

2009 ANNUAL REVIEW

SOUTHWESTERN MEDICINE



MAKING SENSE OF THE SENSES | EATING RIGHT | HYPERTENSION | MINIMIZING SURGERY
THE WONDER HORMONE | GENETICS AND LUNG DISEASE

C O N T E N T S

MAKING SENSE OF THE SENSES 2

At UT Southwestern, researchers are gaining a better sense of our senses – the intimate conduits through which we experience the world.

PRESSURE POINTS 12

UT Southwestern is uniquely positioned among academic medical research centers to study cardiovascular diseases like hypertension.

THINKING SMALL 20

At UT Southwestern, surgeons are finding new ways to minimize incisions.

LEPTIN – THE WONDER HORMONE 30

Recent findings by UT Southwestern researchers suggest that insulin isn't the only agent effective against type 1 diabetes.

DECODING THE FAMILY TREE 38

A software program created by a UT Southwestern surgical oncologist has revolutionized cancer risk assessment globally.

GENERATIONAL INHERITANCE 46

One extended family is providing genetic clues to lung disease.

READING, WRITING AND EATING RIGHT 52

UT Southwestern students and faculty are taking their expertise on the road – helping youngsters learn to choose the right foods to promote healthy eating habits.

THE CLINICAL FRONTIER 60

SEED THERAPY PINPOINTS BREAST TUMORS 60

BREATHING EASES CANCER THERAPY 61

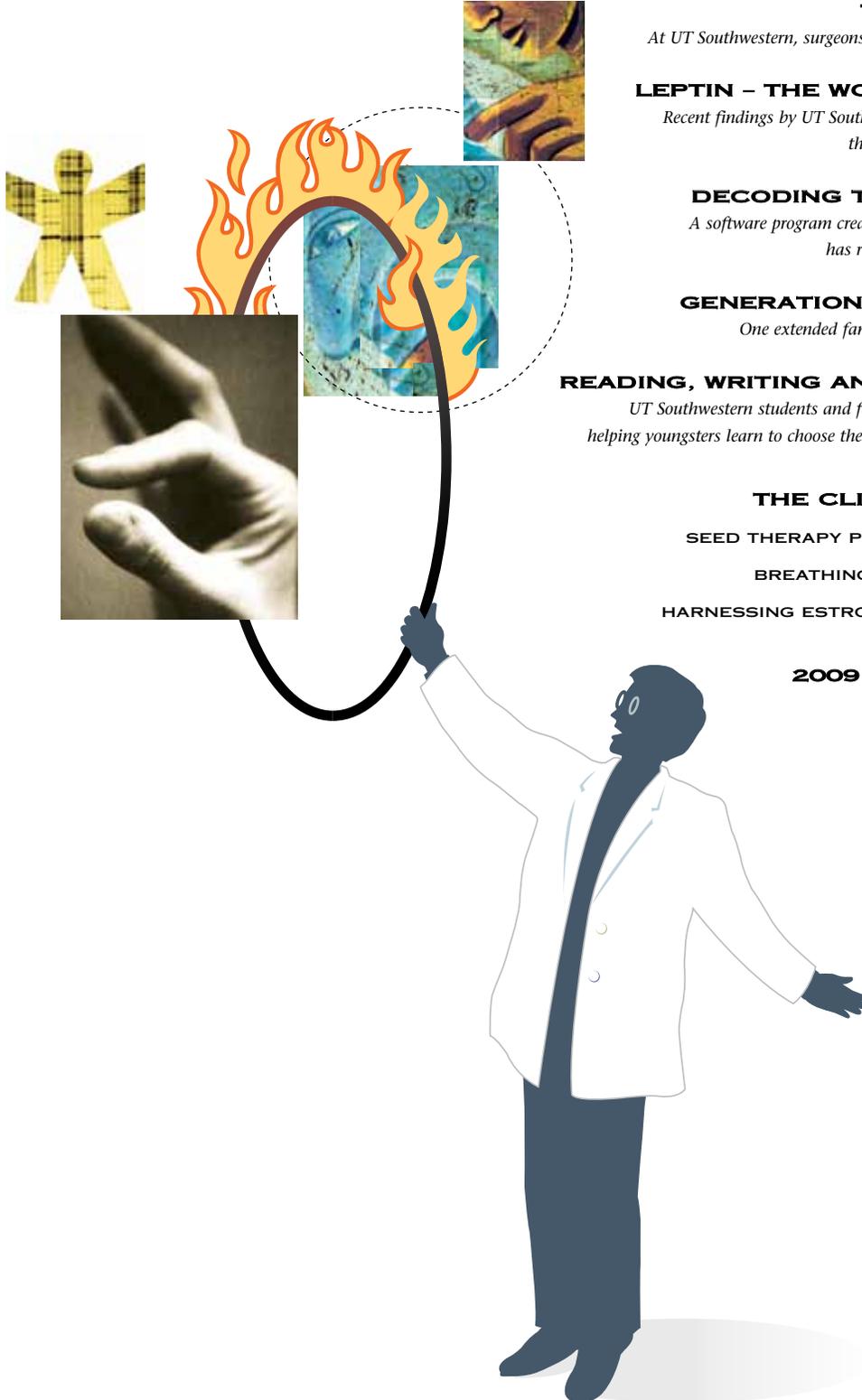
HARNESSING ESTROGEN FOR SEVERE TRAUMA 62

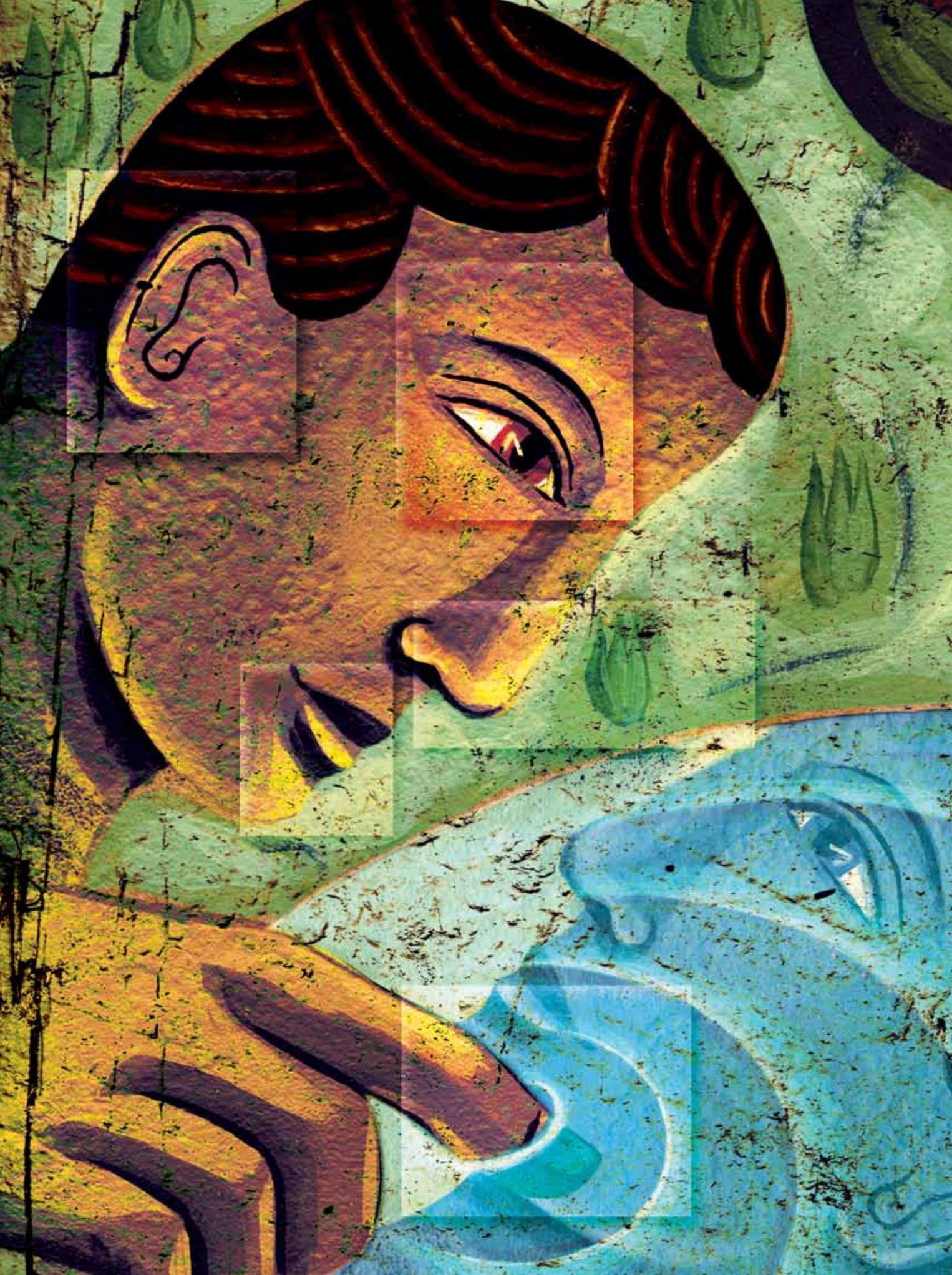
2009 ANNUAL REVIEW 63

HIGHLIGHTS OF THE YEAR 64

FINANCIAL STATEMENT 74

GIFT REPORT 77





Making **Sense** *of the* **Senses**

Our five senses – taste, touch, smell, hearing and sight – are the intimate conduits through which we experience the world. We carry them with us wherever we go, often without a second thought – until something goes wrong and that smooth flow of sensory information is suddenly disrupted.

At UT Southwestern Medical Center, researchers are gaining a better sense of our senses, with an eye toward a better understanding of biology, as well as an ear to the ground for clues to fight disease. From renewing feeling to the feet of diabetic patients, to exploiting an insect's smelling ability to fight malaria, here's a taste of some of the research happening in UT Southwestern laboratories and clinics.

by **Amanda
Siegfried**



The sweet smell of... pheromones?

Dr. Dean Smith, associate professor of pharmacology and neuroscience, is an expert on how insects smell. Not how they smell to us, but how they themselves detect pheromones, which are hormones secreted by one animal and perceived by another animal of the same species. This insect equivalent of “smelling” mediates a variety of behaviors, such as feeding, mating and colonizing.

Dr. Smith has spent countless hours observing the behavior of fruit flies whose ability to detect pheromones has been altered genetically. With the eager help of graduate students who now handle the bulk of fly-watching duties, Dr. Smith and his colleagues have overturned the prevailing theory of how pheromones work at the molecular level to trigger behavior in fruit flies.

The perception of smell begins with small airborne chemicals called odorants. In humans, when these chemicals come in contact with the nose, they attach directly to receptors on nerve cells there. This attachment triggers a series of signals that travel to the part of the brain that identifies the odor signal – that is, one “smells” the odorant. The brain then associates the odor with a positive or negative experience and triggers a behavioral response.

One of Dr. Smith’s key discoveries was that the fruit fly *Drosophila melanogaster* requires an additional step in the smelling process. A

certain kind of protein in its antennae acts as an intermediary between an incoming pheromone molecule and the brain cells that interpret that chemical signal as a smell. Without this critical protein – called an odorant-binding protein – an insect’s ability to detect and interpret certain pheromones is impaired.

Dr. Smith’s lab has concentrated on the fruit-fly pheromone called cVA (11-cis vaccenyl acetate). Male flies produce cVA, but both males and females react to it. Males are repelled by it; females attracted to it. It is involved in clustering, mate recognition and sexual behavior.

The researchers closely examined the interaction of cVA with nerve cells in the antennae of *Drosophila*. Holes in the antennae allow cVA to enter a fluid-filled chamber that surrounds these nerve cells. Observations showed that when the pheromone enters the antennae, the nerve cells fire.

The fluid surrounding the nerve cells also contains a free-floating odorant-binding protein called LUSH, which was known already to bind to cVA. The prevailing theory was that LUSH proteins act solely as carriers, picking up any cVA molecules that enter the antennae, transporting them to the nerve cells and releasing the pheromone cargo to bind directly to the nerve cells.

In their experiments, however, Dr. Smith’s group found that the pheromone does not attach directly to nerve cells, as was previously



While Dr. Smith’s studies have led to a greater understanding of how chemical signals result in the sense of smell in this relatively simple insect system, the impact of his findings on human health could be enormous.

Developing new ways to control insect populations could help fight diseases such as malaria, a mosquito-borne illness that each year infects up to 500 million people worldwide and kills more than 1 million, most of them young children in sub-Saharan Africa.

Other researchers recently have identified odorant-binding proteins in mosquitoes, which carry malaria, yellow fever and dengue fever. Dr. Smith said that if his work with cVA and LUSH translates to mosquitoes, then agents might be developed to target the sex-pheromone signaling system and disrupt mating. He

recently received a \$1.2 million grant from the National Institutes of Health (NIH) to study genes associated with olfaction.

“Right now, the way we manage insects is with poisons that are very toxic to people as well,” Dr. Smith said. “If we could find agents that interact with these binding proteins, it might be possible to target specific species, or just one species of mosquito, without the use of chemicals hazardous to our own health.”

In good taste

Anyone who has had a stuffy nose knows that the senses of smell and taste work together. Without smell, a meal just doesn’t taste as good. The act of chewing forces air up through the nasal passages, carrying the scent of the food along with it and intermingling both smell and taste.

Without the sense of smell, humans can still taste, but they are limited to the basic taste sensations chemically picked up by the tongue: salty, sour, sweet, bitter and umami, which is a savory sensation typically associated with the food additive monosodium glutamate (MSG).

UT Southwestern researcher Dr. Elizabeth Parks suspects there might be another basic taste sensation to add to the human palate: the taste of fat.

“This is really an emerging field, and a radical idea,” she said.



“What’s odd is, rodents like the taste of fatty acids, but humans typically don’t. Food companies work very hard to reduce their presence in the products we buy.”

—Dr. Elizabeth Parks

“Right now, the way we manage insects is with poisons that are very toxic to people as well. . . . it might be possible to target specific species, or just one species of mosquito, without the use of chemicals hazardous to our own health.”

—Dr. Dean Smith



thought. Rather, the pheromone first must dock onto LUSH. This docking action causes LUSH to change shape so it can fit – like a key in a lock – into a receptor on the surface of a specific olfactory neuron, which then sends the appropriate behavioral signal to the bug’s brain.

Interestingly, in 2004 UT Southwestern alumna Dr. Linda Buck shared the Nobel Prize in physiology or medicine with Dr. Richard Axel for their discovery of a very large family of about 1,000 genes for odorant receptors in mammals.

“Without LUSH as a bridge, the cVA pheromone can’t get its signal to the neuron, and the fly doesn’t behave normally,” Dr. Smith said. “The nerve cell’s receptor is designed to work only when cVA and LUSH are bound together. It’s a very unusual pathway that allows even single pheromone molecules to activate the nerves.”

To verify his theory, Dr. Smith created a mutant version of LUSH that was shaped to activate the nerve-cell receptors in the total absence of pheromone, proving that the LUSH-binding protein is what really activates the receptors, not the pheromone.

Dr. Smith’s team of dedicated fruit-fly watchers revealed that mutant flies lacking the gene that makes the LUSH protein can no longer detect and respond to the cVA pheromone. The result: sexually confused flies. Mutant males try to mate with other males, while females that can’t detect cVA are much less likely to mate.



“The intestines seem to be like a bus station, with buses constantly leaving with at least a little bit of fat on board, bound for the blood.”

—Dr. Elizabeth Parks

Dr. Parks, associate professor of clinical nutrition, investigates how taste affects the intestine and liver to maintain energy balance in the body. Her research suggests that the elusive taste of fat plays a key role.

But what does fat taste like?

“It doesn’t taste like butter. Although butter has fat as its base, there are other wonderful compounds in butter that give it its distinctive taste,” Dr. Parks said.

Fat consists of triglycerides, which are chemicals that contain three fatty acids. Dr. Parks believes that what people can taste are individual fatty acids in foods.

“What’s odd is, rodents like the taste of fatty acids, but humans typically don’t,” she said. “If you put dissolved, isolated fatty acids in your mouth, the taste would be astringent and unpleasant in some ways. Food companies work very hard to reduce their presence in the products we buy.”

Based on her own experiments and those of colleagues at Purdue University, Dr. Parks said evidence is mounting that the taste of fatty acids triggers biochemical signals in the body that determine how fat is processed. Understanding these processes is important, Dr. Parks said, because the preferred consumption of high-fat foods is a driving force in the U.S. obesity epidemic.

“We need to understand why people like to eat fat,” she said.

The researchers hypothesize that the taste of fat, most likely picked up by the tongue, sends a signal to the brain, which then signals the intestine, Dr. Parks said. Cells in the intestinal wall are thought to store fat and release it into the blood. When the “fat taste” signal from the brain reaches the intestine, the intestine begins releasing stored fat into the blood and also releases hormones that cause the body to gear up for fat metabolism.

The hypothesis is bolstered by experiments, including one done by Dr. Parks’ collaborators at Purdue that involves mashed potatoes. Researchers asked test subjects first to swallow a few capsules full of oil – a “fat load” that contained a known quantity of fat. After a set amount of time with no other food, subjects then placed a bite of mashed potatoes – a carbohydrate – on their tongues and spit it out, without swallowing. At the same time, the researchers monitored subjects’ levels of blood fats, or blood triglycerides. In the next

experiment, the bite of potatoes had butter on it, and two other tests were run with bites containing the fat substitutes Olestra and Simplese.

Blood analyses showed that immediately after tasting buttered mashed potatoes, triglycerides in the blood spiked, even though no new food had been eaten. When the potato was tasted alone or with fat substitutes, the increase in blood triglycerides was extremely delayed.

In other experiments, Dr. Parks has found that as a morning meal is eaten after a night-long fast, between 13 percent and 20 percent of fat initially released into the blood is from dinner the night before; subsequently, a good portion of the fat eaten at breakfast enters the body after lunch.

Dr. Parks said this delay in meal-fat absorption has been quite surprising to physiologists who believed that 99 percent of fat was absorbable immediately.

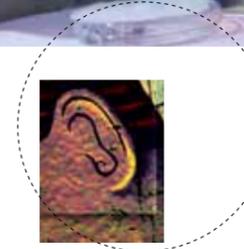
“It might be that you need to taste the fat in breakfast in order to send the proper signal that will prepare the body to quickly and efficiently process the fat from the meal that you are going to be eating,” Dr. Parks said. “Furthermore, we know that fat in food causes a feeling of satiety – contentedness with being full. If we can figure out how the taste of fat relays that message, we might be able to enhance this effect so we feel full while eating less.”

Dr. Parks said the blip in the blood triglycerides when food is put in the mouth is a key piece of the puzzle and helps pull together the connection between the taste of fat, intestinal physiology and metabolism. The fact that the body doesn’t absorb all the ingested fat right away but instead retains some in the intestinal cells is an intriguing finding, she said.

“The intestines seem to be like a bus station, with buses constantly leaving with at least a little bit of fat on board, bound for the blood,” Dr. Parks explained. “Sometimes, there is only one ‘fat’ passenger on board, but the whole system appears to be primed to respond to a large fat load when and if it comes.

“So when someone begins to eat a fat-laden dessert, it’s as if that first taste of fat alone signals the body, ‘She’s eating flan! Big fat load coming, get ready to absorb this!’” she said.

Dr. Parks is a member of UT Southwestern’s Task Force for Obesity Research, a team of scientists and clinicians who are investigating the behavioral, molecular and metabolic mechanisms behind obesity and metabolic disorders. In 2007 the team received a



\$22 million grant from the NIH to enhance its groundbreaking efforts to attack obesity from every angle, from studying fat cells to developing medicines. The group seeks to solve difficult problems by blending approaches from multiple biomedical research disciplines.

Dr. Parks said gaining a better understanding about how the sense of taste interacts with the enjoyment of food and why we eat what we do will lead to new strategies for weight management.

“We’re combining seemingly disparate areas of metabolism, intestinal physiology and taste,” she said. “I think it’s very cool to finally put all these different observations into one experimental approach, where we provide strong evidence for the taste of fat.

“By demonstrating potential interrelationships between all these factors, we hope to stimulate the study of new concepts regarding the role of food taste in energy balance,” she said.

Engineering hearing

Dr. Karen Pawlowski, assistant professor of otolaryngology – head and neck surgery, understands multidisciplinary challenges well. She is working to understand a specific genetic defect linked to deafness, while at the same time tapping into her background in ecology as she collaborates with engineers to make cochlear implants – devices that aid the hearing-impaired – safer and longer-lasting.

“Many researchers think that this might be the key, that deafness occurs because of deranged stereocilia.”

—Dr. Karen Pawlowski

According to the National Institute on Deafness and Other Communication Disorders, approximately 36 million American adults report some degree of hearing loss. Depending on the type and cause of hearing loss, some adults – and particularly children – might benefit from a cochlear implant, which helps restore an individual’s ability to perceive and understand sounds.

To appreciate the challenges involved in fixing hearing problems, it helps to look at the complexity of the ear’s anatomy, which parallels the complexity of its task. It must transform sound waves in the environment into electrical signals that the brain can interpret as voices, jackhammers, fire alarms or music.

After traveling into the outer ear, sound waves hit the eardrum and cause it to vibrate, which in turn vibrates tiny bones in the middle ear. Those vibrations eventually propagate to a complex, fluid-filled structure deep in the inner ear called the cochlea.

The cochlea is shaped like a snail: it is a long hollow tube wound in a spiral a little smaller than a dime in diameter. Along the length of the interior of the cochlea are rows of hair cells. Each of the nearly 20,000 cells has about 100 stereocilia – tiny, delicate hair-like structures – projecting off its top and into the fluid of the cochlear tube. The underside of each cell is attached to about 20 nerve cells.

Mechanical vibrations from the ear bones cause the fluid in the cochlea to move back and forth, and the stereocilia move with this action as well. The hair cells transform the wave-like fluid motion into electrical impulses, which are then sent via the auditory nerve to the brain, where the signals are interpreted as sound.

If the delicate hair cells are damaged, hearing loss or complete deafness can occur.

A rare genetic mutation can result in a condition called Usher syndrome, which results in both deafness and blindness. Individuals who inherit this mutation are usually born deaf or become deaf shortly after birth, and many are totally blind by age 20.

Dr. Pawlowski has worked with animal models of Usher syndrome and is investigating how the genetic mutation affects hair cells.

“Normally on hair cells, the stereocilia are connected to each other and arranged in a specific V-shaped pattern. In our mouse model of Usher syndrome, the stereocilia are not arranged correctly,” she said. “Many researchers think that this might be the key, that deafness occurs because of deranged stereocilia.”

Without the correct arrangement of cell components, hair cells in the animal begin to fall apart and die, Dr. Pawlowski said. As this happens, the nerve cells connected to those hair cells are no longer stimulated, resulting in deafness. Without stimulation, the nerve cells also can die.

Dr. Pawlowski said that while humans with Usher syndrome experience a similar loss of hair cells in the cochlea, researchers elsewhere have determined that human nerve loss is not as severe as what is seen in the mice.

“It’s likely that the first thing that happens in humans with Usher syndrome is the stereocilia become deranged. At some point, the hair cells actually die,” Dr. Pawlowski said. “If we could stop the process at the derangement

stage and prevent it from cascading through the whole system, there might be more intact tissue to work with in order to come in with some kind of therapy.”

One type of therapy for the hearing-impaired is a cochlear implant, a small electronic device that is surgically implanted in the inner ear and activated by another device worn outside the ear. Unlike a hearing aid, it does not make sound louder or clearer. Instead, the implant bypasses damaged parts of the auditory system, in particular damaged hair cells, and employs an electrode coiled inside the cochlea to electrically stimulate the auditory nerve.

According to the Food and Drug Administration, as of 2009, approximately 188,000 people worldwide have received implants. In the U.S., roughly 41,500 adults and 25,500 children have received them. UT Southwestern surgeons perform more than 100 cochlear implant surgeries each year.

In about 1 percent to 5 percent of patients, however, a gunky mix of bacteria called a biofilm adheres to various surfaces of the implant, including the electrodes in the cochlea. Well-developed biofilms, which form as a way for the bacteria to defend themselves against attack by the body’s defenses, are a potential cause of chronic infections. Currently, the only effective treatment for biofilm-related infections is to remove the implant, treat the infection with antibiotics, and clean and replace the implant, a procedure that is costly and stressful for the patient.

Thanks to her background in ecology, Dr. Pawlowski has the expertise to tackle the problem.

“When I was a biology undergraduate in the 1970s, I was interested in ecology, and biofilms in the environment were all the rage,” she said. “The human body is a pretty harsh environment, so finding them in there on these implants is not that surprising.”

Working with engineers from UT Arlington, Dr. Pawlowski is investigating how changing the surface properties of cochlear implants might affect the growth of biofilms. They also are investigating whether passing a small DC current through the electrodes of implants might “shake off” the bacteria that grow there.

“My idea is to use a current that is small enough to not interfere with the hearing signal, yet large enough to irritate the bacteria in such a way that they detach from the electrode’s surface and, hopefully, die,” Dr. Pawlowski said. “The trick is to find just the right current. But for now, we’re still figuring out how biofilms perform under normal circumstances.”



