling services are available, and the center has the latest state-of-the-art diagnostic equipment.

This past November, the Moncrief Cancer Center in Fort Worth began treating patients with a TomoTherapy system utilizing image-guided radiation therapy, making it the first cancer center in Texas to offer this revolutionary technology.

"The Tarrant County facility provides a range of treatments and services that might otherwise not be available to those areas," said Dr. Pistenmaa. "And, patients from the Fort Worth area will soon be able to participate in more UT Southwestern trials and research programs."

In its latest cooperative venture, UT Southwestern is reaching out to patients north of Dallas. Richardson Regional Medical Center has invited UT Southwestern to join forces to establish a comprehensive cancer center for patients in North Dallas, Richardson, Plano, Garland and surrounding areas. The new 50,000-square-foot Richardson Regional Cancer Center–UT Southwestern Medical Center, slated for completion in late 2005, will be located on Richardson Regional's George Bush/Renner Campus. It will focus on advanced technologies to treat prostate, breast, lung, gastrointestinal, and head and neck cancers. A full spectrum of services, including prevention, screening, treatment and follow-up care will provide patients with access to all oncology specialties in one location.

The partnership allows Richardson Regional to expand medical and surgical services as well as radiation oncology services, while also incorporating a strong clinical trials component within its program.

North Dallas and Collin County residents will benefit from direct access to UT Southwestern faculty physicians, who will become part of the medical staff at the Richardson facility.

"UT Southwestern's mission to provide access to exceptional clinical care and services to citizens of North Texas will be strengthened significantly as a result of our affiliation with Richardson Regional Medical Center," said Dr. Willis Maddrey, UT Southwestern's executive vice president for clinical affairs. "More patients will now have access to the latest therapies, including some that are being offered only in a few selected sites around the country."

Combined, UT Southwestern's programs in Dallas, Fort Worth, Weatherford and Richardson provide a look into the future of radiation oncology at UT Southwestern. Featuring the latest equipment and best doctors and staff, the goal is not just to treat the cancer but to treat patients with cancer.

"In the next few years, I expect us to be widely recognized as one of the top 10 radiation oncology programs in the country," said Dr. Choy. "To do that, we will continue to recruit talented researchers and invest our resources in the latest technology for patient care and research. We have the framework in place. Now, it's time to put the rest of the parts together."

Mrs. Goltz knows firsthand about the quality of care and treatment at UT Southwestern. And, she's doing her part to spread the word.

"I tell everyone about this place – my friends, family and anyone who is interested in my treatment," said Mrs. Goltz. "I tell them that they should be as lucky as I have been in receiving the best care and being treated by the best doctors and best nursing staff." ❋

*For more information about radiation oncology treatment, please call 214-645-8525.*

UT Southwestern's experts are adapting strategies for combating pediatric depression – and it's –

# Not Child's Play

By Staishy Bostick Siem

RYAN HAS HAD TROUBLE FOCUSING on class work since preschool. Making friends and participating in team sports adds to his difficulties.

Now, the 14-year-old Irving resident knows why – he suffers from clinical depression and attention deficit hyperactivity disorder (ADHD). But the decade it took to reach that diagnosis – a decade of not fitting in and damaged self-esteem – took its toll.

He is not alone. About 2 million children and adolescents in the nation fight the same demons – and many, like Ryan, go undiagnosed.

"There is still a stigma associated with mental illnesses, and, as a result, children with these illnesses continue to be under-recognized, undertreated and underserved," said Dr. Graham Emslie, professor of psychiatry and head of the department's child and adolescent division at The University of Texas Southwestern Medical Center at Dallas.

"We are working to overcome this stigma so that children can be properly identified and get the treatment they need," said Dr. Emslie, a nationally renowned expert on treating children's psychiatric disorders.

A TYPICAL CHILD who is referred for psychiatric treatment at UT Southwestern suffers from not just one but two or three of the most common mental illnesses among children: depression, learning disabilities and ADHD, the latter characterized by either inattentiveness, impulsive behavior or both.

While all children get the blues or have trouble sitting still once in a while, a surprising number of kids have more serious problems. It is estimated that 5 percent of children and adolescents suffer from clinical depression, and 3 percent to 5 percent suffer from ADHD. About one-third of these children suffer from both illnesses, like Ryan.

"In pre-K at 4, he couldn't sit still," Ryan's mother, Yvette Jefferson, said. "He was a very poky, touchy, feely kid. We thought he just liked to show his emotions, but then he developed a stuttering problem and started blinking a lot. It turns out that he had ADHD, and his brain was working faster than he could get things out. But even after his ADHD was treated, I could look at him and tell that something was still not quite right."

Ryan's ADHD was diagnosed when he was 6. But it would take eight more years – eight years of trouble at school and fractious relationships with his parents and friends – before he would be diagnosed with depression.

"I called the psychiatric clinic at Children's Medical Center Dallas and just needed to talk to someone," Ms. Jefferson said. "They said, 'It might also be depression. Let's go ahead and run some tests,' and bingo – that was it."

Psychiatrists try to determine which illness – depression or ADHD – is dominant so treatment will be most effective. This is difficult because many symptoms overlap.

Children under stress, those who have experienced a loss, or those who have attention, learning or conduct disorders are at a higher risk for depression. Depression can cause children's school work to slip. It can also overshadow the usual ADHD symptoms.

On the other hand, ADHD can be exacerbated by stress and makes focusing in school and completing homework difficult. Children suffering from ADHD often find it challenging to make friends, which can lead to depression.

But regardless of which illness is dominant, one thing is certain – treatment cannot be delayed.

"We must treat these children quickly to prevent them from having long-term problems," said Dr. Emslie, who holds the Charles E. and Sarah M. Seay Chair in Child Psychiatry. "Problems that aren't under control by high school could cause children to become at risk for suicide attempts, eating disorders, and drug, alcohol and tobacco abuse."

**"Problems** that aren't under control by high school could cause children to become at risk for suicide attempts, eating disorders, and drug, alcohol and tobacco abuse."

*— Dr. Graham Emslie*

Guidelines for treating ADHD and depression have been developed by researchers at UT Southwestern and serve as a model nationwide.

The guidelines, or algorithms, are known as the Children's Medication Algorithm Project (CMAP) and outline the best means for treating children with severe problems within Texas' publicly funded mental health-care system. CMAP was developed in cooperation with the Texas Department of Mental Health and Mental Retardation by evaluating current research and talking to community psychologists, psychiatrists and patients.

It includes both a medication and psychotherapy component, said Dr. Carroll Hughes, professor of psychiatry and rehabilitation counseling. Family education is another big part, with a lot of resources available on the Texas Department of State Health Services Web site, www.dshs.state.tx.us/mhprograms/CMAP.shtm.

"Many people automatically think we are just focusing on medication treatment. We're not," Dr. Hughes said. "The good thing about CMAP is that there are nonmedication alternatives, too. So many kids get better just talking about their problems.

"WE WOULD be the first to say that if you can get by without medication, do it. CMAP is so much more than just advising doctors which pills to hand out."

UT Southwestern researchers have recently found that a combination of medication and cognitive-behavior therapy is best for treating depression. Cognitive-behavior therapy is a form of psychotherapy that emphasizes the role of thinking in creating subsequent feelings and behaviors.

The study, published in *The Journal of the American Medical Association* and designated the Treatment for Adolescents With Depression Study (TADS), found that teenagers suffering from depression improved more with a combination of an antidepressant and cognitive-behavior therapy than they did when treated with either separately.

Cognitive-behavior therapy may also play a crucial role in helping children avoid depression relapse, said Dr. Betsy Kennard, associate professor of psychiatry. Depression is a chronic illness, and 30 percent of children who have experienced one episode of depression will have another episode within a year; 50 percent to 60 percent are at risk of a recurrent episode in five years. Experts at UT Southwestern are investigating ways to augment treatments beyond medication in order to curb the high rate of relapse.

"Cognitive-behavior therapy is a form of 'talk' therapy," Dr. Kennard said. "Basically, we are teaching kids to manage their mood by changing their thinking and behavior patterns. They are learning to be their own therapist, in a way, by anticipating what will put them under stress, learning to manage those factors and also to control their mood."

Ms. Jefferson said Ryan has been helped immensely with this approach and is now able to play on his school football team and hold a part-time job.

*Continued on page 47*

**Ryan** (pictured above) has been helped immensely (with cognitive behavior therapy) and is now able to play on his school football team and hold a part-time job.

*Continued from page 31*

"JUST HAVING SOMEONE help us get through this is great," she said. "We both look forward to going and talking to them. His progress is at a very slow pace, but he's getting there. Problems he didn't recognize before, he recognizes now. He tries to think before he acts."

TADS showed that depressed teens treated only with cognitive-behavior therapy did little better than teens given placebos.

These findings come at an important time. Many in the medical community are weighing the risk of prescribing antidepressants to children, citing a concern that the medications may cause suicidal thoughts and behaviors. As a result, the Food and Drug Administration recently decided that antidepressants should come with their strongest warning – a black box on the label – that they can sometimes lead to danger.

"Recent controversies over using antidepressants in adolescents bring up the issue of assessing the risk versus benefit," Dr. Emslie said. "If there were non-medication therapies that worked as well as antidepressants for adolescents, then there would be plausible treatment alternatives. This study shows that not to be the case at this time."

