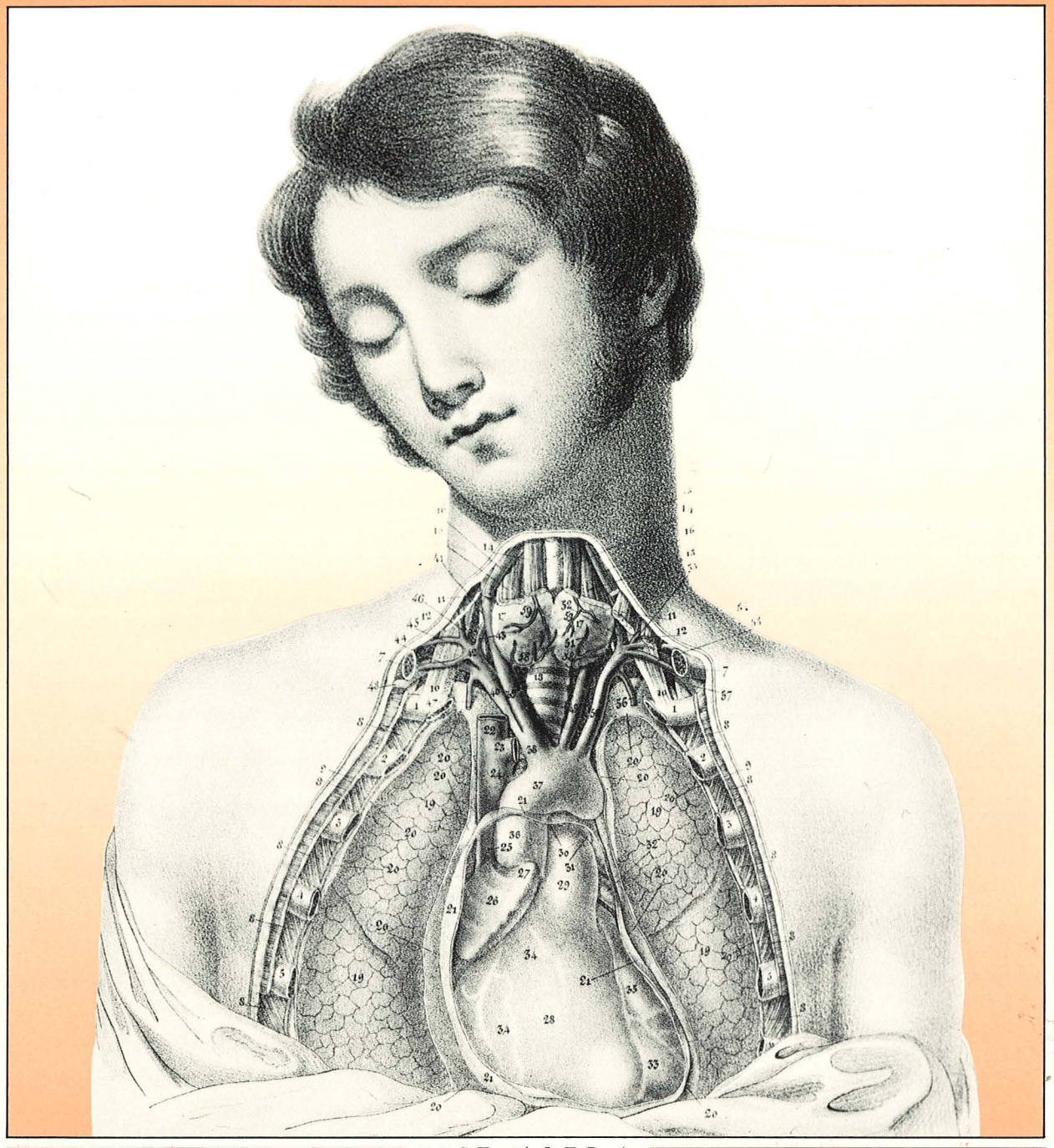
BIOLOGUE

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT DALLAS



VOL.5 NO.1

THE COVER shows a plate from the Manuel d'anatomie descriptive du corps humain *by Jules Cloquet, published in Paris in 1825, now in the History of Health Sciences collection of the UTHSCD Library. Cloquet's five-volume manual includes three volumes of exquisitely detailed lithographs constituting the most complete atlas of human anatomy available at the time. Although lithographers in Cloquet's day could produce only black-and-white prints, every illustration in each copy of the* Manuel *was delicately watercolored by hand after printing to achieve the greatest accuracy and clarity. The print on our cover, reproduced in monochrome for technical reasons, shows the general anatomy of the upper thorax. It was drawn by M. Haincelin and printed by lithographer G. Frey, Germain-trained master artists working in Paris.*

Cover Design: Randy Padorr-Black

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1985 (2)

The University of Texas Health Science Center at Dallas
BioLogue
Vol. 5, No. 1

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ALL OF THE ABOVE

Drew Gaffney, UTHSCD cardiologist, brings a multitude of professional talents to the space program

The lab in the Danciger Research Building was crowded long before the morning sun hit the windows. Cardiologists, reporters, technicians and astronauts were crammed into the shadows among the ceiling-high stacks of monitors and computer-linked oscilloscopes, dodging the tangle of tubes and wires hung from the beams. Without disturbing the hurry-up-and-wait atmosphere, Drew Gaffney opened the door just wide enough to slip into the room.

As the group organized itself around him, Gaffney greeted everyone individually, listening as if discussing each problem were the only reason he piloted a rented plane from NASA headquarters near weather-bound Houston back to UTHSCD—around the storm systems that grounded commercial flights.

Dr. Drew Gaffney, Space-Shuttle astronaut. . .

Then, with an unhurried exit, he disappeared for an hour-long teleconference with the Johnson Space Center, to settle the fate of a malfunctioning equipment system.

Drew Gaffney, M.D., leads several pairs of double lives. He is cardiologist and commercial pilot; researcher and clinician; carpenter who built his own house and Payload Specialist for the Space Shuttle flight scheduled for early 1986. And somehow, without fuss or fluster, he manages to orchestrate these parallel lives and give full attention to each.

Part of the trick is tenacity; Drew Gaffney plans for the long term. "When I was three or four years old," he recalls, "I came in from playing and announced that I was going to be a doctor. I stayed with that."

Gaffney's early decision on a medical career stayed with him through undergraduate studies in psychology and premedicine at the University of California at Berkeley, which included a year at the University of Madrid, and carried him through medical school at the University of New Mexico at Albuquerque, where he took his M.D. in 1972.

Training for a busy career in medicine might seem like more than enough to take on at an early age, but even as a boy growing up in Carlsbad, New Mexico, Gaffney was equally determined to study aviation. "In fact, I had figured out that I could go to the Air Force Academy and go to medical school through the Academy, when the family physician convinced me that my eyes weren't good enough for me to be a pilot. And I didn't want to be a back-seater—so I dropped the Air Force idea. I'm sure now that he was exerting some vocational guidance."

Gaffney outgrew his optical far-sightedness but never gave up his long-range plans to learn to fly. He is now a full-fledged commercial pilot, licensed to fly and to teach flying. Even after he began his practice as a cardiologist, Gaffney recalls, "I worked out a deal with a charter air service where I was a pilot. I would fly either as a co-pilot on a little turboprop or as a pilot flying freight. It's usually at night, and you're out loading mailbags in the dark. You're in a different world, and you are a totally different person; it gets you out of the stereotype, out of the box you get into sometimes.

"And believe me," he laughs, "being a physician is no plus in the world of pilots! It's something you try to keep hidden."

It isn't easy to think of two fields less similar than aviation and cardiology. But through his internship and residency in Ohio and four years at UTHSCD as a

Fellow in Cardiology and as a Faculty Associate, Gaffney never surrendered the thought of combining his widely different interests.

His future work at UTHSCD was to make this combination possible in a spectacular way.

After a year as a visiting scientist at the University of Copenhagen, Gaffney returned to UTHSCD in 1979 to take up his present position as Assistant Professor of Internal Medicine and of Health Care Sciences. He joined the research team of Dr. Gunnar Blomqvist, Professor of Internal Medicine and Physiology at UTHSCD. For the past 10 years, Blomqvist has been investigating the effects of weightlessness on the cardiovascular system.

Blomqvist and Gaffney wondered why astronauts develop low blood pressure in space. The weightlessness caused by a "zero-gravity" environment is part of the answer; freed from the pull of the earth, body fluids move from the legs to the chest cavity, and the extra fluid is excreted.

But the astronauts' problem is far more complex than simple dehydration. "A tennis player loses that much fluid in a game and doesn't have the same trouble," notes Blomqvist. "Something happens to the control mechanisms so the body can't make the adjustments it normally makes."

For the astronauts, this regulatory impairment, with the reduction of fluid in the body, reduces the heart's pumping capacity to a level sufficient for living in a weightless state but insufficient for normal life on earth.

> Gaffney stuffed the NASA application under the seat of a plane and flew to Washington to make the deadline.

When an astronaut returns to the earth's gravitational pull during re-entry, the reduced blood supply is drawn back suddenly into the lower extremities and away from the brain. On ground-controlled capsule flights in the past, astronauts sometimes blacked out because of this abrupt shift. Shuttle astronauts, who must remain alert to pilot their ships back to earth, wear "anti-g suits," trousers that automatically inflate to counter the pressure of the downward blood flow and prevent blackouts.

. . . and working UTHSCD cardiologist.

Still, the astronauts' blood pressure remains low for some time after their return to earth. During the readjustment period after a space flight, it can be "low enough to cause problems," according to Gaffney.

In 1977, a notice from the National Aeronautics and Space Administration appeared on a UTHSCD bulletin board soliciting experiments to be performed on the Spacelab that can be carried in the cargo bay of the Space Shuttle.

Blomqvist, as the principal investigator of the proposed study, developed with Gaffney an application for a series of cardiovascular measurements to be made before, during and after the long Shuttle flights. These readings would provide the first systematic overview of the changes in blood flow and other cardiac action caused by prolonged weightlessness.

To make the deadline in 1978, Gaffney stuffed the proposal under the seat of a plane and flew to Washington. He hand-delivered the bulging package to NASA, spent the afternoon touring the National Air and Space Museum and flew back to Dallas to await the result.

The result was announced officially six years later. The experiments would be performed on board the Shuttle, inside the Spacelab that the ship carries as a payload. Gaffney himself would supervise as a "Payload Specialist" on board the orbiting spacecraft.

Gaffney describes the Spacelab experiments in the same manner as he speaks of everything else, quickly, quietly, in perfectly punctuated sentences. Even technical jargon slips into its grammatical place and becomes understandable. Clarity of this kind is notoriously rare in professionals but even more striking in Gaffney's case. His conversation remains intelligible, although a single sentence may contain words from any or all of a half-dozen fields; he is equally fluent in the languages of cardiology, aviation, politics, aerospace, administration and several other professions.

"The goal is to understand regulatory mechanisms of blood pressure. Space travel provides an environment with no gravity, which takes that variable out. We use the zero-g environment and the return from it, which is where the problem occurs, to get a better idea of regulatory mechanisms."

This study has already benefited patients here on earth. Specifically, Gaffney cites the value of "what one learns about physiology both in the process of preparing for the flight and in studies that were done as groundwork. We studied lots of patients with orthostatic hypotension caused by many factors—heart disease, diabetes and so forth—and learned a lot about how you maintain blood pressure in an erect posture and about how to help patients do so, especially those with low blood pressure."

Gaffney spends most of his time now preparing for the experiments to be performed aboard the Shuttle. Some of the data will be gathered by fairly conventional means, such as attaching electrodes and drawing blood samples. The heart rates and blood pressures of the astronauts will be monitored continuously during the flight; this will give a basic history of changes during weightlessness.

Tests designed to measure changes in the heart's pumping capacity will be run before, during and after the flight. The inhalation of tracer gases will allow measurement of the blood volume through the heart, and cross-sectional echocardiographic images of the beating heart will be compiled by computer to achieve a measurement of the heart's pumping capacity.

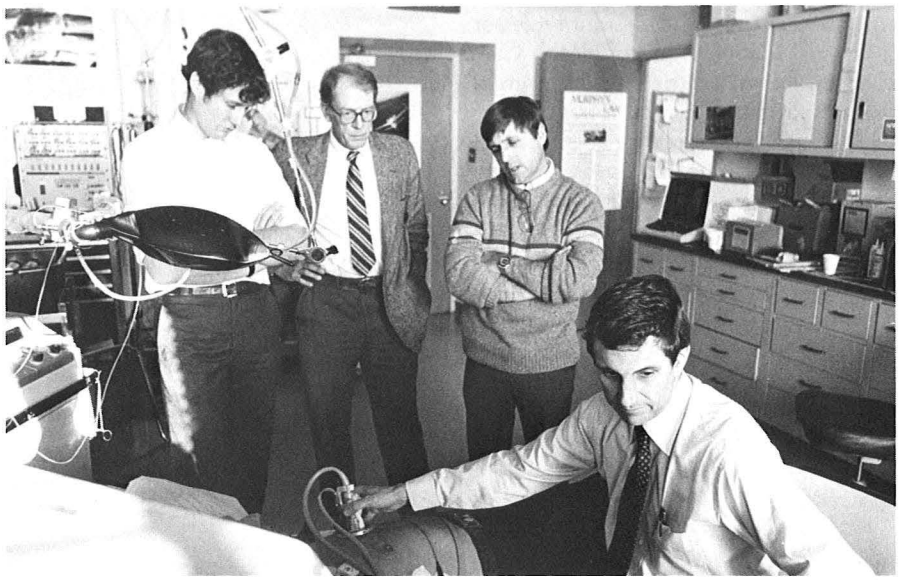
Among the less conventional, state-of-the-art experiments planned for the Shuttle is the System for Venous Occlusion Plethysmography, or "SVOP." This procedure, developed by Blomqvist and Gaffney with Dr. Jay Buckey, Fellow in Internal Medicine at UTHSCD, and Rick Summers of Garland Instruments, quantifies changes in blood flow by measuring changes in limb volume.