“The eye is so unique, and corneal transplantation is so unique. If we can figure out this mystery, then we can improve corneal transplants. Ultimately, perhaps we also can translate our findings to more problematic types of transplants, such as heart, lung, liver or kidney.” —Dr. Jerry Niederkorn

The eyes have it

The eyes are said to be the window to the soul, but for Dr. Jerry Niederkorn, they offer insights into the intricacies of the human immune system.

For 30 years, Dr. Niederkorn, professor of ophthalmology and microbiology, has been studying the unique way the immune system operates in the human eye. In any other tissue or organ (the brain is an exception), an insult from a virus, bacterium or other foreign substance causes the immune system to mount a defense. Special cells are mustered to attack the invaders, and the infected cells, and the response causes inflammation.

“Flu is a good example of this mechanism,” Dr. Niederkorn said. “The immune system overreacts to the presence of the flu virus. It kills the virus, but in such a violent way that some flu symptoms are actually a result of this overzealous immune response and not the virus itself.”

Infections that occur in the throat, or lungs, or as a result of a cut elicit such inflammatory responses. They might make a person feel uncomfortable, but recovery is likely.

“If that type of inflammation occurred in the eye, you would be blind,” said Dr. Niederkorn, who holds the George A. and Nancy P. Shutt Professorship in Medical Science.

Most tissues in the body can regenerate new cells after illness or injury – the eye cannot. A one-cell-thick layer of cells that form the inner surface of the cornea of the eye is a key area that must be protected – if these cells are damaged, the cornea becomes opaque and blindness can result.

To protect eyesight, the eye and the immune system have struck a compromise, Dr. Niederkorn said. The eye does not respond to day-to-day exposure to environmental agents, foreign substances and pathogens. Instead, when exposure occurs, the eye sends out signals to the immune system to remain calm.

This suppression of inflammatory response is called “immune privilege.”

“Immune privilege is so well-developed because it must protect that single layer of cells forming the inner surface of the cornea,” Dr. Niederkorn said. In fact, his research has shown that the immune regulation of the eye is controlled in the anterior chamber, a fluid-filled area positioned directly behind the cornea and in front of the lens.

Immune privilege has its limits, however. The limiting factor is when the eye and the immune system perceive an insult involving the eye to be life-threatening.



For example, a type of herpes virus that causes fever blisters also causes a very severe form of ocular inflammation. In this case, the eye and immune system “agree” that the virus is so dangerous that it’s better to allow inflammation in the eye and risk blindness rather than the alternative.

“If immune privilege were to be left in place, you would not have this inflammation of the eye. Instead, you would have encephalitis and death,” Dr. Niederkorn explained. “Because the danger to the body from the virus is so severe, the eye unshackles the immune system.”

Immune privilege has an unexpected benefit not foreseen by nature. Each year, more than 35,000 corneal transplants are performed in the U.S., and about 200 at UT Southwestern, yet less than 10 percent of these grafts will fail, even though donor matching is not performed routinely.

“If you place a corneal transplant on your arm, your immune system will kill it quickly,” Dr. Niederkorn said. “But if you place a new cornea where a damaged one had been, it has a 90 percent chance of being accepted. That’s because the transplant is being placed right over the anterior chamber, where immune privilege is regulated.”

The recipient eye perceives the new cornea as a non-life-threatening foreign object, so the immune system is suppressed and the graft accepted.

Dr. Niederkorn focuses his efforts on why this type of transplant is so successful, as well as potential ways to improve upon the success rate. His studies over the years have been supported in large part by Research to Prevent Blindness, a leading voluntary health organization supporting eye research directed at the prevention, treatment or eradication of all diseases that threaten vision. Dr. Niederkorn is particularly interested in the 10 percent of patients who reject corneal transplants. What is happening in these patients to cause a loss of immune privilege in the eye?

Clinicians have observed that corneal transplant patients who have inflammation of the eyes due to allergies or allergic disease are at a higher risk for rejection of the transplant. Allergies can cause an immune response in the conjunctiva, a thin layer of tissue covering the eyeball.

“What is it about allergic diseases that creates this high risk for graft rejection?” Dr. Niederkorn asked. “What causes that corneal transplant to lose its immune privilege?”

One hypothesis is that allergic diseases affect a type of immune cell called a cytotoxic T-lymphocyte. These cells normally attack and kill other cells infected with viruses, but because of immune privilege, they usually leave the eyes alone.

“We suspect that for some reason, in people with allergies, that component of the immune privilege is short-circuited, or reprogrammed, and the people develop cytotoxic T-lymphocytes that will kill implanted corneal cells,” Dr. Niederkorn said.

“The eye is so unique, and corneal transplantation is so unique. If we can figure out this mystery, then we can improve corneal transplants. Ultimately, perhaps we also can translate our findings to more problematic types of transplants, such as heart, lung, liver or kidney.”

Happy feet

Just as immune privilege protects the eye, the skin helps protect the body by detecting potentially harmful objects and forces, such as pets’ claws, rough gravel and heat from a flame. It does this through the sense of touch.

In nearly half of all patients with diabetes, however, the sense of touch on the bottom of the feet is compromised by a condition called diabetic neuropathy. Multiple factors are likely involved in the development of the condition, and myriad approaches have been tried to alleviate it.

The majority of patients with diabetic neuropathy initially complain of severe tingling and pain at the toes, which further progresses up the feet and legs with time. Paradoxically, however, many patients also begin to lose sensation altogether.

“It seems contradictory,” said Dr. Shai Rozen, assistant professor of plastic surgery who is studying whether surgery can help restore feeling. “They have severe pain, but on the other hand, they can develop a decreased sense of touch on the bottoms of their feet.”

Losing that sense of touch results in an inability to detect injuries such as cuts or punctures to the feet, which, left unnoticed, might put patients at risk for infections that can progress quickly, often leading to amputation. Also, an infection can cause uncontrolled high blood sugar.

Dr. Rozen explained that diabetic neuropathy patients might have decreased balance, partially because of a loss of proprioception, the ability to sense where one is relative to space. Also, the small muscles in their feet that help maintain balance and proper pressure distribution in the bottom of



the feet lose innervation, or nerve stimulation. This contributes to a loss of balance and a flattening of the arch on the bottom of the foot.

“When the arch flattens, you suddenly have a different-shaped foot, and the pressure points change,” Dr. Rozen said. “Now areas that are not designed to take pressure suddenly have to bear pressure,” which can generate wounds on the bottom of the feet.

Dr. Rozen is working with a multidisciplinary team of 11 investigators in five specialties on an ambitious study to evaluate whether a very delicate surgical procedure can relieve pressure on key areas of the legs and feet and, hopefully, restore at least some level of sensation. The study is the first of its kind to evaluate systematically whether the surgical procedure is effective at reducing pain, restoring sensation and, ultimately, reducing the number of infections and amputations associated with diabetic neuropathy.

“Currently we have only anecdotal evidence that this type of surgery might be effective,” Dr. Rozen said. “Patients in general have done well, reporting reduced pain and improved sensation. But this type of data needs to be scientifically evaluated and verified, and that’s what we have set out to do.”

The long-term study, which will take four to five years to complete, is funded in part by the NIH and private funds. It involves endocrinologists, who are diabetes specialists; neurologists; physical medicine and rehabilitation experts; pain management clinicians; and plastic surgeons.

“The lay community tends to view plastic surgeons as concentrating on cosmetic surgery, which we certainly do, but many of the procedures we do are reconstructive surgery as well,” Dr. Rozen said. “A majority of the

microsurgical procedures that are done in medicine, such as connecting millimeter-sized blood vessels to one another, are done by plastic surgeons. From that perspective, the diabetic neuropathy study fits well within the realm of plastic surgery.”

Medicine at its best

Dr. Rozen’s study, and many others that relate to the five senses, are perfect examples of the type of cross-disciplinary research that takes place every day on the UT Southwestern campus. By taking a comprehensive approach to understanding and treating disease and health conditions, researchers and clinicians can provide the most advanced, scientifically validated care to patients in North Texas.

But advances in medicine often start from examining, listening to and learning from the patients themselves, a concept many people tend to forget.

“In translational research, clinicians start from the patient’s bedside with a problem, then go on from there to solve it, whether through clinical studies or heading to the lab,” Dr. Rozen said. “Translational research is in essence the ability to connect and create a fruitful interaction between the bedside clinical problem and the basic science.

“This type of research could not be done successfully without the cooperation of many investigators in different disciplines,” he said. “You have to have the right people on board who are all interested in solving a problem. There’s no question that it must be done at an academic medical center like UT Southwestern.” ♦

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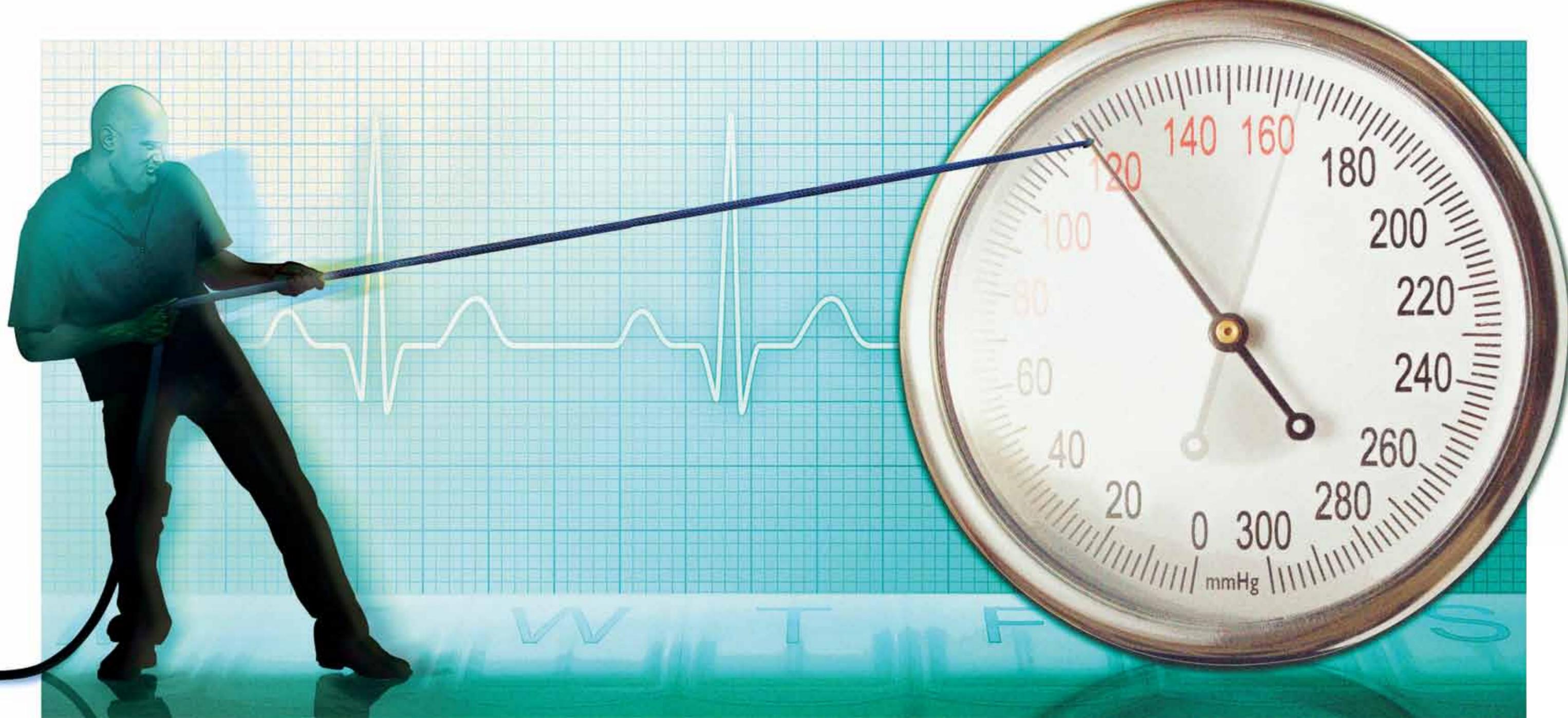
academic medical center

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—Dr. Shai Rozen



The skin helps protect the body by detecting potentially harmful objects and forces. It does this through the sense of touch.



PRESSURE POINTS

BY KATHERINE MORALES

In a plastic box labeled with the days of the week, Michael Meyers lines up his daily doses of medicine required to treat his hypertension.

Ten milligrams of this, 20 milligrams of that – once a day, twice a day, Monday through Sunday.

Mr. Meyers, 58, is among millions of Americans who go through similar routines. Hypertension, or high blood pressure, is one of the most common cardiovascular diseases in the country affecting one in every four Americans. Like many others, Mr. Meyers must battle it constantly on multiple fronts, not only through his daily doses of medicine, but also by thinking about everything he eats and fitting regular exercise routines into his daily duties as a pastor for two churches in Dallas.

“I GUESS I NEVER REALIZED that [hypertension] could go on for a long time without any serious symptoms. I’d had headaches and felt run-down, but I thought it was all because of stress.”

— MICHAEL MEYERS, patient

THINKING BACK on the last 10 years, Mr. Meyers can’t pinpoint exactly when his blood pressure began creeping up. It probably started affecting him a few years before he had it diagnosed, but minimal symptoms kept him from noticing until he went in for a routine checkup with his family doctor.

Often called “the silent killer,” hypertension can go undetected for years, until it’s found during regular checkups or until it causes major health complications.

“I knew it ran in my family, but I was very surprised when they told me I had it,” Mr. Meyers said. “I guess I never realized that it could go on for a long time without any serious symptoms. I’d had headaches and felt run-down, but I thought it was all because of stress.”

Mr. Meyers began a regimen of medications and began exercising regularly in hopes that he could get hold of the disease. He soon found out that tackling high blood pressure can be as hard as catching a fish with your bare hands. Just when he and his doctors thought they’d found a good system of managing it, it resurged.

It all came crashing down one night when Mr. Meyers thought he was having a heart attack. His wife, Gloria, rushed him to a local hospital where doctors told him, after a battery of tests, that he was not having a heart attack. The diagnosis was a huge relief, but Mr. Meyers felt the symptoms were too close to the real thing.

“It was sort of the last straw,” Mr. Meyers said. “I wasn’t having a heart attack and that was good news, but the hypertension was not well-controlled; I thought I needed to see a new doctor.”

His wife asked for recommendations for blood pressure specialists before he was discharged from the hospital, and the cardiologist on staff gave them a name: Dr. Shawna Nesbitt.



FINDING HELP

Dr. Shawna Nesbitt, associate professor of internal medicine at UT Southwestern Medical Center, specializes in researching and treating this complex disease. She also serves as the medical director of the hypertension clinic at Parkland Health & Hospital System.

Every day, Dr. Nesbitt sees dozens of patients like Mr. Meyers, and she, along with her colleagues, is studying new methods of intervention before the disease can lead to complications such as heart attacks, strokes and kidney damage. She studies the epidemiology of hypertension and cardiovascular risk, with a special area of interest in hypertension among African-Americans – a population disproportionately affected by high blood pressure.

“There is no one-size-fits-all approach to treating hypertension,” Dr. Nesbitt said. “Understanding behaviors and being able to relate to patients is as important as developing a medication strategy.”

The day Mr. Meyers came home from the hospital, he called Dr. Nesbitt’s office to make an appointment. Prior to his visit, the side effects from the medication he was taking to help control his high blood pressure were almost as bad as the chest pain he mistook for a heart attack.

The primary causes of hypertension cannot always be defined. For those who have primary hypertension, there may be myriad reasons why it manifests itself, including genetic predisposition, lifestyle factors such as smoking and obesity, even vitamin deficiencies.

Mr. Meyers suspects it was a combination of factors in his case, including family history (his grandparents on both sides had hypertension), the stress of his job and his lifestyle.

“My other doctor couldn’t get the combination of medicines really under control. I was having dry mouth and headaches – a lot of headaches,” he said. “When I came to Dr. Nesbitt’s clinic, I thought it would be the same old thing, but that wasn’t the case.”

He and Dr. Nesbitt basically started from scratch. She took her time, sat down with him for nearly an hour and talked about everything related to his high blood pressure.

“She explained to me the different methods of how it could be done, and we decided on a path to take,” Mr. Meyers said. “I was most concerned about the medicine’s side effects, and she thought of some different combinations.”

But one thing was clear when he left that day: He had to keep fighting or the disease would win. Coming to UT Southwestern was fortuitous for Mr. Meyers.

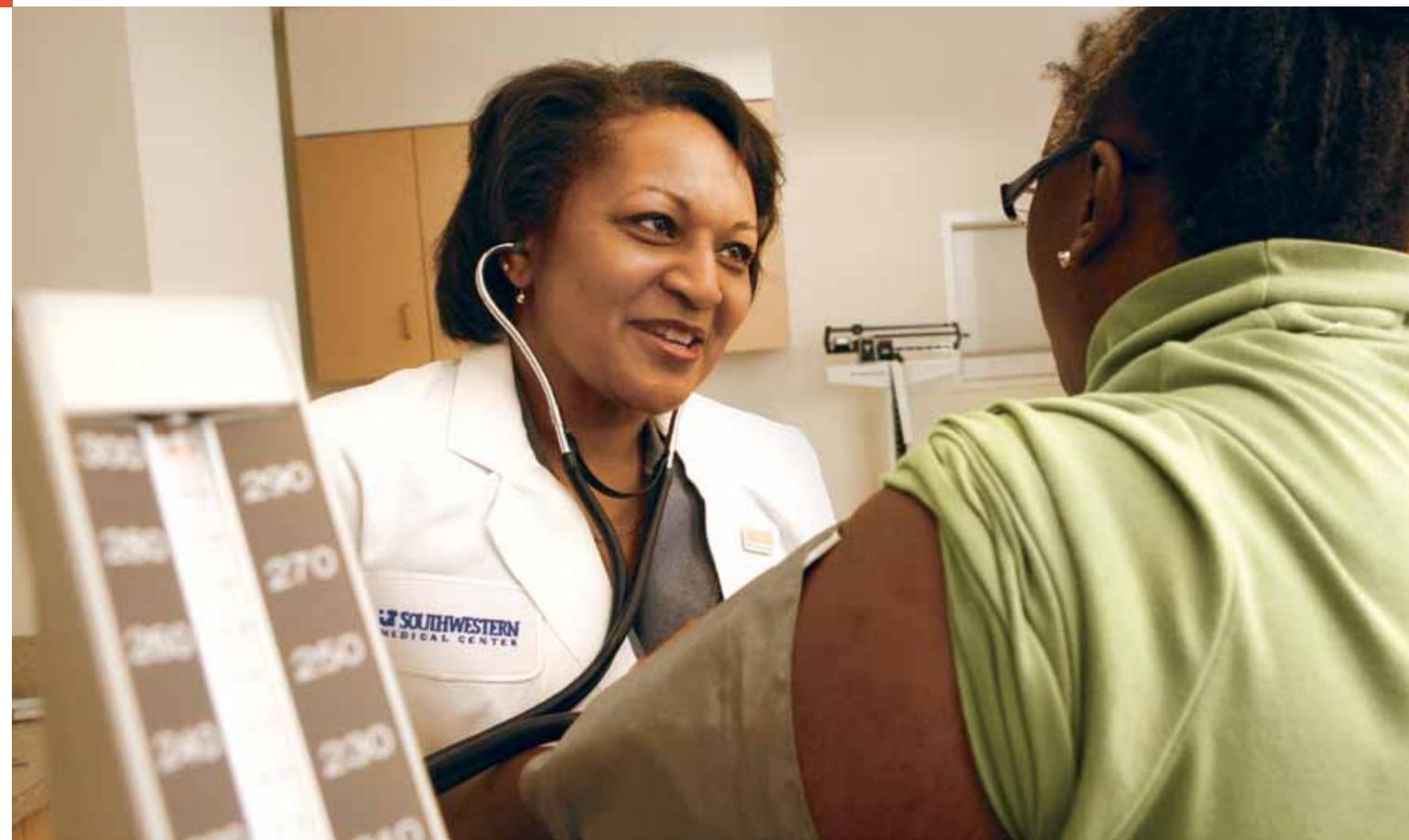
CENTER FOR RESEARCH

UT Southwestern is uniquely positioned among academic medical research centers to study cardiovascular diseases like hypertension.

UT Southwestern is home to the Dallas Heart Study, which allows UT Southwestern researchers to study factors that contribute to heart disease in a large multi-ethnic group of Dallas County residents.

“THIS IS AN OPPORTUNITY for us to investigate early treatments and to see if we can prevent patients from needing lifelong therapy for hypertension.”

— DR. SHAWNA NESBITT





“WE HAVE DISCOVERED that C-reactive protein is not merely a marker of the risk of hypertension; it actually induces hypertension.”

— DR. WANPEN VONGPATANASIN

As part of the Dallas Heart Study, researchers have obtained detailed medical histories from more than 6,000 Dallas residents; more than half of the participants provided blood samples and underwent multiple imaging studies to examine the heart, and the information has been studied and used to identify new drug targets for the prevention and treatment of heart disease.

Dr. Nesbitt previously served as the director of cohort follow-up for the Dallas Heart Study.

She also is the national coordinator for the Trial of Preventing Hypertension (TROPHY) study. The study, funded by the National Institutes of Health, is a four-year trial, including more than 70 sites and more than 800 patients.

As part of her work with the TROPHY study, she's looking into whether treating elevated blood pressure earlier keeps patients from developing full-blown hypertension. Early findings showed that treating pre-hypertension with medication and lifestyle modifications reduced the risk of patients progressing to hypertension. Those classified as having pre-

hypertension have a blood pressure between 120 and 139 systolic and 80 to 89 diastolic – just below the designation of hypertension.

Present guidelines recommend that pre-hypertension be managed with changes in the patient's lifestyle through weight loss, salt restriction, exercise and dietary modification. Dr. Nesbitt collaborated with researchers at several institutions to find out if treatment with angiotensin-receptor blockers, or ARBs, could prevent the development of hypertension in what was the first human study involving treatment of pre-hypertension with an ARB.

“I think this is the tip of the iceberg in the further study of new treatment protocols for pre-hypertension,” Dr. Nesbitt said. “We've typically waited until people have hypertension before we treated them, and it's really hard to stave off the disease's progression when you treat it later in its development. This is an opportunity for us to investigate early treatments and to see if we can prevent patients from needing lifelong therapy for hypertension.”

Mr. Meyers tried mightily to keep his weight under control and to keep up with regular exercise. In a fit of exasperation, Mr. Meyers said he recalled walking into a scheduled appointment with Dr. Nesbitt and declared, “That's it. I'm going to get down to 170 pounds if it kills me.”

He said that Dr. Nesbitt looked at him and asked, “Mr. Meyers, when was the last time you weighed 170 pounds?”

“I told her, that I'd weighed that much when I was 18, and she just smiled and said, ‘I don't think that's a reasonable goal.’”

As much as she appreciated Mr. Meyers' desire to radically alter his weight, she also knew the success rates of such undertakings were extremely small.

“Unfortunately, the long-term maintenance of a lifestyle change is dismal. Patients typically don't stick to it,” Dr. Nesbitt said. “Which is why we, as physicians, need to understand how to treat the disease in the context of what a patient can reasonably achieve.”

Even without the radical weight loss, Mr. Meyers said he can now manage his disease and feels healthier than he has in the last 10 years.

“It is a team effort with a doctor and patient,” Mr. Meyers said. “She's the best teammate I could've ever asked for.”

Continued on page 18

“HYPERTENSION IS BECOMING A MORE FREQUENT PROBLEM as numbers of patients with uncontrolled hypertension are increasing in the United States, despite the rapid development of new blood pressure medicines.”

— DR. VONGPATANASIN



HORMONES AND HYPERTENSION

Dr. Richard Auchus, professor of internal medicine, was recently named director of the Houston J. and Florence A. Doswell Center for the Development of New Approaches for the Treatment of Hypertension. His research involves studying the effects of hormones on hypertension, specifically a disease process called primary aldosteronism and genetic forms of hypertension caused by abnormal steroid hormone production.

Primary aldosteronism, once considered a rare condition, is now studied more vigorously because it may be the underlying cause of high blood pressure in a significant number of patients. Dr. Auchus says the subtle abnormalities associated with the condition are challenging to diagnose, and more research is needed to develop better ways to diagnose and treat this condition.

Aldosterone is a hormone created by the adrenal glands and increases reabsorption of sodium and water. Aldosterone also controls the release of potassium in the kidneys. Changes induced by aldosterone in the blood include increased blood pressure, which can occur with adrenal tumors.

“Obviously, hypertension is affected by many things – variations in hormone levels being one of them,” Dr. Auchus said. “What we're doing in the translational model is studying human adrenal tumors and developing cell lines from these tumors in hopes that we can better understand what makes them work.”

Dr. Auchus, holder of the Charles A. and Elizabeth Ann Sanders Chair in Translational Research, is an endocrinologist and enzymologist and a noted expert on steroid hormone biology and related diseases. Dr. Auchus performs basic, clinical and translational research on the biochemistry and physiology of how steroid hormones are made as well as how their production is regulated.

His lab focuses on principles related to human disease, with the goal of improving the diagnosis and treatment of conditions such as infertility, hypertension and intersex disorders.

“I’M HAPPY TO SAY today that my blood pressure is controlled.”

— ROSEMARY CANNON, patient

EACH PATIENT IS UNIQUE

Dr. Nesbitt’s patients range in age from their 30s to their 80s, and none has the same story. Some suffered for years with multiple symptoms and other chronic illnesses; some had a more typical onset of hypertension in middle age like Mr. Meyers; still others are diagnosed in their 30s.