UT Southwestern recently became one of five centers in the nation, funded by the National Institute of Mental Health, to embark on studies of depressed adolescents who have attempted suicide and are considered to be at very high risk for another attempt. They are recruiting patients for this study, the first of its kind. Frequently, teens are still in the hospital when they are enrolled. Most previous research has focused on lower-risk children who have never made a suicide attempt.

More than a half-million teens attempt suicide each year, with 2,000 – almost half suffering from major depression – dying. Experts hope to identify the most effective treatments for depression and determine what will prevent relapse and future suicide attempts.

"This is an exciting time to work with children with psychiatric disorders," Dr. Kennard said. "We are adapting strategies for use with teens that have been found to be effective in depressed, suicidal adults. These kids are also helping us prepare to treat future generations – what we are learning today will make us even better."

Another new realm of research at UT Southwestern is to use new functional magnetic resonance imaging (fMRI) technology to study brain activity. Imaging gives researchers the ability, for the first time, to view specific areas of the brain and cellular processes in children with both ADHD and depression without exposing them to damaging radiation.

"The functional magnetic resonance imaging technique will help us understand which brain systems get activated when depressed people make decisions," said Dr. Uma Rao, professor of psychiatry and head of the pediatric psychiatry research program. "Before, we weren't able to do this without exposing children's growing brains to radiation; hence, we had to rely on other measures that cannot reliably tell us what really goes on in the brain."

"Our future hope is to prevent depression," said Dr. Rao, who holds the Sarah M. and Charles E. Seay Chair in Child Psychiatry. "We hope to integrate biological and social realms, such as social support systems and environmental stresses, to see how they interact and develop treatments for different subgroups of depressed people. Interventions could be tailored to individuals."

Depression is often a precursor to substance abuse and nicotine dependence. Dr. Rao said many 12- to 14-year-olds who experiment with drugs, alcohol or cigarettes – even those who are depressed – never become addicted. She hopes to use the fMRI and other technologies to predict those who will.

For adolescents who have already begun smoking, Dr. Rao hopes that imaging could even be used to dictate which method of treatment might be most effective for a particular child: medication, behavioral treatment or a combination of both. Armed with this information, health-care providers might be able to help adolescents recover sooner, avoiding more serious addictions.

"Nicotine is a gateway drug," Dr. Rao said. "It can quickly lead to tobacco addiction and more hard-core drug use."

For this reason and others, pinpointing signs of mental illness as early as possible is crucial for positive long-term outcomes in children and adolescents.

"If you notice that there is something wrong with your child, seek medical advice and talk to someone," Ms. Jefferson said. "Ryan was constantly in trouble at school, but people would say, 'There's nothing wrong with your child.' The people at Children's and UT Southwestern said differently, and that has saved us. We have come a very long way with their help." ❊

*For more information on pediatric psychiatry, please call 214-456-8918.*

**"We are adapting** strategies for use with teens that have been found to be effective in depressed, suicidal adults. These kids are also helping us prepare to treat future generations – what we are learning today will make us even better."

*—Dr. Betsy Kennard*

UT Southwestern researchers are searching for clues to what makes the most menacing microbes on the planet tick in hopes of eliminating them altogether.

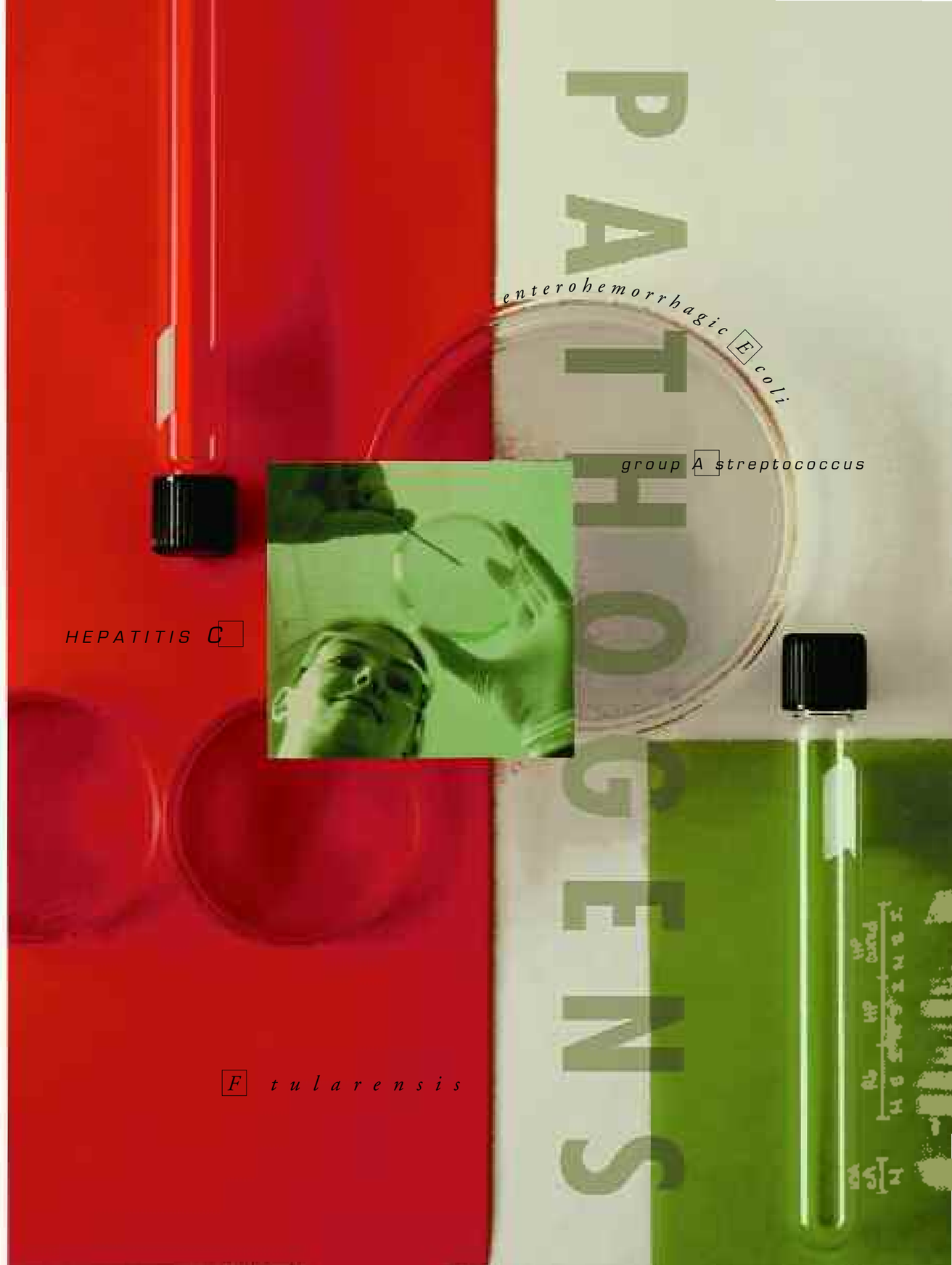
# MEGA MYSTERIES IN A MICRO WORLD

Infectious agents like plague and smallpox have been staples of human pestilence throughout history, as populations moved and wars raged. On an ever-shrinking planet of globe-trotting tourists and international business, new pathogenic players continue to emerge – West Nile virus, Ebola, hepatitis C, new *Escherichia coli* strains and severe acute respiratory syndrome (SARS). Throw into this mix of old and new dangers the threat of bioterrorism – from anthrax, ricin or tularemia – and you have a recipe for alarm.

At The University of Texas Southwestern Medical Center at Dallas, researchers work with the bugs that cause some of the nastiest illnesses on Earth – syphilis, tularemia, gastroenteritis and bloody diarrhea, flesh-eating strep – dissecting and analyzing in excruciating detail every gene, protein, membrane and colony, searching for weaknesses that could be exploited for new drug therapies or treatments.

"The research focus here is on things that are important, whether it's bioterrorism or human disease," said Dr. Kevin McIver, assistant professor of microbiology.

By Amanda Siegfried



"That's what fascinates me: Not only what the pathogen does, but how does it work at that basic level?"

—*Dr. Kevin McIver*

## Battling Biothreats

Spurred by the federal government's post-Sept. 11 emphasis on national biodefense, UT Southwestern's Department of Microbiology received a five-year, $8.7 million grant in 2003 from the National Institutes of Health (NIH) to pursue studies of *Francisella tularensis*, the bacterium that causes tularemia. Before the Sept. 11 terrorist attacks, little research was being done anywhere on this pathogen. Only a handful of labs around the world were responsible for most of the last 20 years of knowledge, or lack thereof, of this highly infectious agent, which, as a Class A bacterial biothreat, is in the "most dangerous" category.

"Embarrassingly little is known about the organism, not even how it attaches to cells, or how it gets inside cells, and what happens when it does," said Dr. Michael Norgard, chairman of microbiology and holder of the B.B. Owen Distinguished Chair in Molecular Research. "How does tularemia take over the machinery of the cell? How does it destroy cells? How does it liberate its toxicity? Why is it so virulent?"

When the NIH issued a call for proposals to conduct research on potentially nefarious bioagents, UT Southwestern's microbiologists had no experience in tularemia (nor did other researchers).

Now, five UT Southwestern projects overseen by six faculty members focus on different aspects of the bacterium's basic biology and its ability to cause infection. In addition to Dr. Norgard and Dr. McIver, these researchers are Dr. Vanessa Sperandio, assistant professor of microbiology; Dr. Simon Daefler, assistant professor of internal medicine and microbiology; Dr. Kayla Hagman, assistant professor of microbiology; and Dr. Eric Hansen, professor of microbiology.