The SVOP assembly is a small instrument pack that can be strapped to an astronaut's leg. A slim, lubricated loop of mylar, anchored to a small pulley on the side of the pack, wraps snugly around the leg. As blood flow in the leg changes, the mylar band responds to the resulting changes in the limb's size, feeding the measurements into the instrument pack's magnetic tape for storage or "downlinking" to Houston for immediate interpretation.

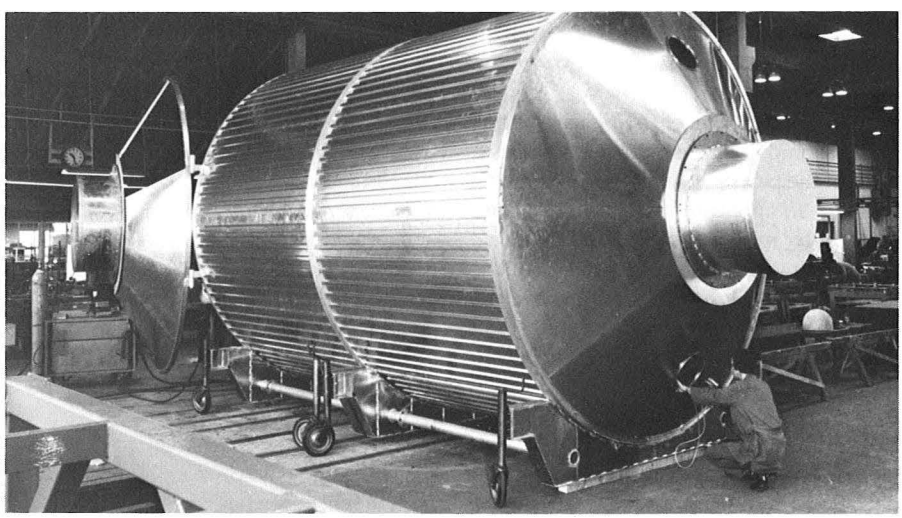
The periodic SVOP readings taken during the flight can be compiled later into a schedule of an important aspect of the body's cardiovascular adaptation to weightlessness.

The same mechanism will be used to measure changes in venous "compliance," the elasticity of the leg's veins. Blood flow in the limb is gradually changed by varying the tension on strategically placed cuffs, while the corresponding differences in the veins' distention are recorded.

"The question is," says Gaffney, "what are the veins like when you come back to earth? Are they more stretchable? Less? These changes in venous distensibility might help explain blood pooling in women, which can occur with birth control pills or with the menstrual cycle and in pregnancy, or in patients with varicose veins, which can cause fainting spells."



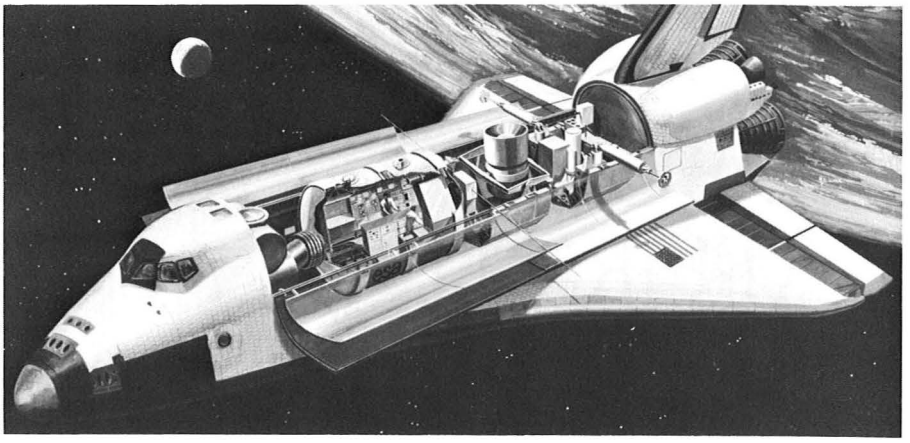
In the UTHSCD Space Medicine Lab: Jay Buckey, M.D.; Gunnar Blomqvist, M.D., Principal Investigator; Bill Williams, Ph.D., Payload Specialist Candidate; Gaffney.



Full-scale mock-up of the Spacelab. Within the 13-foot diameter unit, Gaffney will run his experiments during the flight.

The largest possible Spacelab that can be bolted into the cargo bay of the Shuttle is a metal cylinder only 23 feet long and 13 feet in diameter. Inside, it is only about the size of a small camping van. Most of the interior is full of life-support and other machinery. Equipment taken aboard must be minimal in size and quantity, and must be designed for maximum strength and simplicity. The Shuttle mission runs only about a week, so time is extremely limited; there is no opportunity to repeat a failed experiment. Scientific procedures in space therefore take on something of the ritualized precision, the economy of movement, of a high-tech tea ceremony.

But Gaffney is quick to point out that these same constraints have already improved the quality of health care here on earth. "You take equipment that is large, and you learn to make it smaller so that you can take it to more places, and that makes the equipment more available." Electrocardiograms and blood pressure



The Spacelab in earth orbit, carried aboard the Shuttle. In this cutaway view, two Payload Specialists can be seen conducting experiments.

monitors, he notes, have already been improved through space-aimed research.

"The problem is that you have one chance to do something. You want it safe, and you want it to work. Things of no consequence here in a lab are of enormous consequence in space. If you accidently start a fire in the lab here, you just put it out and do the experiment again; but if you start a fire in the Spacelab, you might have to abort the whole mission. You can prepare for 10 years," he says, "and you get only one chance to do it."

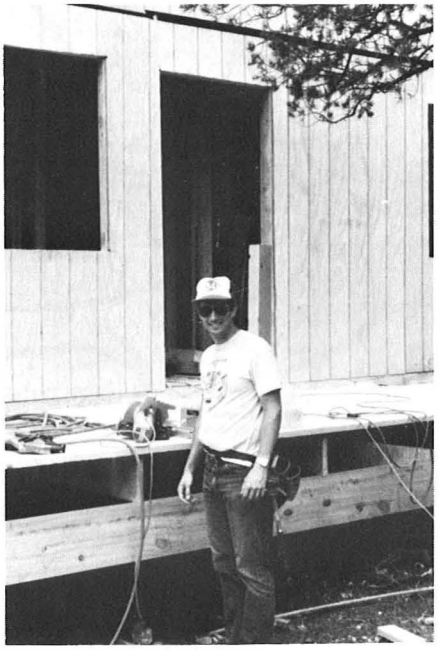
For that single chance to confirm 10 years of work, the equipment developed by the Blomqvist-Gaffney team —and Gaffney himself—will be shot into space at 17,000 miles per hour on a rocket booster 16 stories tall.

If Gaffney is nervous about the prospect, it doesn't show. He seems to be enjoying his space-related research just as he enjoys any of his other occupations: relaxed, but with a lively sense of wonder at the fresh horizons constantly swinging into view.

As remarkable as his steady nerves is his high level of organization. Working with the space program not only meant taking on an extra job, it required Gaffney's moving his family to a new, temporary home near the NASA base outside Houston. But despite the extra work load and the long hours of travel involved, Gaffney is able to schedule time for all of his interests and keep everything in perspective.

"In terms of priorities," Gaffney explains, "I consider myself first a clinician and second a researcher." To achieve this combination of medical careers, Gaffney admits, "You have to be willing to work evenings and weekends, and get good people to work with, because being a cardiologist is a full-time occupation."

And he hasn't cut down on his flying. In fact, Gaffney has recently taken on learning to fly aerobatics, which is much more demanding than conventional flying. It's a challenge just learning to fly the old "tail draggers"—so called because their third landing gear is under the tail instead of under the nose as on more recent planes. To gain the experience needed to fly the Decathalon stunt plane, Gaffney says, "I went out and found an old, old plane—a Cessna 140 that's two months older than I am.



Building in New Mexico: "People born in a city have no idea how may stars there are."

"It has no radio, no lights, and one big seatbelt that pulls across both occupants. It only has a bench seat that doesn't adjust." The 38-year-old plane is light-years behind the Shuttle, but there's no telling which one Gaffney will enjoy more.

Gaffney also finds time to spend with his wife and two daughters at their vacation home in the mountains of New Mexico. The idea of building the house himself came naturally to him: "My father and grandfather built the house I lived in as a child. In fact, I don't think we ever lived in a house that we didn't build or add some rooms to.

"I bought some land, thinking I'd build on it when I retired. My brother, who is a school principal who builds houses during the summers, called me a few days later and asked, 'Do you have your plans yet?' So I went in a very short time from having no intention of building to actually building my house."

The house stands in the same region as the White Sands observatory and allows Gaffney an excellent opportunity to investigate his newest interest—not surprisingly—astronomy. "It made no sense to go there and not know anything about it," he jokes, although admitting that the Shuttle's 160-mile-high orbit would hardly put him in interstellar space. When his older daughter recently began to study astronomy in grade school, Gaffney got involved and began studying with her.

"We're just beginning to learn about constellations," he reports. "We got a small, hand-held telescope, just to see if her interest will hold. If it does, then maybe we'll get a bigger one."

Even if his daughter loses interest, it sounds as if there's a sizable telescope in the Gaffney family's future. "It's a really neat feeling," Gaffney admits, "to be up in the mountains and see the stars from a house that you built yourself. People born and raised in a city have no idea how many stars there are."

Astronomer now, as well as cardiologist, researcher, stunt pilot and astronaut— what is it that holds all of these diverse interests together? "The bottom line," Gaffney says, "is that people should enjoy what they are doing. Everybody has the wherewithal to find something they enjoy doing. Then getting up in the morning is easy.

"I try to teach my daughters that you can do anything you want if you prepare for it. And you can't prepare in a specific way—I didn't learn to fly in order to become an astronaut—but you can get things in place if you study and work for it. Their world will be a much bigger and brighter place if they approach it with the idea that everything's possible."

Everything's possible. If anybody can prove that, Drew Gaffney can. ■

—KEVIN ORLIN JOHNSON

THE SUPER UNSATURATES

In the fight against heart disease, olive oil may be a better weapon than popular polyunsaturated oils like corn oil and safflower oil

A new study comparing the effects of different types of fats on cholesterol levels in the blood showed that both monounsaturates such as olive oil and polyunsaturates result in markedly lower cholesterol levels than saturated fats—fats found in meats, egg yolks, butter and cream. But monounsaturates are preferable because they are just as effective as polyunsaturates, do not have the possible side effects of polyunsaturates and may actually be superior in lowering certain types of cholesterol.

"We knew that the rate of cardiovascular disease was very low in the Mediterranean region where people cook primarily with olive oil. Unfortunately, a thorough clinical comparison of monounsaturates and polyunsaturates had not been made, so no one knew whether monounsaturates lowered cholesterol levels as effectively. Now we know they do," said Scott M. Grundy, M.D., Ph.D., Professor of Internal Medicine and Biochemistry and Director of the Center for Human Nutrition at UTHSCD.

Grundy's partner in the research effort was Dr. Fred H. Mattson of the Department of Medicine, University of California—San Diego in La Jolla. The clinical studies were conducted at the Veterans Administration Medical Centers in Dallas and San Diego.

> A high level of LDL in the blood accelerates the development of fatty deposits that clog arteries.