Latrice Clark was only 35 when she found out her blood pressure was dangerously high. Though it’s rare to develop hypertension at such an early age, it’s not uncommon. Ms. Clark described the diagnosis as devastating.

“I guess I thought I was too young to have something like this,” she said. “I knew there was no going back.”

She overcame her initial disbelief and sought treatment quickly, where she learned about all of the lifestyle choices that she now had to monitor compulsively. Reading food labels and tracking her salt were among the first and foremost changes she made. With the help of anti-hypertensive medicine, her blood pressure stabilized; however, she noticed an unpleasant side effect.

“I started noticing this rash on my hands, and it was so bad,” Ms. Clark said. “It spread up to my face, and it was really hard for me to go to work because of the way I looked. My doctor at the time tried a few other combinations, but nothing worked.”

What seemed like a mild irritation at first became nearly unmanageable for Ms. Clark. The rash spread to her face, hands and neck and was scaly and itchy to the touch. She feared going into work everyday because of her appearance.

“It was getting so bad, that I thought about just quitting the medicine,” Ms. Clark said. “My doctors kept trying different combinations, but nothing worked.”

When a co-worker of Ms. Clark’s suggested she come to UT Southwestern, she made an appointment with Dr. Nesbitt. Within a few weeks, they hit upon the cause of her debilitating rash.

“It was just an ingredient in the kinds of high blood pressure medicines I was taking,” Ms. Clark said. “If Dr. Nesbitt hadn’t taken the time to find that out, I don’t know what would have happened to me. I don’t know that I could’ve kept taking the medicines I needed to save my life.”

RESEARCH IN PROGRESS

At UT Southwestern, physicians not only work at treating hypertension after it begins, but also perform multitudes of clinical trials, where they test the effectiveness of various drug and lifestyle therapies.

Dr. Wanpen Vongpatanasin, associate professor of internal medicine and holder of the Norman and Audrey Kaplan Chair in Hypertension, studies neural control of blood pressure and the influence of various hormones and anti-hypertensive agents on the autonomic nervous system’s control of blood pressure. Autonomic brain functions include those that are largely involuntary, such as digestion and maintenance of body temperature.

“We are assessing nerve activity that controls blood flow to the skeletal muscles in patients with high blood pressure during treatment with thiazide diuretics, which are often a first-line drug treatment for hypertension,” Dr. Vongpatanasin said.

Thiazide diuretics have long been used for treatment of high blood pressure but are also known to have side effects that raise blood glucose and the chances of developing adult-onset diabetes. Reasons, Dr. Vongpatanasin said, may be due to depletion of the body’s potassium stores, which reduces the ability of the pancreas to release insulin.

The key, she said, is finding a treatment that effectively reduces blood pressure and does not adversely affect blood-sugar levels.

“Our research thus far suggests that spironolactone, another diuretic that counteracts the effects of aldosterone hormone responsible for causing us to retain salt and water, is equally effective in lowering blood pressure without causing increases in nerve activity that can heighten insulin resistance,” Dr. Vongpatanasin said.

Dr. Vongpatanasin and her research team also examined the role of C-reactive protein (CRP) in the onset of hypertension. CRP is widely regarded as a risk factor for hypertension and other forms of cardiovascular disease.

“We have discovered that C-reactive protein is not merely a marker of the risk of hypertension; it actually induces hypertension,” said Dr. Vongpatanasin.

Her team studied mice with an engineered gene for CRP that was under the regulation of a second gene responsive to changes in dietary carbohydrate intake. The levels of circulating CRP, which is produced by the liver, were manipulated by altering the mice’s diets, and the effect on blood pressure was determined.

In this manner the actions of CRP were segregated from the actions of other mediators of inflammation.

They discovered that when the gene that causes increases in CRP was turned on, the blood pressure went up, and, when turned off, CRP levels went down, and the blood pressure fell.

“Hypertension is becoming a more frequent problem as numbers of patients with uncontrolled hypertension are increasing in the United States, despite the rapid development of new blood pressure medicines,” Dr. Vongpatanasin said. “Therefore, understanding the mechanisms of hypertension is crucial to improving blood pressure control.”

THE TEAM APPROACH

Rosemary Cannon, 56, said her early diagnosis of hypertension 17 years ago surprised her because she maintained a healthy weight and had no symptoms whatsoever.

“It truly made me realize why hypertension is called the silent killer,” she said. “I had no symptoms at all – no headaches, no swelling, nothing.”

Her only clues were family histories, rife on both sides with hypertension. Still, she thought if she kept her weight down and led a healthy lifestyle she might avoid it. But it crept up anyway, and Ms. Cannon spent the next decade on a variety of medications trying to stabilize her blood pressure.

“It wasn’t until I was diagnosed with diabetes at 48 that I really was done playing around with this,” Ms. Cannon said. “I felt it was the right time to move to a hypertension specialist, and that’s how I met Dr. Nesbitt.”

Those already afflicted with hypertension have a higher likelihood of developing other diseases such as heart failure, kidney disease and diabetes. These co-morbidities create a need for a cohesive approach to treating patients like Ms. Cannon.

“When I first came in for a visit, Dr. Nesbitt asked if I had time to stick around,” Ms. Cannon said. “She looked at my chart and made a couple of phone calls, and pretty soon, I was set up with a cardiologist, a nutrition specialist and an endocrinologist for my diabetes.”

The team approach to Ms. Cannon’s treatment, she said, made a profound difference in her life. All of her health information is easily accessible to her treating physicians, and they can communicate with each other on any special issues pertaining to Ms. Cannon’s conditions.

“For the longest time, I thought I was just tired and worn out,” Ms. Cannon said. “I’d gotten so used to feeling this way, that I thought it was normal. It wasn’t until my hypertension was well-managed, that I realized what I’d been missing all of these years.”

She supplemented her doctors’ appointments with diabetes education through counseling sessions available at UT Southwestern University Hospitals. There, they showed her appropriate portions for her meals and reviewed what she’d been eating. In addition the registered dietitians cautioned her about foods the body rapidly converts to simple sugars, explained which foods are likely to keep her full longer and talked about how to lower sodium levels.

“I’m happy to say today that my blood pressure is controlled,” she said. ♦

For more information about hypertension treatment, please call 214-645-2800.





[Surgeons find new ways
to minimize incisions.]

thinking small

SURGERY, which meant cutting open patients to heal them in 1985, was about to change forever. > That year a German surgeon removed a person's gallbladder for the first time ever without slicing the skin and muscles in order to operate directly on the patient. His new way – laparoscopy – was named for the slender, tubular endoscope inserted through an incision in the abdominal wall. > In little more than two decades, the number of minimally invasive surgeries performed through a few small holes went from zero to an estimated 3 million annually. Some expect that number to grow by 20 percent a year as more and more types of surgeries can be done via minimally invasive procedures. >

By **Russell Rian**

The question surgeons are asking themselves today are no longer: “Are such surgeries feasible, and are they safe, but how few holes do we need? Can we do it without making any incisions by using natural orifices?”



For UT Southwestern Medical Center’s Dr. Jeffrey Cadeddu, who performed the nation’s first single-incision kidney removal, the latest question he asked himself is: “Can we guide surgical instruments magnetically through the body better than we can guide present-day instruments?”

His idea for magnetic surgical tools was inspired by a television show featuring teens who used magnets to hold studs on their lips rather than getting their lips pierced.

Now surgeons and engineers at UT Southwestern and UT Arlington are in the testing phase of their magnetic instruments; other UT Southwestern physicians are developing ways to perform smaller one-hole surgeries and dreaming up even less-invasive procedures.

Thirst for less

Today’s thirst for the latest minimally invasive methods tracks back to that 1985 operation, according to Dr. Edward Livingston, chief of GI/endocrine surgery and holder of the Dr. Lee Hudson-Robert R. Penn Chair in Surgery, who recently wrote papers on the foundations and future of laparoscopic surgery.

He said that initial laparoscopic accomplishment by the German doctor was reviled broadly at the time by the surgical community, which deemed it dangerous and unnecessary. Yet it was quickly followed in 1987 by a French surgeon who deployed the first laparoscopic video-camera during another gallbladder surgery. The news was again greeted with widespread skepticism by surgeons, who became even more outspoken due to higher complication rates initially reported.

Minimally invasive surgery was dismissed as a passing surgical fad, and its speedy demise widely predicted.

“But it did not happen that way,” said Dr. Livingston. “Patients were intrigued by the notion that they could undergo major

abdominal surgery without a large incision. The complication rates were still low and of little interest to patients, whereas the prospect of a large, painful scar was very real. Patients went in droves to those surgeons offering the new approach, even bypassing the well-respected institutions and surgeons.”

Surgeons took notice. As more and more patients defected to laparoscopic surgeons, more and more surgeons clamored for the added training necessary at places like the UT Southwestern Center for Minimally Invasive Surgery.

“Although there was a lot of skepticism initially about whether it would be better than the good old-fashioned, time-honored operation, it is better,” said Dr. Robert Rege, chairman of surgery and a renowned laparoscopic surgeon himself, who was instrumental in launching UT Southwestern’s minimally invasive surgery center.

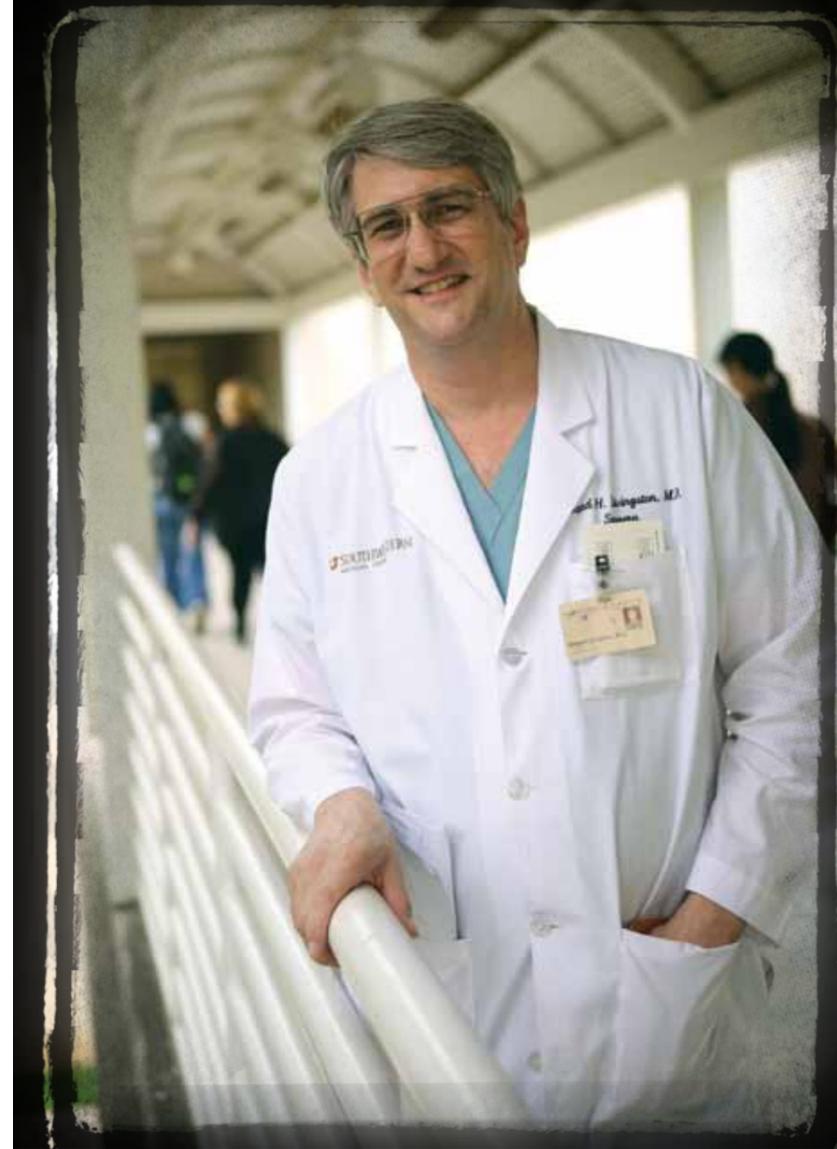
“Yes, it has its own problems. But they’re not more than the open operation; they’re less,” said Dr. Rege, who holds the Hall and Mary Lucile Shannon Distinguished Chair in Surgery. “Take a specific group – geriatric patients. There was worry about the stresses of putting carbon dioxide in the abdomen so you can visualize what you are doing. But it’s the safest operation for an elderly person who needs to have his or her gallbladder out with many fewer major side effects and many fewer respiratory and cardiac side effects. Minimally invasive surgery brought a lack of invasiveness that was and is good for most people.”

Experience that counts

UT Southwestern has since become home to some of the world’s most respected minimally invasive surgeons in a multitude of surgical fields and has established two nationally distinguished minimally invasive surgery centers.

The Southwestern Center for Minimally Invasive Surgery is one of the most comprehensive educational facilities in the southwestern United States, a multidisciplinary clinical, research and teaching facility that provides laparoscopic surgery in more than a dozen fields, including bariatrics, breast surgery, burn and trauma care, cancer and sarcoma surgery, colorectal, GI, endocrine and hernia surgery, and oral surgery.

The center’s \$2 million training laboratory was one of the first seven facilities across the United States and Canada and the first in Texas, to garner accreditation from the American College of Surgeons. Dr. Rege also was among the committee members who



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—Dr. Robert Rege

helped draft the tough new standards designed to ensure safety, reduce errors and recognize skilled laparoscopic surgeons.

UT Southwestern’s Clinical Center for Minimally Invasive Treatment of Urologic Cancer is staffed by UT Southwestern urologists, offering patients minimally invasive alternatives to conventional cancer surgery and radiation therapy, such as for early-stage tumors of the prostate, kidney and testicles, bladder cancer, and benign conditions, such as adrenal masses, complex renal cysts and abdominal fibrosis.

Research at the center focuses on expanding the uses of minimally invasive techniques to include the treatment of advanced stages of malignancies and evaluating the effectiveness of newly developed treatments. The center also plays an active role in developing technologies and in assessing new surgical tools.

UT Southwestern has tapped those with national expertise in the minimally invasive field, such as Dr. Livingston. He was among the first in the nation to learn minimally invasive surgical techniques at a California Veterans Affairs hospital while the concepts were still in their infancy and still being rejected at renowned medical centers.

Since then, UT Southwestern has home-grown some of its own national experts, such as Dr. Daniel Scott, director of the Southwestern Center for Minimally Invasive Surgery and associate professor of GI/endocrine surgery.

Dr. Scott had been involved in minimally invasive surgical research since 1999 when, as a resident and fellow at UT Southwestern, he helped pioneer new laparoscopic techniques and joined the team of UT Southwestern surgeons who performed the first laparoscopic Roux-en-Y gastric bypass in Texas.



Dr. Daniel Scott helped pioneer new laparoscopic techniques and joined the team of UT Southwestern surgeons who performed the first laparoscopic Roux-en-Y gastric bypass in Texas.

Dr. Scott, holder of the Frank H. Kidd Jr., M.D., Distinguished Professorship in Surgery at UT Southwestern, went on to establish Tulane University's first laparoscopic center, created a state-of-the-art simulation and training laboratory there, and initiated a robotic general surgery program.

Dr. Cadeddu, professor of urology and radiology and director of the Clinical Center for Minimally Invasive Treatment of Urologic Cancer at UT Southwestern, has spent years pioneering minimally invasive techniques. He has written a definitive text in the field, titled *Laparoscopic Urologic Oncology*, and was the first in Texas to use radiofrequency ablation to treat kidney tumors. He also performed the first laparoscopic prostatectomy in North Texas.

Other experts continue to arrive.

Dr. Mayra Thompson, associate professor of obstetrics and gynecology and a noted laparoscopic surgeon, performed UT Southwestern's first single-incision hysterectomy, also believed to be the region's first. In addition, Dr. Thompson has completed a single-incision oophorectomy, the removal of the ovaries.

Minimally invasive methods have now become the gold standard in some fields.

UT Southwestern surgeons perform laparoscopic surgeries in dozens of fields. The more common include:

- > Gastrointestinal surgery, such as removing appendices and gallbladders;
- > Colon and rectal surgery for Crohn's disease, colitis, polyps, diverticulitis and inflammatory bowel disease;
- > Heart surgery for aortic valves, atrial fibrillation and coronary bypass;
- > Vascular surgery such as balloon angioplasty, stenting and endovascular repairs;
- > Gynecologic and urological surgeries, from hysterectomies to kidney stones;
- > Neurosurgery for brain tumors, herniated discs and carotid angioplasty;
- > Orthopaedic surgery in hips, knees, ankles, shoulders, elbows, wrists, hands and spine;
- > Sinus, throat, and head and neck surgeries to remove polyps and tumors; and
- > Plastic surgery for breast reconstruction after cancer, tummy tucks, face lifts and nose restorations.

Multidisciplinary reach

In UT Southwestern's Clinical Center for Minimally Invasive Treatment of Urologic Cancer, physicians are targeting early-stage tumors of the prostate, kidney and testicles, while a new program in bladder cancer

treatment is also under development. In addition, patients with benign conditions such as adrenal masses, complex renal cysts and abdominal fibrosis often have lesions that are amenable to minimally invasive techniques.

Linda Gnade had kidney cancer when she sought the help of Dr. Cadeddu for a partial nephrectomy, in which the tumor is cut off and the kidney repaired through a few small incisions.

"We have a reputation for doing this operation, so it is very much standard of care and routine," said Dr. Cadeddu, holder the Ralph C. Smith, M.D., Distinguished Chair in Minimally Invasive Urologic Surgery. "Laparoscopy is often easier on the patient than traditional surgery: less pain, smaller scars and faster recovery – the difference being one day in the hospital for a laparoscopy versus four to five days for conventional surgery."

Ms. Gnade said, "I have 85 percent of my kidney left, and there is no sign of any remaining kidney cancer at all. There was a time I didn't think I'd be alive right now. I'm very happy to be here, and I'm happy to be a success story and able to tell you about it."

For patients who have experienced heart valve damage and whose specific condition permits it, UT Southwestern surgeons can provide minimally invasive heart valve surgery.

Head and neck surgeons have found several successful niches for minimally invasive techniques as well. In UT Southwestern's unique Comprehensive Skull Base Program, otolaryngologists and neurosurgeons use laparoscopic techniques to go through the sinus cavity, which allows them to avoid opening the face and leaving the patient with a large scar.

At UT Southwestern's Clinical Center for Voice Care, otolaryngology surgeons perform microsurgery of the vocal folds, a minimally invasive procedure in the throat to remove polyps or cysts causing hoarseness.

Neurosurgeons are able to use minimally invasive approaches for some brain tumors.

"Minimally invasive approaches, with and without endoscopy, are being used in the management of a variety of intracranial tumors," said Dr. Bruce Mickey, vice chairman of neurological surgery and director of the Annette G. Strauss Center for Neuro-Oncology at UT Southwestern. He also is a professor of otolaryngology – head and neck surgery and holder of the William Kemp Clark Chair in Neurological Surgery.

Orthopaedic surgeons have found minimally invasive techniques to restore knees, repair the spine and even fix fractures.



"The Magnetic Anchoring and Guidance System affords a much greater range of motion inside the abdominal cavity, allowing the surgical team more easily to position instruments in their optimum locations."

—Dr. Jeffrey Cadeddu



"The minimally invasive technique has really taken off in orthopaedic surgery and trauma, and its been supported by research that we published years ago that showed it preserves blood supply to the bone and, therefore, helps the bone heal," said Dr. Joseph Borrelli, chairman of orthopaedic surgery and holder of the Doctor Charles F. Gregory Chair in Orthopaedic Surgery.

Spine surgeons also use laparoscopy.

"Less invasive methods have been used for many years in certain spinal operations," said Dr. Michael Bolesta, associate professor of orthopaedic surgery who is part of UT Southwestern's multidisciplinary spine center team, medical director of the Multi-Disciplinary

Spine Clinic at Parkland Memorial Hospital, chief of orthopaedic spine service at Parkland and an adjunct faculty member in biomedical engineering at UT Arlington. "More recently, surgical robots and stereotactic techniques have been developed to improve accuracy of percutaneous procedures."

Interventional radiology also has blossomed, making many open operations a thing of the past. Utilizing imaging techniques such as CT scans, X-rays and ultrasound, teams of interventional radiologists and surgeons can do a number of targeted, through-the-skin procedures, such as stenting of ducts and vessels, draining fluids, performing angioplasty and embolization to treat a variety of problems, including aneurysms, cancerous tumors, varicose veins and uterine fibroids.

"The beauty of interventional radiology is that we're providing treatment that helps a lot of patients avoid major surgery," said Dr. Bart Dolmatch, professor of radiology and head of interventional radiology at UT Southwestern. "Any one of a number of treatments – restoring blood flow to blocked arteries, treating blood clots, or preventing clots from going to the heart or lungs – are all being done simply through a puncture or small incision rather than conventional surgery. In some cases we're providing treatment where surgery isn't a good option or is impossible."

New frontiers

New advances are now revolutionizing the laparoscopic field with the use of robots, single-incision surgery and the just-emerging field of natural orifice surgery.

And again, UT Southwestern surgeons are leading the way.

With funds from the Friends of UT Southwestern University Hospital - Zale Lipshy, the medical center purchased one of the first da Vinci robotic systems, sporting four robotic arms controlled by a surgeon.

UT Southwestern surgeons performed several urologic surgeries using the unique robot and have since expanded to other areas, including bariatric and gastrointestinal surgery, some cancer surgeries and even microvascular surgeries.

Surgeons sit at controls using a joystick and foot pedals to operate the arms, which include a camera offering 3-D, high-resolution vision in color and up to 10 times magnification of the surgical area, and surgical instruments on its other three arms.

The number of procedures has expanded to a variety of cancers, including those affecting

the prostate, ovaries, cervix, bladder, colon, esophagus, pancreas and stomach as well as coronary artery bypass grafting and valve replacement.

UT Southwestern surgeons were the first in North Texas to perform robotically assisted laparoscopic gastric-bypass weight-loss surgery and colon-resection surgeries.

The obstetrics and gynecology service has adopted the robot for benign gynecological conditions as well as for gynecological oncology.

"I also do robotic surgery for benign conditions such as myomectomies in large uteri as well as hysterectomies and prolapse repair," said Dr. Thompson.

In prostate removal, for example, studies showed the use of robotics resulted in significantly shorter hospital stays – up to half the time according to one study – and less time on a catheter. Studies also showed significantly less blood loss and fewer complications – 15 percent for open surgeries compared to 5 percent for robotic-assisted procedures.

"Robotic operations cannot make an average surgeon great," said Dr. Claus Roehrborn, chairman of urology and holder of the E.E. Fogelson and Greer Garson Fogelson Distinguished Chair in Urology. "A great surgeon is an experienced surgeon who knows the anatomy, knows the disease he is dealing with and knows the limitations of the procedures he can perform."

One-hole surgeries

Melanie Willhite wanted laparoscopy after learning that she would need gallbladder surgery to treat her recurring abdominal pain, sometimes so intense that she could not stand.

A skilled golfer who wanted a quick return to the greens, Ms. Willhite seized the opportunity at UT Southwestern to become the first in North Texas to have a single-incision gallbladder surgery, done entirely through the bellybutton, leaving no visible scar.

"There were a lot of advantages to doing it through one hole, including less scarring and the possibility for quicker healing," said Ms. Willhite, 28 at the time of her surgery. "I'm young. I also wanted to get back on the golf course as soon as possible."

Traditional laparoscopic surgery involves inserting a camera into one tiny incision and special surgical tools through three or

Continued on page 28

[Researchers Provide New Treatment, Insight on Age-Old Appendicitis]

WENDY TURNER THOUGHT SHE HAD THE FLU. > "I was nauseated and had fever. The next day I had pain on my right side. I thought I was getting better, but my husband made me go to an emergency-care place. I had a computed tomography scan, and they found out I had acute appendicitis," the 34-year-old recalled. "It was pretty bad apparently, and they said I should go to an emergency room right away."

SHE HEADED directly to UT Southwestern University Hospital's emergency room, where doctors offered Ms. Turner something few surgeons in the world could – an opportunity to avoid the impending appendectomy scar.

"They explained this new procedure in which I would have only one incision in the navel," she said. "I had heard of laparoscopic surgery but not about single-incision surgery, so I was a little nervous.

"Anytime you hear something that's new, you're a little unsure, but when you're at UT Southwestern, you're at a good place. I know they are not going to be performing new surgeries on patients that have not been reviewed thoroughly, so I agreed."

She was discharged later that day, a small bandage over her bellybutton.

"It is nice not to have a scar, especially with it being an emergency surgery," she said.

Hers was one of the first single-incision appendectomies at UT Southwestern, where some 25 such surgeries have now been completed.

Disappearance of the traditional scar in appendectomies, one of the most common general surgeries of all, mirrors the overhaul in understanding about this quirky little organ and its associated disease, appendicitis.

The appendix, first noted in the late 1700s, is a dead-end tube, usually around eight centimeters, located near the junction between the large and small intestine. Appendicitis occurs when the appendix becomes obstructed, but doctors are unsure why that happens. The

condition afflicts about one in 10 people during his or her lifetime.

"Though appendicitis is fairly common, it still remains a frustrating medical mystery," said Dr. Edward Livingston, chief of GI/endocrine surgery. "While we know surgical removal is an effective treatment, we still don't know the purpose of the appendix, nor what causes it to become inflamed."