Dr. Norgard, who also studies the bacteria that cause Lyme disease and syphilis, believes that his group has the collective experience needed to shed light on poorly understood pathogens that could be used as bioterrorism agents.

Tularemia is a classic example. It's easy to deliver and is highly infectious; it takes just one inhaled organism to cause illness. And it's no secret that tularemia is more easily weaponized than anthrax, a primary factor in the government's urgency to find ways to combat it.

The natural reservoir for *F tularensis* is in wild animals, where it causes characteristic liver damage in those infected – common knowledge to hunters, who call it "rabbit fever." Dr. Norgard, whose hunting exploits of yesteryear landed him the wild turkey and the bobcat that now grace his office, said hunters and outdoors people who accidentally inhale the bacteria from a carcass can come down with flu-like symptoms.

Left without treatment, the bacteria can change the normal programming of the human host in a way that allows it to hide and flourish inside one of the body's defense mechanisms – a macrophage, which normally engulfs and kills bacteria. But *F tularensis* likes being in the macrophage. It tricks it somehow, allowing the bacterium to grow and proliferate to the point where it causes severe, debilitating and even life-threatening infection. Dr. McIver is determined to understand how it does this.

"There are no known secreted proteins from this organism, which is how other bacteria change their environment, such as inside the macrophage, to make it a 'happy place,'" Dr. McIver said. "But nobody has really looked for this in tularemia, and that's my task – to seek out and identify these secreted proteins and then use genetics to knock them out and determine what exactly they do. If they exist, they could offer a target for drug therapy."

Dr. McIver's other focus is group A streptococcus, responsible for the sore-throat ailment typically striking victims aged 5 to 20. In most cases, strep throat is self-limiting – wait seven to 10 days, and 99 percent of cases in kids will get better on their own.

Even so, most doctors start patients with suspected strep on antibiotics right away. Why? Because the immune response the body mounts to the strep can cross-react with the body's tissues, causing an autoimmune disorder called rheumatic fever, leading to swelling of tissues, particularly in the heart and joints.

"If you never get a strep infection, you'll never get rheumatic fever," Dr. McIver explained. "It's difficult, however, to study this phenomenon in lab animals because you can't give mice rheumatic fever by infecting them with strep. Their immune system is different from ours."

There are a variety of strains of strep, and like *Staphylococcus aureus*, they can cause a skin infection or other problems. Strep infection, which also has been linked to certain tic disorders such as Tourette's syndrome, can quickly turn virulent, negatively affecting the body's cells.

"In some cases, the strep bacteria will leave benign areas of the body like the throat, get into the bloodstream and invade deep tissues, where it elicits severe and often fatal disorders, including necrotizing fasciitis – flesh-eating disease," said Dr. McIver, who as a child had frequent bouts with strep throat. But that's not what drove him to specialize in strep and bacterial genetics.

"From the research end, we're interested in the regulation of those genes that are turned on under certain conditions, allowing this switch from a throat strain to an invasive disease that is much more severe and can afflict a completely different population – adults," he said.

"You have to understand the big picture – the disease, the host, the interaction – and at the same time, get down to the DNA sequence that some protein binds to, or the protein-protein interactions. That's what fascinates me: Not only what the pathogen does, but how does it work at that basic level?"

Genetic studies – the core of research efforts on many pathogenic species – are a main focus of UT Southwestern's microbiology labs. A genetic profile of the tularemia bacterium, for example, would aid researchers in identifying weaknesses, but little information is available about that bug's genome.

Because it's such a hot pathogen, the research effort on *F tularensis* requires the strictest of safety precautions, including using UT Southwestern's new biosafety level 3 (BSL3) facility designed specifically for work on highly virulent agents. Prior to the building of the BSL3 lab, Dr. Norgard's group worked with nonvirulent strains of *F tularensis,* which was not optimal but allowed the team to do some pilot experiments and practice on procedures.

Most of the viruses and bacterium the faculty work with can be handled using routine microbiological practices and conventional barriers like gloves and gowns. Most bugs don't pose a risk unless you eat them, spray them in your eyes or accidentally inject yourself.

"Because it is airborne and particularly virulent, *F tularensis* poses a more difficult problem, and in part that's why there is so little known about it," Dr. Norgard said.

## Friend or Foe?

In contrast to the largely uncharted territory of the tularemia bacterium's genome, the genetics of the *E coli* bacterium have been mapped in detail. As one of the workhorse organisms of the biomedical research enterprise, *E coli* has been poked and prodded, dissected and analyzed to the point that almost all the information about the benign versions of this creature, such as its genetic structure and biological functions, is freely available on the Internet.

But one strain of *E coli*, which goes by the unwieldy designation of enterohemorrhagic *E coli* O157:H7, or EHEC for short, is so nasty that it takes only five individual bacterium to make a person sick.

"Because it is airborne and particularly virulent, F tularensis poses a more difficult problem, and in part that's why there is so little known about it."

—*Dr. Michael Norgard, standing in front of a biosafety level 3 lab*

"A little bit of knowledge here and there gets you to a vaccine or a treatment. But it takes a lot of effort from a lot of different research groups, a lot of different brains, to figure out how to combat these pathogens."

—*Dr. Vanessa Sperandio*

Compare that to cholera, in which a person must ingest a colony of millions of bacteria before becoming ill. The consequences of EHEC infection include severe bloody diarrhea and – in the elderly, children and the immune-compromised – kidney failure or even death from a condition called hemolytic uremic syndrome, which shuts down a person's kidneys.

The bacterium's natural home is in cattle, which are immune to its effects. It is estimated that 73,000 Americans contract this horrible bug each year, primarily through contaminated meat and other food. About 60 die. The first outbreak of infection from EHEC was in 1982 from a West Coast fast-food restaurant. Since then, outbreaks of this emerging infectious disease have been traced back to radish sprouts, a water park and unpasteurized cider.

Understanding what makes this *E coli* strain so virulent is a high priority for Dr. Sperandio. Her research focuses on how bacteria living inside us – both the good and the bad – communicate with each other and with their host. She is particularly interested in intercepting the signals EHEC uses to cause disease.

With about ten times as many bacterial cells as human cells in the body, sorting out the key messages from the din might seem a daunting task. The skin, mouth and gut are covered with bacteria, by some estimates 500 to 1,000 different species. The ones that live peacefully inside a human host are called commensals. They assist in food digestion and protect against pathogenic invaders. Benign strains of *E coli* live unnoticed in the colon.

But like the black sheep of the family, it's the cousin EHEC that Dr. Sperandio is most concerned about.

"Once this bacterium is ingested and colonizes the bowel, it receives a signal from your body that it's now in the proper environment to begin the process of making you sick," she said. "Our focus has been on trying to understand the signals it is receiving and how those signals turn on the genes that activate the bacterium's virulence factors."

Dr. Sperandio and her group discovered that EHEC picks up hormone and hormone-like signals both from the host and from the friendly flora normally living in the colon. The pathogen picks up two signals from the colon, from epinephrine and norepinephrine, Dr. Sperandio said.

"These hormones seem to initiate a very complex signaling cascade inside of this *E coli* that regulates different genes," she said.

Some of these activated genes create a whip-like flagellum on the bacterium so it can swim through mucus. Once this mechanism shuts down, another signal, secreted by the "good" bacteria living inside the human body, activates genes that tell the *E coli* to begin making several toxins and a syringe-like apparatus to inject the toxin into cells. It's the concerted effect of these toxins that results in severe diarrhea.

But that's not even the worst this pathogen can do. If you try to kill it – with antibiotics, for example – the outcome of the disease may be worse.

"Without treatment, EHEC will give you diarrhea that will resolve itself in a week. It's uncomfortable, but you are not going to die," Dr. Sperandio said. "But when you assault EHEC, you signal the bacteria that it's in trouble, and it triggers its own SOS response."

The SOS signals the bacterium to release shiga toxin, the same toxin as the Class A biothreat ricin.

"This toxin goes through the intestinal barrier and travels in your bloodstream to the kidneys, killing those cells point blank," Dr. Sperandio said. "Once you have hemolytic uremic syndrome, unless you dialyze it out within a matter of days, there's really nothing doctors can do for you."

Dr. Sperandio was named a 2004 Ellison Medical Foundation New Scholar in Global Infectious Disease Research. Through this program, scholars early in their careers receive $50,000 a year for five years from the nonprofit foundation to support research in areas that are often underfunded or not funded by traditional sources.

Dr. Sperandio has found that beta-blockers, used currently to treat high blood pressure and congestive heart failure, can block the signaling cascade in EHEC, at least in a petri dish. Further tests of beta-blockers in animals may eventually lead to human treatments.

"The reason I like working with microbial pathogens is that you can do so much in a short amount of time – genetics, biochemistry, you name it," Dr. Sperandio said. "A little bit of knowledge here and there gets you to a vaccine or a treatment. But it takes a lot of effort from a lot of different research groups, a lot of different brains, to figure out how to combat these pathogens."

One of those brains belongs to Dr. Michael Gale, associate professor of microbiology and one of the world's leading experts on the hepatitis C virus. Recruited to UT Southwestern in 1999 as the first Nancy C. and Jeffrey A. Marcus Scholar in Medical Research, in Honor of Dr. Bill S. Vowell, Dr. Gale also became a 2004 Burroughs Wellcome Fund Investigator in Pathogenesis of Infectious Disease, an honor that carries a five-year, $400,000 award that supports his research on the control of hepatitis C virus replication. In addition, he is another Ellison Medical Foundation New Scholar in Global Infectious Disease Research, named in 2001.