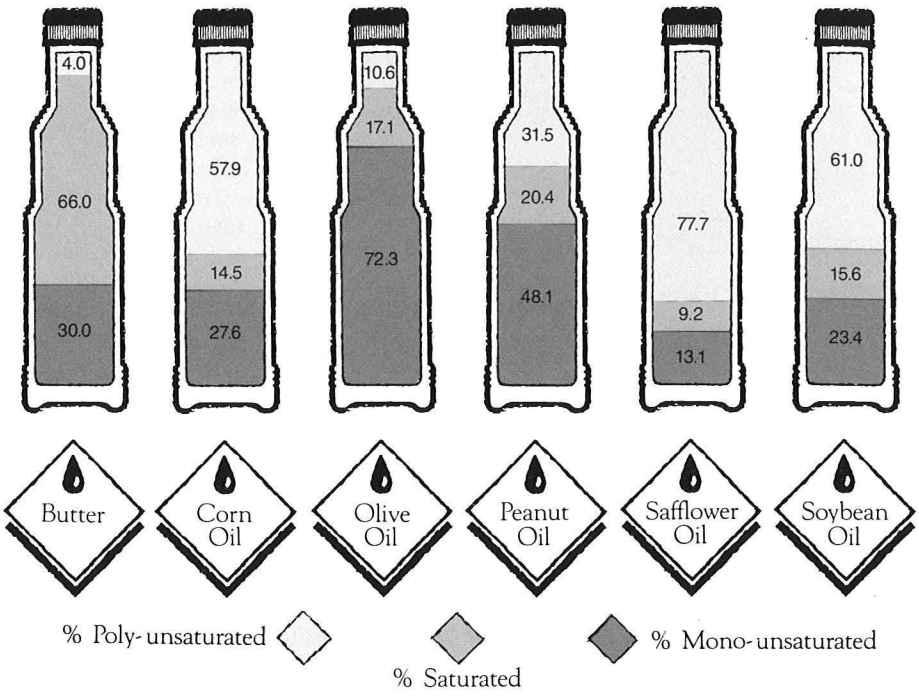
In the tests, 20 patients consumed three liquid diets in each of which the predominant fatty acid type was saturated, monounsaturated or polyunsaturated. The fats totaled 40 percent of the calories in each diet, roughly equal to the percentage of fats in an average American diet. Each diet was consumed for four weeks; during the third and fourth weeks blood samples were taken and analyzed for total cholesterol and total triglycerides. They were also analyzed for the lipoproteins LDL-C, HDL-C, and VLDL-C, which are various combinations of protein with cholesterol or triglycerides.

Grundy and Mattson found that monounsaturates and polyunsaturates had almost identical effectiveness in reducing the levels of total cholesterol in the blood. A high blood cholesterol level results in a gradual accumulation of fatty deposits in blood vessels throughout the body. This narrows the vessels, reducing the blood flow to the heart and posing a direct threat of heart disease.

But recent research into cholesterol metabolism has described several types of lipoproteins that carry cholesterol through the blood and has shown that some types of lipoproteins are harmful while others are harmless.

For example, the cholesterol carried in low density lipoprotein (LDL) is deliv-

Olive oil is currently the best source of monounsaturated fat for human consumption available in the United States. It is 71 percent oleic acid. Peanut oil is second, with 46.5 percent oleic acid. Following is a comparison of several common dietary sources of fat:



ered to the cells for storage. A high level of LDL in the blood accelerates the development of fatty deposits that clog arteries. Both the monounsaturated and polyunsaturated diets lowered the harmful LDL cholesterol about 17 percent from the level produced by the saturated fat diet.

In addition to lowering total cholesterol and LDL cholesterol, the diet highest in polyunsaturated fat frequently lowered the high density lipoprotein (HDL) level. HDL transports cholesterol from the body's tissues to the liver where it can be converted for use by the body or processed for elimination. A high level of HDL cholesterol, indicating that cholesterol is being used efficiently, is desirable. The fact that polyunsaturates lowered the HDL cholesterol level seems undesirable, according to Grundy.

The monounsaturated fat diet reduced the HDL cholesterol level less often than the polyunsaturated diet. Although the results in this area of the test were not conclusive, they were promising.

"We think the results of the overall tests prove that monounsaturated fats are as effective as polyunsaturates in lowering cholesterol levels in the blood," Grundy said. "We will be studying the HDL aspect further. It would indicate several advantages of olive oil over polyunsaturates."

The American Heart Association currently recommends that cholesterol intake should be reduced to 250-300 milligrams per day and that total fat in the diet should be limited to 30 percent of daily calories. The group also suggests limiting saturated fats to less than 10 percent of calories and increasing polyunsaturated fats to a maximum of 10 percent of calories.

> Grundy and Mattson found that monounsaturates and polyunsaturates had almost identical effectiveness in reducing the levels of total cholesterol in the blood.

However, the nutrition committee of the American Heart Association is reluctant to advocate an increase in polyunsaturated fats (for example, to 15-20 percent of total calories) because no sizable population has consumed such large quantities of polyunsaturated fats for a long period of time. Therefore, the long-term safety of polyunsaturates has not been proven.

Monounsaturated fats have now been shown to have the same cholesterol-lowering advantage and several other possible advantages over polyunsaturates. Monounsaturates have a demonstrated history of use in the Mediterranean region, where olive oil is the primary source of dietary fat and where coronary heart disease is low.

"Furthermore," says Grundy, "monounsaturated fats are synthesized normally by the body and are less likely to have some of the side effects that have been postulated to occur with polyunsaturated fats, like promoting the development of cancer, suppressing the immune system and changing the cell membranes drastically. So we think that all these side effects could be avoided by the use of monounsaturates. Another big advantage is that monounsaturates have a more stable shelf life, so they don't go rancid nearly as fast as polyunsaturates. And then in our study we learned that they didn't lower the HDL as often as polyunsaturates.

"We're not saying that monounsaturates should replace the polyunsaturates completely. The body requires a small amount of polyunsaturated oil—it's what we call an essential fatty acid. Polyunsaturates also serve as a source of the prostaglandins in the body. Prostaglandins are extremely active biological substances which affect organs as diverse as the prostate gland or the uterus, the brain, lung, kidney, thymus and pancreas, and therefore are really quite important. Our problem with polyunsaturates is giving large amounts."

Concluded Grundy, former head of the Nutrition Committee of the American Heart Association, "The kind of very low-fat, high-carbohydrate diet favored in the Orient probably just isn't realistic for many Americans. But it appears that it would be prudent to limit the calories supplied by fats to 30 percent of the daily total. At this level, saturates should be kept below 10 percent of total calories, monounsaturates should be kept at 10-15 percent of calories, and polyunsaturates from 5-10 percent." ■

—TOMMY JOY BOSLER

A LEGACY OF LIFE

It's never too late to share the "gift of life" with others through transplantation, research or medical education

Give my sight to the man who has never seen a sunrise, a baby's face or love in the eyes of a woman. . .

Give my heart to a person whose own heart has caused nothing but endless days of pain. . .

Give my kidneys to one who depends on a machine to exist from week to week. . .

Take my bones, every muscle, every fiber and nerve in my body, and find a way to make a crippled child walk. . .

Explore every corner of my brain. Take my cells, if necessary, and let them grow so that, someday, a speechless boy will shout at the crack of a bat and a deaf girl will hear the sound of rain against her window. . .

If you do all that I have asked, I will live forever.

Robert Test
To Remember Me

Most people don't realize that no one is ever too young or too old to be an organ donor, says Dr. Charles R. Baxter, Professor of Surgery at The University of Texas Health Science Center at Dallas. "That's because if an organ is not appropriate for transplant, there is always a need for teaching and research."

UTHSCD has pioneered the transplantation of organs. Dr. Paul Peters, Chairman of the Division of Urology, performed Texas's first kidney transplant in 1964. "For 18 years," says Peters, "we were the only game in town. There were 11 teams in the U.S. when I started here in the 60's. Now there are more than 250 in all."

In fact, renal transplants have become relatively common. More than 30,000 have been performed since the procedure became a clinical reality in the 1950's. In Dallas there is now an average of one every other day. Every effort is made to use donated kidneys for transplant, but, say UTHSCD urologists, those kidneys that cannot be transplanted are needed for research.

Dr. Charles R. Baxter

The newest transplant procedure being performed by UTHSCD doctors is liver transplant. In 1984 Melissa Lively, a toddler from Missouri City, Texas, received a new liver—the first successful liver transplantation in the state. Little Melissa made a speedy recovery and was soon seen taking walks through the corridors of Children's Medical Center, which works with the Health Science Center in the joint pediatric liver transplant program.

Such visceral organs—kidney, liver, heart—need to be used quickly after donation. But some organs can be stored for future use: skin, corneas and bone are all "bankable."

Baxter, who serves as Medical Director of the bankable organ transplant program sponsored by UTHSCD and the Lions Sight and Tissue Foundation, also heads the Parkland Memorial Hospital Burn Center. A member of the new federal Task Force on Organ Transplantation, he is himself a trailblazer in the use of donated human skin to save victims of major burns. In 1973 he treated an eight-year-old Dallas girl whose burns covered more than 92 percent of her body. Young Sherry White became the first person ever to survive such extensive burns. Baxter says that Sherry, now a Dallas housewife with a child of her own, would never have made it without the large amount of donor skin that was available at the time.

It is no exaggeration to say that skin saves lives. This "living bandage," which is removed from the back of the legs and upper back of deceased donors, is kept in a liquid nitrogen freezer until it is used. The donor skin is applied to a wound and held in place with pressure dressings for the first 72 hours after surgery. The dressings are then removed and a little gauze covering placed over the donor graft until a covering of the patient's own skin is formed or the wound is healed.

Baxter and his associates are also involved in major research requiring donor skin. One project that has recently drawn national attention is a method of "seeding" the burn wound with the patient's own skin. The procedure uses a composite graft of cells from the patient's epidermis, the top layer of skin, and donor dermis, the structural skin just below the epidermis. The donor cells form a stable scaffolding that lets the epidermal cells

grow and cover the wound as it is healing. So far, results of studies involving small sheets of skin grown from the patient's own cells have been outstanding; currently, the team is looking at larger wounds.

"In fact," says Baxter's co-worker Ellen Heck, Executive Director of the Lions Sight and Tissue Foundation and the Skin Transplant Center for Burns, "facilitating research is a major goal of our bankable organ program. Although we see that bankable organs are made available to physicians for their patients whenever possible, there are times when it is not possible to use them. Sometimes vital tissue has deteriorated so that it is not suitable for transplantation. Occasionally, it may be accidentally damaged during the delicate removal process."

But this does not mean that these donations have been to no avail: bankable organs unsuitable for transplant are still needed for teaching and research. Many ophthalmological surgeons in private practice request eye tissue for research; on the UTHSCD campus, the Department of Ophthalmology currently has half a dozen research projects that need corneas or whole eyes, but which do not require tissue that meets the standards for transplantation. In addition, Dr. James McCulley, Chairman of Ophthalmology at UTHSCD, notes that there is always a need for eyes and the surrounding bony structure for teaching, especially for teaching surgical procedures. Using such donated tissues, ophthalmology residents can learn procedures by actually performing surgical operations, and experienced eye surgeons can practice new procedures.

Last year, Heck reports, tissue from 66 eyes was used for research; 292 corneas were supplied for transplantation. The small circular structures, which look much like contact lenses, are stored in a protective solution in small bottles and refrigerated. Unlike skin, which can be frozen for long periods of time, corneas must be transplanted within four days.

One local cornea transplant patient is Mary Galen Thomas of Fort Worth, Publications Coordinator for the Tarrant County Junior College District. Thomas, whose vocation is dependent upon her vision, is a victim of keratoconus—a cornea with a bulging center that becomes increasingly conical. "It's like a growing ice-cream cone," she says.

The condition becomes increasingly painful as the corneal tissue stretches. Contact lenses can sometimes help the condition by serving as a brace on the cornea, but, in Thomas's case, nothing seemed to work for very long. Transplantation became necessary when other approaches to her vision problem failed.

A gift of skin for transplantation gave this child a chance at life.

The 40-year-old editor received her first donor cornea late in the summer of 1984. Although she doesn't know when surgery for her other eye will be necessary, she accepts that it's just a matter of time. Her surgeon, Dr. McCulley, is preparing research toward a new procedure that may remove the necessity for such radical surgery for keratoconus and similar problems. Its development, though, is some time away, and the research is as dependent upon organ donation as the transplant surgery itself.

Besides helping to restore the precious gift of sight and save the lives of the badly burned, the bankable organ program at UTHSCD plays an important role in supplying bone tissue used to relieve the pain and crippling of many orthopedic patients. Bone is taken from the iliac crest of the pelvis and used for various types of bone replacement. One of these surgeries is anterior spinal fusion, a procedure in which donor bone is used to form a latticework for new bone growth so that a

spine damaged by disease or trauma will grow back together. The small piece of donor bone—cut to the required size, washed to remove cells, dried and sterilized—is inserted to replace the patient's missing spinal bone or disc. Bone treated in this way is easily stored in the organ bank since it requires no refrigeration.

On the other hand, fresh frozen donor bone is needed for hip and knee replacement. Using human bone to replace the damaged portion of joints allows the recipient's bone to regenerate and incorporate the donor bone, while the recipient's own joint cartilage continues to live and function. Researchers who perform such implantation consider the procedure much superior to implanting plastic or metal joints, particularly for younger, more active patients who put too much stress on the cement that holds the artificial joint, causing it to loosen.

In addition to supplying bankable organs for research, teaching and therapy at UTHSCD, the program provides tissue needed elsewhere in the United States. According to Heck, the UTHSCD program supplied some 89 shipments of skin for burn patients last year—about 790 square feet for transplant. Locally, skin was provided for the Parkland Burn Center and the hospital's physical therapy area and for the Department of Physical Medicine and Rehabilitation at UTHSCD; many other hospitals in the region drew on the UTHSCD skin bank for tissue, as did burn units throughout the country.

> Dedicated volunteers are important in trying to see that donated tissue is available for transplant.