"Though appendicitis is fairly common, it still remains a frustrating medical mystery."

— DR. EDWARD LIVINGSTON

For a quarter of a century, appendicitis was generally on the decline, but in 1995, Dr. Livingston, also professor of biomedical engineering at UT Arlington, and other UT Southwestern researchers uncovered an unexpected rise in appendicitis cases.

As they began to look into this relatively unstudied disease, their analysis led to other unanticipated findings.

Examining three decades of data, UT Southwestern researchers discovered that emergency surgery may not always be necessary. It's a significant finding, because appendicitis remains the most common reason for emergency general surgery, leading to some 280,000 appendectomies annually.

"Patients still need to be seen quickly by a physician, but emergency surgery is now in question," Dr. Livingston said.

Evidence from sailors at sea without access to immediate surgery and from some children's hospitals, whose practice did not call for emergency surgery, hinted that non-perforated appendicitis may resolve without surgery, said Dr. Livingston.

Seasonal variations and clustering of appendicitis cases support the theory that appendicitis may be a viral disease, like the flu, Dr. Livingston concluded.

Statistical data reveals peaks, which may be outbreaks of appendicitis during the 1980s and 1990s. In addition, researchers uncovered some seasonal trends for appendicitis, documenting a slight increase in appendicitis cases during the summer.

Researchers are now trying to pin down the reason, such as whether environmental or pathogenic factors are at play. So far, researchers have been able to rule out flu, several other common infections and several types of intestinal viruses as a direct cause.

Until the physicians can sort it all out, surgical advances to hide the scars will have to suffice.

"I've seen some pretty ugly scars from appendectomies," said Ms. Turner. "So anytime you can minimize scarring, that's a good thing."

For more information on appendicitis surgery, please call 214-645-2900.

●
UT Southwestern surgeons were the first in North Texas to perform robotically assisted laparoscopic gastric-bypass weight-loss surgery and colon-resection surgeries.





“What’s important is that you’re in the hands of a good surgeon. The well-trained surgeon will be well-versed in your disease and all of its treatments and will use minimally invasive or open surgery depending on what is appropriate for your situation.”

—Dr. Robert Rege (center)

four other tiny incisions. The single-incision procedure uses just one tiny incision through which the camera and all the surgical tools are inserted.

A day after her surgery, Ms. Willhite was enjoying spaghetti, a favorite meal she had forsaken due to her gallbladder problems. Within a week, she was back to putting and in two weeks out swinging at golf balls.

Experienced single-incision surgeons are in great demand as more and more patients hear about them.

“Patients are really enthusiastic about it and often come in inquiring about bellybutton surgery because we’re the only ones in the region doing it,” said Dr. Livingston, who also directs the Clinical Center for the Surgical Management of Obesity. “Since UT Southwestern is a medical school as well as a hospital, we’re now getting lots of requests from other area surgeons for continuing medical education courses to teach these techniques.”

The fast-paced move toward further minimizing minimally invasive surgery is no better reflected than with Joe and Dawn Wear of Azle, both of whom underwent bariatric weight-loss surgery.

Mrs. Wear chose a minimally invasive approach for her stomach-restricting LapBand surgery. This procedure requires only a handful of tiny scars less than an inch in length in the abdomen rather than a huge scar across the belly and is in high demand at the Clinical Center for the Surgical Management of Obesity.

Her husband, who had been heavy since childhood and weighed about 300 pounds before surgery, said he was motivated by his 3-year-old daughter, Kylie, to have the surgery a year later.

Mr. Wear, a registered nurse, opted for single-incision surgery.

“I didn’t want all the incisions, and I wanted faster healing time,” Mr. Wear said. “The only way to advance medical technology is to give it a try, so I’m glad I could help.”

Dr. Scott completed the two-and-a-half-hour procedure on Mr. Wear in April 2008. It was the first such surgery in Texas. Mr. Wear began losing weight – 30 pounds in his first month – achieving similar results as his wife with fewer scars, less pain during recovery and a quicker discharge.

The next step

The final step for minimally invasive surgery may be natural orifice transluminal endoscopic surgery, called NOTES, a procedure in which no external incisions are made.

Instead, surgeons use special flexible endoscopic instruments to go through a natural hole such as the throat, anus or vagina to enter the abdominal cavity. Surgeons hope the advantages of having no external incisions to heal will translate into faster and less painful recoveries, less infections and, of course, no scars.

“NOTES may be the next frontier for minimally invasive surgery,” Dr. Scott said. “It alleviates all the scars.”

Though NOTES is still in the experimental stage, Drs. Cadeddu and Scott have been at the forefront, using porcine models to pioneer needed techniques and instrumentation for what is truly “scarless surgery.”

UT Southwestern also sponsored the area’s very first NOTES conference, an initial gathering of scientists and engineers to collaborate on the scientific and medical challenges this new type of surgery poses and what will be needed to overcome them. Chief among those challenges will be new-and-improved surgical instruments.

Tools for the future

UT Southwestern surgeons have teamed up with UT Arlington engineers and one of the country’s leading surgical device manufacturers, Ethicon Endo-Surgery, to develop Dr. Cadeddu’s magnetically controlled tools that can benefit all areas of laparoscopic surgery.

The investigational surgical device platform includes a wide range of magnetically controlled instruments designed to give surgeons greater maneuverability and range-

of-motion while reducing the number of entry ports into the abdominal cavity required for surgery. The Magnetic Anchoring and Guidance System (MAGS) uses magnets outside the abdomen that attract magnets attached to instruments inserted inside the abdomen, allowing internal movement.

“The magnetic maneuverability affords a much greater range of motion inside the abdominal cavity, allowing the surgical team more easily to position instruments in their optimum locations,” explained Dr. Cadeddu.

The technology may help solve fundamental problems of guiding instruments through the abdomen for natural orifice surgery.

“This is powerful technology and a very innovative concept,” said Dr. Scott. “These new instruments are much better than most of the currently available technology – offering much better stability and maneuverability.”

In early animal studies, surgeons were able to successfully remove a kidney using MAGS.

Physicians at UT Southwestern have been working over the past several years with engineers from UT Arlington’s Texas Manufacturing Assistance Center, the Texas affiliate of the National Institute of Standards and Technology’s Manufacturing Extension Partnership and part of the Automation and Robotics Research Institute. The team created several generations of prototypes that are the basis for this technology development effort with Ethicon Endo-Surgery.

No one is exactly certain which of the new territories or technologies in laparoscopic surgery will take hold, Dr. Rege said.

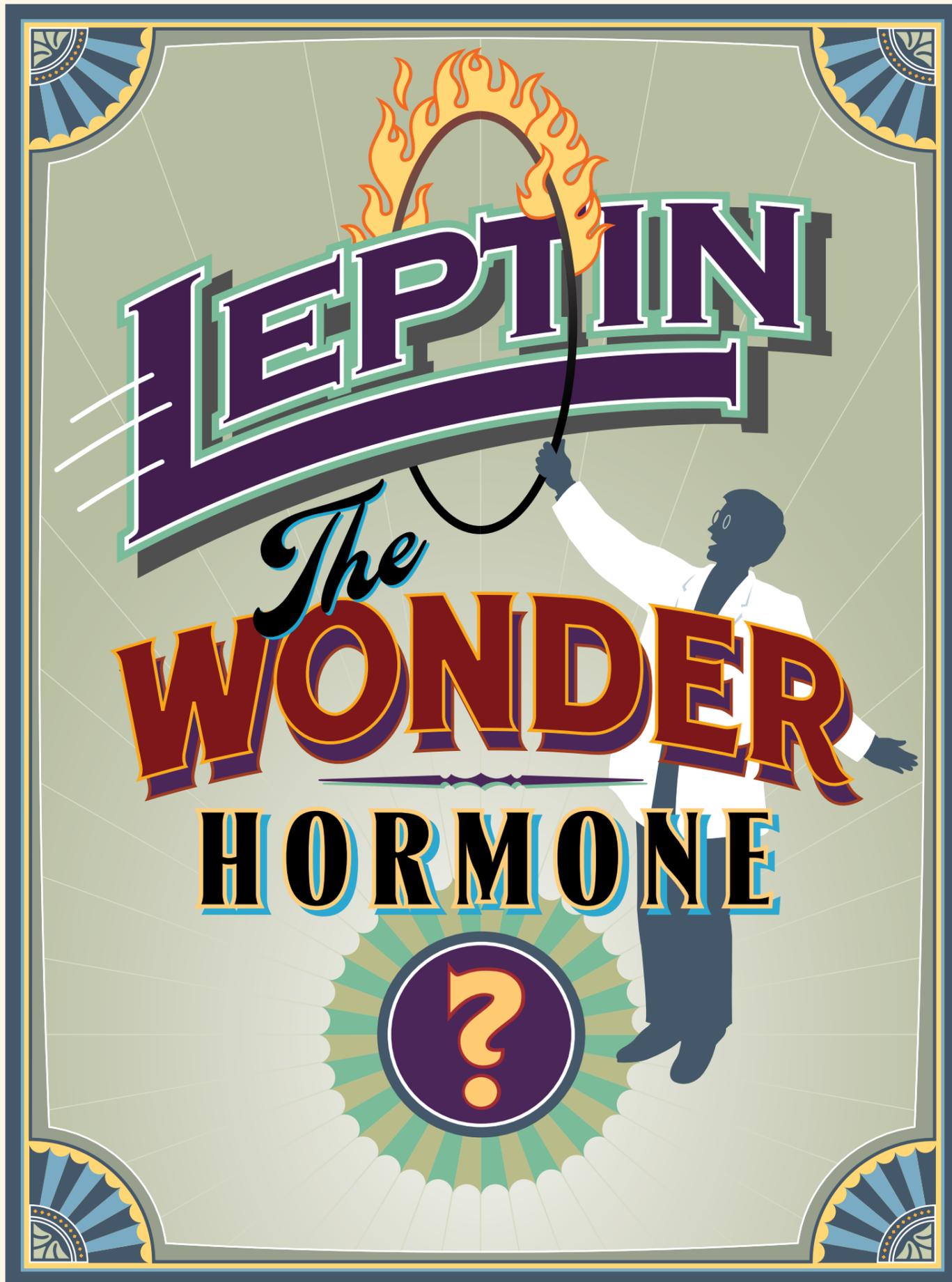
“Fortunately, there are centers that are interested in this, that are making great progress, that are studying what is the proper thing to do, and we’re one of them,” he said.

The technology constantly changes. But the critical factor in the equation will remain the surgeon, whatever tools are in his hands, Dr. Rege said.

“What’s important is that you’re in the hands of a good surgeon,” he said. “The well-trained surgeon will be well-versed in your disease and all of its treatments and will use minimally invasive or open surgery depending on what is appropriate for your situation.” ♦

For more information on minimally invasive surgery, please call 214-645-2900.





Since the discovery

of insulin in 1922, type 1 diabetes in humans has been treated by injecting insulin to lower high blood sugar levels and prevent diabetic coma. Until then, starvation was the only known option.

Recent findings by UT Southwestern Medical Center researchers suggest that insulin isn't the only agent that is effective.

Leptin, a hormone produced by the body's fat cells, also lowers blood glucose levels and maintains them in a normal range for extended periods for people with type 1 diabetes, also known as insulin-dependent diabetes.

While it's premature to know whether leptin might someday replace insulin as a treatment for diabetic patients, recent findings by a team of diabetes researchers at UT Southwestern suggest that leptin could at least handle some of insulin's job requirements and do it for longer than the three or four hours injected insulin is active biologically.

"Before the advent of insulin, everyone died within a matter of months," said Dr. Roger Unger, professor of internal medicine and holder of the Touchstone/West Distinguished Chair in Diabetes Research at UT Southwestern. "There was no such thing as a long-term survivor. With insulin, people live 30, 40, even 50 years with fewer complications. My hope is that you could give leptin for one type of action – glucagon's (hormone that raises sugar levels) suppression, for example – and insulin for another."

Newly discovered

Compared to insulin, leptin is but a toddler in the world of science and medicine. First discovered by Rockefeller University researchers in 1994, the hormone originally was envisioned as a wonder bullet that would eliminate the obesity epidemic in humans. The hypothesis didn't pan out as expected, but that hasn't stopped scientists, including many at UT Southwestern, from trying to figure out how leptin does play a role in weight regulation.

By Kristen Holland Shear

Based on the Greek word leptos, meaning thin, leptin plays a key role in regulating energy intake and energy expenditure functions such as appetite and metabolism. Researchers believe that nature designed leptin to sense when too much fat has been accumulated.

Several UT Southwestern researchers said the system worked beautifully until the mid-20th century, when the constant abundance of “cheap, high-caloric, yummy food” became commonplace in Western countries, particularly the United States.

“Evolution was unprepared for the change in the American diet to processed fast food and drive-through lanes,” said Dr. Unger, who has investigated diabetes, obesity and insulin resistance for more than 50 years. “We have 200 million overweight people in this country, and of those, 50 million already have metabolic syndrome and probably another 50 million just haven’t been diagnosed. The challenge is that this is an entirely self-inflicted disease that wouldn’t occur if we went back to our lifestyle of 100 years ago.”

Dr. Masashi Yanagisawa, professor of molecular genetics and an investigator of the Howard Hughes Medical Institute at UT Southwestern, agreed, calling the current situation “completely abnormal.”

“Most mammalian species, including humans, have evolved in a continual dearth of food,” Dr. Yanagisawa said. “So, whenever food is plentiful, we are designed to gobble up as many calories as possible. But, if animals or humans get too obese, it’s easier to be caught by predators, and, in the case of humans at least, chronic obesity causes a host of other problems. That’s why nature invented leptin – to counterbalance all those other systems which tend to make you fatter.”

“Chronic obesity causes a host of other problems. That’s why nature invented leptin – to counterbalance all those other systems which tend to make you fatter.”

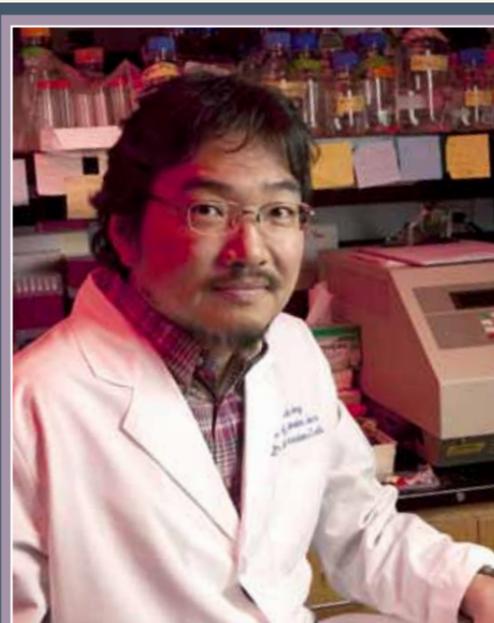
Leptin, Dr. Yanagisawa said, performs this counterbalancing mechanism by constantly monitoring the amount of fat an individual has accumulated so that the level of leptin in the bloodstream remains proportional to the amount of body fat. When too much fat has accumulated, then leptin sends a signal to the brain that it is time to stop eating and burn more calories.

“Even if you have a high-caloric diet, the leptin system should tell you that you are satiated before you become obese,” he said. “But that’s obviously not always the case. In humans and in mice, it’s well known that those diets help you put on weight.”

The problem, he said, is that while leptin levels do rise in diet-induced obese mice or obese patients, at some point the hormone becomes ineffective at conveying to the brain that food is no longer needed. Why this happens remains a mystery, but Dr. Yanagisawa believes that the natural brain chemical known as orexin may play a role.

Dr. Yanagisawa’s team recently published a study showing that mice with an abundance of orexin don’t gain weight when fed a high-fat diet. The study, published in the January 2009 issue of *Cell Metabolism*, reported that orexin works by increasing the body’s sensitivity to leptin, suggesting that finding a way to boost the orexin system may prove useful as an anti-obesity therapy.

“Obese people are not deficient in leptin,” Dr. Yanagisawa said. “They have tons of leptin



Dr. Masashi Yanagisawa

floating around. The problem is that their brains aren’t very sensitive to it.”

He said determining how to re-sensitize someone’s brain to leptin could help reduce the prevalence of obesity. “We believe the orexin system might do the trick,” said Dr. Yanagisawa, who holds the Patrick E. Haggerty Distinguished Chair in Basic Biomedical Science.

Helping the obese

Leptin may not be a magic hormone or drug for obesity, but the hormone has caused dramatic improvements in the lives of some patients, particularly those with generalized lipodystrophy – or low blood leptin levels – and congenital leptin deficiency. Patients with congenital leptin deficiency are born without leptin and are typically extremely obese.

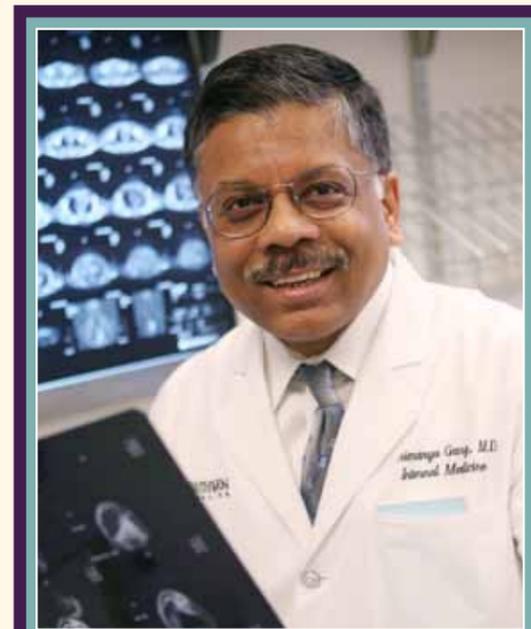
“Leptin could realistically be considered a wonder hormone for patients with lipodystrophies and leptin gene mutations,” said Dr. Abhimanyu Garg, chief of nutrition and metabolic diseases in the Center for Human Nutrition at UT Southwestern.

Generalized lipodystrophies are associated with metabolic abnormalities such as diabetes, high blood lipids (triglycerides or fat) and an accumulation of fat in the liver. Current treatment consists of high-dose insulin plus triglyceride- or lipid-lowering medications.

In a landmark study published in the February 2002 issue of *The New England Journal of Medicine*, Dr. Garg’s team and his collaborators at the National Institutes of Health reported that leptin replacement therapy not only controlled severe insulin resistance and lowered triglyceride levels in patients with severe lipodystrophy but also decreased fat accumulation in the liver, an abnormality for which there has been no effective therapy.

Nine females, eight of whom were diabetic, participated in the 17-week study. All participants received leptin injections under the skin twice a day for four months. After four months of therapy, six of the eight diabetic patients no longer required insulin therapy to control their diabetes, and two required much lower doses.

“That was a very dramatic result,” said Dr. Garg, who has been studying patients with lipodystrophies for more than two decades. “There’s an ongoing debate about the primary site of action of leptin and whether it works in the brain to reduce appetite or in the liver or muscles to improve insulin sensitivity, but our study showed that leptin was extremely helpful for these patients.”



Dr. Abhimanyu Garg

“Leptin could realistically be considered a wonder hormone for patients with lipodystrophies and leptin gene mutations.”

Dr. Garg, who holds the Endowed Chair in Human Nutrition, said several participants from the original four-month trial have yet to reintroduce insulin to their treatment regimens. Some do take both insulin and leptin, but he stressed that the amount of leptin the patients take is minimal compared to that given as part of past obesity studies.

“Since many of the original participants have now been taking leptin for five or six years, we’ve begun studying the efficacy and safety of its long-term use,” Dr. Garg said. “We’ve also expanded the studies from those with generalized lipodystrophies to patients with partial lipodystrophies.”

Dr. Garg said studying the safety of using leptin long-term will remain a priority, particularly because the hormone is not Food and Drug Administration-approved. He said it remains up to Amylin Pharmaceuticals, which holds the rights to the leptin molecular franchise and clinical program, to pursue FDA approval.

“So far, we’ve found it very safe, but as for anything, we need to continue to be vigilant,” Dr. Garg said. “Additionally, there have been reports that some patients respond well initially but then the response goes down, so we also need to understand why that happens and whether those patients are developing leptin antibodies or resistance.”

Effects on the brain

Understanding how leptin acts in the brain, particularly the hypothalamus region, is of particular importance to Dr. Joel Elmquist, professor of internal medicine, psychiatry and pharmacology at UT Southwestern. The hypothalamus is known to control food intake and energy expenditure.

“There’s obviously the disease angle, but from a very basic point of view, leptin has turned out to be a very useful tool to figure out how complex systems in the hypothalamus work,” said Dr. Elmquist, who holds the Maclin Family Professorship in Medical Science, in Honor of Dr. Roy A. Brinkley.

He said deciphering how leptin works in the brain is critical because the brain is the hormone’s primary site of action. Peripheral actions do exist, but “the brain is clearly a primary site of action for leptin,” Dr. Elmquist said.

Using mouse genetics, Dr. Elmquist’s team previously identified some of leptin’s key targets in the brain, including a group of brain cells called pro-opiomelanocortin, or POMC, neurons. The POMC neurons, which are found in the hypothalamus, play an important role in suppressing appetite and inducing weight loss.

“By manipulating leptin receptors only in those particular neurons, we get maybe 15 percent to 20 percent of the obesity you would see with total leptin deficiency, suggesting that the effects of leptin to regulate feeding and body weight probably are more distributed across the brain,” he said.

Research is ongoing but Dr. Elmquist’s team currently is using different mouse models to determine how the central nervous system may handle this job. He also is using mouse genetics in combination with electrophysiology to understand how neurons respond to leptin and to identify the cellular mechanisms through which leptin acts.

“One of our key questions is trying to figure out how leptin and insulin act on these POMC cells to regulate glucose levels, including those regulated by the liver.”

Another project currently under way, he said, involves studying the molecular mechanisms of leptin resistance in order to explain why obese people remain largely invulnerable to the benefits of leptin.

“If you give lean rodents a very low dose of leptin, you can melt away all the fat, sparing the lean body mass,” he said. “However, the same dose of leptin has no effect on obese animals. In theory, leptin could be a good drug treatment for obesity in humans, but only if researchers are able to decipher why obese people are so resistant to the beneficial effects of leptin in the first place.”

Studying fat

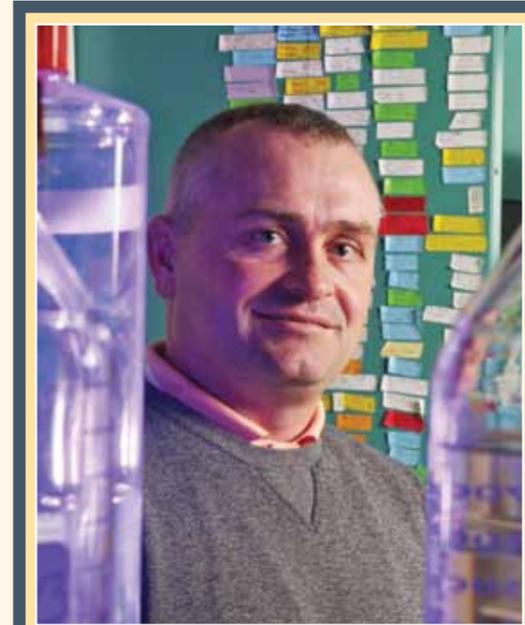
A five-minute walk from where Dr. Elmquist’s team is tackling the central actions of leptin, another group of researchers has focused its efforts on the site of leptin’s origin – fat.

Largely perceived as a useless storage bin until the early 1990s, fat tissue has been found to release hormones, including adiponectin, that play integral roles in metabolism and obesity. Adiponectin levels decline as a person accumulates more fat, making the levels a good predictor of future risk of developing diabetes, heart disease and cancer, said Dr. Philipp Scherer, professor of internal medicine and cell biology, director of the Touchstone Center for Diabetes Research and holder of the Gifford O. Touchstone Jr. and Randolph G. Touchstone Distinguished Chair in Diabetes Research.

Prior research by Dr. Scherer has shown that an expanded fat mass, when stored in the right places, can help prevent diabetes and reduce the risk of heart disease. He currently is trying to understand if – and how – fat may also play a role in leptin resistance.

“At this point, no one has figured out how to overcome this resistance,” said Dr. Scherer, who discovered the hormone adiponectin in 1994.

Continued on page 36



Dr. Joel Elmquist

"Leptin could be a good drug treatment for obesity in humans, but only if researchers are able to decipher why obese people are so resistant to the beneficial effects of leptin in the first place."

Stemming Diabetes

UT Southwestern Medical Center is the only study site in the southwestern U.S. where researchers are trying to determine whether adult stem cells may help newly diagnosed patients with type 1 diabetes better manage their disease.

In type 1 diabetes, also known as insulin-dependent diabetes, the pancreatic beta cells that produce insulin are destroyed by an autoimmune process. Individuals with type 1 diabetes must regiment their diets and take insulin multiple times a day to control blood sugar levels and prevent diabetic coma. The autoimmune disease, which is usually diagnosed before the age of 40, affects about 1 million people in the U.S.

Dr. Philip Raskin, professor of internal medicine at UT Southwestern and holder of the Clifton and Betsy Robinson Chair in Biomedical Research, said the multicenter national study aims to determine whether an investigational drug called Prochymal can be used to treat patients newly diagnosed with type 1 diabetes in addition to their usual insulin dose.