## Keeping One Step Ahead

Hepatitis C may have been in the human population for a long time, but it was only first identified on a molecular level and cloned in 1988. "For decades, people dropped dead from liver failure, but we didn't know why," Dr. Gale said. "Scientists finally figured out it was hepatitis C."

An estimated 200 million people worldwide are infected with the virus.

Hepatitis C is a blood-borne pathogen, transmitted very efficiently through needle sticks and intravenous drug use. Prior to 1994, before the nation's blood supply was screened for the virus, large numbers of people were exposed through surgical procedures and blood products. Nonetheless, it spread quickly throughout the world as medical procedures became more attainable by different communities. The disease maintains a reservoir in people who engage in IV drug use and high-risk sex.

The insidiousness of the virus can be seen in how it slowly – over 30 years – attacks the liver. As the virus grows in liver cells, the body's immune system attacks and kills infected cells. But the liver is a unique organ – it can regenerate. As the immune system destroys virus-laden cells, they grow back. Nodules begin to form on the liver, become highly prolific and turn cancerous. Eventually the whole liver becomes scarred – a condition leading to cirrhosis – until it shuts down completely.

"It's a remarkable virus," Dr. Gale said. "Most viruses will infect you, make you sick for a couple of weeks, and either go away or kill you. This one has adapted so that it doesn't go away, and it doesn't kill the host too soon."

Hepatitis C is very sloppy when it replicates, making mistakes as it copies its genetic material. These errors lead to lots of mutations. In fact, it mutates so rapidly that an infected person may have 20 genetically distinct viruses in their blood.

"That means this virus has remarkable adaptive potential, and because of that, it's very hard to treat. It adapts and mutates around any therapy we throw at it, so it's always one step ahead of us," Dr. Gale said.

*Continued on page 48*

"If you feel artistic, science is the place to be. What turned me on to viruses was that they are so powerful – these little pieces of DNA or RNA can kill you. It's just incredible. Figuring out how they work is a great mystery."

—*Dr. Michael Gale*

## Mega Mysteries in a Micro World

*Continued from page 37*

Nonetheless, his lab is making tremendous strides toward understanding the bug better, with the goal of finding a treatment or cure. Part of the challenge is that hepatitis C makes the body work against itself.

When a person is infected with a virus, cells produce a chemical called interferon, which, as it names suggests, interferes with virus replication by turning on crucial genes inside cells. That achy, tired feeling that accompanies the flu is due to the interferon the body makes and circulates through the blood to combat the virus.

In 2003 Dr. Gale and his group analyzed human liver cells containing a replicating hepatitis C virus genome and discovered that a viral protein, called the NS3 protease, blocks the cell's ability to produce interferon. When treated with an experimental protease inhibitor drug, the NS3 was stymied. This allowed the host cell to once again produce interferon, restoring the body's natural immune ability to kill the virus on its own. Research groups elsewhere are now studying the drug's effectiveness in humans with hepatitis C.

Clinical investigators at UT Southwestern also are applying knowledge gained by Dr. Gale's studies. Comprising the largest group of hepatitis researchers in Texas, investigators at UT Southwestern's Clinical Center for Liver Diseases are developing new techniques for assessing and treating diseases of the liver. Under the direction of Dr. William Lee, professor of internal medicine, center researchers participate in many national clinical trials to develop and improve treatments that may slow the progression or eradicate hepatitis C and other liver diseases.

With support from the pharmaceutical industry and major grants from the National Institutes of Health and the Food and Drug Administration, Dr. Lee's group promotes "translational" research, which links basic laboratory science with patient studies.

For example, Dr. Lee, with Dr. Gale, is currently examining the earliest changes observed in the hepatitis C virus itself after interferon therapy is begun. These early patient-derived samples demonstrate that the virus changes rapidly during this critical period and provide hints as to why some patients respond to treatment and others do not.

"Mike Gale's groundbreaking work is now linked directly to our patient material and the evidence for response to therapy," said Dr. Lee, holder of the Meredith Mosle Chair in Liver Disease. "The potential synergies between our groups using this approach are tremendous."

Another surprising finding Dr. Gale has made – through collaborative studies with UT Southwestern Nobel laureates Dr. Michael Brown, director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease, and Dr. Joseph Goldstein, chairman of molecular genetics – is that statin drugs can kill the hepatitis C virus, at least in a test tube. Dr. Gale and his group found that this cholesterol-lowering prescription drug blocks a normal process called prenylation, by which a fatty acid is added to proteins found in cells. It appears that in order to replicate, the virus needs to interact with a particular cellular protein that has been prenylated. Blocking prenylation with statins thus shuts down the virus.

"We are working toward identifying the prenylated cellular protein that the virus needs to make more copies of itself," Dr. Gale said. "This protein would present us with another therapeutic target. But the beauty of it is, it's not a viral target, it's a target within the human cell. And that cell is not going to mutate like the virus does, which should make treatment more effective."

While scientists are beginning to get a leg up in their battle against emerging and re-emerging infectious diseases, Dr. Gale is philosophical as he encourages his students and colleagues to be creative in their approaches.

"The beauty of science is that it's like art," Dr. Gale said. "If you feel artistic, science is the place to be. What turned me on to viruses was that they are so powerful – these little pieces of DNA or RNA can kill you. It's just incredible. Figuring out how they work is a great mystery." ❄

# Clear as a bell

*By Katherine Morales*

**Charles McManus** loves to twirl his wife around the dance floor. The two routinely go to a local senior center, dressed for an evening of square-dancing and socializing.

But in recent years Mr. McManus, 75, began habitually missing steps during his dance routines – not because he'd lost his rhythm, but because he was slowly losing his hearing.

"I always missed steps because I couldn't hear," Mr. McManus said.

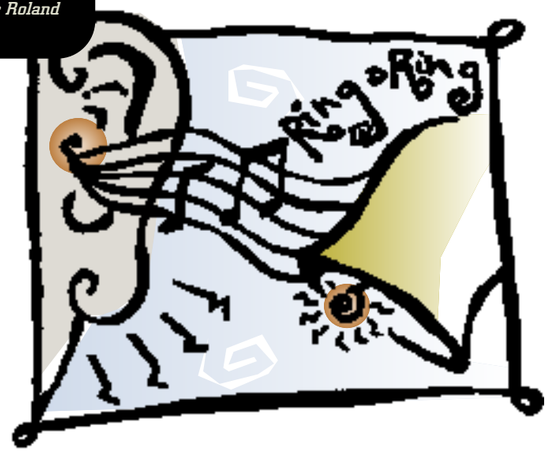
He experimented with a variety of hearing aids to improve his high-frequency sensory hearing loss – a chronic condition common in older people.

"It's a very common type of hearing loss as people get older," said Dr. Angela Shoup, assistant professor of otolaryngology – head and neck surgery at The University of Texas Southwestern Medical Center at Dallas. "Many older Americans suffer some degree of sensory hearing loss."

In fact, more than one-third between the ages of 65 and 74 do.

Mr. McManus first turned to the traditional devices designed to amplify sound, but he still struggled. Devices that fit inside his ear canal created uncomfortable side effects. Outer-ear devices were quite noticeable.

"Most importantly, patients say sounds are clearer. This is an important evolutionary step in hearing-aid technology."
—— *Dr. Peter Roland*




Finally, he came to the Department of Otolaryngology - Head and Neck Surgery at UT Southwestern, where he learned of a new device called the RetroX, which sends amplified sound directly to the ear canal through a small titanium tube implanted behind the ear at the base of the skull.

"This new hearing aid is smaller, less visible and more comfortable than others," said Dr. Peter Roland, chairman of otolaryngology - head and neck surgery and holder of the Arthur E. Meyerhoff Chair in Otolaryngology/Head and Neck Surgery. "Most importantly, patients say sounds are clearer. This is an important evolutionary step in hearing-aid technology."

Patients like Mr. McManus often complained of loud, hollow or buzzing noises created by what is called a canal ocular effect.

"It's very disconcerting for patients with hearing loss," Dr. Shoup said.

Because the titanium tube in RetroX doesn't block the ear canal, that particular side effect is greatly diminished or eliminated.

The RetroX comes with a receiver, no bigger than a dime, which clips to the end of the implanted tube. The entire device weighs less than an ounce and is much less noticeable than a traditional behind-the-ear hearing aid. The receiver transforms sound into vibrations, which are sent to the inner ear by the vibrating bones of the skull.

"UT Southwestern is a leader in using new technology to assist patients with hearing loss," Dr. Shoup said. "We have participated in many clinical trials for partially implantable devices."

The RetroX is one of several cutting-edge options available for patients at UT Southwestern and has only become clinically available in the last few years, Dr. Shoup said.

As for Mr. McManus, he said sounds are clearer and he has an easier time at business meetings and, of course, at dancing.

"The music sounds better," he said. ❄

*For more information on hearing loss, please call 214-648-2432.*

# Getting hip to health

*By Staishy Bostick Siem*

**Barney videos** playing on the television and Lego blocks in the waiting room may make the medicine go down better for young pediatric patients, but for teenagers – who still require the care of a pediatrician – it can be humiliating.

But when 17-year-old Brittni Lawhorn visited her mother's doctor instead of her own pediatrician, she still felt out of place.