In order to assure that families of donors will not be contacted more than once, the Bankable Organ Transplant Program at UTHSCD works closely with Dallas' Southwest Organ Bank, the third largest free-standing organ retrieval agency in the country. Southwestern furnishes vital organs for transplantation.

Dedicated volunteers are important in trying to see that donated tissue is available for transplant. A group of ham radio

Cornea transplant patient Mary Galen Thomas of Fort Worth has resumed work as an editor after successful surgery for keratoconus.

operators takes to the airwaves in the early morning hours every day in search of available corneas that have no local matches and are being offered to other parts of the country, or in search of skin for major trauma when it is not locally available. East-coast hams make calls in their area starting at about 6 a.m.; at 6:45 it's time for the Midwest operators, including those in Texas, and later others farther west take their turn.

AirLifeLine of Texas, a non-profit, volunteer organization of pilots, delivers skin and eyes when there is neither the time nor the opportunity to use commercial airlines.

A major reason for Dallas' exemplary history in organ donation is the cooperation of the Dallas Medical Examiner's office. Dr. Charles Petty, UTHSCD Professor of Pathology and Director of the Southwestern Institute of Forensic Sciences, serves as Chief Medical Examiner and can accurately be called a crusader for the cause.

A quiet, lanky man with a slow smile, Petty says that he needs "to feel I provide things for the living." The pathologist first became interested in transplant when he was Chief Resident in Pathology at Peter Brent Brigham in the early 50's, when the first kidney transplants were being done there.

But before that, Petty became involved in blood banking. "In a sense," he says, "this is a form of tissue transplant. Transplantation is really an off-shoot, an extension, of blood banking."

Petty says that a generous act on the part of his father pointed the way to his interest in blood and organ donation. "In about 1933 or 1934," he recalls, "a friend had an accident on a sled. He flew off and came down on a tree stump, rupturing his spleen. He needed blood—a person-to-person transfusion. In those days, they connected a tube from the donor to the patient. My father volunteered."

Now Petty volunteers, writing about organ donation for professional journals, speaking on the subject at medical meetings and working toward perfecting the cooperation among the Health Science Center, the Lions group and the organ banks. His interest played a major part in convincing the Dallas County Commissioners to allocate space in Parkland Hospital to the Bankable Organ Program so that the two entities can work closely together on a day-to-day basis.

Petty also works with another program in which donors can help—the Willed Body Program at the Health Science Center. The program is part of a state network, regulated by law, that manages body donation. If the family of a donor wishes, funeral arrangements may be made in advance as part of the donor plan, or the donor's ashes can be buried at the memorial on the UTHSCD campus grounds.

The Willed Body Program is invaluable in the teaching of anatomy. Dr. William Gonyea, Professor of Cell Biology and Director of Anatomy, points out that the faculty at the Health Science Center is dedicated to inculcating in first-year med-

Research is an on-going part of the bankable organ program, according to researcher Ellen Heck, shown at work.

ical students a feeling of reverence and respect as they approach the study of the human body. Gonyea sees the introduction to anatomy as the student's first encounter with the doctor-patient relationship; this relationship, he feels, "insures that we demonstrate the proper respect for the dignity of the deceased individuals and for the feelings of the relatives who reside in the community."

Gonyea says that many people have the mistaken idea that if they give their bodies for medical education and research they cannot be organ donors. However, arrangements can be made that will allow both kinds of donation. In addition, there are many special educational and research needs that donations serve; for example, many graduate residency programs have in-depth studies of anatomy, and surgical subspecialties are constantly learning new procedures.

If you are interested in any of these ways of giving, the most important thing to do is inform your immediate family of your wishes. Also, sign the donor's certification on the back of your Texas driver's license or carry a donor card. Presently, corneas are the only organs that may be released for transplant by a justice of the peace or county coroner in Texas; most often, donations will be made after the closest surviving relative has been consulted.

Another way to donate is through The Living Bank, the only national donor registry and referral service. The Bank is a non-profit organization funded by donations, and about 150,000 to 200,000 persons are currently enrolled in its registration program. In the event of a death, family members can call The Living Bank International at any hour, and Bank representatives will immediately contact the proper institution. ■

—ANN HARRELL

For more information on local donor programs or to register, contact:

UTHSCD Organ Transplant Services
(214) 688-2609

Kidney Foundation of Texas
(214) 934-8057

The Living Bank International registry and referral service, Houston
(713) 528-2971 in Texas
1 (800) 528-2971 out of state

THE TWINKLE OF AN EYE

"We at the Health Science Center simply couldn't carry out research without organ donors," says Dr. James McCulley, Chairman of the UTHSCD Department of Ophthalmology. And, in fact, McCulley's department is a good example of the need for organ donations for research. Some of the research projects in Ophthalmology are:

■ **Research on improved preparation and sterilization techniques for corneas.** Infection is a major problem in cornea transplantation. McCulley says that, because the Dallas eye bank is the only one in the United States that routinely does sterile procedures before and after the application of antibiotics, it is a natural place for this kind of research.

■ **Looking for more effective antibiotics to ward off infection following cornea transplant.** Drugs currently being used do not seem to be warding off strep infections. Therefore, researchers are looking at new combinations of drugs used prophylactically.

■ **Use of infant corneas for transplant.** Standard use of corneas for transplant consists of using these organs from donors aged two and up. However, McCulley has been transplanting corneas from donors less than one year of age in certain patients who are aphacic (born without the crystal-like lens) and cannot have interocular lenses or who have had cataracts removed. While it has been found that these young lenses are able to enhance the "plus power" in the cornea for magnification, it is not yet determined how effective their use will be in the long run.

■ **Improvement of tissue culture media.** Organ bankers feel that a week is the maximum storage time for corneas to be used in transplantation. McCulley says that his goal is the development of a culture that would keep the cornea viable for 10 days. Then both the patient and the surgeon would have more flexibility in scheduling the transplant procedure.

■ **Development of a transplant of healthy donor cells that have repopulated in culture.** McCulley says that his work in repopulating cells from a donor's cornea endothelial layer (layer of cells lying on the basal membrane) has proven successful in rabbits. However, the tissue adhesive used in this work has some toxic properties. While the adhesive does not seem to have hurt the rabbits, a non-toxic glue is needed for human experimentation. Researchers are also seeking another way of attaching the new cells to the cornea tissue. One way might be to take out the cornea, coat its back with the new cells and then replace it surgically.

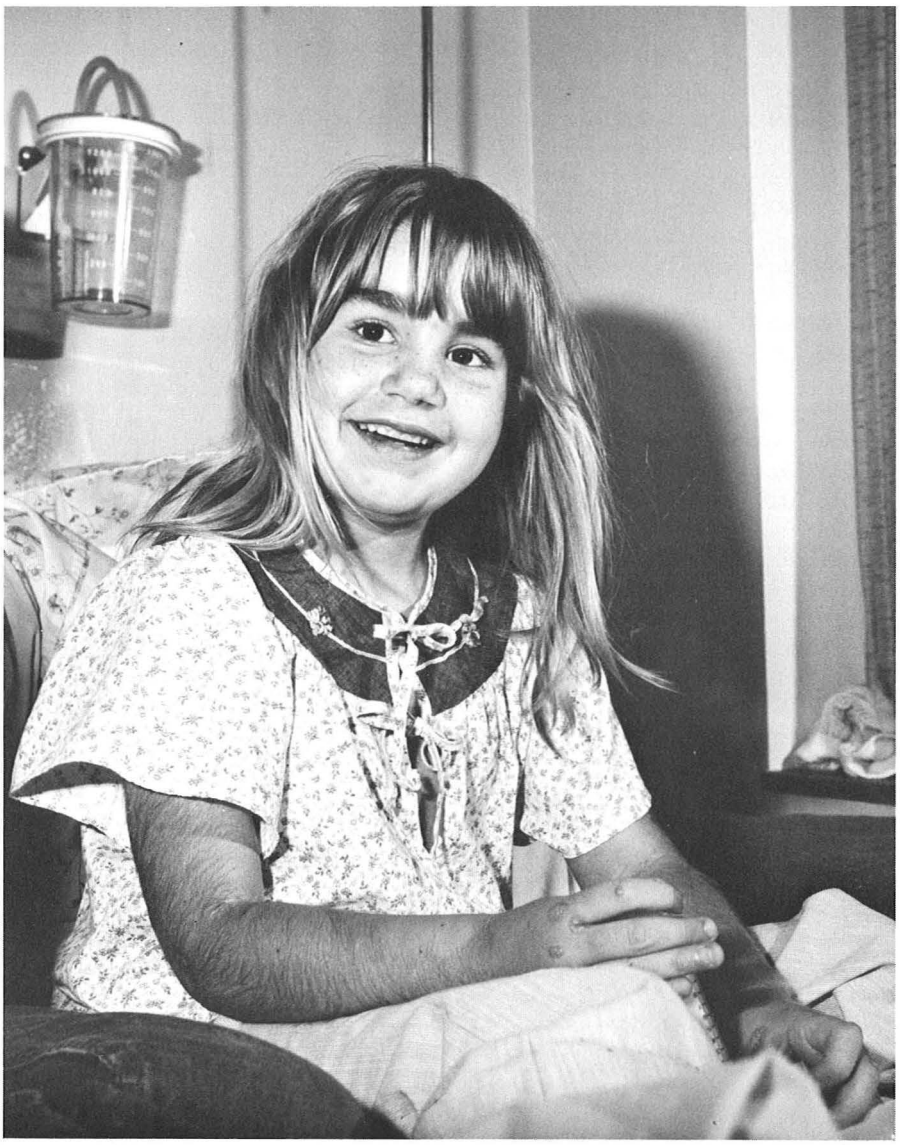
■ **Repopulation of endothelial cells using the patient's less-than-healthy cells.** The donor in this case, says McCulley, needs to be younger than 30 in order to grow new cells for the corneal layer. These young cells, which are stimulated to divide, will heal and fill in the spaces as they spread out.

■ **Rejection studies.** "If we can define which types of antigens are more likely to reject the repopulated cells, we can remove them. Also, we may learn to manipulate cells so the antigens' reaction will be less vigorous," says McCulley. This could perhaps be done by using mixed cells from several sources so less challenge would be offered to the host. "The antigens might recognize 'spots' of cells (and leave them alone), and the others could fill in empty areas."

■ **Refractive surgery in order to enhance power.** This surgery would provide a way of reshaping the removed cornea before replacing it. Half the cornea might be removed and a donor or synthetic cornea sandwiched in to correct farsightedness. Another possible procedure might be taking a cornea and altering the curvature before replacing it. The sutures would be placed only in the part of the eye not used for vision, and the scar would be on the outside of the area away from the cornea.

CLOUDS BREAK FOR STORMIE

The world's first heart/liver transplant patient has made a remarkable recovery thanks to diagnosis and treatment at UTHSCD



Stormie Jones first came to the Health Science Center in July 1983 as just another child with an undiagnosed condition. She returned the following summer for follow-up testing after becoming the world's first recipient of a dual heart/liver transplant.

Stormie Jones's unprecedented simultaneous heart/liver transplant on Valentine's Day, 1984, was heralded as a major step forward for medical science. Yet this important medical achievement could not have occurred had it not been for more than a decade of research by a group of scientists at UTHSCD.

Scientists here are among the world's leading authorities in cholesterol metabolism. UTHSCD has been the site of important breakthroughs at the basic science level in this field and is one of only a few research centers in the country where physicians have extensive clinical experience in studying the hereditary disease that almost destroyed Stormie's life. Their discoveries and recommendations forged the way towards the historic Pittsburgh surgery.

Six-year-old Stormie was referred to UTHSCD in the summer of 1983 by a physician in her home town of Cumby, Texas. Dr. David Bilheimer, Professor of Internal Medicine, examined her and knew instantly the yellow, wart-like lesions dotting her body were a symptom of a rare genetic disease. These lesions were plaques of cholesterol pocketed beneath her skin—a sign that her body's cholesterol level had risen out of control. Having treated people with this condition for more than 10 years, Bilheimer realized that the child faced the high risk of a heart attack.

Stormie was diagnosed with "familial hypercholesterolemia," a disease characterized by the inability of the body to regulate its cholesterol supply. Unregulated, cholesterol can narrow and clog coronary arteries. The resulting plaque buildup on artery walls causes atherosclerosis, which chokes the supply of blood and oxygen to the heart. This can ultimately lead to heart attacks and strokes.

One in 500 Americans suffers from the milder form of this disease, heterozygous FH, in which the person is born with one mutant gene. This condition, which produces two to three times the normal plasma cholesterol level and premature heart disease and strokes, is treatable with drugs and diet.

Stormie had the more serious form of the disease—the one-in-a-million homozygous form—in which she inherited two abnormal genes, one from each parent. Patients with homozygous FH have extremely elevated cholesterol levels (six to eight times the normal level) and often suffer heart attacks within the first decade of life. Most die from heart disease before age 20.

When Stormie was diagnosed, she

had no history of heart problems and no symptoms of angina, the chest pain that often precedes a heart attack. She was admitted to a research ward at UTHSCD for evaluation and placed on a low-cholesterol diet. Her impaired ability to metabolize cholesterol showed that she was typical of several other homozygous FH patients Bilheimer had studied. Although doctors here were working to understand and treat the disease, there was still no cure; even existing standard treatments made prognosis for the disease poor.