“Our hope is that the infusion of adult stems cells will help stabilize the pancreatic beta cells so that they continue to produce insulin,” said Dr. Raskin, who receives support from the Irma and Irwin Grossman Fund at Southwestern Medical Foundation. “This is by no means a cure for type 1 diabetes, but the addition of these stem cells could make the disease more easily managed.”

Prochymal, developed by Osiris Therapeutics, is a formulation of adult mesenchymal stem cells designed to control inflammation, promote tissue regeneration and prevent scar formation. These cells, which can develop into bone, muscle and fat, are derived solely from healthy, adult volunteer bone marrow donors. Studies have shown that adult mesenchymal stem cells have a very low risk of rejection, similar to blood type O, the universal donor type.

The formulation to be evaluated in the UT Southwestern study is currently in expanded human clinical trials for graft-versus-host disease and Crohn’s disease, but this is the first time it will be tested in patients with type 1 diabetes.

Research has shown that when adult mesenchymal stem cells are injected into an animal, the cells home in on and begin to repair any damaged tissues. If there is no damage, the stem cells return to the bone marrow.

Dr. Raskin said that while Prochymal has not been investigated in patients with type 1 diabetes, he believes that the stem cells will target the pancreas because of the inflammation and tissue damage caused by the autoimmune process.

The clinical study, scheduled to be completed this year, is evaluating 60 participants randomly assigned to receive either the stem cell formulation or a placebo.

He said researchers speculated that individuals became leptin-resistant partly because of a defense system in the body called the blood-brain barrier, which prevents many substances in the blood from penetrating into the brain.

"But I think it's more than that. There's actual resistance that develops in the hypothalamus," Dr. Scherer said.

Findings from a recent UT Southwestern study suggest that fat from certain digested foods makes its way to the brain. Once there, the fat molecules cause the brain to send messages to the body's cells, warning them to ignore the appetite-suppressing signals from leptin and insulin.

"What we've shown in this study is that someone's entire brain chemistry can change in a very short period of time. Our findings suggest that when you eat something high in fat, your brain gets 'hit' with the fatty acids, and you become resistant to insulin and leptin," said Dr. Deborah Clegg, assistant professor of internal medicine at UT Southwestern. "Since you're not being told by the brain to stop eating, you overeat."

Dr. Scherer said these results could play a role in unraveling the mechanisms involved in leptin resistance, but their practicality has yet to be shown.

"You can avoid eating fatty foods, but that doesn't really work for most people," he said. "There really isn't a practical way to avoid this leptin resistance. If we're able to pharmacologically reduce the levels of resistance, perhaps that would enable leptin to unleash its full power in the brain again."

Though consuming excess calories usually spurs insulin resistance and diabetes, Dr. Scherer's team also has shown that the combination of too much of the hormone adiponectin and too little leptin enables mice to store excess calories in fat tissue instead of in liver, heart or muscle tissue — places where excess fat can lead to inflammation, diabetes and heart disease.

In other words, the mice get morbidly obese but are insulin-sensitive with normal blood-glucose levels.

Dr. Scherer is now looking into how leptin may play a role in breast cancer, particularly among post-menopausal women. While there's no epidemiological connection between the

size of an individual's mammary fat pad and tumor incidence, Dr. Scherer said early findings suggest that both the quality and location of the fat play a significant role.

"The quality of the mammary fat can be affected negatively by the kinds of things that we experience in other fat pads," he said. "They can be inflamed; they can be fibrotic. All these conditions will lead to an increased production of leptin."

Forecast: New treatments

Using anything other than insulin to treat type 1 diabetes patients may sound far-fetched to some, but Dr. Unger believes that adding leptin to standard insulin treatment may revolutionize diabetes care.

In a *Proceedings of the National Academy of Sciences* article published in 2008, Dr. Unger and his colleagues reported that terminally ill rodents with type 1 diabetes were restored to full health with a single injection of leptin.

"Many scientists, including us, thought it would be a waste of time to give leptin in the absence of insulin. We've been brainwashed into thinking that insulin is the only substance that can correct the consequences of insulin deficiency," he said.

The mechanism of leptin's glucose-lowering action appears to involve the suppression of glucagon, a hormone produced by the pancreas that raises glucose levels. Normally, glucagon is released when the glucose, or sugar, level in the blood is low. In insulin deficiency, however, glucagon levels are inappropriately high and cause the liver to release excessive amounts of glucose into the bloodstream. This action is opposed by insulin, which tells the body's cells to remove sugar from the bloodstream.

In type 1 diabetes, which affects about 1 million people in the U.S., the pancreatic islet cells that produce insulin are destroyed. Type 1 diabetics must take insulin multiple times a day to metabolize blood glucose and regiment their diets. In comparison, patients with non-insulin dependent, or type 2, diabetes make insulin, but their bodies don't respond well to it. Type 2 diabetes affects between 18 million and 20 million people in the U.S.

Dr. Unger said his team hypothesizes that leptin combats diabetes not only by suppressing glucagon's action on the liver, but also by boosting the insulin-like actions of IGF-1 (insulin-like growth factor-1), a hormone that promotes growth and mimics insulin.

"One of the things that happens when a child gets type 1 diabetes is their growth is stunted until they're given insulin," Dr. Unger said. "The same is true with these mice. However, we found that if you take a diabetic rat that's not receiving insulin and make it hyperleptinemic, it almost catches up growth-wise."

Dr. Unger said that while insulin treatment can significantly prolong the lives of those with type 1 diabetes, it is not without complications. "People who live that long almost always develop coronary artery disease, likely as a result of the chronically high insulin levels required to meet their insulin needs," he said.

That's why his team believes that adding leptin to standard insulin therapy may be extremely beneficial.

"We've shown that both insulin and leptin reverse the effects of untreated diabetes. Insulin reverses the damage by putting the fatty acids back into the fat cells, whereas leptin forces those fatty acids to leave the body as carbon dioxide and water, creating a much healthier environment," Dr. Unger said.

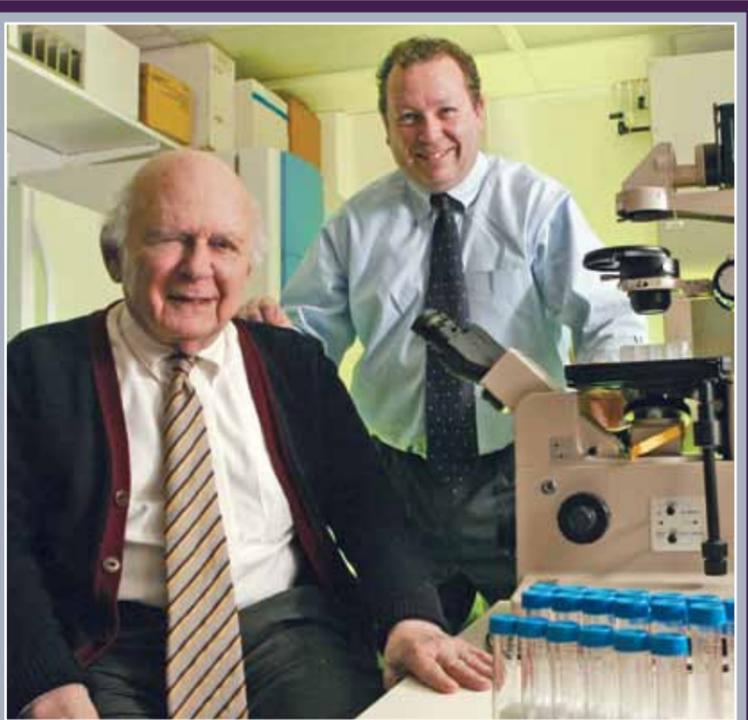
The goal, he said, would be for leptin to suppress the glucagon, thus freeing up the insulin to satisfy the needs of peripheral tissues.

"We believe, based on previous findings in animal models, that if you add leptin to a suboptimal dose of insulin, you could completely normalize blood sugar levels without injecting astronomical doses of insulin," he said.

The next step, Dr. Unger said, is to begin clinical trials to see whether bihormonal therapy using both leptin and insulin is as successful in humans as in the mouse models. A gift from Mr. and Mrs. Kent Foster is expediting this work.

"We think that insulin monotherapy should go into the dustbin of history with the other 'Roaring 20s' items including flappers and speakeasies," he said. "The challenge will be proving that our theory is correct." ♦

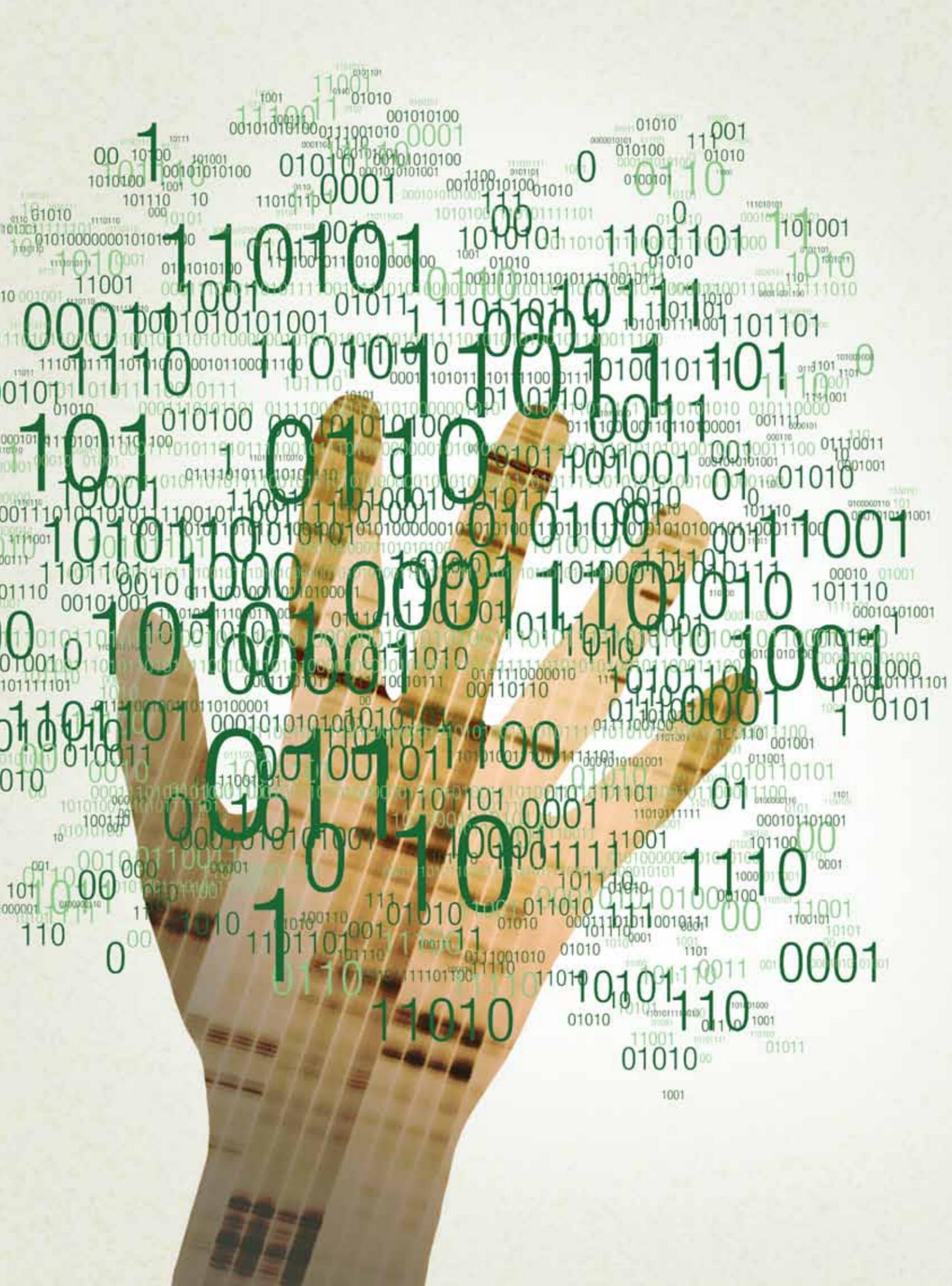
For more information about diabetes treatment, please call 214-645-6455.



Dr. Roger Unger and Dr. Philipp Scherer

"We believe...that if you add leptin to a suboptimal dose of insulin, you could completely normalize blood sugar levels."

- Dr. Unger



Decoding the family tree:

Using computers to assess cancer risk

Optimism and hard work have paid off for Dr. David Euhus in ways far greater than he ever imagined. A surgical oncologist, he knew little about computers or their languages when he was asked 14 years ago to create a risk assessment program that could predict who might develop breast cancer.

BY CONNIE PILOTO



The small software program that Dr. Euhus created in his “spare time” as a junior faculty member at UT Southwestern Medical Center has developed today into a robust engine that can not only assess the risk of breast cancers, but also ovarian, uterine, pancreatic and colon cancers.

The program, known as CancerGene, has revolutionized cancer risk assessment globally and is used in more than 4,000 medical centers in more than 75 countries.

Dr. Euhus, himself a breast cancer surgeon, distributes the program to high-risk clinics and academic medical centers free of charge.

“The goal of the program is to reduce the incidence of cancer,” said Dr. Euhus, professor of surgical oncology and director of the Mary L. Brown Breast Cancer Genetics and Risk Assessment Program at the Harold C. Simmons Comprehensive Cancer Center.

Genetics revolution

An explosion of basic-science studies on genes and diseases has resulted in significant advances in clinical genetics.

CancerGene has revolutionized cancer risk assessment globally and is used in more than 4,000 medical centers in more than 75 countries.

As part of the genetics revolution, the cancer and genetics clinic at the Simmons Comprehensive Cancer Center helps families who may have an inherited predisposition for cancer understand their risk, as well as their options for prevention, early detection and treatment.

UT Southwestern’s cancer genetics program began in 1992 under the direction of Dr. Gail Tomlinson. Dr. Tomlinson, who is currently a clinical associate professor of internal medicine at UT Southwestern and chief of hematology/oncology at UT Health Science Center at San Antonio, created a cancer genetics registry. She was studying the hereditary forms of the disease before many of the cancer genes that individuals are tested for today were even discovered.

Back then, about 40 families a year were seen at the clinic. The practice began growing in 2000, when insurance companies started paying for testing and more genes had been discovered.

Today, the Simmons Comprehensive Cancer Center genetics program is one of the largest in the nation and is the only research-based clinical program in the Dallas-Fort Worth area offering testing and counseling for all identified types of cancer.

The clinic is directed by Dr. Euhus, holder of the Marilyn R. Corrigan Distinguished Chair in Breast Cancer Surgery, and staffed by five board-certified genetic counselors who also see patients at eight satellite clinics, including Parkland Memorial Hospital, John Peter Smith Hospital and Moncrief Cancer Institute in Fort Worth, and Children’s Medical Center Dallas.

Today more than 1,000 patients are seen annually at the clinics, which also provide genetic counseling for patients who do not have insurance through grants from cancer foundations and charities.

Although 70 percent of the referrals to the clinics are for hereditary breast cancer, UT Southwestern provides counseling and testing for all hereditary cancers, including pediatric genetic syndromes.

While most genetic testing is done in adulthood, there are some pediatric cancers that have a hereditary link, such as retinoblastoma.

Linda Robinson, a genetic counselor and supervisor of the clinic, said that up to 30 percent of all cases of cancer have a familial component, and approximately 5 percent to 10 percent of all cancers may be due to a known, major, inherited-cancer-predisposition syndrome.

“Many people assume that if an immediate family member or other close relative has cancer, their risk for inheriting any kind of cancer themselves is automatically increased,” Mrs. Robinson said. “But, that’s not true. Just because cancer is in your family doesn’t mean it’s genetic.”



Dr. David Euhus directs the Mary L. Brown Breast Cancer Genetics and Risk Assessment Program.



A love of genealogy led patient Dinah Eivens to the discovery of a family link to colon cancer.

She said that only genetic testing can reveal whether a person has an inherited tendency to develop a particular cancer.

At the clinic, genetic counselors obtain a detailed family medical history from the patient and discuss the inherited nature of the cancer as well as other risk factors, such as environment, lifestyle and diet.

The information is then entered into the CancerGene database to generate a statistical analysis detailing a patient's risk for developing cancer.

"New genes are discovered every year that can predict your risk of cancer based on test results and family history and ancestry," Mrs. Robinson said. "In some cases, we can tell patients what probably caused the cancer in their family and trace the gene back in time. It's like putting together the pieces of a very important puzzle."

Depending on the results, genetic testing may be recommended. The test consists of obtaining a small sample of blood or saliva, which is sent for laboratory testing.

Mrs. Robinson and her staff counsel patients who are undergoing genetic testing so that they understand their options and can prepare emotionally for the results.

A positive result means a patient should undergo preventive screenings earlier and with more frequency and develop an aggressive game plan with their physician.

The test is highly recommended for individuals with a personal history of early-onset cancer or a strong family history of the disease.

"For every one person who tests positive for a cancer gene, we can find on average four other family members with the gene," Mrs. Robinson said. "This is the true beauty of genetic testing. You're able to provide yourself and other family members with the gift of early detection and piece of mind."

Family tree offers clues

A love of genealogy led Dinah Eivens to the discovery that her family carries a mutation for an inherited form of colon cancer.

A Fort Worth native, Mrs. Eivens was researching her ancestry to determine if she had any links to Native Americans on the maternal side of her family. She knew there were links on the paternal side.

A short time after posting her query on a genealogy message board, she received a message asking if there was a history of cancer in her family.

"Yes, we've had some cancers over the years," she replied.

The person who made the inquiry was a genealogist for the Ohio State University Comprehensive Cancer Center, and he was conducting research on the American Founder Mutation, a common cause of Lynch syndrome.

Lynch syndrome is hereditary and greatly increases a person's risk for developing cancers of the colon, uterus and ovaries.

The mutation was discovered in 2003, and researchers suspect it is about 500 years old, suggesting that it arose in Europeans or perhaps Native Americans. Most of the families with the mutations are clustered in Kentucky, Ohio and Texas.

The Ohio State genealogist helped Mrs. Eivens with her research, and she in turn shared the incidences of cancer in her family.

There appeared to be a link: Mrs. Eivens' grandmother was in her early 50s when she died of uterine cancer, and several cousins had died from colon cancer.

Researchers asked Mrs. Eivens if she would be willing to undergo genetic testing for the mutation as part of a clinical trial. She agreed and had her physician ship a kit with her blood to Ohio.

The researchers also asked Mrs. Eivens to speak with a genetic counselor and referred her to UT Southwestern.

Mrs. Eivens, 50, met with Sara Pirzadeh, a UT Southwestern genetic counselor who works

medical management? How could it affect their family, kids and siblings as well as their extended family?"

For Mrs. Eivens the results mean that every year she will undergo a colonoscopy as well as a screening of the lining of the esophagus, stomach and upper duodenum.

Because individuals with Lynch syndrome also are likely to develop cancer of the ovaries and uterus, Mrs. Eivens also decided to undergo a hysterectomy.

"My grandmother died from uterine cancer; my mother had issues and underwent a hysterectomy in her 40s; and one of my aunts had cancer of the ureter, which is also associated with Lynch syndrome," Mrs. Eivens said. "I have a chance

The Simmons Comprehensive Cancer Center genetics program is one of the largest in the nation and is the only research-based clinical program in the Dallas-Fort Worth area offering testing and counseling for all identified types of cancer.

at the Simmons Comprehensive Cancer Center and Moncrief Cancer Institute.

Mrs. Eivens tested positive for Lynch syndrome. "It's hard, and you can't help but think about it often," Mrs. Eivens said. "But for me, knowledge is power. There are things that I can do to prevent the cancer, catch it early or control it."

After finding out the news, Ms. Pirzadeh created a letter so that Mrs. Eivens could send it to her family telling them that a family member had tested positive for a gene associated with a cancer syndrome. The practice is standard and encourages family members to speak with a genetic counselor and to consider being tested themselves.

Several of Mrs. Eivens' family members sought the expertise of Ms. Pirzadeh and decided to be tested. One of Mrs. Eivens' aunts has also tested positive for Lynch syndrome.

Family members sometimes choose not to be tested. After genetic counselors run the statistical models, which include family history and the incidences of cancer in the family, the patient and counselor weigh the options together.

"We discuss what the test can tell us," Ms. Pirzadeh said. "How could it change a patient's

to prevent the cancer or catch it early. This might save my life."

Mrs. Eivens said she is more concerned about ureter cancer since her aunt, who tested



Sarah Pirzadeh, genetic counselor

positive for Lynch syndrome, has had it twice. Also, the screening tests for ureter cancer are not as precise as those for other cancers.

"Having Lynch syndrome has greatly heightened my awareness of all cancers inherited or not," Mrs. Eivens said.

Educating the community

The UT Southwestern genetics clinic keeps a database of all patients who have tested positive and educates them about new discoveries and protocols.

Every year the clinic holds a hereditary breast and ovarian cancer conference for patients who have tested positive for the *BRCA 1* or *BRCA 2* gene. Last year, they added a conference for patients with hereditary colon cancer.

Physicians, researchers and genetic counselors discuss the latest research and screening recommendations.

"The conferences help keep our patients informed with the latest information," Ms. Pirzadeh said.

Recently, the UT Southwestern genetic counseling group was asked to help create an awareness campaign about genetic services in Texas.

As part of the campaign, they edited the content on genetics for the Texas Department

The program used a statistical model known as the Gail model to predict risk and was even programmed to play music while Dr. Euhus entered data.

"It became more austere as the practicality set in," Dr. Euhus said.

Serendipity struck a short time after creating the program.

"I remember the moment clearly," Dr. Euhus said. "I was on trauma call at Parkland Memorial Hospital, and it turned out to be an unusually quiet night."

Dr. Euhus was paging through a stack of journals when he came across an article detailing a new model for predicting *BRCA 1* and *BRCA 2* gene mutations, which were recent discoveries at the time. Mutations of these genes are linked to hereditary breast and ovarian cancer.

The model – called BRCAPRO – was written in an impossibly complex programming language.

Dr. Euhus started looking at ways he could adapt the model. Frustrated, he decided to call the researchers who had created it. He said he was surprised by their reaction.

"They were happy to hear from a clinician," Dr. Euhus said about the researchers, members of the BayesMendel lab, whose core group now



Up to 30 percent of all cases of cancer have a familial component, and approximately 5 percent to 10 percent of all cancers may be due to an inherited-cancer-predisposition syndrome.

of Health Web page and developed brochures and public service advertisements.

How it began

After searching for ways to assess risk and finding no information back in 1995, Dr. Euhus said, he "decided to put something together that we could actually use to measure a woman's risk."

He turned to a computer and taught himself how to program it.

"That was an adventure in itself," Dr. Euhus recalled. "I learned several computer languages and created a small program."

works from the Harvard University School of Public Health and develops methodologies, models and software for predicting who may carry a cancer-susceptibility gene. "At the time, there was no one in the world that could use their model – it was entirely conceptual and mathematical."

After a series of discussions, the researchers sent Dr. Euhus the computer code for the statistical model. He has since become one of their collaborators.

"At the time, it appeared to be an impossible task," Dr. Euhus said. "I worked on it every day, and then the pieces fell into place, and I had mastered it."

Dr. Euhus remembers the night he distributed the first version of the program to about 25 researchers who wanted it as soon as it was available.

"I e-mailed CancerGene version 1, and at the bottom of the e-mail I wrote, 'Please God, let this work,'" he said.

Minutes later, Dr. Euhus started receiving e-mail responses: "Your prayers are answered, it works."

Evolution to the Web

Dr. Euhus regularly updates the models and redistributes new versions of the computerized program to all its subscribers.

As technology and science have evolved – there are more than 40 genes now related to hereditary cancer syndromes – so has the CancerGene program.

While the first versions of the program were for a desktop, Dr. Euhus has just developed one for the Web.

"Desktop programs are going away," Dr. Euhus said. "This is the next evolution of CancerGene."

The Web-based program has all the functionality of CancerGene but will allow Dr. Euhus to update the program more easily and is patient-friendly.

"As science progresses there are new factors that need to be added to the statistical models, and the program becomes more accurate at making predictions," Dr. Euhus said.

Beginning this year, when patients make appointments with genetic counselors, they will be given access to a Web site where they can enter their family history from their home or office. Before the Web-based model was created, a genetic counselor compiled a detailed family and past medical history during the visit.

Entering the information before a visit allows the counselor and patient to spend more time talking instead of collecting information. It also allows patients who may be unsure of some aspect of their family history to call relatives and gather the needed information before walking into the clinic.

"The program asks some background questions about the family, and then it drills deeper and starts asking more questions about



Genetic counselor Linda Robinson says new genes are discovered every year that can predict a person's risk of cancer.

specific relatives," Dr. Euhus said. "When a patient is done, the program generates a full family tree."

Patients can also access their page and modify and update information, as well as print their family tree and medical history to share with relatives.

"The new program will allow us to be more efficient and spend more time counseling each patient," Mrs. Robinson said. ♦

For more information about genetic counseling at UT Southwestern, please call 214-645-4673.



Generational inheritance:

how one family is providing genetic clues to lung disease

BY CONNIE PILOTO

Jimmy Sasser has grown accustomed to the sad phone calls.