Enter Dr. Laura Scalfano, assistant professor of pediatrics at The University of Texas Southwestern Medical Center at Dallas. Dr. Scalfano directs an adolescent medicine clinic at Children's Medical Center Dallas and specializes in treating the unique needs of those between the ages of 11 and 21.

Adolescent medicine isn't exactly new – it's been a certified subspecialty of pediatric and internal medicine since 1994 and of family practice since 2001. Still, it is a relatively small field with only about 600 certified adolescent medicine subspecialists in the United States, according to the Society for Adolescent Medicine.

"The difference is just amazing," said Carolyn Lawhorn, Brittni's mother. "The people in the clinic, the way Brittni is treated, the way she is encouraged have helped just as much as the medicine. Dr. Scalfano has empowered Brittni to take control of her health."

Treating adolescents takes a special approach, and empowering teens is a big part of the job, Dr. Scalfano said.

"They are going through such a complex stage of development," she said. "You have to get them to take ownership of their health because ultimately it's their decision whether to make changes – be it in their diet to lose weight or sticking with a particular treatment regimen. Parents can't be responsible forever."

Dr. Scalfano also tries to prepare adolescents for adulthood by giving them a more active role in the decision-making process.

"It's not just Mommy taking them to the doctor. They are making decisions under the guidance of their parent," Dr. Scalfano said. "When children become adults, they are often expected to take charge of their health care overnight. I try to bring about that transition gradually."

Brittni said she has begun to see this same transition in herself since she became Dr. Scalfano's patient.

"I used to have my mom do everything," she said. "I would ask her, 'What do I need to eat?' and 'What do I need to do?' Now, I know what to do and do it."

In fact, Brittni has even begun motivating her mother to make some healthier lifestyle changes. The two have recently taken up walking for exercise, Mrs. Lawhorn said.

Physicians who specialize in adolescent medicine are also prepared to broach touchier topics that not all pediatricians, especially those who treat primarily young children, often deal with.

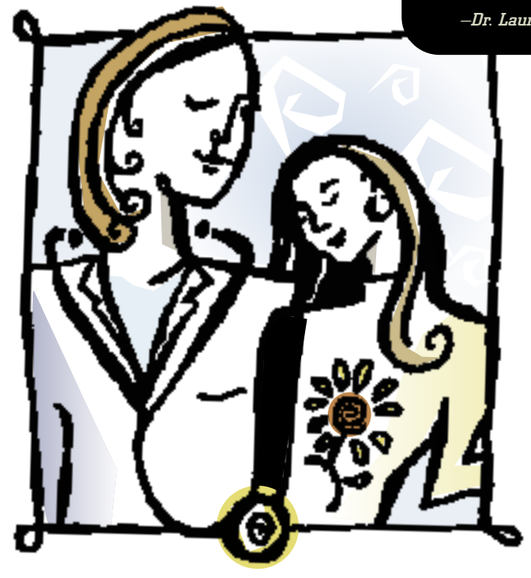
"You have to anticipate their needs. They aren't going to tell you about potentially risky behavior; you have to ask," Dr. Scalfano said. "You also have to listen and be patient and earn their trust."

Brittni said she is just happy she found a physician who takes the time and makes the effort to understand her.

"I would hope that no one else would have to go through what I did at first," she said. "I am glad I found someone so encouraging and someone who wants to help me out. Dr. Scalfano listens, and it's obvious that she cares for her patients." ❄

*For more information on the UT Southwestern adolescent medicine clinic, please call 214-456-6500.*

"When children become adults, they are often expected to take charge of their health care overnight. I try to bring about that transition gradually."
*—Dr. Laura Scalfano*



2004

# ANNUAL REVIEW

# HIGHLIGHTS
*of the year*

## FALL 2003

### MEDICAL CENTER, PRIVATE INVESTORS FORM COMPANY TO DEVELOP NEW DRUGS

Research pioneered at UT Southwestern has led to the formation of Reata Discovery Inc., a Dallas biopharmaceutical company with $5.2 million in startup financing and statewide and international business partnerships.

Reata, created by an unusual public-private partnership, is different in that its drugs in development are further along in the Food and Drug Administration's approval process than those of most startup firms, and it possesses platform technologies aimed at discovering new drugs to treat both cancer and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases and amyotrophic lateral sclerosis.

Discoveries from UT Southwestern, as well as partnerships with UT M.D. Anderson Cancer Center and several Asian companies, are at the heart of the company's technologies. Reata is developing four new classes of low-molecular-weight compounds discovered by its founding scientists, most of whom are UT Southwestern faculty members. Reata, based in Dallas, also features a unique small-molecule discovery program focused on identifying new drugs.

### LOU GEHRIG'S DISEASE CASES ELEVATED AMONG GULF WAR VETERANS

An unusually high number of veterans of the 1991 Gulf War are becoming ill and dying of amyotrophic lateral sclerosis (ALS), which typically does not strike until decades later in life, according to Dr. Robert Haley, chief of epidemiology at UT Southwestern.

A study published in *Neurology* shows that veterans of the first Gulf War under the age of 45 have developed ALS, or Lou Gehrig's disease, as much as three times more frequently than those of comparable ages in the general population.

Another study by the Department of Veterans Affairs – published in the same issue of the journal – confirms Dr. Haley's findings using a different method. The VA undertook its study in 1998, one year after Dr. Haley began his investigations. The papers by Dr. Haley and VA researchers represent the first peer-reviewed studies establishing the increased incidence of ALS among Gulf War veterans.

### HALF OF YOUNG CANCER PATIENTS FACE MAJOR MEDICAL PROBLEMS LATER

Nearly half of childhood cancer survivors have at least one fairly significant health problem later in life caused by their cancer or cancer treatment, according to a landmark study of nearly 10,000 survivors at UT Southwestern and other institutions.

The study in *The Journal of the American Medical Association* also found that women are 40 percent more likely than men to suffer long-term problems.

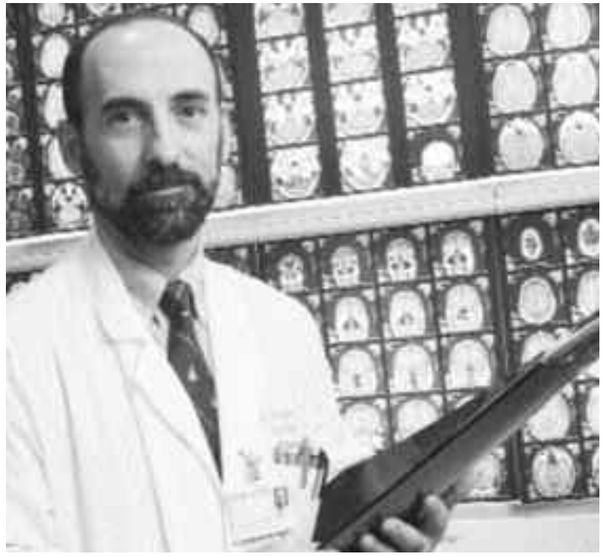
Dr. Kevin Oeffinger, professor of family and community medicine and senior author of the multicenter Childhood Cancer Survivor Study said he hopes the findings will lead to implementation of new guidelines for providing health care for pediatric cancer survivors as they grow older.

### DIAGNOSING MS SOONER

The notoriously long and difficult process of confirming the diagnosis of multiple sclerosis has become simpler, a researcher at UT Southwestern reported in *Neurology*.

Dr. Elliott Frohman, lead author of the paper and head of the multiple sclerosis program, and his colleagues said data suggest that advanced applications of magnetic resonance imaging scans can be used in concert with clinical observations to identify the complex neurological disorder more quickly.

DR. KEVIN OEFFINGER CHECKS THE BLOOD PRESSURE OF A CHILDHOOD CANCER SURVIVOR, 20-YEAR-OLD CHRIS SLOGGETT. DR. OEFFINGER HOPES A NEW STUDY WILL LEAD TO GUIDELINES FOR CARING FOR PATIENTS WHO HAVE SURVIVED CHILDHOOD CANCERS.



DR. ELLIOT FROHMAN BELIEVES THAT ADVANCES IN MRI TECHNOLOGY WILL MAKE IT POSSIBLE FOR DOCTORS TO ELIMINATE THE COMPLEXITIES OF DIAGNOSING MS AND SPEED UP THE PROCESS.

New technology produces MRI scans that show white matter abnormalities in the brain that provide definitive evidence of the disease's progression, eliminating the need for time-separated clinical observations. Using this new method, Dr. Frohman said, diagnosis can be confirmed as early as a patient's first attack.

### CANCER SOCIETY AWARDS TOP HONOR TO PARADA

Dr. Luis Parada, director of the Center for Developmental Biology, has been awarded 2003's only American Cancer Society basic research professorship, making him one of 20 such designated professors nationwide.

The research professorship carries a five-year award of $60,000 per year with the possibility of a five-year renewal. The professorship provides flexible funding for established full-time investigators in mid-career who have made watershed contributions to cancer research and are expected to continue to provide leadership in their research areas. The ACS grants no more than two basic research professorships and two clinical research professorships a year.

DR. LUIS PARADA

The ACS said, "In awarding Dr. Parada this professorship, the society recognizes his extraordinary ability to integrate the fields of molecular genetics, embryonic development and signal transduction in ways that will provide critical insights into how brain cancers arise, develop and progress, thus paving the way to better treatments for these devastating tumors."