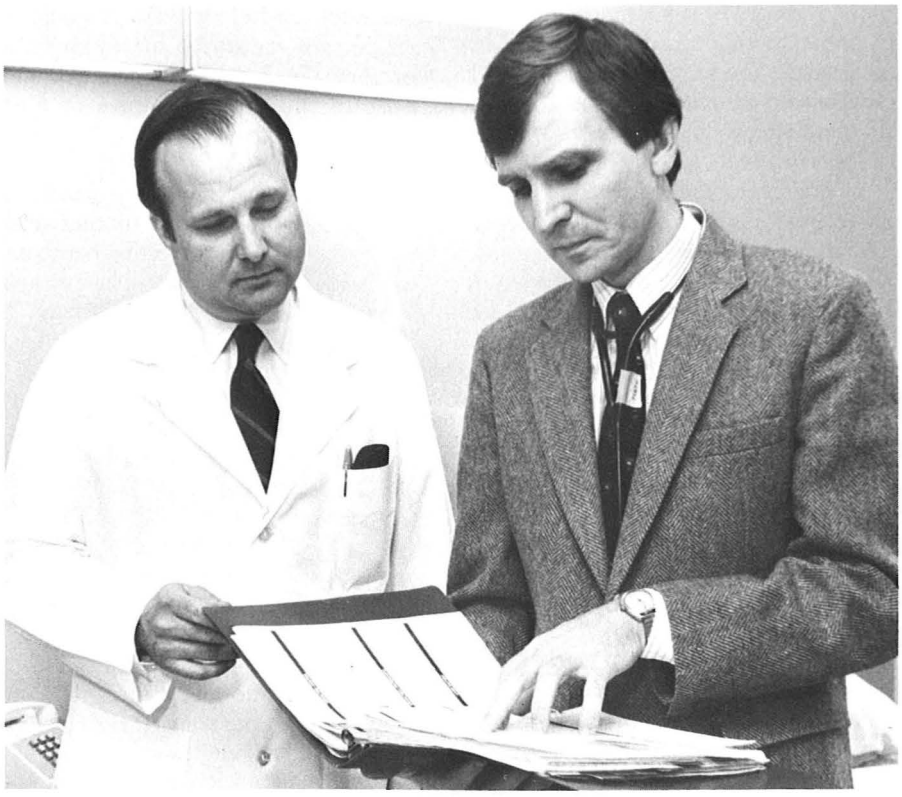
UTHSCD geneticists Drs. Joseph Goldstein and Michael Brown were the first to identify a major genetic mechanism responsible for cholesterol metabolism in 1973. Goldstein is Professor and Chairman of Molecular Genetics and Professor of Internal Medicine; Brown is Professor of Molecular Genetics and Internal Medicine and Director of the Center for Genetic Diseases. They discovered tiny structures that are located on the surface of cells which remove potentially harmful cholesterol from circulation. These structures are receptors for low-density lipoprotein, molecules that carry approximately two-thirds of the body's cholesterol through the bloodstream. In a healthy person, receptors admit LDL molecules carrying cholesterol into the cell's interior so that the cholesterol necessary to build cell walls can be retained.

The importance of the liver in this process was largely established by Dr. John Dietschy, UTHSCD Professor of Internal Medicine. From animal experiments, he and his associates determined that the liver is the major organ for cholesterol regulation—clearing at least 75 percent of the LDL cholesterol from the body. His studies showed that the liver contains more than half of the body's LDL receptors. This high concentration of LDL receptors and its large size enable the liver to take up and degrade more LDL cholesterol than any other organ.

This process goes awry in people with homozygous FH.

In Stormie's case, none of her body's cells contained LDL receptors. LDL cholesterol, therefore, soared to life-threatening levels—eight times the normal level for a child her age.

While Stormie's case was serious, her heart appeared normal during her stay at the UTHSCD research ward in September and early October of 1983. She was treated with an experimental drug, Mevinolin, to lower her cholesterol levels. The drug had been shown effective in lowering the cholesterol levels of heterozygous FH patients by 20-25 percent. It worked in heterozygotes by stimulating the single normal gene to produce more receptors. While Stormie had no normal gene, and therefore no chance of producing more receptors, doctors hoped the drug would suppress LDL synthesis. "I told her family, 'The drug may or may not work,' " Bilheimer recalls.



Dr. David Bilheimer (left) was the first physician to accurately diagnose young Stormie Jones's rare genetic disease. Dr. Brian Firth (right) was brought into the case to determine the extent of damage to her heart after she suffered two heart attacks brought on by her disease. The two physicians continue to monitor Stormie's progress at regular intervals at the Health Science Center.

Then, on October 12, Stormie suffered a heart attack. Shortly afterward, she developed renewed severe chest pains that were controlled by morphine and "huge doses of nitroglycerin," according to UTHSCD Cardiologist and Associate Professor of Internal Medicine Dr. Brian Firth. Firth and Dr. Gary Turner, a specialist in pediatric intensive care medicine, performed an emergency cardiac catheterization to see if their suspicion was correct—that she had severe coronary artery disease. The doctors discovered that Stormie had a dominant left coronary artery so that most of her heart was being supplied by one artery instead of the normal two. After Firth and Turner found a major blockage in the left coronary artery caused by cholesterol deposits, they knew that surgery was necessary. Presbyterian Hospital surgeons Drs. Larry Mills, Melvin Platt and David Fosdick performed surgery to bypass the blocked artery, thereby restoring a better blood flow to Stormie's heart.

Firth says that performing a cardiac catheterization and coronary angiography on such a young child who was in such an unstable state was "very scary. It was a first for most of us—those doing the coronary angiography and bypass surgery. It was most unusual in a six-year-old girl."

The fact that her heart was dependent on one coronary artery for most of its blood supply hastened Stormie's medical deterioration. "I think that's why she got so sick so fast," Bilheimer said. "I have seen other homozygous patients who had heart attacks but they didn't have a dominant left coronary artery, so they had a more balanced blood supply to the heart. Therefore, if you closed off part of one artery, enough of the heart would be supplied by the other to get through it. In her case, most of her heart was endangered when she developed pain."

Within six weeks of her cardiac bypass operation, Stormie had another heart attack. After performing another cardiac catheterization, Firth determined that a

second coronary bypass was needed; again, the operation was performed by Mills, Platt and Fosdick. The second heart attack had also damaged the mitral valve between the two left chambers of the girl's heart; this was replaced with a prosthetic valve.

The doctors reasoned that if Stormie received a normal, donated liver containing receptors, her disease would stabilize; but they feared that her severely damaged heart would not withstand the trauma of a liver transplant.

"She had had two heart attacks and two operations within six weeks as well as the insertion of a prosthetic valve," Firth recalls. "The immunosuppressives you would have to give to prevent rejection of a transplanted liver would increase the risk of infection on the artificial valve.

"Additionally, it was not the heart of a six-year-old; it was more like the heart of someone who was 60."

Doctors here and at Pittsburgh began to consider a combined heart-liver transplant as Stormie's only hope. Without the double procedure, her chances for survival were slim. "I wouldn't have put any money on her surviving a year. Actually, I wouldn't have put any money on her surviving three or four months," says Firth.

"It became clearer and clearer," recalls Bilheimer, "that the way her heart was behaving she wouldn't live another year. So, it was a matter of subjecting her to an immediate risk from the transplant or just waiting until the inevitable end came."

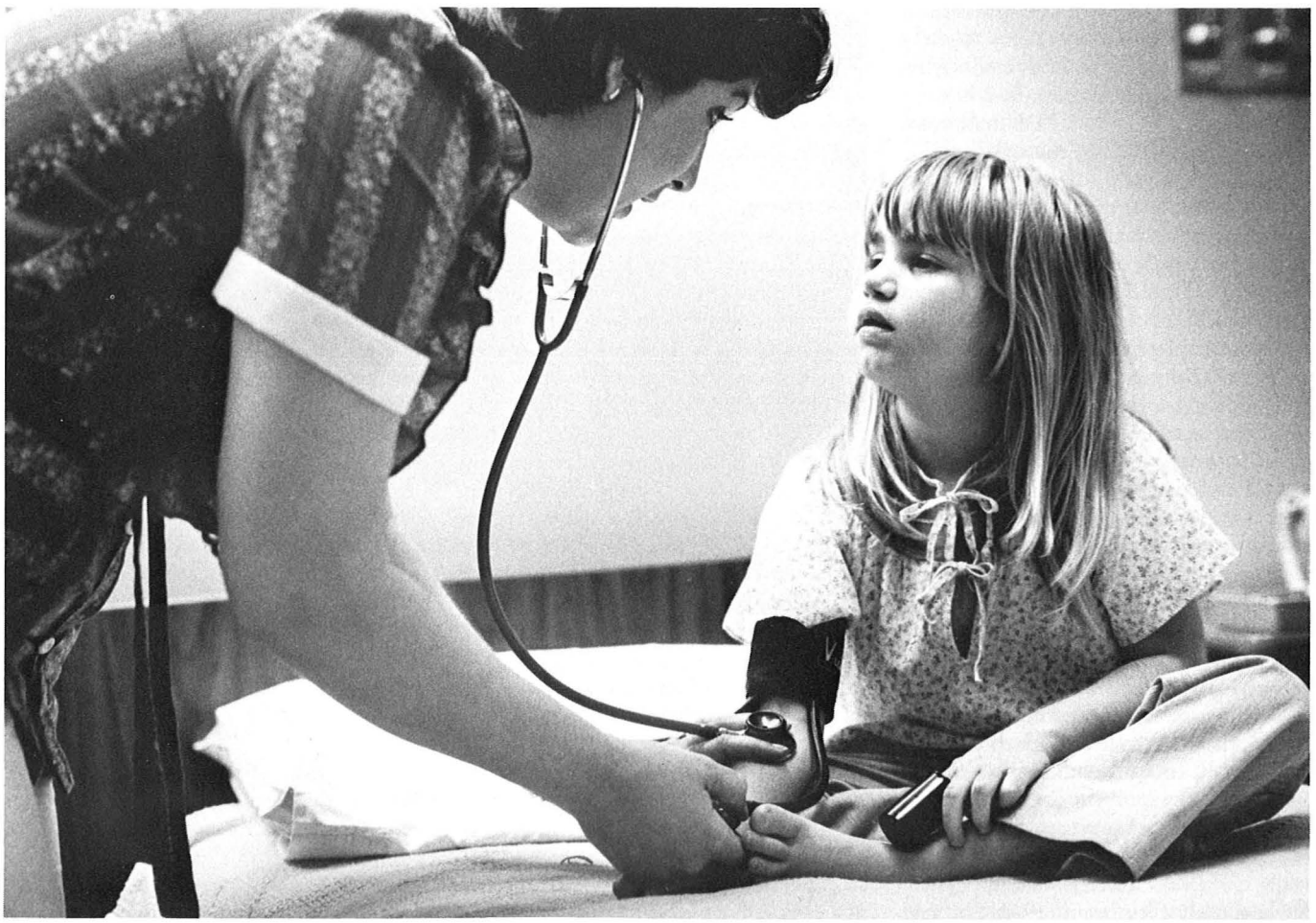
In late December, Bilheimer arranged for Stormie to be rushed to Children's Hospital of Pittsburgh for evaluation by the surgeon who pioneered liver transplantation, Dr. Thomas Starzl. Because of Stormie's critical condition, the decision was made to attempt the dual transplant. She remained in the Pittsburgh intensive care unit until transplant surgery was performed February 14, 1984.

Since the medical procedure had never been done before, doctors didn't know how Stormie would come through the grueling 18-hour surgery. But doctors in Dallas and Pittsburgh watched Stormie make a tremendous recovery. "She recovered more quickly than most people who receive one transplant, and she had two organs transplanted," recalls Bilheimer.

"She has done extraordinarily well," Firth adds. "She has had no major episodes of rejection or significant infections. And we are continuing to taper down her immunosuppressive drugs, which further lowers the risk of infection."

Studies performed since the surgery confirmed the liver's central role in the disease. Bilheimer estimates that the new liver gave Stormie 60 to 65 percent of the necessary receptors, "Which," he says, "is roughly what we anticipated from animal studies." By supplying her body with the means to control cholesterol, Stormie's new liver reduced her cholesterol level by 81 percent, according to an article which appeared December 27 in *The New England Journal of Medicine.*

"No one knew how many LDL receptors were on the human liver; we only had animal experiments to go on. We could have been dead wrong. Stormie was the first to have a liver transplant for this disease, and because of that, she was the



Doctors and nurses at the General Clinical Research Center at UTHSCD took care of Stormie prior to her double transplant at Children's Hospital at Pittsburgh. Since her return to the Dallas area, the medical staff here continues to adjust her anti-rejection medication and see that she follows a low cholesterol diet.

Being a six-year-old survivor of an historic operation brought national media coverage to both Stormie Jones and her mother Lois "Susie" Jones Browning. Throughout the pre- and post-operative period the child was followed closely by radio, television and news reporters.

first person to give us quantitative data on the numbers of receptors contained on the human liver," Bilheimer says.