- In September 2008 he received the news again: Another relative – his 49-year-old nephew, Charles E. Sasser – had died from idiopathic pulmonary fibrosis, or IPF.
- He was the eighth member of Jimmy Sasser's family to die from the fatal lung disease. Another nephew would die a year later. A niece is currently in the first stages of the disease. She is the 10th member of Jimmy Sasser's family to develop IPF.



here was a link, Mr. Sasser always believed, between his family and the fatal disease that had claimed the lives of so many of his relatives.

"There has to be a connection," he recalls telling his wife after his nephew's death.

Days later, Jimmy Sasser was the one making phone calls. He contacted the Pulmonary Fibrosis Foundation in Chicago and shared his story with members of the advocacy group. They referred him to Dr. Christine Garcia, assistant professor in the Eugene McDermott Center for Human Growth and Development and of internal medicine at UT Southwestern Medical Center.

A physician-scientist, Dr. Garcia treats patients with IPF, and in her UT Southwestern laboratory, she leads a team of scientists who study the genetics of the inherited form of the disease.

"I called Dr. Garcia and left a message," Jimmy Sasser said. "I told her about my family and how many had died from the disease."

Dr. Garcia returned his call. They discussed the history of the disease in his family, and they agreed to meet – at Charles E. Sasser's memorial service.

Cause and effect

Pulmonary fibrosis is a lung disorder characterized by a progressive scarring and deterioration of the lungs, which slowly robs its victims of their ability to breathe.

About 500,000 people in the U.S. have pulmonary fibrosis, and more than 40,000 patients die of the disease each year. About one in every 50 IPF patients, or approximately

is the only center in Texas to be a part of this network, which is coordinated by Duke University, said Dr. Jonathan Weissler, director of the James M. Collins Center for Biomedical Research and holder of the James M. Collins Professorship in Biomedical Research.

"We don't have any medicines to treat this disease," Dr. Garcia said. "If a patient is younger than 65, lung transplantation is an option, but most people who develop IPF are older than that."

Defying the odds

Genetics were slowly working against Francis Moran – so slowly that he thought he might escape familial IPF.

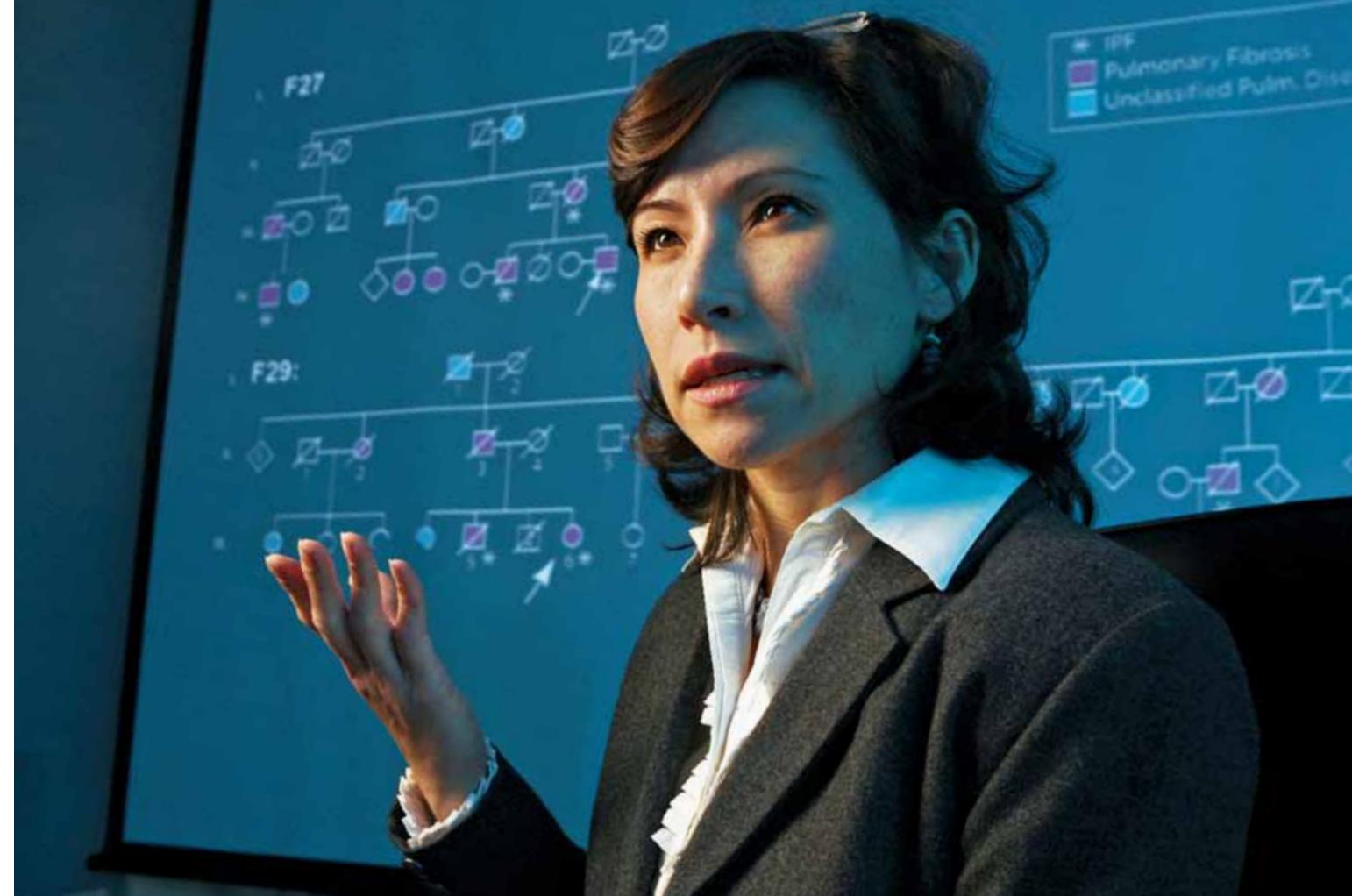
The disease had stricken other members of his family. Both his mother and his brother fought the disease before it claimed their lives at ages 54 and 40, respectively.

"Once I hit my 50th birthday, I was still free of symptoms, and I had a lot of confidence that I wouldn't get a thing," Mr. Moran said. But a couple of years later, in 2003, he found out that he was in the first stages of familial IPF.

Mr. Moran sought the expertise of Dr. Fernando Torres at UT Southwestern. Dr. Torres, an associate professor of internal medicine, specializes in complex pulmonary diseases like Mr. Moran's. Dr. Torres suggested the possibility of a lung transplant and referred Mr. Moran to other lung experts at UT Southwestern, including Dr. Garcia.

Mr. Moran was placed on a regimen of medication to keep his health as stable as possible until a transplant became necessary.

"This is the kind of disease that can remain stable for a while, but when the patient's health



Dr. Christine Garcia treats patients with IPF and leads a team of scientists who have discovered the genes responsible for the inherited form of the disease.

home in Honey Grove, Texas, on Feb. 10, 2009. The couple's two grown children also joined them.

Dr. Michael DiMaio, associate professor of cardiovascular and thoracic surgery and holder of the Laurence and Susan Hirsch/Centex Distinguished Chair in Heart Disease, and Dr. Michael Wait, professor of cardiovascular and thoracic surgery, together performed the bilateral transplant.

"I was very blessed to have matched to donor lungs so quickly after I was put on the list," Mr. Moran said.

Hunting the culprits

Researchers don't know what causes IPF. They suspect it might be a combination of genetic susceptibility and environmental influences such as smoking, said Dr. Garcia, who has been studying the inherited form of IPF for five years.

But not all patients who develop IPF smoke. Aware that his mother and brother had died from IPF, Mr. Moran never touched a cigarette, but he still developed the disease.

"There are a lot of questions that still need to be answered," Dr. Garcia said. "The ultimate goal is to find a cure or develop a medication that can stem the progression of this pulmonary condition."

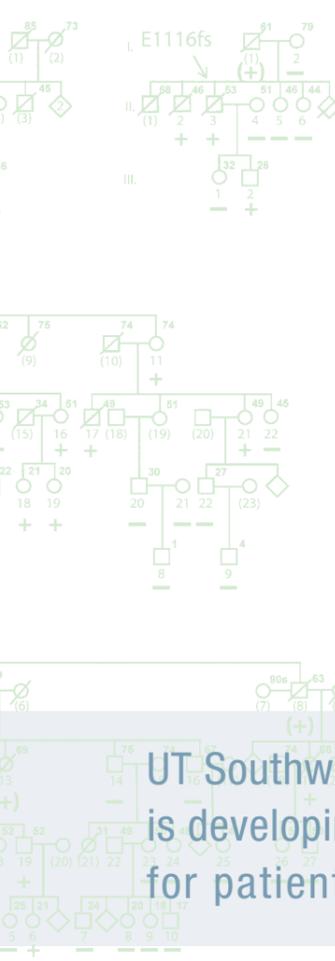
To do that, Dr. Garcia and her team have been working to identify the genes and genetic variants that underlie the disease.

"We know there are multiple genes involved," Dr. Garcia said.

And she has found some of them. Dr. Garcia and her team have identified three of the genes that are linked to IPF.

In 2007, in their search for a gene causing the disease, Dr. Garcia and her colleagues studied two large families in which multiple individuals were affected with IPF.

This led to the discovery of mutations in genes called *TERT* and *TERC*. These two genes are normally responsible for producing the telomerase enzyme, which elongates the lengths of DNA at the ends of chromosomes, called telomeres.



UT Southwestern is one of 22 centers of excellence in the U.S. that is developing and conducting clinical trials to find effective therapies for patients with both the early and advanced stages of IPF.

2 percent, have an inherited or familial form of the disease.

IPF typically strikes people in their 50s and older. There is no cure except lung transplantation. Death usually occurs within three years of diagnosis.

UT Southwestern is one of 22 centers of excellence in the U.S. that is developing and conducting clinical trials to find effective therapies for patients with both the early and advanced stages of IPF. UT Southwestern

begins to decline, it declines rapidly," Dr. Torres said. "In 2008 he began to deteriorate, and we knew that a lung transplant was really the only way for him to recover."

Three weeks after being placed on the list for a double-lung transplant, Mr. Moran and his family were notified that a match had been found.

Mr. Moran and his wife, Sarah, drove to UT Southwestern University Hospital from their



Ten members of Jimmy Sasser's family have been stricken with IPF.

Many in the Moran family who carried this mutation had not only IPF but also lung cancer, especially adenocarcinoma with features of bronchioloalveolar cell carcinoma.

It is known that people with IPF have a higher risk for developing lung cancer, and Dr. Garcia suspects that mutations in the *SFTPA2* gene are associated with both IPF and lung cancer. Another family harboring a different mutation in the *SFTPA2* gene also had members that exhibited IPF and lung cancer.

Dr. Garcia and her team are now working on molecular studies in cells to determine why these gene mutations put patients at risk for either of these diseases. They also are working to develop an animal model of pulmonary fibrosis.

Gene pool aids research

Dr. Garcia says she would not have discovered the genes that are linked to IPF without the help of families who have an inherited form of the disease.

To date, more than 300 families and more than 2,000 people have donated DNA samples to aid Dr. Garcia's research – from children to octogenarians.

"They feel strongly about wanting to help because so many people in their families have died," Dr. Garcia said. "Their participation has allowed us to make important discoveries and is helping us unravel the mysteries of this disease."

Collecting DNA samples at family gatherings eases the burden for family members who would otherwise have to travel to a medical office to have blood drawn and also allows researchers to gather samples from numerous relatives at the same time.

Dr. Garcia has traveled to family reunions and gatherings across the state. She and her team arrive prepared to collect blood samples, inquire about family and medical histories, and answer questions.

"I talk to them about our research," Dr. Garcia said. "And I tell them that I will protect their privacy, and part of that protection includes that I will not tell them – or anyone else – if they have the gene mutation."

Genetic tests may help in the future if a medication were to be developed to slow the progression of the disease.

Some family members who have a genetic mutation for IPF never develop the disease. Others who have the gene develop pulmonary fibrosis. What determines who develops pulmonary fibrosis is still being studied.

During family meetings Dr. Garcia allays fears and reminds them that they can't change their genetics, but they can definitely change their environment.

Because half of the people who develop IPF are ex-smokers, she makes sure all generations hear this key message: "If you're smoking, quit. If you don't smoke, take care of your lungs. Don't pick up welding or carpentry as a hobby without wearing a mask. Protect yourself."

Back at the laboratory, the DNA is processed and analyzed in hopes of finding new clues about the disease.

Generations of grief

Jimmy Sasser told Dr. Garcia he was willing to do whatever she needed to help her better understand the disease that has haunted his family for generations.

His nephew, Charles, was dead. His niece, Linda Sasser Lawrence, had died two years earlier after undergoing two lung transplants. She was 56.

"My brother has lost two children to IPF – Linda and Charles – and his daughter is in the first stages of the disease," said Jimmy Sasser, who also is a father of three and lost one of his three daughters 26 years ago from unrelated causes.

In 2000 his sister, Shirley Sasser Butler, died. She was 69. Her daughter, Peggy Butler Martin, died in 2008. She was 57.

"Peggy knew she had the same disease, but she didn't tell any family members," Jimmy Sasser said.



To date, more than 300 families and more than 2,000 people have donated DNA samples to aid Dr. Garcia's research – from children to octogenarians.

In the spring of 2009, Mrs. Butler's son, Dan E. Butler, died from IPF. He was 54 and hoping to get a lung transplant.

"My faith has helped me get through this," Jimmy Sasser said. "You just have to take each day as it comes. You could be depressed or think the worst, but that won't get you anywhere."

Hope amid tears

After his initial conversation with Dr. Garcia, Jimmy Sasser started calling and writing to relatives. He told them about Dr. Garcia's research, asked them to participate and let them know she would be attending the upcoming memorial service.

On Oct. 18, 2008, family and friends gathered at the Tuloso-Midway Baptist Church in Corpus Christi to celebrate the life of Charles E. Sasser, a refinery worker, self-employed auto mechanic, father and grandfather.

Dr. Garcia and a member of her laboratory also attended. When the service ended, Jimmy Sasser and a group of family members crowded into a room near the church sanctuary.

He introduced Dr. Garcia. Shortly after she finished answering questions, family members began lining up to donate their DNA.

"More research is needed," Mr. Sasser said. "And maybe our family can help be a part of the cure."

Months later, his nephew, Dan, who would die eight months later, took a cue from his uncle and organized a family reunion in Saledo, Texas, so that family members who weren't able to attend the church service could participate in the genetic study.

"In all, about 40 members of the family have participated," Jimmy Sasser said. "Two of my cousins – one living in Colorado Springs and the other from Florida – also agreed to be involved. Their mother died from the disease."

Recently, Jimmy Sasser drove to UT Southwestern from his home in Bryan, Texas, to undergo a battery of pulmonary tests. Doctors determined he did not have IPF.

"It was a relief," said Jimmy Sasser, who is 76. One of his daughters also was evaluated, and she does not have the disease that has claimed the lives of so many of her cousins.

Jimmy Sasser's youngest daughter has not been tested.

"We just have to hope that she doesn't have it," Jimmy Sasser said. "She's 49."

For more information about IPF, please call 214-645-2800.



Reading Writing and Eating Right

UT SOUTHWESTERN STUDENTS AND FACULTY ARE TAKING THEIR EXPERTISE ON THE ROAD — PROMOTING HEALTHY EATING HABITS BY HELPING YOUNGSTERS LEARN TO CHOOSE THE RIGHT FOODS.

A sea of dark-haired fourth-graders squirmed on the hard gymnasium floor as Trevor Turner, a third-year medical student at UT Southwestern Medical Center, started to tell them why he was interrupting gym class at Dallas’ Ignacio Zaragoza Elementary School.

The children, dressed in red T-shirts and dark blue pants, giggled and whispered as Mr. Turner and Joseph Spellman, another third-year medical student, distributed electronic clickers to each of the 51 students crowding one end of the gym.

Every day, nearly one-third of the nation’s children between the ages of 4 and 19 eat fast food, a worrisome statistic that experts say can result in an extra 6 pounds of weight gain each year, a major contributor to obesity and type 2 diabetes in children. More than 9 million – 6 percent of children between 6 and 19 years old – are already considered overweight or obese, three times the number reported in 1980, according to the Centers for Disease Control and Prevention.

Mr. Turner and Mr. Spellman, part of a UT Southwestern outreach program, hope that by teaching these Zaragoza Elementary youngsters about nutrition and which foods are good for them, the children can avoid the fate of so many of their peers.



“What is the most important thing you can do to be healthy?” Mr. Turner asked them once everyone had a clicker. The students immediately started pointing their clickers at the answers on the screen, like they were attending the television show “Who Wants to Be a Millionaire.”

Their choices were: 1) Avoid sweetened drinks, 2) eat fruits and vegetables, 3) get physical activity each day, and 4) limit serving sizes or eat breakfast.

Though only their first answer counted, most of the students kept clicking well past the 10 seconds allocated to answer the question.

“Most of you said ‘eat fruits and vegetables,’ but it’s great that somebody voted for each of these categories because they’re all important,” Mr. Turner said. “Today, however, we’re going to focus on why you should eat at least five fruits and vegetables a day.”

The presentation, “Getting Enough Fruits and Vegetables,” is the first in a series of interactive slideshows targeting components of the American Medical Association’s recommendations to combat childhood obesity. The program is also one example of how UT Southwestern’s Center for Human Nutrition has gradually begun shifting its scope from studying not only just what to eat, but also to all aspects of obesity.

By Kristen Holland Shear



JOSEPH SPELLMAN AND CHILDREN FROM ZARAGOZA ELEMENTARY

"Research has shown that children who eat a healthy, balanced diet with a variety of fruits, vegetables, meats and dairy products become adults who do the same."

— Dr. Linda Michalsky



Groundbreaking basic science continues at a frenzied pace, but Center for Human Nutrition faculty members have recently stepped up their efforts to share the knowledge gleaned in the lab with the larger community.

Clinical nutrition students enrolled in the UT Southwestern School of Health Professions have traditionally taken part in and promoted obesity-prevention efforts. Now their peers enrolled in medical school also are stepping up to the plate.

Under the leadership of Dr. Linda Michalsky, assistant professor of clinical nutrition and the obesity-prevention outreach coordinator, medical students have been visiting elementary schools throughout the Dallas Independent School District to tout the importance of eating fruits and vegetables. In addition, Bernadette Latson, director of clinical dietetics, has spearheaded a partnership with North Dallas'

Episcopal School of Dallas, and Dr. Jo Ann Carson, professor of clinical nutrition, has recently evaluated a program developed by KERA, Dallas' local public broadcasting station, to promote healthy lifestyles in families with young children.

Faculty members have further strengthened the center's ties to Dallas' Cooper Institute, the research arm of Dr. Kenneth Cooper's famed Cooper Clinic in North Dallas. To this end, Dr. Jonathan Cohen, professor of internal medicine and a member of the Eugene McDermott Center for Human Growth and Development, has already started using 40 years of data collected from clinic patients to identify new genetic sequence variations and new genes that contribute to disease risk.

New school promotions

Convincing children who may have limited access to fruits and vegetables to eat more of them isn't as simple as sending a few medical or clinical dietetic students armed with health tips into schools once or twice a year. It's probably not enough to provide boxes of fresh produce, either.

Yet, both activities are considered vitally important tools for medical professionals working to prevent and combat obesity. The key, Dr. Michalsky said, is that both strategies promote rather than force change.

Dr. Michalsky said that although the federal government requires school districts to offer fruits and vegetables at breakfast and lunch, it's up to each student to choose what goes on his or her plate.

"We want to get the children to select fruits and vegetables," said Dr. Michalsky, who developed the program – called Balancing Exercise and Nutrition for Students (BEANS) – in cooperation with DISD's nutrition services department. "Research has shown that children who eat a healthy, balanced diet with a variety of fruits, vegetables, meats and dairy products become adults who do the same. While a single program may not cause immediate behavior change, hearing a consistent message will help."

The PowerPoint presentation takes about 20 minutes. The clickers record each student's answers so that researchers can track in real time whether students grasp a concept as well as whether they intend to eat more produce.

About 10 minutes into the presentation at Zaragoza Elementary, Mr. Turner asked the students, "Who can tell how much a serving is?"

A handful of students shouted out, "It's gigantic."

"How can you eat five if it's gigantic," Mr. Turner replied. "One serving is like the size of a deck of playing cards."

The other questions included:

- Are fresh fruits and vegetables always better for you than canned, frozen or dried? (Answer: No.)
- How many fruits and vegetables should you eat each day? (Answer: At least five.)
- How can you eat more fruits and vegetables? (Answer: Ask for them.)

Dr. Michalsky said the idea behind BEANS is not only to educate, but also to promote real behavior change.

"Although we want to address knowledge and misinformation, such as the idea that fresh fruits and vegetables are always best, our ultimate goal is to reduce obesity," she said.

That's why, when speaking at Zaragoza, Mr. Turner asked not only about the students' favorite pizza toppings, but also what vegetables they might be willing to add to their next slice. Suggestions of spinach, mushrooms and tomatoes tumbled out of the students' mouths as quickly as pepperoni had when asked about their favorite topping.

The idea, Dr. Michalsky said, is to show children that even a small change, like consistently adding a few mushrooms or spinach leaves to a slice of pizza, can make a big difference in their overall health.

"There really are no bad foods," she said. "We're not asking children to give up pizza, french fries and hamburgers. We're just encouraging them to add more fruits and vegetables to their plates."

Dr. Michalsky said the presentation and the overall program remain a team effort.

Students, faculty and staff associated with the UT Southwestern School of Health Professions and UT Southwestern Graduate School of Biomedical Sciences all contributed to the effort, but Dr. Michalsky said Heidi Prather, a fourth-year medical student, instigated the development of BEANS in late 2008. Roshni Nelson and Elizabeth Smith, two biomedical communications students, jazzed up the PowerPoint with animated jumping beans and fanciful illustrations of fruits and vegetables.

The obesity-prevention outreach program falls under the umbrella of UT Southwestern's Taskforce for Obesity Research. In 2007 the multidisciplinary group received a \$22 million grant from the National Institutes of Health to enhance its efforts to attack obesity from every angle.

The taskforce is one of nine interdisciplinary research consortia sponsored by the NIH Roadmap for Medical Research, a series of initiatives designed to transform the nation's medical research capabilities. The UT Southwestern group is the only one focused on obesity.



"We're not asking children to give up pizza, french fries and hamburgers. We're just encouraging them to add more fruits and vegetables to their plates." — Dr. Linda Michalsky



"Students want to know about optimum protein intake, the healthiest fat to eat and how to carbohydrate-load before a marathon event." — Bernadette Latson



Dr. Scott Grundy, director of the Center for Human Nutrition and chairman of clinical nutrition, said community outreach is a vital component of the obesity, diabetes and metabolic disease research under way at UT Southwestern.

"Our hope is that by partnering with the DISD, we'll be able to have a real impact on the community in terms of reducing childhood obesity," said Dr. Grundy, holder of the Distinguished Chair in Human Nutrition. "Not every student who participates in the program will start asking for fruits and vegetables, but there will be a few who adjust their eating habits as a result of this program. We want to promote this type of behavior change."

Building food consciousness

UT Southwestern's clinical nutrition experts aren't only interacting with public school students; they're also seeking to support healthy living in private schools such as the Episcopal School of Dallas.

Ms. Latson said the partnership with ESD began more than two years ago when the North Dallas school officially launched its Wellness for Life campaign.

Designed to foster the development of lifelong physical activity and nutrition habits, the \$30 million capital campaign reflects the school's commitment to educating the whole child. Besides supporting the construction of a 100,000-square-foot athletic and wellness center, the funds will be used for a new dining commons, a new kitchen and meal-serving area.

The new dining commons, Ms. Latson said, will be set up much like a college cafeteria. The kitchen will double as a lab for students and parents alike to learn about nutrition and cooking techniques from area experts.

Ms. Latson said that clinical nutrition faculty members have helped plan and design the new space. They've also had a hand in planning the menus for the Lower School and will assist with the development of a nutrition-based curriculum.

"Another way we're supporting their efforts is by maintaining good nutritional content on their Wellness for Life website," Ms. Latson said. "One of our faculty members manages the 'Ask the Dietitian' component of the site and serves as a consulting dietitian for the school."

The questions asked run the gamut from "How can I spot hidden sugar in packaged and prepared food?" to "Is organic milk healthier than regular milk?"

As the partnership evolves, Ms. Latson said she sees her team becoming more involved in helping ESD leaders incorporate nutrition-based information throughout the Lower, Middle and Upper School curriculums.

"There are many ways nutrition can be integrated into all aspects of the curriculum," she said.

In third grade, for instance, students study the importance of vitamins, minerals, fats, carbohydrates, proteins and fiber. They also talk about the difference between foods that can be eaten every day and those that should be considered "treats," as well as how different foods work to fuel their bodies.

Continued on page 58

A HEALTHY GENE PULL



DR. JONATHAN COHEN

A new partnership with a renowned Dallas fitness center that has 40 years of data on runners and other fit volunteers could put Center for Human Nutrition

investigators several laps ahead in their research.

In spring 2009, with a gift from a local philanthropist, nutrition center leaders announced a partnership with the Cooper Institute to develop a joint scientific medical research program aimed at improving health and preventing the development of chronic diseases, like Alzheimer's, diabetes, cancer and a range of cardiovascular conditions.