## WINTER 2003-2004

### CAMPAIGN CONTRIBUTIONS TOP $300 MILLION MARK, ANONYMOUS DONOR MAKES $50 MILLION GIFT

Record-setting new gifts and pledges to UT Southwestern's *Innovations in Medicine* capital drive brought the total raised by November 2003 to $301 million, and the enthusiastic donor response persuaded campaign leaders to raise the overall goal from $450 million to $500 million. The additional $50 million will go to the Clinical Services Initiative component of the drive.

A new $50 million anonymous contribution – the largest gift in the medical center's history and the largest single philanthropic donation ever to a Dallas organization – enabled the campaign total to top $300 million in less than three years – more than twice the entire goal of UT Southwestern's last major campaign, which ended in 1995.

The record-setting gift is being used to enhance the quality of clinical care and service received by UT Southwestern's patients as well as to find treatments and cures for diseases through basic research. The goal of the Clinical Services Initia-

tive, announced in February 2003, is to develop a system for delivering a superior medical experience for patients at the center's clinics and hospitals.

### FAMILY COUNSELING CENTER JOINS WITH UNIVERSITY

The Family Studies Center of Dallas – a nonprofit counseling center founded by Dr. W. Robert Beavers in 1973 – has come under the UT Southwestern umbrella as a new division of the Department of Psychiatry. Dr. Beavers, who has joined the UT Southwestern faculty as a professor of psychiatry, is one of the country's foremost authorities on family dynamics and a leading proponent of family-based therapy.

The board of directors of the Family Studies Center voted to transfer its assets to Southwestern Medical Foundation to support the center at UT Southwestern. In addition, Dr. Beavers has established a $1.3 million charitable remainder trust, which will create a chair in his name to support future directors of the UT Southwestern Family Studies Center.

DR. W. ROBERT BEAVERS

The center, which is devoted to advancing family approaches to treating mental disorders, not only serves patients and their families, but also works with affiliated hospitals and other community agencies to promote the application of family interventions. The center will serve as a training facility for psychiatry residents, psychology graduate students and medical students, as well.

### MANGELSDORF WINS NOTED GERMAN PRIZE

Dr. David J. Mangelsdorf, professor of pharmacology and biochemistry and an associate investigator in the university's Howard Hughes Medical Institute, has been awarded Germany's highly respected Heinrich Wieland Prize for his research on lipids.

The prestigious international science award is given annually to one individual for research in the fields of biochemistry, chemistry and physiology of fats and lipids and their clinical importance. Dr. Mangelsdorf's research focuses on the mechanisms of nuclear receptor proteins that serve as sensors in protecting human cells against unusually high and possibly toxic levels of lipids, such as cholesterol and fatty acids. These lipid-sensing proteins play a central role in the maintenance of physiological levels of lipids consumed with food.

Three other UT Southwestern scientists have received the Wieland Prize since its inception in 1963. Nobel laureates Dr. Michael Brown, director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease, and Dr. Joseph Goldstein, chairman of molecular genetics, claimed the award in 1974 for their research in lipoprotein

DR. DAVID J. MANGELSDORF

receptors and the genetic control of cholesterol metabolism. Dr. John Dietschy, professor of internal medicine, received the Wieland Prize in 1983 for his research into the regulation of cholesterol balance in tissues.

### DRUG COMBO DELAYS PROSTATE SYMPTOMS

For men who suffer from enlargement of the prostate, also called benign prostatic hyperplasia (BPH), combining two classes of drugs reduces the risk of symptoms significantly worsening and other complications by 66 percent, according to research led by UT Southwestern investigators.

A five-year, multicenter study in *The New England Journal of Medicine* provides the first scientific evidence that combining alpha-blocking doxazosin with the drug finasteride is significantly more effective than using either treatment alone, said Dr. John McConnell, executive vice president for health system affairs and lead author of the study. The clinical trial involved more than





DR. JOHN MCCONNELL (LEFT) AND DR. CLAUS ROEHRBORN, CHAIRMAN OF UROLOGY, LED A NATIONAL STUDY INVOLVING 3,000 MEN WITH BENIGN PROSTATIC HYPERPLASIA.

3,000 men and 20 major medical centers across the United States and was the largest study of its kind ever conducted.

Use of finasteride alone or the combination therapy significantly reduced the risk of acute urinary retention and the need for surgical intervention. A surprising finding of the study was that the alpha-blocker doxazosin was not effective in reducing the long-term risk of acute urinary retention or need for surgical therapy.

### SÜDHOF WINS METLIFE AWARD IN ALZHEIMER'S

Dr. Thomas Südhof, director of the C. Vincent Prothro Center for Research in Basic Neuroscience and the Gill Center for Research on Brain Cell Communication, has been named co-recipient of the MetLife Foundation Award for Medical Research in Alzheimer's Disease in recognition of his contributions to understanding the illness.

Dr. Südhof is internationally known for his studies into the mechanism by which neurons communicate in the brain. In 2001 he made a breakthrough discovery about the role of a protein involved in the onset of Alzheimer's. More recently, he found that a specific group of brain proteins, alpha-neurexins, is essential to activate communication between neurons, and, without this group of proteins, all functions of the central nervous system are disrupted.

DR. THOMAS SÜDHOF

In 2004 Dr. Südhof and his colleagues published a study in *Neuron* that offered the first evidence that lack of a protein known as RIM1 alpha causes profound deficits in the learning process. The discovery is a major step in understanding the molecular events that underlie learning and memory – complex processes that can be impaired in human neuropsychiatric disorders, such as Alzheimer's disease, mental retardation and schizophrenia.

When this molecule was deleted, the mice became "incredibly stupid," said Dr. Südhof. He hopes that further study of the protein's role in learning and memory will lead to potential treatments for some neuropsychiatric disorders.

**SPRING 2004**

### GREEN FOUNDATION ESTABLISHES CENTER FOR SYSTEMS BIOLOGY

A major grant from the Cecil and Ida Green Foundation, representing the final distribution of the foundation's assets by its trustees, was combined with a specific bequest from the late Mr. Green through his trust to provide $12.8 million to UT Southwestern.

The gift was used to establish a center that will utilize information technology to enable scientists to link basic research on molecules and cells with analysis of the function of entire biological systems. The Cecil H. and Ida Green Comprehensive Center for Molecular, Computational and Systems Biology is directed by Dr. Alfred Gilman, chairman of pharmacology and one of four Nobel laureates at UT Southwestern.

The emerging field of systems biology focuses on how individual

parts of an organism – from small-scale molecules and proteins to larger-scale cells and tissues – work in concert to produce a functioning – or in the case of disease, malfunctioning – life form. In systems biology, experts in scientific disciplines – including biology, physics, mathematics and computer science – come together to create models of biological systems that consider not only the individual parts but also how they react to each other and to changes in their environment.

### NEW NIH CENTER TO TEST CHILDREN'S DRUG REACTIONS

Pediatric researchers at UT Southwestern received a $2 million grant from the National Institutes of Health to establish a pharmacology research study center at Children's Medical Center Dallas to study how children react to drugs.

The NIH-funded pediatric pharmacology research center, one of 13 in the United States, will provide the infrastructure and support that researchers need to study drug therapies in infants and children. The investigators will evaluate the safety, tolerability, dosing schedules, and effectiveness of new and existing drugs in pediatric patients.

Dr. George McCracken, professor of pediatrics, and Dr. Hasan Jafri, assistant professor of pediatrics, will co-direct the center.

### FETAL LUNGS' SIGNAL MAY INITIATE LABOR

A protein released from the lungs of a developing mouse fetus initiates a cascade of chemical events leading to the mother's initiation of labor, researchers at UT Southwestern found.

The research, which has implications for humans, marks the first time a link between a specific fetal lung protein and labor has been identified, said Dr. Carole Mendelson, professor of biochemistry and obstetrics and gynecology and senior author of the study published in the *Proceedings of the National Academy of Sciences*.

The initiation of term labor is carefully timed to begin only after the embryo is sufficiently mature to survive outside the womb. Previous studies suggested that the signal for labor in humans may arise from the fetus, but the nature of the signal and actual mechanism was unclear, said Dr. Mendelson, co-director of the North Texas March of Dimes Birth Defects Center at UT Southwestern. In the new study, researchers found evidence that a substance secreted by the lungs of a developing fetus contains the key signal that initiates labor. The substance, called surfactant, is essential for normal breathing outside the womb.

DR. CAROLE MENDELSON; DR. JENNIFER CONDON, INSTRUCTOR OF BIOCHEMISTRY; AND DR. PANCHARATNAM JEYASURIA, A RESEARCH FELLOW IN INTERNAL MEDICINE (LEFT TO RIGHT), HAVE FOUND EVIDENCE IN MICE THAT A SUBSTANCE SECRETED BY THE LUNGS OF A DEVELOPING FETUS CONTAINS THE KEY SIGNAL THAT INITIATES LABOR.

### RESEARCH MAY LEAD TO NEW WAY TO PREVENT NARCOLEPSY

Researchers at UT Southwestern discovered a new potential avenue for curing human narcolepsy, and the work may also lead to more effective ways for insomniacs to boost their wakefulness during the daytime.

Artificially reintroducing a brain chemical called orexin into mice that lack the ability to produce the chemical on their own rids the mice of their narcolepsy symptoms, the researchers discovered and reported in *Proceedings of the National Academy of Sciences*. The genetically engineered mice in the study lacked a particular type of nerve cell in the brain that produces orexin. Most researchers believe that in humans, a lack of or deficiency in orexin causes narcolepsy, a rare disease in which people uncontrollably fall asleep, are excessively sleepy during the day and experience sudden muscle weakness called cataplexy.