"And, she's the first patient who's had a joint heart/liver transplant, which is of importance in this disease. Ideally, we would like to proceed with liver transplantation to lower the cholesterol in these patients as soon as they are discovered and before their hearts are damaged by atherosclerosis," says Bilheimer. "Unfortunately, we still lack long-term experience with liver transplantation and the use of Cyclosporin, the major anti-rejection drug. This uncertainty with the status of the liver transplant itself is holding us back from proceeding before a double transplant is required, and we try to control the cholesterol level in these patients by other means. If liver transplantation and long-term treatment with Cyclosporin appear increasingly safe, this operation is likely to be performed earlier and more often in patients like Stormie."

While Stormie's case is extreme—it is estimated that only about 30 people in the country suffer from homozygous FH—the medical community is learning much from her. "Her disease is very rare," says Dietschy, "but what we learn from Stormie about managing cholesterol may be very important for all the people who suffer from disorders of the heart and blood vessels."

Through Stormie, doctors have developed a major scheme of understanding that not only confirms preliminary findings but extends treatment options for many people. "She is teaching us a great deal," Bilheimer says. "Findings from her care represent a major step forward in our understanding of lipoprotein metabolism. And she solidifies our understanding about medications because we inferred from animal studies that medications worked primarily on the liver; and indeed the liver is a pivotal organ in regulating lipoprotein metabolism in man."

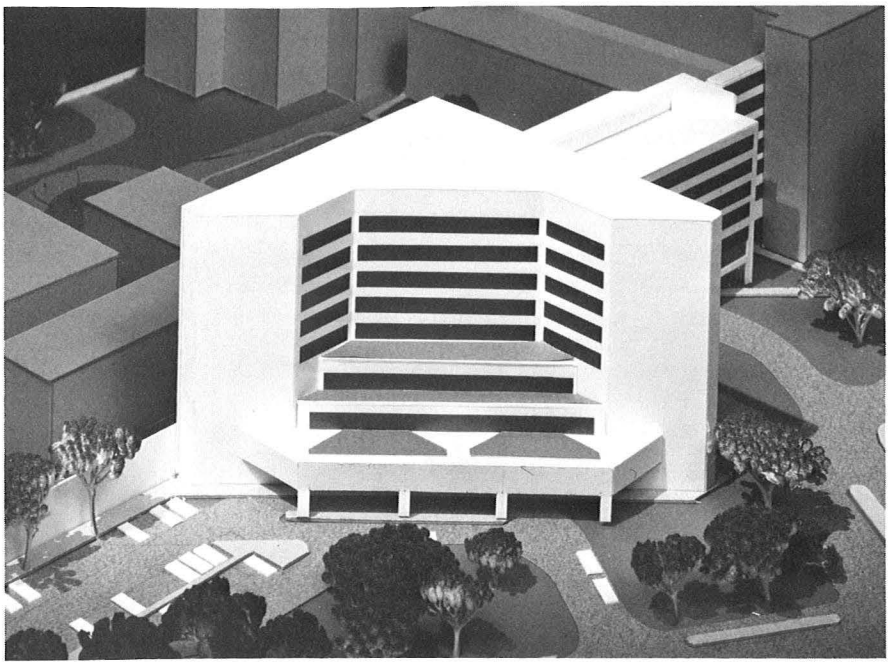
Doctors continue to see their most famous patient regularly at the Health Science Center for routine check-ups and adjustment of anti-rejection medication.

If research continues at its present rate, doctors may eventually be using gene therapy to replace expensive transplants in patients like Stormie. Already, Brown and Goldstein have isolated the human gene that orders cells to make LDL receptors. The next step is finding a way to reproduce copies of the normal LDL gene.

"Then," observes Bilheimer, "we have to figure out a way to get that gene into liver cells and get it turned on to order cells to produce the LDL receptors properly. If that can be done, we will have another and probably better way to help patients like Stormie." ■

—CAROL FLOYD

NOTE: Stormie Jones is the first patient who has had a joint heart/liver transplant, and, while she has done well, two subsequent patients did not survive the operation. This extreme operation is being reserved for those patients who have no other treatment options. One concern is the long operating time for the double transplant, and surgeons are now considering staging the operation. In the staging procedure, a donor heart would first be inserted, and, after several weeks or months of recovery time, a donor liver would be inserted.



TO HEAL AND TO TEACH HEALING

A proposed University Medical Center to adjoin Parkland Hospital would augment UTHSCD's clinical programs and provide specialized patient care

In many ways, a university hospital is the keystone of a region's health-care system. In support of the area's general-practice primary-care facilities and secondary-care specialists, university hospitals provide the region with highly specialized medical equipment and personnel—the "tertiary" care essential to the diagnosis and treatment of unusual health problems.

Beyond this, university hospitals have a strong commitment to research. Here, new methods of diagnosis and treatment can be developed in ways that are not possible in a public primary-care facility. And, most of all, university hospitals are for teaching. Every health-care professional needs to practice applying skills learned in lecture and laboratory; only in a hospital can this experience be gained.

Because they have a triple mission of research, teaching and innovative patient care, university hospitals have always been prime sites for major medical breakthroughs. Diphtheria, typhus, measles and other epidemic diseases have been conquered by work done at American university hospitals during the past century. Techniques as basic as blood transfusion, as vital as organ transplantation and as spectacular as artificial-heart implantation were developed or improved at teaching hospitals.

Developments such as these reach even the poorest and remotest countries and raise the quality of human health care around the world. But within the United States, not all regions can share the highly specialized tertiary health care that university hospitals supply, and not all medical schools can provide their students with the vital experience of studying in a teaching hospital. As recently as 1982, the Association of American Medical Colleges found that teaching hospitals "are disproportionately concentrated in the Northeast (*i.e.*, New England and Mid-Atlantic Census Regions)" and "are relatively underrepresented in the South and West."

Texas, in fact, has remarkably few teaching hospitals in proportion to its area and population. Within The University of Texas System, there is only one state-supported university hospital complex, The University of Texas Hospitals at Galveston. Other UT System medical schools, including UTHSCD, have

arrangements with independent hospitals that can provide basic clinical experience for medical students but are not primarily dedicated to teaching and research.

Dallas, in particular, is the only major American city with no university-based tertiary-care referral center. The need for a teaching hospital in the north central Texas region has been articulated several times during the past 20 years. Most regional health-care professionals have required the referral services that only such a facility can provide; medical educators recognize that it is entirely possible, given existing training facilities in the area, for medical students to complete their entire medical training without encountering the kinds of patients that dominate private practice.

This need found its most recent expression in a 1981 report by the UTHSCD Clinical Priorities and Planning Committee, which pinpointed a university hospital as the top priority for the school. But such a facility seemed destined to remain a dream. Since the construction of the Galveston Center in 1922, The University of Texas System Board of Regents and the Texas State Legislature have allocated no public funds for teaching hospitals.

But private philanthropy has always been strong in Dallas. When the Health Science Center's needs were expressed in the community in 1982, a group of Dallas leaders organized to meet the challenge. This group—University Medical Center, Inc.—was headed by Ben A. Lipshy of Zale Corporation as Chairman of the Board with Ralph B. Rogers of Texas Industries, Inc. as Vice Chairman.

> Dallas is the only major American city with no university-based tertiary-care referral center.

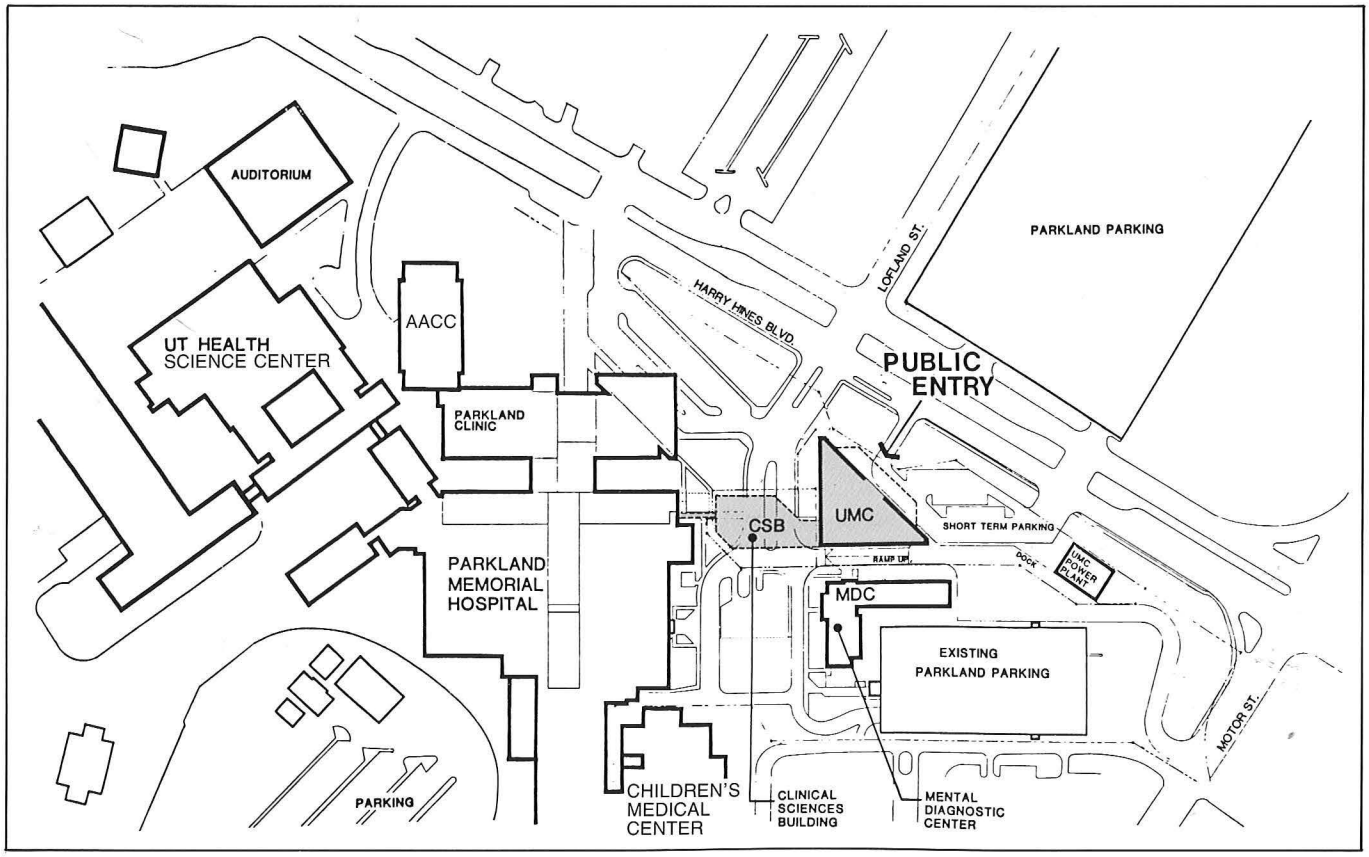
With the support of UTHSCD President Charles Sprague, the Zale Foundation funded a year-long feasibility study of the proposal. This accomplished, University Medical Center, Inc. set about to raise funds necessary for construction of a $40 million hospital.

UMC, which would own and operate the new hospital, elected Michael Romaine, Ph.D. as president of the facility.