The Cooper Institute, a preventive medicine research and educational nonprofit located at the Cooper Aerobics Center, maintains one of the world's most extensive databases on exercise and health, known as the Cooper Center Longitudinal Study. This database contains detailed clinical information, such as imaging and blood studies from patients who volunteer to participate in research studies at the Cooper Clinic. Data from more than 250,000 records from almost 100,000 individuals has been collected since Dr. Kenneth Cooper founded the institute and clinic in 1970. The blood samples are processed at UT Southwestern for DNA isolation in this collaboration known as the Cooper Institute – UT Southwestern BioBank.

"UT Southwestern investigators have the needed expertise in genetics and the technology to perform the genetic analysis, while the patients in the Cooper Center Longitudinal Study represent a valuable resource where

that expertise can be applied," said Dr. Jonathan Cohen, professor of internal medicine at UT Southwestern and holder of the C. Vincent Prothro Distinguished Chair in Human Nutrition Research.

One advantage of the database, Dr. Cohen said, is that its makeup of predominantly fit individuals will allow researchers to identify genes associated with being healthy.

"UT Southwestern investigators have the needed expertise in genetics and the technology to perform the genetic analysis, while the patients in the Cooper Center ... represent a valuable resource."

— Dr. Jonathan Cohen

The UT Southwestern group is spearheaded by Dr. Scott Grundy, director of the Center for Human Nutrition, with Dr. Cohen providing expertise in human genetics.

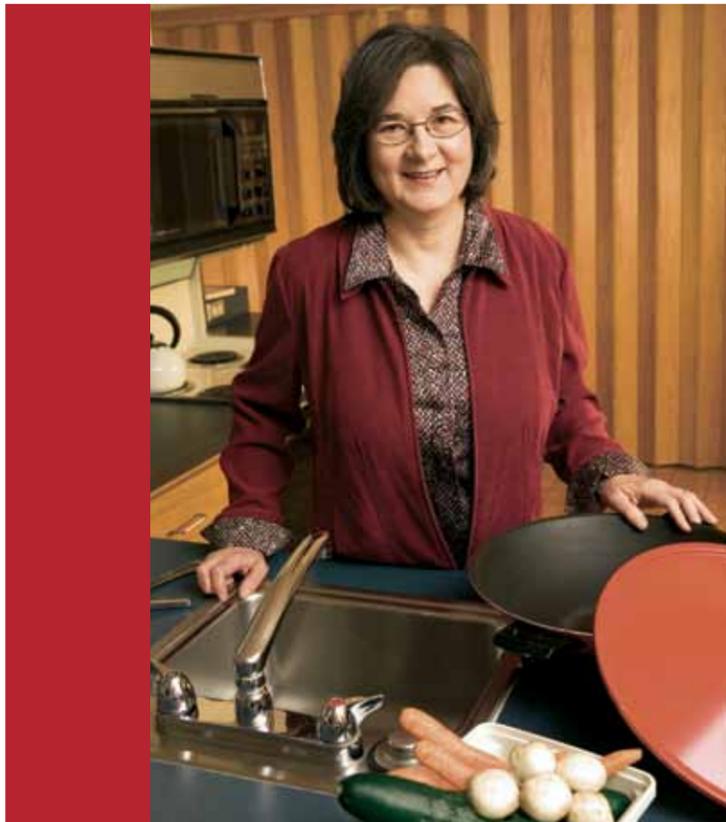
Dr. Cohen said the group hopes to use information gleaned from the database to identify genes that confer protection against diseases, much like what they've

been able to do from the UT Southwestern Dallas Heart Study.

The Dallas Heart Study, a large, long-term investigation of Dallas-area residents, aims to bring the latest in discoveries from UT Southwestern laboratories to the community in an effort to improve the diagnosis, prevention and treatment of heart disease. Data gathered from participants in the Dallas Heart Study have led to many new insights, including the discovery of cholesterol-lowering genetic mutations in some people who are significantly less likely to develop heart disease later in life.

"People with genes that increase their cholesterol levels are most likely to be found in a lipid clinic," Dr. Cohen said. "But people who have genes that lower their cholesterol levels are not likely to end up in a hospital or lipid clinic. The best way to find these genes is in a large sample of healthy people, and the Cooper database is a unique resource for these investigations."

By Kristen Holland Shear



"In the 1970s, only 5 percent of young children were obese. Now it's more than twice that at 12.4 percent, paralleling the obesity trends we're seeing in adults and school-age children."
 — Dr. Jo Ann Carson



The opportunities increase as the students become involved in athletics and upper-level science classes, Ms. Latson said. "The role of nutrition in performance is of great interest to all outstanding athletes, coaches and trainers," she said. "Students want to know about optimum protein intake, the healthiest fat to eat and how to carbohydrate-load before a marathon event. They also want to know about hydration and electrolyte balance – basic nutrition concepts they can apply to their own lives right away."

She said schools like the ESD are great places to pilot nutrition and health-related projects for larger public school districts because they generally have a high level of commitment and the resources to follow through.

"I think (Dr.) Roger Unger said it best when he was talking about pediatric obesity," she said, referring to a longtime diabetes researcher at UT Southwestern. "He said, 'If we just talk about obesity in adults, it's like putting out the fire after the house has burned down.'"

Healthy babies, too

Dr. Carson has spent much of the past two years evaluating Little Bites, Big Steps, an early childhood education initiative developed locally to reach parents and caregivers of children, from infants to 5-year-olds.

The fact that obesity is taking hold in children still in diapers is not lost on Dr. Carson, who has promoted good nutrition in Dallas for decades.

"In the 1970s, only 5 percent of young children were obese," said Dr. Carson. "Now it's more than twice that at 12.4 percent, paralleling the obesity trends we're seeing in adults and school-age children."

"When you translate that into dollars the state of Texas might spend on health care costs, it really is important to attack obesity from a prevention standpoint early-on. Parents and other primary caregivers play an important function as role models for these young children," she said.

Funded by the National Recreation Foundation, Little Bites, Big Steps is one component of KERA's larger Ready for Life project, which was launched in January 2000 to provide parents, caregivers and the larger North Texas community with information about early childhood development research. The five-hour curriculum offers parental guides in English and Spanish, as well as a facilitator guide to support use of 12 short video segments that model healthy food and activity habits for families with young children. (See www.readyforlife.org)

Dr. Carson said she became involved with the program when it was initiated in Dallas and nine other sites nationwide. "I was asked to evaluate the program's implementation in those communities," she said.

The task wasn't easy, particularly given that each community started the program in multiple ways based on its needs and resources.

In Dallas, for example, the program was offered by Avance-Dallas, a nonprofit dedicated to strengthening at-risk Hispanic communities by supporting and educating parents. Participants attended weekly classes where they learned how to identify healthy foods and about the importance of regular exercise. Parents and caregivers enrolled in the program also were required to carry out six health projects in their neighborhoods and lead six health days at their local schools. One such visit involved a group of parents dressing up as avocados, strawberries, grapes and a carton of milk to teach kindergarteners and first-graders about healthful food choices.

Overall, the program reached more than 10,000 parents and child-care workers across the 10 sites nationwide; more than half the participants were Hispanic or African-American. The typical participant was a mother aged 20 to 35 or a child-care provider over age 35 with some high school or college education; 10 percent reported an education of sixth-grade or less.

Dr. Carson said the findings showed that the knowledge and skill levels of participants improved as a result of the program. The findings also suggested that participants started eating more family meals together, using the nutrition label more often, involving children in food preparation, and limiting television and computer time. Hispanic parents in Dallas, for example, changed from saying they would make sure their child finished the food on his or her plate to accepting the child's cue that enough had been eaten.

"Assessing the program over less than a year in each site prevented us from gauging whether a program like this reduces obesity," Dr. Carson said. Instead, the evaluation focused on the audience reached, improvements in knowledge and skills, and indications of behavior change.

"If we're going to spend money trying to do things in the community, we need to know that they work," she said. "That's why it's important to look both at the process – how well it did work – and whether it made a difference in terms of outcome."

"When you translate that into dollars the state of Texas might spend on health care costs, it really is important to attack obesity from a prevention standpoint early-on. Parents and other primary caregivers play an important function as role models for these young children."

— Dr. Jo Ann Carson

Just the first course

Back at Zaragoza Elementary, Mr. Turner and Mr. Spellman have shifted gears.

"Who can name one fruit or vegetable that's red?" Mr. Turner asked the students.

"Strawberries," one student blurted out.

"Tomato," said another.

Red apples and watermelon also made the list.

"That's a good start," he said. "What about something that's green?"

Dr. Michalsky, who was seated along the gym wall, said she wanted to reach out to elementary school students, in particular, because their minds are like sponges.

"This is an attempt at promoting self-efficacy," she said. "I don't think this is going to effect immediate behavior change, but we might eventually see some shifts in obesity patterns if the message from school, local and national leaders is consistent."

She said one obvious benefit of BEANS is that it can be as big or small as desired.

"Right now, we're only offering a single presentation, but we hope to expand the offerings within the next year and add some classroom-based activities that teachers can lead," she said. "Ultimately, I would love to go into the classrooms and have the same group of kids for six weeks. We might be able to witness real change if given that opportunity." ♦

(special section)

Seed Therapy Pinpoints Breast Tumors

By Connie Piloto

A small, radioactive pellet – about the size of a grain of rice – is helping guide surgeons to the exact spot in the breast where a hard-to-detect mass or suspicious lesion is located.

The new technique provides pinpoint accuracy and allows surgeons to remove possible breast-cancer tumors with greater precision.

Physicians at UT Southwestern Medical Center are the first in Texas to begin using the procedure, in which a capsule, or “seed,” containing a small amount of radioactive material is inserted into the mass. Once lodged, surgeons use a wand that detects radioactivity to locate the mass and find the best pathway for removal.

“The new technique is also less-invasive for the patient,” said Dr. Roshni Rao, assistant professor of surgical oncology in the George N. Peters, M.D., Center for Breast Surgery at UT Southwestern and the first surgeon in the state to start using the technique.

Dr. Rao, who specializes in breast cancer, teamed up with Dr. Michael Ulisse, associate professor of radiology, to use this new procedure. Several other U.S. medical centers currently perform the procedure.

This technique replaces a process in which a radiologist would lance a thin, hooked wire into the breast to help guide the surgeon to the location of the mass. While one end of the wire was lodged at or near the mass, the other end protruded from the patient’s skin.

Often, Dr. Rao said, the entry site of the wire was distant from the ideal site where a surgeon would prefer to make an incision. The wire also did not always take a direct path to the lesion.

“The seed procedure pinpoints the location of a nonpalpable tumor more accurately than the wire, and it is more efficient,” said Dr. Rao, who performs the procedure in the Harold C. Simmons Comprehensive Cancer Center.

The old, wire method, requires patients to undergo the preoperative procedure just hours before surgery because if left in longer, the wire could become dislodged.

“With the seed technique, the patient can have the seed inserted up to three days before surgery,” Dr. Ulisse said.

For patient Joan Hollers, 61, the preoperative procedure was quick, easy and painless.

After a mammogram had detected a suspicious mass in her left breast, Ms. Hollers consulted with Dr. Rao, who decided on the seed procedure.

Dr. Ulissey numbed Ms. Hollers’ breast before inserting the radioactive seed, which gives off less radiation than the amount emitted by a standard X-ray.

“I felt the prick of what felt to me like a tiny needle,” said Ms. Hollers. “I went home with a small Band-Aid and went to work the next day.”

Several days later, the Rowlett resident returned to the hospital so that Dr. Rao could remove the suspicious mass.

Dr. Rao removed the mass in Ms. Hollers’ left breast. Then, she underwent chemotherapy for a cancerous tumor that was found in her right breast. Once she was done with the therapy, Dr. Rao surgically removed the tumor.

Throughout the surgeries and therapy, Ms. Hollers has remained optimistic.

“When I got the news that I didn’t have cancer anywhere else in my body, I told myself, ‘I’m not dying from this disease,’” said Ms. Hollers, a mother of three and grandmother of eight. ♦

For more information about seed therapy, please call 214-645-4673.



Breathing Eases Cancer Therapy

By Kristen Holland Shear

After seven months of weekly chemotherapy, followed by surgery to remove any remnants of her stage 2 breast cancer and six weeks of radiation therapy, Carol Baker has a message for anyone facing a cancer diagnosis.

“If you could just think of your diagnosis and the time you spend in chemo as respite care, you could enjoy it,” said the 60-year-old English-as-a-Second-Language ministry leader at Park Cities Presbyterian Church. “The word ‘cancer’ freaks some people out, but for me, and apparently only me, my favorite day of the week ended up being the days I went in for my chemotherapy treatments.”

Though Ms. Baker’s initial breast cancer diagnosis and the resultant treatment plan were pure textbook, not all cancer patients fare as well. But a new diagnosing technique may also provide relief for those facing breast cancer.

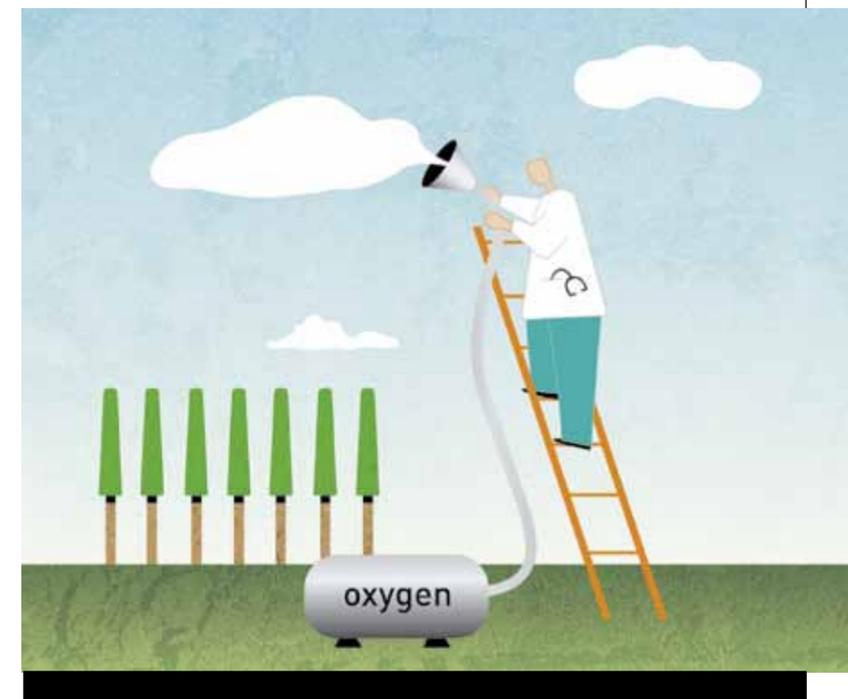
The new test, being developed at UT Southwestern, ultimately may help oncologists determine quickly and easily the best treatment plan for even the harder-to-treat cases. The patient need only be able to breathe in oxygen while undergoing an MRI scan.

Prior research has shown that the amount of oxygen present in a tumor can be a predictor of how well a patient will respond to treatment. Tumors with little oxygen tend to grow stronger and resist both radiotherapy and chemotherapy. Until now, however, the only way to gauge the oxygen level in a tumor was to insert a huge needle directly into it.

The new technique, known as BOLD (blood oxygen level dependent) MRI, can detect oxygen levels in tumors without the need for an invasive procedure.

“The patient simply inhales pure oxygen, which then circulates through the bloodstream, including to the tumors,” said Dr. Ralph Mason, professor of radiology and a member of the Harold C. Simmons Comprehensive Cancer Center. “Using MRI, we can then go in and estimate how much oxygen a particular tumor is taking up, providing us some insight into how the tumor is behaving and what sort of treatment might be effective.”

The most important finding, Dr. Mason said, is that BOLD MRI performed as well as the standard, yet more invasive, procedure for viewing tumors. That method, known as FREDOM (fluorocarbon relaxometry using echo



planar imaging for dynamic oxygen mapping) MRI, requires the injection of a chemical called a reporter molecule directly into the tumor and is only suitable for research.

“The BOLD technique appears to indicate accurately the oxygen levels in tumors,” Dr. Mason said. “Because BOLD is immediately applicable to patients, this holds promise as a new method for predicting response to therapy.”

BOLD MRI has been used extensively in studying brain function, but the procedure only recently has been used to assess blood oxygenation and vascular function in tumors.

Physicians at UT Southwestern are already testing BOLD MRI in patients with cervical, prostate, and head and neck cancer. They have proposed using it in lung cancer patients as well, Dr. Mason said.

For her part, Ms. Baker said anything that helps other cancer patients is a step in the right direction.

“Coming here has been respite care for me, but I don’t want to belittle the experiences of others who may not have had it as easy,” she said. “Hopefully, this new technique will be able to help ease the pain for others.” ♦

For more information about clinical trials involving BOLD MRI, please call 214-648-7031.

“The new technique is also less-invasive for the patient.”

—Dr. Roshni Rao

“The patient simply inhales pure oxygen, which then circulates through the bloodstream, including to the tumors.”

—Dr. Ralph Mason

(special section)

Harnessing estrogen for severe trauma

By Aline McKenzie

Testosterone is the ultimate symbol for rough, tough, fighting men.

But if research at UT Southwestern pans out, estrogen may prove to be a wounded soldier's best friend.

Women, generally, can endure much more serious injury than men, said Dr. Jane Wigginton, assistant professor of emergency medicine. Likewise, men would be less likely to survive the severe blood loss that might occur with a difficult childbirth.

So Dr. Wigginton wants to harness estrogen as a simple, inexpensive treatment to reduce brain damage and better ensure recovery in cases of severe traumatic head injury and other major physical insults. Trauma is the No. 1 killer of Americans under 40, she said.

In two current studies, men who arrive at the emergency room with either traumatic brain injury or shock from blood loss receive a single shot of the hormone.

"This extremely simple treatment has incredible potential, not only in a day-to-day hospital setting but also for military situations, as a way to stabilize wounded soldiers while being transported to definitive care centers," she said. "It's so cheap and so easy to give. I expect a rapid transition from the study phase

"It's so cheap and so easy to give. I expect a rapid transition from the study phase to acceptance as standard of care."

—Dr. Jane Wigginton

to acceptance as standard of care."

Estrogen probably exerts its protective effect in the mitochondria, the so-called "powerhouses" inside cells that provide the vital energy that keeps us alive. Mitochondria bristle with receptors on which estrogen can latch, and this works in all cells in the body.

Studies in animals have shown that estrogen keeps injury-induced inflammation from spreading and harming neighboring cells. Experimentally, it may reduce damage from a stroke by 65 percent, Dr. Wigginton said. The UT Southwestern head-injury study, which has enrolled more than two dozen patients, is the first human test of estrogen's healing effects. The researchers plan to extend the study to patients suffering from burns and other critical conditions.

Funding for this groundbreaking study came from an anonymous donor who wished to support pioneering high-impact research.

Another UT Southwestern study is addressing the problem of microscopic, yet devastating, brain injury that can occur when a person is jerked to a sudden stop.

A driver or cyclist can employ any number of airbags, seat belts, helmets or other safety devices, but there's no way to protect delicate brain tissues from massive internal shearing forces as the head slams from full speed to zero.

This type of scenario can cause a severe, but difficult-to-detect injury, called diffuse axonal injury (DAI), which may account for up to half of traumatic brain injuries.

This injury doesn't show up on CAT scans, which use X-rays, but Dr. Ramón Díaz-Arrastia, professor of neurology, and his colleagues have developed a way to use MRI to detect it.

These efforts are in the early stages. The researchers, working with people who had suffered severe, closed-head injury, simply took an MRI "snapshot" of three parts of the brain rich in nerves that link one region to another.

They then used a new type of data analysis to measure water movement in the nerves, a sign that a nerve had stretched and was leaking fluid. After six months, the patients with more severe DAI had worse outcomes.

"This is not a tool for treating patients," Dr. Díaz-Arrastia said. "But if we can find a way to diagnose reliably a common, but hard-to-detect injury, we can better tailor the treatment to the problem." ♦

For more information on the estrogen study, please call 214-648-3942; or the DAI study, please call 214-648-6721.



2 0 0 9

A

N N U A L

R E V I E W

64

HIGHLIGHTS OF THE YEAR

74

FINANCIAL STATEMENT

77

GIFT REPORT

FALL 2008

PODOLSKY BECOMES THIRD PRESIDENT OF MEDICAL CENTER

Dr. Daniel K. Podolsky, former chief academic officer of Partners HealthCare and chief of gastroenterology at Massachusetts General Hospital, became the third president of UT Southwestern after Dr. Kern Wildenthal stepped down after 22 years in that role.

Dr. Podolsky, associated with Harvard Medical School throughout his career, said he came to UT Southwestern to build on the remarkable accomplishments already made at the medical center. An experienced investigator, clinician and administrator, Dr. Podolsky said he is committed to ensuring that the medical center remains at the vanguard in its basic research programs while working to ensure its clinical programs and clinical and translational research are also similarly innovative and of outstanding quality.



PAUL M. BASS JR.



DR. DANIEL PODOLSKY IS WELCOMED TO CAMPUS BY UT SOUTHWESTERN STUDENTS ON SEPT. 2, 2008, HIS FIRST DAY AS PRESIDENT.

Dr. Podolsky, a member of the Institute of Medicine, holds the Philip O'Bryan Montgomery Jr., M.D., Distinguished Presidential Chair in Academic Administration and the Doris and Bryan Wildenthal Distinguished Chair in Medical Science.

EXCHANGE PARK BUILDINGS RENAMED FOR PAUL BASS

The buildings on the 24-acre Exchange Park site in Dallas, acquired by UT Southwestern, were renamed the Paul M. Bass Administrative and Clinical Center. The \$38 million acquisition fills important needs for faculty offices and additional administrative, educational and clinical space.

The complex, located adjacent to UT Southwestern's North Campus on Forest Park Road, was renamed in honor of Mr. Bass, chairman emeritus of Southwestern Medical Foundation. Mr. Bass served as the foundation's chairman of the board from 1995 to 2008. Under his leadership, the foundation's assets increased more than

\$500 million, from \$126 million to \$647 million. He died March 9, 2010.

With this additional property, UT Southwestern now encompasses approximately 9 million square feet of laboratory, clinical, educational and administrative space, and covers 387 acres. The site includes the Bass Center Tower 1 (formerly the AT&T Building), a 10-story office building with 175,000 square feet; and the Bass Center Tower 2 (formerly the Frito Lay/American General Building), a 14-story office building with more than 470,000 square feet.

GENE VARIANT RAISES LIVER DISEASE RISK

Individuals who carry a specific form of the gene *PNPLA3* have more fat in their livers and a greater risk of developing liver inflammation, according to researchers led by Dr. Helen Hobbs, director of the Eugene McDermott Center for Human Growth and Development and an investigator for the Howard Hughes Medical Institute.

The researchers also found that Hispanics are more likely to carry the gene variant responsible for higher liver-fat content than African-Americans and Caucasians.

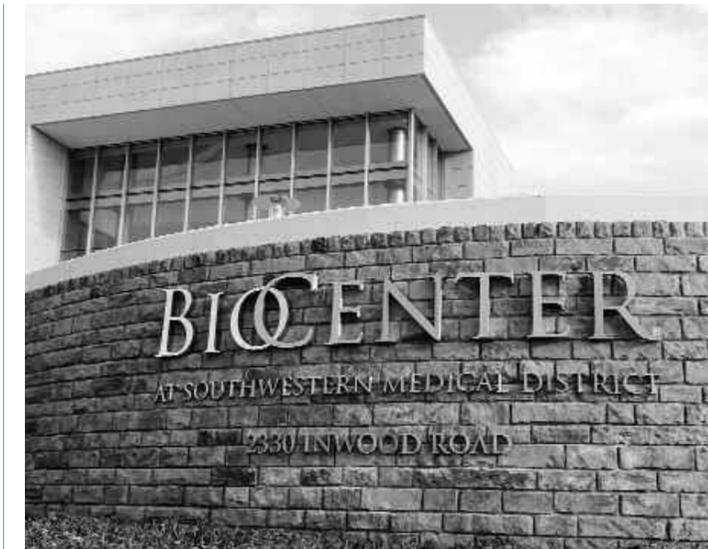
The findings, published in *Nature Genetics*, provide a gene-based explanation for the results of a 2004 UT Southwestern study that determined that the propensity to develop nonalcoholic fatty liver disease differs among ethnic groups. It is the most common form of liver disease in Western countries. Previous research has shown that it may affect as many as one-third of adults in America.

BIOTECH PARK TO SPUR RESEARCH, MEDICAL CARE

UT Southwestern is spurring innovations in patient care and aiding the area's economic growth with a new biotech park, called BioCenter at Southwestern Medical District, to develop university technologies and attract existing biotech companies to North Texas.

The 13-acre site, located on the east side of the medical center's campus on Inwood Road, was purchased from the city of Dallas. The first of four buildings is ready for occupancy. Ultimately it will contain up to 500,000 square feet of laboratory, office and research space and will serve the full spectrum of the biotechnology and biodevice industry, providing a nurturing environment for early-stage and mature companies alike, said Dr. Dennis Stone, vice president for technology development.

He said the purpose of the site is not only to develop UT Southwestern technologies to the point of commerciali-



BIOCENTER AT SOUTHWESTERN MEDICAL DISTRICT IS OPEN FOR BUSINESS.

zation, but also to provide commercial space for existing or start-up life-science companies that want to locate close to the university and its many resources.