These experiments provide a strong proof of the concept that introducing into the brain a molecule that mimics the effect of orexin will be the fundamental cure for human narcolepsy, said Dr. Masashi Yanagisawa, an investigator in the Howard Hughes Medical Institute at UT Southwestern, professor of molecular genetics and the paper's senior author.

### NATIONAL ACADEMY OF SCIENCES ELECTS WANG

Dr. Xiaodong Wang, a professor of biochemistry who discovered the biochemical pathway responsible for cell death, was elected to the National Academy of Sciences, one of the highest honors attainable by an American scientist.

Dr. Wang became the 15th UT Southwestern faculty member serving on the prestigious organization. There are now 19 NAS members at Texas medical institutions, with more than 75 percent working at UT Southwestern.

Earlier in the year, Dr. Wang was awarded the prestigious National Academy of Sciences Award in Molecular Biology, an honor given annually for a recent notable discovery in molecular biology by a young scientist. Dr. Wang was selected on the basis of his biochemical studies of apoptosis, or cell death, a phenomenon in which cells activate a self-destruction program. As the body generates new cells, older cells must activate their self-destruction program. In the case of cancer cells, they are unable to maintain a balance and grow uncontrollably.

DR. XIAODONG WANG



DRS. MATTHEW PORTEUS, LEIGHTON JAMES AND MICHELLE GILL (LEFT TO RIGHT)

## SUMMER 2004

### PRC PRESENTS THREE RESEARCHER AWARDS

The President's Research Council presented its 2004 Distinguished Young Researcher Award to three especially promising new faculty members at UT Southwestern.

The recipients – Dr. Michelle Gill, assistant professor of pediatrics; Dr. Leighton James, assistant professor of internal medicine in nephrology; and Dr. Matthew Porteus, assistant professor of pediatrics and biochemistry – were each given a $60,000 award.

Dr. Gill is studying how respiratory syncytial virus, a common childhood respiratory infection, affects the immune system. She is interested in how the virus may alter the function of a specific immune cell, thereby affecting the chain of command in the immune response to the virus.

Dr. James is studying a specific pathway that leads to kidney damage in people with diabetes. In diabetics, high levels of glucose in the blood lead to insulin resistance. He has discovered that overstimulation of the hexosamine pathway, in which glucose is converted to a different molecule, leads to increased activity of inflammatory and injury pathways in the kidney.

Dr. Porteus is developing gene-therapy techniques for diseases such as sickle cell anemia. He has established a rapid technique by which a mutation in a gene can be specifically corrected by swapping the mutation, or irregular sequence, with the normal sequence.

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

### 369 EARN DEGREES FROM THREE SCHOOLS

Diplomas were received by 204 Southwestern Medical School students and 35 Southwestern Graduate School of Biomedical Sciences students at June 5 commencement ceremonies.

Former New York Yankee third baseman Dr. Robert W. "Bobby" Brown, a retired Fort Worth cardiologist and former star player with the New York Yankees, gave the commencement address.

The top award to a graduating medical student, Southwestern Medical Foundation's Ho Din Award, was presented to Dr. William "Will" Schmalstieg by Shirley Pollock, a Foundation trustee.

Andrew Shulman received the Nominata Award, given to the outstanding graduate school student.

Southwestern Allied Health Sciences School conferred degrees on 61 students at its inaugural winter commencement. Another 69 received degrees at August graduation exercises.

### BRAIN IMAGING PROVES EFFECTIVE FOR DIAGNOSING ALZHEIMER'S

Nearly a century after Alzheimer's disease was first identified, there has been no foolproof way to diagnose the illness in a living patient. But a new method used by doctors at UT Southwestern is almost 100 percent accurate when combined with clinical assessment.

Testing blood flow in a specific region of the brain may boost the degree of diagnostic certainty in difficult cases from 90 percent to almost 100 percent, said Dr. Frederick Bonte, director of the Nuclear Medicine Center at UT Southwestern.

DR. FREDERICK BONTE

A study in the *Journal of Nuclear Medicine* showed that single-photon emission computed tomography can be used to identify a characteristic sign of Alzheimer's disease and distinguish it from a group of illnesses known as frontotemporal diseases, which comprise the second-leading cause of dementia.

### BRAINS OF DEPRESSED PEOPLE CONTAIN EXTRA NERVE CELLS

Individuals who suffer from severe depression have more nerve cells in the part of the brain that controls emotion, UT Southwestern researchers discovered.

Postmortem studies of patients diagnosed with major depressive disorder (MDD) showed a 31 percent greater than average number of nerve cells in the portion of the thalamus involved with emotional regulation. Researchers also discovered that this portion of the thalamus is physically larger than normal in people with MDD. Located in the center of the brain, the thalamus is involved with many different brain functions, including relaying information from other parts of the brain to the cerebral cortex.

The findings, published in *The American Journal of Psychiatry*, are the first to directly link a psychiatric disorder with an increase in total regional nerve cells, said Dr. Dwight German, professor of psychiatry.

SEVERELY DEPRESSED INDIVIDUALS HAVE MORE NERVE CELLS IN THE PART OF THE BRAIN THAT CONTROLS EMOTION, RESEARCHERS AT UT SOUTHWESTERN HAVE FOUND. DR. DWIGHT GERMAN WAS CO-AUTHOR OF THE STUDY.





The study results support the hypothesis that structural abnormalities in the brain are responsible for depression, said Dr. German.

### EXPERT PANEL UPDATES CHOLESTEROL GUIDELINES

The National Cholesterol Education Program (NCEP) updated its guidelines for treatment of blood cholesterol, suggesting that people at risk for heart attack and stroke would benefit from more intensive cholesterol-lowering therapies.

Dr. Scott M. Grundy, director of the Center for Human Nutrition at UT Southwestern, said the new guidelines are based largely on results from five major clinical trials involving cholesterol-lowering medications called statins. These results make possible changes to the 2001 guidelines issued by the NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, which Dr. Grundy chaired.

For high-risk patients, the guidelines issued in 2001 called for doctors to prescribe cholesterol-lowering drugs along with dietary therapy as necessary to reduce low-density lipoprotein (LDL) cholesterol levels to less than 100 milligrams per deciliter. Recent clinical trials allowed the panel to identify a subgroup of very high risk patients who may benefit from even more intensive lowering of LDL. For those, the new recommendations give physicians the option of reducing LDL cholesterol to less than 70 mg/dL.

For people who are at moderately high risk, the panel recommended reducing LDL cholesterol to less than 130 mg/dL. Recent clinical trials, however, strongly suggest that moderately high-risk

DR. SCOTT GRUNDY

people will receive additional benefit if their LDL levels are reduced to less than 100 mg/dL.

### NEW APPOINTMENTS FOR 2003-2004

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

■ Dr. William M. Behrendt was named vice president for human resources. He oversees all personnel at UT Southwestern Medical Center including the University Hospitals and Clinics. Dr. Behrendt had served as senior vice president of human resources at CareGroup HealthCare System and Beth Israel Deaconess Medical Center in Boston. He earned a doctorate in clinical psychology from Washington University in St. Louis.

■ Bruce Fairbanks was named vice president for health system financial affairs. Mr. Fairbanks is the former chief clinical financial officer and senior financial strategist for the University of California, Davis, where he worked from 1997 until joining the medical center. Mr. Fairbanks, a Colorado State University graduate, has a Master of Business Administration in management from the University of Southern Mississippi.

■ Dr. Larry Gentilello was named chairman of the division of burn/trauma/critical care and first holder of the C. James Carrico, M.D., Distinguished Chair in Surgery for Trauma & Critical Care. Dr. Gentilello was on the faculties of the University of Washington School of Medicine and Harvard Medical School before joining UT Southwestern. He received his medical degree from Albert Einstein College of Medicine in New York.

■ Dr. Alfred Gilman, Nobel laureate and chairman of pharmacology, was named interim dean of Southwestern Medical School. Dr. Gilman remains head of pharmacology and 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 directing the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational and Systems Biology. 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. Dr. Gilman earned an M.D. and Ph.D. in pharmacology from Case Western Reserve University.

■ Dr. Beth Levine was named chief of infectious diseases in the Department of Internal Medicine and holder of the Jay P. Sanford Professorship in Infectious Diseases. Her primary research focus is neurovirology. She was a faculty member at Columbia University College of Physicians and Surgeons prior to joining UT Southwestern. She received her medical degree from Cornell University in 1986 and completed her residency at Mount Sinai Hospital in New York City.

■ Dr. Dennis McKearin was named associate dean for the Medical Scientist Training Program. Associate professor of molecular biology and chair of the genetics and development program in the Southwestern Graduate School of Biomedical Sciences, Dr. McKearin earned a Ph.D. in biochemistry from the University of Illinois at Urbana/Champaign. His research focuses on the molecular genetics and biology of stem cells, as well as the mechanisms of germ cell differentiation.

■ Dr. Milton Packer was named director of the new Center for Biostatistics and Clinical Science. He also holds an appointment as a professor of internal medicine and has been named the first holder of the Gayle and Paul Stoffel Distinguished Chair in Cardiology. Dr. Packer came to UT Southwestern from Columbia University College of Physicians and Surgeons, where he was chief of circulatory physiology and professor of medicine and pharmacology. After receiving his medical degree from Jefferson Medical College in 1973, he was a medical resident at the Albert Einstein College of Medicine of Yeshiva University and completed his fellowship in cardiology at Mount Sinai School of Medicine of New York University.