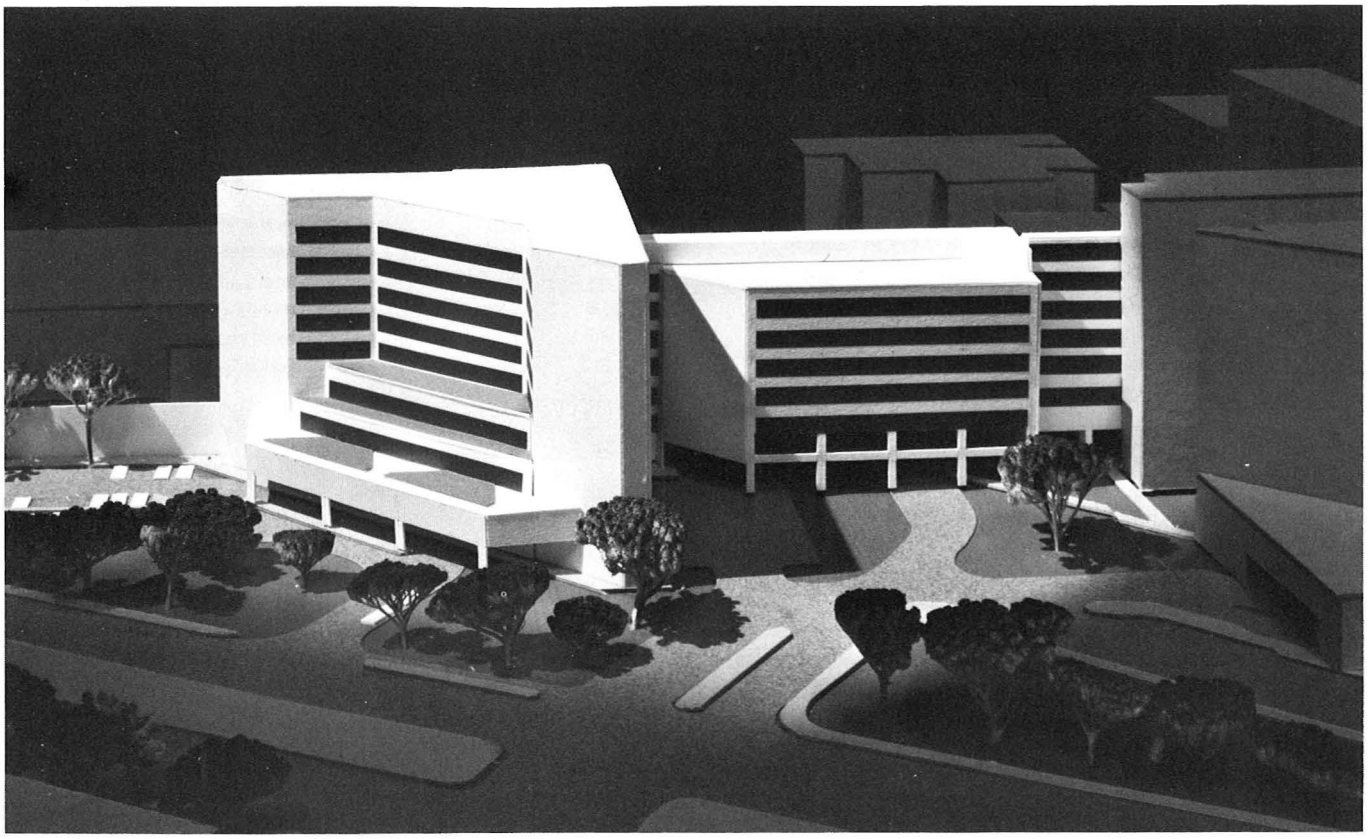
The principal idea was, said Mr. Lipshy, "to respond to a long-existing need to provide an enhanced clinical setting for the education of physicians and for performing research to enable the treatment of complex medical problems. Such a university-related facility will also provide a resource of top scientific expertise to be shared with the community."

Naturally, creation of any new hospital—even a small teaching hospital—has a major impact on a local health-care system, and the study considered carefully every aspect of the project. From the beginning, the school's close relationship with Parkland Memorial Hospital was a major factor to be considered: together, UTHSCD and Parkland have built one of the highest-ranked teaching, research and treatment complexes in the world.

"We are firmly committed," said President Sprague, "to the principle that to be feasible, a new university hospital must be beneficial to both the Health Science Center and to Parkland. While Parkland is the principal teaching facility of the medical school, its mission of service to the indigent population of Dallas County restricts its use by non-indigent and out-of-county



Site proposed for the University Medical Center



The University Medical Center and adjoining Clinical Sciences Building will serve goals of teaching and healing.

patients and the physicians who may wish to refer such patients to the medical school faculty because of its special skills and resources.

"Consequently," he added, "access and facility limitations diminish the faculty's ability to serve the community at large, and keep the faculty, students and house staff from necessary educational experiences across the full spectrum of human conditions. In addition, with a university hospital, faculty would be able to receive referrals from outside the county, a service that Parkland is prohibited from offering except on a very limited basis."

The study defined the medical scope of the proposed hospital, outlined its organization and operation, and evaluated several sites. The medical scope of the new hospital would be limited since the primary mission of the University Medical Center is to complete the educational and research programs of UTHSCD; the Center is not planned as a primary patient-care facility. The 159-bed hospital would be geared for tertiary care, accepting referrals of patients from other physicians. This referral system would bring patients from all over the region—indeed, from all over the world—to the facilities that their treatment requires, including specialized intensive care units, isolation areas, and facilities for chemotherapy and advanced radiological diagnosis. Moreover, it would form a broader base for educational and clinical research; it would bring UTHSCD medical students a crucially important opportunity to study the wide variety of diseases and conditions that they will meet in practice. This bringing together of patient and student under the supervision of the faculty sums up the mission of a university hospital: to heal and to teach healing.

In order to combine its missions of teaching and innovative patient care with its strong emphasis on research, the University Medical Center would be governed independently by University Medical Center, Inc. Close cooperation between UTHSCD and the Center will provide the Center's patients with access to the school's faculty while facilitating teaching and clinical research by the faculty. Operational services, the day-to-day management of the Center, will be provided on contract from Parkland, and certain services will be shared by the two hospitals.

Thus, the University Medical Center will stand on its own, organizationally, alongside Parkland and UTHSCD. In more concrete terms, construction of the Center is planned for a site that reflects this system of affiliations; the Center would stand just up the street from UTHSCD, east of Parkland at the corner of Lofland and Harry Hines. A new clinical sciences building—an $8 million complex including 10 stories of academic offices for faculty, laboratory and support space, seminar and conference rooms—is planned by The University of Texas to link University Medical Center with Parkland and allow the further development of training and research in burn treatment, diabetes, hypertension, developmental biology, pediatric trauma and other fields.

In recent years, UTHSCD has developed excellent new facilities for teaching and research. The school has also developed an excellent center for out-patient care, the Aston Ambulatory Care Center. But the lack of suitable in-patient clinical facilities has been felt most keenly.

"There is no more pressing need," says President Sprague, "than for adequate clinical facilities for in-patients who represent a broad spectrum of disorders. Such a facility is essential for the continued evolution of the school, a basic step in the achievement of our full potential as a comprehensive biomedical institution."■

—KEVIN ORLIN JOHNSON

SWEET MYSTERY OF LIFE

A special section on current research into the causes and treatment of diabetes

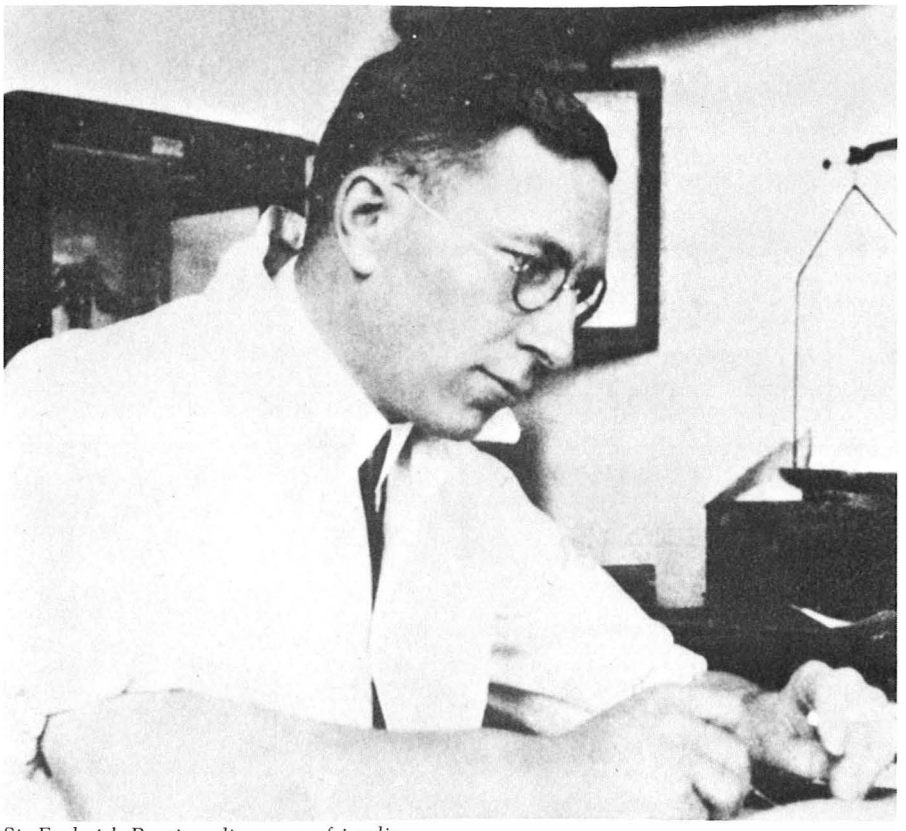
Records of diabetes are as old as written language. But for thousands of years, the chilling prognosis for the diabetic was the same: "Life is painful. Death is speedy."

No one understood the causes of diabetes, although a few researchers came tantalizingly close to this discovery. In the 17th century, for instance, the Swiss physician J.C. Brunner successfully removed the pancreas of an experimental dog and carefully catalogued the resulting insatiable thirst, passing of excessive urine and other symptoms he knew to be those of advanced human diabetes; but, with experimental methodology in its infancy, neither Brunner nor his contemporaries made the connection.

Two hundred years later, the German scientists Oskar Minkowski and Josef von Mering repeated Brunner's experiments, removing the pancreas from several laboratory dogs. By then, the physiology of diabetes was much better understood; and they, unlike Brunner, were in a position to recognize the result: "After complete removal of the organ," they wrote in 1900, "dogs become diabetic. This state...is a genuine permanent *diabetes mellitus*, which in every respect corresponds to the most severe form of this disease in man."

After this perceptual breakthrough, great strides in diabetology came quickly. Over the following 20 years, man came closer than ever before to finding the causes and treatment of the disease.

In 1901, it was noticed—again, through canine experiments—that tying off the ducts of the pancreas destroyed all of the gland's tissue except the "Islets of Langerhans"—small cell clusters named for the German medical student who had first described them in his 1869 dissertation. Most striking, the ligation failed to produce the expected diabetes in experimental animals.



Sir Frederick Banting, discoverer of insulin.

Confirmation of this discovery's implications came soon after: an histologist examining the tissues of a child who had died of diabetes noticed that the pancreatic islets had degenerated, while the rest of the pancreas appeared normal. By 1916, the English physician Sir Edward Schaefer assimilated these and other recent findings and proposed that the islets secreted a substance that metabolized sugar.

But these advances in themselves offered no treatment for the diabetic. Diabetes had been recognized as a major killer; mortality records had been compiled into detailed statistics to identify high-risk persons in Europe and America, but physicians were still powerless to treat the disease. They concentrated on relieving symptoms: aspirin was prescribed to reduce sugar excretion; opium, morphine and codeine to allay suffering. The 1911 *Encyclopaedia Britannica* still characterized

diabetes as "a very fatal form of disease."

This changed for the first time in 1921. A young Canadian, F. G. Banting, successfully prepared "isletin," an extract of the Islets of Langerhans, from canine pancreatic tissue. This preparation was injected into the bloodstream of a dog dying of diabetes.

Within two hours the dog's blood sugar level had dropped by one-half.

After the treatment proved safe in a year of further successful animal experiments, Banting and his colleague C.H. Best administered their "isletin" to Dr. Joe Gilchrist of Toronto, a severely diabetic patient.

Gilchrist improved as dramatically as the experimental dog. For the first time in history, a treatment for diabetes had prolonged human health and life. Banting and Best renamed their discovery "insulin," from the Latin *insula*, meaning "island." They soon learned that effective insulin could be extracted in ample quantities from sheep pancreases. Within a few years, animal insulin came to mean life and hope to millions of diabetics.

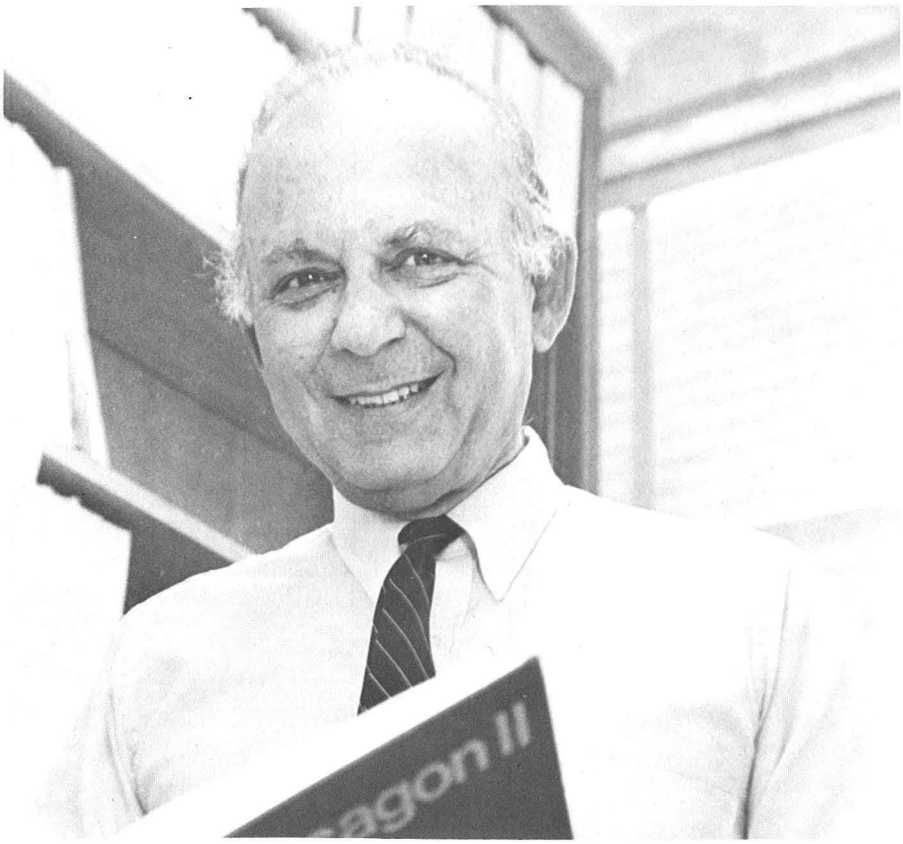
But insulin is not a cure. It can only imperfectly maintain the diabetic patient. Insulin does nothing to prevent the ravaging side effects of diabetes: blindness, heart disease, kidney failure, nerve damage and a host of related ills. The University of Texas Health Science Center at Dallas has taken a position of leadership in the quest to cure or prevent diabetes. The three articles in this section spotlight landmark developments in diabetes research at UTHSCD:

■ Investigations leading to the transplantation of the Islets of Langerhans, the insulin-producing cell clusters of the pancreas, a procedure being developed by a Dallas/St. Louis co-operative research team, hoping to make it possible to restore the diabetic's insulin-producing ability.