MOLECULE HELPS KEEP SALMONELLA, PATHOGENS AT BAY

UT Southwestern scientists have found a potential new way to stop the bacteria that cause gastroenteritis, tularemia and

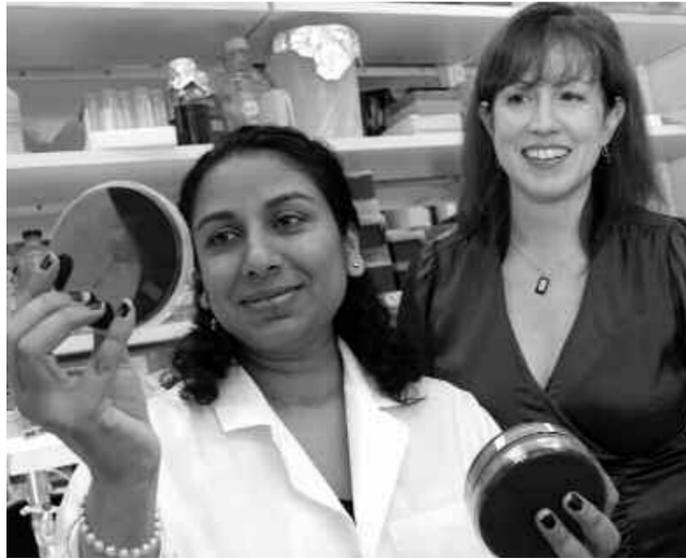
severe diarrhea from making people sick.

The researchers, led by Dr. Vanessa Sperandio, associate professor of microbiology and biochemistry, reported in *Science* that the molecule LED209 interferes with the biochemical signals that cause bacteria in our bodies to release toxins.

Though many antimicrobial drugs are already available, new ones are needed to combat the increasing microbial resistance



DR. VANESSA SPERANDIO LED RESEARCH THAT UNCOVERED A POTENTIAL NEW WAY TO STOP THE BIOCHEMICAL SIGNALS THAT CAUSE BACTERIA TO RELEASE TOXINS. THE TEAM'S INVESTIGATION COULD PROVIDE A NOVEL APPROACH TO COMBATING ILLNESS.



DR. SHIPRA VAISHNAVA (FRONT) AND DR. LORA HOOPER DISCOVERED A MECHANISM THE GUT USES TO KEEP HARMFUL BACTERIA OUT OF THE BODY.

to antibiotics. In addition, treating some bacterial infections with conventional antibiotics can cause the release of more toxins and may worsen disease outcome.

Scientists have known for decades that millions of potentially harmful bacteria exist in the human body, awaiting a signal that it's time to release their toxins. Without those signals, the bacteria pass through the digestive tract without infecting cells. What hasn't been identified is how to prevent the release of those toxins, a process that involves activating virulence genes in the bacteria.

In the new study, UT Southwestern researchers describe how LED209 in mice blocks the QseC sensors in *Escherichia coli*, *Salmonella* and *Francisella tularensis* bacteria, preventing them from expressing virulence traits. In 2006, the UT Southwestern researchers were the first to identify the receptor QseC sensor kinase, which is found in the membrane of a

diarrhea-causing strain of *E. coli*. This receptor receives signals from human flora and hormones in the intestine that cause the bacteria to initiate infection.

WINTER 2008-2009

GUT'S DEFENSIVE AGENTS CONTROL BACTERIAL TRANSFER

How and under what circumstances the gut activates its defensive mechanisms in mice to prevent illness has been discovered by scientists, including Dr. Lora Hooper, associate professor of immunology and microbiology, and Dr. Shipra Vaishnava, lead author of the research and postdoctoral fellow in immunology.

It has been known for decades that microbial cells in the human gut outnumber the body's own cells by about 10 to 1. Some microbes are beneficial, helping us break down food we can't otherwise digest; others

can cause disease and illnesses such as food poisoning if they escape the gut and invade body tissues.

The findings, published in the *Proceedings of the National Academy of Sciences*, showed for the first time that the Paneth cells, which line the guts of mammals, including humans, play a major role in making sure that bacteria – both good and bad – remain in the right places. Dr. Hooper likened the cells to border patrol agents.

The findings of the study might offer researchers new clues about the pathologic features of inflammatory bowel diseases, a group of chronic disorders in which the intestines become inflamed.

EARLY-CAREER SCIENTISTS SINGLED OUT BY HHMI

Dr. Russell DeBose-Boyd, associate professor of molecular genetics, was appointed a Howard Hughes Medical Institute Early Career Scientist early in 2009.

He was one of 50 researchers named in a national competition by the institute to be in the program's inaugural group of scientists. The \$200 million



DR. RUSSELL DEBOSE-BOYD



DR. NIMA SHARIFI

Early Career Scientist initiative is aimed at supporting scientists who have run their own laboratories for two to six years and are ready to move their research programs in innovative directions. Each Early Career Scientist receives \$1.5 million in research funding over a six-year appointment to HHMI.

Dr. DeBose-Boyd's work focuses on how the body regulates and controls cholesterol production. He was supported by the Perot Family Foundation until this HHMI award.

Dr. Nima Sharifi, assistant professor of internal medicine, also was singled out by the HHMI with an Early Career Physician-Scientist Award.

Dr. Sharifi was one of 11 researchers named in a national competition to be part of the program, which aims to increase the number of researchers translating basic science discoveries into improved treatment for patients. Established in 2006, the program supports more than 50 physician-scientists. Each Early Career Physician-Scientist receives \$375,000 in research

funding over a five-year period from HHMI.

Dr. Sharifi's research focuses on how advanced prostate cancer – the second leading cause of cancer death in men – becomes resistant to androgen deprivation therapy. The most well-known androgen is the male sex hormone testosterone.

SERVICES, CARE REDUCE PARKLAND PREMIE RATE

Parkland Memorial Hospital, the primary teaching facility of UT Southwestern, has cut its rate of preterm births by more than half in the past 15 years, even as national rates are rising, researchers reported.

The drop at Parkland Memorial Hospital, from 10.4 percent in 1988 to 4.9 percent in 2006, was associated with a program of coordinated and easy-to-access care – including prenatal programs – for the largely minority, indigent population served by the county hospital, said Dr. Kenneth Leveno, professor of obstetrics and gynecology and lead author of the study in *Obstetrics & Gynecology*.

The researchers studied data from more than 260,000 women served at Parkland from 1988 to 2006. They began their analysis

in response to a 2006 report on preterm births by the Institute of Medicine that stated that the national rate of prematurity was 9.4 percent in 1981 and 12.5 percent in 2004, representing a 33 percent increase.

SPRING 2009

MOLECULE PROMPTS REPAIRS AFTER HEART ATTACKS

A protein that the heart produces during its early development reactivates the embryonic coronary developmental program and initiates migration of heart cells and blood vessel growth after a heart attack, researchers led by Dr. J. Michael DiMaio, associate professor of cardiovascular and thoracic surgery, have found.

The molecule, Thymosin beta-4 (TB4), is expressed by embryos during the heart's development and encourages migration of heart cells. The findings, reported in the *Journal of Molecular and Cellular Cardiology*, suggest that, in mice, introducing TB4 systemically after a heart attack encourages new growth and repair of heart cells. The research findings indicate that the molecule



DR. J. MICHAEL DIMAIO AND DR. ILDIKO BOCK-MARQUETTE, ASSISTANT PROFESSOR OF CARDIOVASCULAR AND THORACIC SURGERY

affects developmental gene expression as early as 24 hours after systemic injection.

Tremendous medical progress has been made to counter the damaging effects of heart attacks, but ordinarily, mammalian hearts are incapable of repairing themselves following damage. They are also limited in their ability to form new blood vessels. Earlier studies demonstrated that TB4 is expressed in the embryonic heart and stimulates cardiac vessels to form. It was, therefore, thought that introduction of TB4 might activate new vessel growth in the adult heart.

RESEARCH IS AIMED AT ERADICATING PARASITES

Discoveries by researchers led by Dr. David Mangelsdorf, chairman of pharmacology, are accelerating efforts to eradicate worm infections that afflict a third of the world's population.

The latest findings, published in the *Proceedings of the National Academy of Sciences*, demonstrate that a biochemical system controlling development and reproduction of *Caenorhabditis elegans*, a common research worm, also provides the same function in several parasitic nematodes, including hookworms. In these parasitic organisms, the activating molecule, called dafachronic acid, signals for the worms to mature from the stage in which they infect a host to the stage in which they start feeding on the host, which is what makes the host sick.

In the study, researchers treated hookworm parasites pharmacologically at the infective larval stage with dafachronic acid, causing them to pass into the "feeding" larval stage outside a host, where



DR. DAVID MANGELSDORF

they had no food supply and died. Treatment of other infectious species had similar effects. Dr. Mangelsdorf, an investigator for the Howard Hughes Medical Institute, said the findings point to a promising therapeutic target for the infectious nematodes.

Many infectious nematode larvae live in the soil, often in areas where proper sanitation is lacking. According to the World Health Organization,

parasitic nematodes infect about 2 billion people worldwide and severely sicken some 300 million, at least 50 percent of whom are children.

FINDING MAY HELP KEEP EMBRYONIC STEM CELLS ALIVE

In a study that could transform embryonic stem cell (ES cell) research, scientists have discovered why mouse ES cells can be easily grown in a laboratory while other mammalian ES cells are difficult, if not impossible, to maintain.

If the findings in mice can be applied to other animals, researchers could have an entirely new palette of tools to work with, said Dr. Steven McKnight, chairman of biochemistry and senior author of the study in *Science*.

According to the research, the activation of a gene called *TDH* in mouse ES cells results in the cells entering a unique metabolic state that is similar to that of rapidly growing bacterial

cells. The gene controls the production of the TDH enzyme in mouse ES cells. This enzyme breaks down an amino acid called threonine into two products. Both of the threonine breakdown products are necessary to keep the ES cells growing and dividing rapidly in a petri dish without differentiating into specific tissues.

The various substances currently used by scientists to keep mouse ES cells alive in the laboratory were found by trying many different combinations until something worked, Dr. McKnight said. But until now, it wasn't known that these culture conditions keyed into keeping the *TDH* gene actively expressed. Other mammalian species have a functional version of the *TDH* gene, suggesting the possibility that the process could also be activated in them.

SUMMER 2009

FORMER GOV. CLEMENTS MAKES 'TRANSFORMATIVE' \$100 MILLION DONATION

Former Texas Gov. William P. Clements Jr. made an unexpected and unprecedented \$100 million gift. This visionary act, intended to have a transformative impact, marks the largest single donation in the institution's history and was given through the Southwestern Medical Foundation.

UT Southwestern officials said the gift, especially noteworthy in Mr. Clements' insistence that there be no restrictions on its use, created the William P. Clements Jr. Fund.

Mr. Clements said his goal was to help encourage and advance scientific discovery and innovation, prepare the next generation of physicians for Texas and the nation, and ensure the delivery of world-class medical care at the academic medical center.

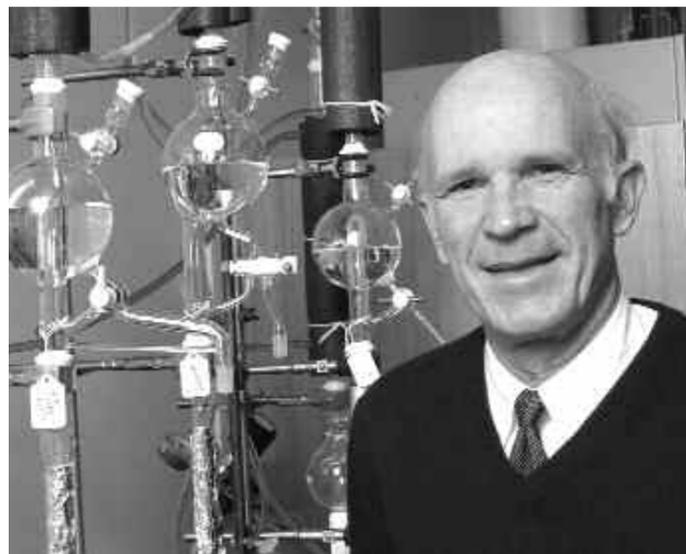


DR. J. GREGORY FITZ

FITZ NAMED MEDICAL SCHOOL DEAN; GILMAN JOINS CANCER AGENCY

Dr. J. Gregory Fitz, chairman of internal medicine, was named executive vice president for academic affairs and provost of of UT Southwestern and dean of the medical school.

The team of UT Southwestern academic leaders that



RESEARCH LED BY DR. STEVEN MCKNIGHT HAS DEMONSTRATED THAT THE ACTIVATION OF A PARTICULAR GENE MIGHT BE A KEY COMPONENT OF WHY MOUSE EMBRYONIC STEM CELLS ARE EASILY GROWN IN A LABORATORY WHILE OTHER MAMMALIAN ES CELLS ARE DIFFICULT, IF NOT IMPOSSIBLE, TO MAINTAIN.



FORMER TEXAS GOV. WILLIAM P. CLEMENTS JR. (CENTER) ACCEPTS THE THANKS OF UT SOUTHWESTERN CONVEYED BY DR. DANIEL K. PODOLSKY, PRESIDENT, AND WILLIAM T. SOLOMON, CHAIRMAN OF THE BOARD OF SOUTHWESTERN MEDICAL FOUNDATION.

conducted a national search identified Dr. Fitz as superbly suited to provide continued academic leadership at the school, said Dr. Daniel K. Podolsky, president of the medical center.

Dr. Fitz is a world-renowned hepatologist who joined the faculty in 2003. He brings to his new responsibilities a record of outstanding academic leadership and significant accomplishment as an investigator and clinician.

Former dean and provost Dr. Alfred Gilman stepped down from those roles to assume the position of chief scientific officer of the Cancer Prevention and Research Institute of Texas (CPRIT) and become professor emeritus of pharmacology at UT Southwestern. In his new role at CPRIT, the Nobel laureate oversees the scientific review and grants review processes of this new state agency. Dr. Gilman had been with the university since 1981, when he was recruited as chairman of pharmacology.

**HOSPITAL SPECIALTIES
SECURE ELITE RANKINGS**

UT Southwestern is nationally ranked in more specialty-care areas than any other health care provider in North Texas on *U.S. News & World Report's* America's Best Hospitals 2009-10 list.

The UT Southwestern specialties and their respective ranks on the list include: urology at 15; neurology and neurosurgery at 20; kidney disorders at 23; and gynecology at 33. Additionally, Parkland Memorial Hospital – staffed by UT Southwestern physicians – ranked 11th in gynecology. UT Southwestern physicians also provide the majority of

specialists for Children's Medical Center Dallas, which was recently named one of the top 10 children's hospitals nationwide in a separate analysis by *U.S. News & World Report*.

The America's Best Hospitals guide identifies 174 out of some 4,800 medical centers nationwide that excelled in one or more of 16 specialties.

**PRC PRESENTS TWO
DISTINGUISHED AWARDS**

The President's Research Council presented its 2009 Distinguished Young Researcher Award to a pair of outstanding UT Southwestern scientists. The recipients – Dr. Carol Elias, assistant professor of internal medicine, and Dr. Kamal Bharucha, assistant professor of pediatrics and pharmacology – each received a \$65,000 award.

Dr. Elias is investigating how the brain integrates nutritional and reproductive cues to regulate many aspects of reproductive physiology. Her research aims to further the understanding and treatment of



DR. CAROL ELIAS

reproductive deficits caused by metabolic dysfunctions.

Dr. Bharucha's research focuses on the control of glucose and lipid metabolism, as well as the regulation of hunger and food-seeking behaviors.

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

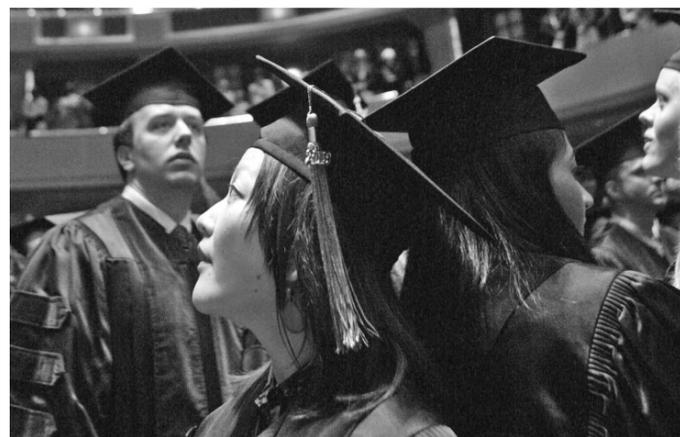
**352 EARN DEGREES
FROM THREE SCHOOLS**

Diplomas were received by 233 UT Southwestern Medical School students and 67 UT Southwestern Graduate School of Biomedical Sciences students in early June commencement ceremonies.

Dr. Tadataka Yamada, president of the Global Health Program at the Bill & Melinda Gates Foundation, addressed the medical school graduates and their guests. The graduate school's address was delivered by Nobel laureate Dr. Alfred Gilman, former UT South-



DR. KAMAL BHARUCHA



UT SOUTHWESTERN MEDICAL SCHOOL GRADUATES

**APPOINTMENTS
FOR 2008-2009**

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

■ Dr. James de Lemos, to the Sweetheart Ball - Kern Wildenthal, M.D., Ph.D., Distinguished Chair in Cardiology.

■ Tim Doke, named vice president for communications, marketing and public affairs.

■ Dr. Ethan Halm, to the Walter Family Distinguished Chair in Internal Medicine, in Honor of Albert D. Roberts, M.D.

■ Dr. Jeffrey Kahn, to the Sarah M. and Charles E. Seay Chair in Pediatric Infectious Diseases.

■ Dr. Carl Noe, named director of the Eugene McDermott Center for Pain Management.

■ Dr. Sharon Reimold, to the Gail Griffiths Hill Chair in Cardiology.

■ Dr. Michael Rosen, to the Mar Nell and F. Andrew Bell Distinguished Chair in Biochemistry.

■ Dr. Joseph Takahashi, named chairman of neuroscience and to the Loyd B. Sands Distinguished Chair in Neuroscience.

■ Dr. Dwain Thiele, to the Jan and Henri Bromberg Chair in Internal Medicine.

■ Dr. Michael White, to the Sherry Wigley Crow Cancer Research Endowed Chair, in Honor of Robert Lewis Kirby, M.D.

■ Dr. Charles Whitten, named chairman of anesthesiology and pain management and to the Margaret Milam McDermott Distinguished Chair in Anesthesiology and Pain Management.

■ Dr. Richard Wu, to the Dallas Heart Ball Chair in Cardiac Arrhythmia Research.

**MAJOR GIFTS
IN 2008-2009**

Philanthropists continued to demonstrate their commitment to UT Southwestern in 2008-2009, providing support for a variety of research and clinical programs.

In addition to the \$100,000,000 donation from former Gov. William P. Clements Jr., as described on page 69, other major new pledges and gifts received in the 2008-2009 fiscal year included:

■ \$2,000,000 from Florence Doswell to Southwestern Medical Foundation to establish the Houston J. and Florence A. Doswell Center for the Development of New Approaches for the Treatment of Hypertension.

■ \$2,000,000 from the Cain Foundation in memory of Lillian and James Cain, to establish the Lillian and James Cain Endowment in Vision Loss to support macular degeneration research and to establish the Lillian and James Cain Endowment in Hearing Loss to support research on cochlear implant treatments.

■ \$1,924,993 from proceeds of the 2009 Sweetheart Ball to establish the Sweetheart Ball - Kern Wildenthal, M.D., Ph.D., Distinguished Chair in Cardiology.

■ \$1,100,000 from an anonymous donor to Southwestern Medical Foundation to foster general clinical care and research programs.

■ \$1,028,000 from an anonymous donor to support a joint research endeavor between UT Southwestern and the Cooper Institute to enable the Eugene McDermott Center for Human Growth and Development to analyze DNA samples gathered by the Cooper Institute, and to support the research activities of Dr. Joseph Takahashi, chairman of neuroscience.

■ \$1,000,000 from an anonymous donor to Southwestern Medical Foundation to support basic medical research at UT Southwestern.

■ \$1,000,000 from the Eugene McDermott Foundation to Southwestern Medical Foundation to establish the Kern and Marnie Wildenthal Family Fund to enable students, faculty and staff of UT Southwestern and UT Dallas to enjoy the artistic and cultural excellence of the metroplex.

■ \$1,000,000 from the Shirley and William S. McIntyre Foundation to Southwestern Medical Foundation to support research and clinical care in neurological disorders at UT Southwestern.

■ \$750,000 from the AT&T Foundation to support entrepreneurial activities at UT Southwestern's BioCenter.

■ \$500,000 from friends, colleagues, family members and former students of Dr. Paul Bergstresser to establish the Paul R. Bergstresser, M.D., Chair in Dermatology, which will foster skin-disease research and clinical care programs.

■ \$500,000 from Ronald Reeder to Southwestern Medical Foundation to create the Ronald Reeder Foundation Fund for Medical Research and Care in Honor of Becky Reeder, Marilyn Reeder, Preston Reeder and David Gann, to support cancer research and to foster programs in gastroenterology, neurology and urology.

■ \$500,000 from Elaine Dewey Sammons to provide additional support to the Elaine Dewey Sammons Chair in Pulmonary Research, in Honor of John E. Fitzgerald, M.D., and the Elaine D. Sammons Cancer Research Fund in Honor of Eugene Frenkel, M.D.

■ \$450,000 bequest from Arthur Gayle Hilley to Southwestern Medical Foundation to establish the A.G. Hilley Scholarship Fund for students.

■ \$432,295 from the Sparrow Foundation to support UT Southwestern's portion of the Center for Advanced ADHD Research, Treatment and Education (CAARTE) initiative – a joint project with UT Dallas and the Shelton School.

■ \$325,000 from the Charles Y.C. Pak Foundation to support research activities in the Neill Walsdorf Sr. Biotechnology Center in Mineral Metabolism and the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research.

■ \$309,150 from an anonymous donor to support research on Alzheimer's disease under the direction of Dr. Ilya Bezprozvanny, professor of physiology.

■ \$300,000 from The Hartwell Foundation to support a three-year research fellowship for Dr. Mala Mahendroo, associate professor of obstetrics and gynecology.

■ \$300,000 from Wilma M. Keahey, through a bequest, to support research on lung cancer, movement disorders and multiple sclerosis.

■ \$260,627 from the Muscular Dystrophy Association from the proceeds of the 2008 "The Affair – Join the Quest to Beat ALS" to support animal models in ALS research under the direction of Dr. Jeffrey Elliott, professor of neurology.

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

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

■ An anonymous donor, through a bequest, to support arthritis research.

■ An anonymous family foundation to Southwestern Medical Foundation to provide unrestricted support for UT Southwestern.

■ An anonymous foundation to support research on multiple sclerosis and ovarian cancer.

■ Dr. Robert C. and Veronica Atkins Foundation to Southwestern Medical Foundation to support the Dr. Robert C. and Veronica Atkins Chair in Obesity & Diabetes Research.

■ Henry Van Beber to Southwestern Medical Foundation to support Alzheimer's disease research.

■ BRAINS (for Autism) to support autism mouse models research.

■ David M. Crowley Foundation to support research on spinal cord injury, peripheral nerve disorders and pain management.

■ Mr. and Mrs. Lawrence B. Dale to support research and clinical care in multiple sclerosis in pediatric patients.

■ Louis Dorfman and Dr. Samuel Dorfman to support clinical research programs at UT Southwestern.

■ Dr. Robert G. Freeman, through a bequest, toward the creation of an endowed chair in dermatopathology.

■ Family and friends of Mauricia and Charles Fugitt to create the Mauricia and Charles Fugitt Family Fund in support of cancer and bone marrow research.

■ The Melchizedek Fund of Communities Foundation of Texas, to Southwestern Medical Foundation, to upgrade the Mark and Jane Gibson Professorship in Cancer Research to a Distinguished Professorship.

■ S. Roger Horchow, in memory of Carolyn P. Horchow and in honor of the staff in the Department of Physical Medicine and Rehabilitation, to support activities through the establishment of the endowed Carolyn P. Horchow Fund for Physical Medicine and Rehabilitation.

■ Howard Hughes Medical Institute to support renovations and improvements to laboratory space.

■ Mary Kay Foundation to support breast cancer research under the direction of Dr. Philip Shaul, professor of pediatrics.

■ Jeffrey Modell Foundation to establish the Jeffrey Modell Diagnostic Program for Primary Immunodeficiencies in the Division of Allergy.

■ Ted Nash Long Life Foundation to support research on Alzheimer's disease and on human cell aging.

■ Mr. and Mrs. C. Lamar Norsworthy III, to Southwestern Medical Foundation to support research in the Department of Neurological Surgery on the treatment of brain-stem bleeding.

■ Rudman Securities Partnership, Ltd. to support the Josephine Rudman Laboratory for Alzheimer's Disease Research.

■ The Sammons Dallas Foundation to St. Paul Medical Foundation to support the Heart, Lung and Vascular Clinical Center.

■ Texas Society to Prevent Blindness, through the proceeds of the 2009 Eye Gala, to support macular degeneration research.

■ Lawrence and Terry Tobin, to Southwestern Medical Foundation, to create the Lawrence L. and Terry P. Tobin Fund for Liver Disease Research, in Honor of Dr. William Lee.

■ Dr. Juan R. Vilaró-Grau, to Southwestern Medical Foundation, to establish the Helen and Juan R. Vilaró-Grau Scholarship Fund.