■ Sharon Riley was named UT Southwestern vice president for hospital operations and CEO, University Hospitals. Most recently, she was chief operating officer of Anne Arundel Medical Center in Annapolis, Md., and she previously served as chief operating officer of the University of Nebraska Medical Center and vice president of Nebraska Health System, which includes the university medical center. Ms. Riley holds a master's degree in health administration from the University of Iowa.

■ Wendell Roberts was named vice president for ambulatory services. Mr. Roberts served the last four years as vice president for ambulatory services at the University of North Carolina Healthcare System. At UNC Mr. Roberts was responsible for the direction and management of ambulatory care services provided on campus and in community-based clinics. A graduate of Appalachian State University, he has a Master of Business Administration from Queens College in New York.

■ Dr. Michael Roth was named associate dean for Southwestern Graduate School of Biomedical Sciences, a position which will allow him to oversee the graduate school's doctoral programs. A faculty member since 1985, his experience includes helping to design the original curriculum for the first-year core course that all graduate students must take. A professor of biochemistry and holder of the Diane and Hal Brierley Chair in Biomedical Research, Dr. Roth earned his doctorate through the cellular and molecular biology program at the University of Alabama at Birmingham.

■ Dr. James Willson was named director of the Harold C. Simmons Comprehensive Cancer Center, associate dean for oncology programs at UT Southwestern, professor of internal medicine and holder of the Lisa K. Simmons Distinguished Chair in Comprehensive Oncology. He was formerly director of the National Cancer Institute-designated Case Comprehensive Cancer Center in Cleveland. A pioneer in colon and rectal cancer research, his work has led to the development of cell and animal models for human colon cancer that have been key to identifying genetic factors in disease progression. His current research focuses on identification of novel molecular targets for cancer therapy. Dr. Willson joined the Case Western faculty in 1987, and, prior to that, served at the University of Wisconsin. He received his medical degree from the University of Alabama, with additional training at the NCI and Johns Hopkins Hospital.

### MAJOR GIFTS 2003-2004

Philanthropists continued to demonstrate their commitment to UT Southwestern in 2003-2004, providing support for a variety of research and clinical programs.

Major new pledges and gifts for programs received in the fiscal year ending Aug. 31, 2004, included:

■ $50 million from an anonymous donor for UT Southwestern's Clinical Services Initiative, neuroscience research and other priorities in the *Innovations in Medicine* campaign.

HIGHLIGHTS

■ $15.4 million from the Simmons Foundation to provide additional support for the Harold C. Simmons Comprehensive Cancer Center.

■ $12.8 million from the Cecil and Ida Green Foundation and from Mr. Green to establish the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational and Systems Biology.

■ $6 million from Sarah and Charles Seay of additional support for the Sarah M. and Charles E. Seay Comprehensive Center for Pediatric Emergency and Intensive Care.

■ $3.25 million from the Perot Foundation in further support of UT Southwestern's M.D./Ph.D. education program and for research in the Department of Molecular Genetics.

■ $2.8 million bequeathed by Pauline E. Weinberger to support research in the Pauline and Adolph Weinberger Laboratories for Cardiopulmonary Research.

■ $1.5 million from the Horchow Family Charitable Trust to bring to Dallas young pediatric researchers as part of the new Endowed Scholars Program in Clinical Science.

■ $1.5 million from Texas Instruments Foundation to provide support for the Texas Instruments Scholars Program in Advanced Imaging Technologies.

■ $1.4 million from the Dr. Bob and Jean Smith Foundation to establish the Dr. Bob & Jean Smith Foundation Distinguished Chair in Neuromuscular Disease Research and to support laboratory research.

■ $1.3 million from Dr. W. Robert Beavers to establish a chair to support future directors of the UT Southwestern Family Studies Center.

■ $1 million from the Barrett Foundation Fund of Communities Foundation of Texas to establish the Barrett Family Center for Pediatric Oncology.

■ $1 million from the Jane & John Justin Foundation of Fort Worth to endow a distinguished chair in urology.

■ $1 million from the estate of Ann Eickenroht Miller for scholarships in memory of her son, Edmund Eickenroht.

■ $1 million from Mr. and Mrs. J. Thomas Walter to establish the Walter Family Distinguished Chair in Internal Medicine, in Honor of Albert D. Roberts, M.D.

■ $700,000 from Mr. and Mrs. Lawrence Lacerte, given through the St. Paul Foundation, for major cardiology equipment and renovations at University Hospital-St. Paul.

■ $700,000 from proceeds of the 2004 Sweetheart Ball to support heart disease research.

■ $600,000 from Centex Corp. to establish a distinguished chair in honor of the company's chief executive officer, Lawrence Hirsch, and a professorship in honor of its director, Paul Stoffel.

■ $550,000 from Sherry Knopf Crasilneck to upgrade a chair in psychiatry honoring her late husband, Albert Knopf, to the level of a distinguished chair.

■ $525,000 from Mr. and Mrs. Louis A. Beecherl Jr. toward the establishment of a Distinguished Chair in Medical Science in honor of Texas Speaker of the House Tom Craddick and his wife, Nadine.

■ $500,000 from an anonymous donor to establish the Fredye Factor Chair in Rheumatoid Arthritis.

■ $500,000 from the Cain Foundation toward endowing a center for clinical research on mobility disorders.

■ $500,000 from the Eugene McDermott Foundation for furnishings and interior design in UT Southwestern's new Biomedical Research Tower.

■ $500,000 from Zale Corp. for the rehabilitation unit at University Hospital-Zale Lipshy.

■ $420,000 from the estate of D.J. Moody to create a fund for medical research.

■ $375,000 from the Texas Stampede to benefit pediatric programs at UT Southwestern.

■ $315,000 from Once Upon a Time….

■ $300,000 from the Leukemia Association of North Central Texas for further support of cancer research.

■ $300,000 from friends and colleagues to establish a chair in urology honoring Dr. Paul C. Peters Sr.

■ $300,000 from Mrs. Elaine Sammons to add to her previous gifts and establish the Elaine Dewey Sammons Distinguished Chair in Cancer Research, in Honor of Eugene P. Frenkel, M.D.

■ $300,000 from the Hansjoerg Wyss Medical Foundation to establish the Hansjoerg Wyss Professorship in Orthopaedic Trauma.

■ $265,000 from the Sid W. Richardson Foundation to establish a cancer pain management program at the UT Southwestern Moncrief Cancer Center in Fort Worth.

■ $260,000 from Mr. and Mrs. John L. Roach for clinical care and research.

■ $250,000 of additional support from Mr. and Mrs. Edward M. Ackerman for research in preventative medicine.

■ $250,000 from Dr. Norman M. and Audrey Kaplan to endow the Norman and Audrey Kaplan Chair in Hypertension.

■ $250,000 from Giant Tiger Stores Limited to support research on muscle metabolic disease.

■ $250,000 from the Wikert Group to fund fellowships to train physicians from developing countries in the research and treatments of infected liver diseases.

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

■ An anonymous couple to establish a fund in honor of Dr. Daniel Foster, former chairman of internal medicine.

■ An anonymous donor for professorships in memory of Dallas physicians Dr. Stanley Gilbert and Dr. José Garcia.

■ The Hon. and Mrs. William P. Clements Jr. for clinical and research programs.

■ Dr. and Mrs. Clay T. Cockerell toward a chair in dermatopathology.

■ Dallas County Medical Society Alliance to support UT Southwestern's STARS program to improve science education in public schools.

■ Dallas Eye Ball 2004 and Prevent Blindness Texas to further research on vision-threatening eye diseases.

■ Ruth Pate Dally to support oncology programs at UT Southwestern Moncrief Cancer Center in Fort Worth.

■ Dr. Robert G. Freeman toward a chair in dermatopathology.

■ Mr. and Mrs. Irwin J. Grossman for diabetes research.

■ The estates of Leone and Charles Orrin Hopper for scholarships.

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

■ Mr. and Mrs. Jeff K. Jensen for diabetes research.

■ Mr. and Mrs. Michael H. Jordan for research on neurodegenerative disease.

■ KidneyTexas Inc. for research on renal disease.

■ Gillson Longenbaugh Foundation to support cancer and neurological research.

■ Tavenner and Carolyn Lupton to establish the T.C. Lupton Family Professorship in Patient Care, in Honor of Dr. John Dowling McConnell and Dr. David Andrew Pistenmaa.

■ Nasher Foundation for cancer research under Dr. Eugene Frenkel.

■ Mr. and Mrs. Charles Nearburg for research on Ewing's sarcoma.

■ Mr. and Mrs. Monroe B. Passis for neurology research.

■ Ruth E. Robinson to establish, in memory of her late husband, the Edgar A. Robinson Family Fund in Cancer Research, in Honor of Eugene Frenkel, M.D.

■ Ron and Phyllis Steinhart for clinical and research programs.

■ Stemmons Foundation for the Clinical Services Initiative.

■ Mr. and Mrs. Richard C. Strauss for clinical enhancement and research.

■ Mr. Theodore H. Strauss and Ms. Sue L. Wayne for the Annette G. Strauss Center in Neuro-Oncology.

■ The Friends of the Texas Ballet Theater to support clinical and research programs.

■ James and Kay McCord Watson for medical research.

■ Mr. and Mrs. J. McDonald Williams for outreach medical programs in underserved areas of Dallas. ❊