■ Dr. Philip Raskin's search for ways to forestall or reverse diabetic complications, which centers on new drug treatment programs and a revolutionary insulin pump.

■ Dr. Roger Unger's discovery of the role of glucagon, insulin's twin hormone, which fundamentally changed the concept of diabetes from that of a one-hormone disease to a two-hormone disease, and the new breed of diabetes researcher working UTHSCD to develop this and other advances. ■

—KEVIN ORLIN JOHNSON



. . . Dr. Roger Unger, discoverer of insulin's twin hormone, glucagon.

ΔIABETEΣ: NAME OF YE BEASTE

In 1562, the English physician William Turner wrote of "the fluxe to the chamber pot called of the beste Physicianes Diabetes, that is when a man maketh water oft and much."

The term *diabetes*, the Greek word for "siphon," had been used for the disease by the ancient Greeks. But in Turner's day it was just beginning to be revived as a useful name for a bewildering array of incurable disorders, all characterized by insatiable thirst and the habitual passing of excessive quantities of urine.

A hundred years later, a fashionable London physician, Thomas Willis, systematically tested the copious output in the time-honored manner of mediaeval uroscopy, and discovered that diabetic urine had either a sweet or an insipid taste.

Willis' work led eventually to the traditional division of diabetes into two main varieties according to the nature of this common symptom: *diabetes insipidus*, in which the discharge of urine was simply increased, and *diabetes mellitus*—"honeyed" diabetes—in which the increased output was noticeably sweet.

Today, the focus on the patient and modern knowledge of the microprocesses involved in diabetes are reflected in the terminology, which speaks of two main types of *diabetes mellitus* patient.

Type I diabetics, also called "juvenile-onset" or "insulin-dependent" diabetics, lack the insulin that normally delivers the carbohydrate-derived sugars to the body's cells.

The body of a Type II or "adult-onset" diabetic is resistant to its own insulin. Therefore the insulin is present in sufficient amounts, but it cannot gain access to the cells to provide them with the sugar they need.

A FUTURE TREATMENT?

Implantation of active Islets of Langerhans offers hope in diabetes

Insulin-dependent diabetes affects an estimated four million Americans. Because of a dysfunction in the pancreas, their bodies are unable to produce insulin, one of the hormones that regulate sugar levels in the blood. These people suffer damage to the smallest blood vessels, capillaries, which results in circulation problems; in advanced stages there may be blindness, kidney failure, nerve degeneration and heart damage. Diabetes and its complications are the third leading cause of death in this country.

Successful transplantation of insulin-producing pancreatic islet cells could provide the key to satisfying the diabetic's need for insulin.

At the threshold of human islet transplants is a Dallas/St. Louis research team who can now cure diabetes in laboratory animals. Their next goal is to cure it in humans.

Dr. Ingemar Dawidson

The pancreatic "Islets of Langerhans" are clusters of about three thousand cells each. They number about 500,000 to one million in normal persons and are scattered throughout the pancreas. Within the islets are several types of cells, including the "beta" cells that make insulin. Normally, when blood sugar becomes too high, beta cells produce insulin, which triggers the metabolization of sugar and lowers the concentration of sugar in the blood. When blood sugar gets too low, other islet cells produce glucagon, a hormone that instructs the liver to release the sugar it has stored. The secretion of insulin and glucagon from islet cells in healthy persons is exquisitely controlled, responding to the body's energy demands from minute to minute.

As few as 15 percent of the insulin-producing islets may be enough to keep a person from developing diabetes. But insulin-dependent diabetics have too few or no functioning islets; therefore, their pancreases cannot produce sufficient quantities of insulin.

"Today, pancreas transplants, either whole-organ or segmental, represent the only alternative for the diabetic," says Ingemar Dawidson, M.D., Ph.D., Assistant Professor of Surgery at UTHSCD, who heads the Dallas research group. "But attempts at pancreas transplant fail about 80 percent of the time. Technical problems account for failure in about 30 percent of the cases; it is particularly important to secure drainage of the ducts of a transplanted pancreas, but it is very difficult to avoid fistulas and leaks, and these lead to infection. Rejection accounts, probably, for the other 50 percent." With the failure rate so high, many surgeons feel that putting a patient through the transplant operation is not warranted.

Transplanting islet cells may offer many advantages over existing forms of treatment, says Dawidson. Islets are relatively easy to transplant and can be manipulated in the laboratory before implantation to prevent rejection.

Transplantation of islet cells involves injecting them into the patient's abdomen. "Right now, the spleen is the best site," explains Dawidson, "because the insulin produced by the islets can easily reach the liver. Eventually, we would like to transplant into the portal vein, which would lead the islets directly to the liver itself, but there are technical problems in the purification process that have to be overcome. Tests have shown that the intrasplenetic site triggers less reac-

tion than others and gives a better functional survival rate."

Islets don't seem to generate so strong an immune response in the body as a whole implanted pancreas. Rejection begins when the recipient's immune system recognizes markers on the surface of transplanted tissue cells; islet cells have fewer surface markers than most tissues.

The team would like eventually to help diabetic patients without putting them on life-long drug programs to suppress this immune response. While these immunosuppressant drugs reduce the risk of rejection after transplantation, they make a person vulnerable to life-threatening infection. In fact, immunosuppressants may pose a greater risk to a person's health than diabetes.

"Animal studies indicate," Dawidson says, "that immunosuppressants are necessary only at first with islet transplantation. The body becomes conditioned to the presence of the islets, and long-term drug therapy may not be needed." Dawidson explains that endocrine cells, including islets, do not grow, divide or reproduce themselves in the adult, so islets successfully implanted should continue to function for the patient's entire lifetime. Already, islets transplanted into experimental animals have remained functional for several years.

> The secretion of insulin and glucagon in healthy persons is exquisitely controlled.

Now, successful islet transplantation for humans appears to hinge upon the isolation of pure pancreatic islets in sufficient quantities. Isolation of the cells is difficult because the islets compose only about one percent of pancreatic tissue. Surrounding the islets are the tough fibers that hold the organ together and the so-called "exocrine" cells that produce enzymes released into the digestive tract through pancreatic ducts.

Early research on ways to isolate islet cells from the rest of the pancreas was begun in 1956 by Dr. Paul Lacy, Chief of Pathology at Washington University in St. Louis. Later, he was joined in development of the islet-transplant concept by surgeon Dr. David Scharp.

Lacy credits his wife, Ellen, with solving part of the purification problem in animal models. She suggested inserting a Velcro strip into a test tube containing islet cells and collagen that had been broken down by the enzyme collagenase. The freed collagen cells attached to the Velcro strip, while the islets floated freely. "We also use screens," says Dawidson, "to separate the cells by mechanical means, on the basis of size. This is an engineering problem, basically, and it will probably be solved by engineering means."

Besides their pioneering efforts in cell separation and purification, Lacy and Scharp were instrumental in testing a cell-separation technique aboard the NASA Space Shuttle Challenger (see sidebar). This technique, taking advantage of the weightless environment of space, allowed a larger and purer yield of islet cells to be harvested.

For the past three years, Dawidson has collaborated with the St. Louis scientists, working on methods of clinical and large-scale islet isolation for transplantation. Particularly, they are interested in developing ways to screen out lymphocytes, the white blood cells that can trigger a rejection response. "The 'passenger' cells that adhere to the islets are a major problem," he says, "because they contain an IA antigen that causes rejection. There are several different ways to separate them because the lymphocytes are more vulnerable than the islet cells. The cells can be cultured in an atmosphere of 95 percent oxygen, which selectively destroys the lymphocytes. Ultraviolet light is another means, or we can use monoclonal antibodies that attack the white cells. We can cryopreserve them—freeze them at very low temperatures for extended periods of time—which also kills the lymphocytes.

"The drawback to all of these separation methods is that whatever you do to kill the lymphocytes kills some of the islets, too. One alternative that we are working on here is reducing the entire pancreas to single cells and separating the types of cells in a special centrifuge. Then the cells would be re-aggregated in a purer state."

While some of the problems of harvesting enough islet cells seem to be resolved, the remaining obstacle is purification. "But," Dawidson says, "recent advances in the isolation techniques indicate that the concept of transplanting insulin-producing tissue in the diabetic patient is a goal that can be achieved." —SUSAN RUTHERFORD

ISLETS IN ORBIT

A major obstacle in the pursuit of islet-cell transplantation as a possible treatment for diabetes is the difficulty of obtaining the cells in sufficient quantity and purity for clinical testing.

The space program has offered a solution. Experiments aboard NASA's Spacelab, a self-contained research facility flown as a payload on the Space Shuttle, have proved that a weightless environment is ideal for refining raw biological materials into effective pharmaceutical products. (See article in this issue, "All Of The Above," a profile of UTHSCD's Dr. Drew Gaffney, who will supervise a series of cardiovascular experiments performed aboard the Spacelab in 1986.)

Live insulin-producing beta cells have been successfully separated from pancreatic tissue aboard the Spacelab, using a modified electrophoresis device developed by Drs. Lacy and Scharp in conjunction with the McDonnell Douglas Corporation.

Inside the device, an electrical field separates the pancreatic tissue into its constituent materials. The pure islet cells are then collected.

Purity levels significantly higher than those obtainable on earth are possible because weightless fluids can't pick up contaminants from touching their containers. And while earth-bound techniques produce only minute amounts, many hundreds of times as much material can be separated in space with relative ease.

Encouraged by the repeated success of the experimental unit during Spacelab missions in 1983 and 1984, McDonnell Douglas plans to fly a fully-automated manufacturing unit, which can produce 24 times as much as the experimental unit, on missions in 1985 and 1986.

By 1988, the company plans to put a full-scale manufacturing plant into permanent orbit. The self-contained facility could be serviced twice yearly by Space Shuttle crews delivering raw materials and collecting refined pharmaceutical products for use on earth.

A BETTER LIFE NOW

Dr. Philip Raskin studies new insulin-pump therapy and a drug to fight nerve damage in efforts to prevent the devastating complications of diabetes

Insulin has made survival possible for diabetic patients. The easy availability of animal insulin means that most diabetics no longer face certain death at an early age. But this same life-saving treatment has introduced new anxieties into their lives.

"The insulin that diabetic patients take keeps them alive, and it helps their bodies use glucose," explains Dr. Philip Raskin, UTHSCD Professor of Internal Medicine. "But insulin doesn't prevent the serious complications of diabetes, such as blindness, kidney failure, nerve damage, and poor circulation that may lead to gangrene."

Deterioration of the circulatory and nervous systems lies at the root of these and many other debilitating complications. Raskin and his associates are currently testing new modes of treatment designed to prevent this deterioration: new drugs may help prevent nerve damage, and a portable insulin pump is proving its value in preventing—or even reversing—damage to the circulatory system.

The insulin pump was designed to mimic closely the body's own blood sugar management. Instead of the sudden shot of insulin delivered by the usual maintenance program, the pump supplies a constant, measured stream of insulin into the patient's system.

Diabetes patient Jim Baxley has been on the insulin pump for four and a half years. "At first," he says, "it was an adventure in a lot of ways." Baxley, who has Type I diabetes (see sidebar), went to a police supply store and rigged a walkie-talkie box with a strap from a shoulder holster. That way, he could wear the pump hidden under his jacket.

Dr. Philip Raskin with the new insulin pump, part of a program to prevent or reverse the complications of diabetes

"It has so little metal I could go through airport security without any problem," he recalls. "But in the New Orleans airport, the security guard spotted the strap, and he came over and talked to me for about five minutes.

"I'm sure he was checking me out, but he never asked. And I was going to make him ask."

Since that time, rapid advances in pump technology have developed a pump only about as big as a pocket calculator, too small to be noticed.

The pump is central to studies looking for an answer to a major question in diabetology: will tight control of blood su-

gar levels reduce the complications of diabetes?

So far, the pump has given some encouraging answers. With a regimen of dietary management and blood glucose monitoring, the pump has indeed allowed the study's 13 patients to achieve near-normal blood sugar levels.

More strikingly, these patients showed a reversal in the width of the "capillary basement membranes" in the tiny blood vessels that nourish the body's muscles. The thickening of this basement membrane, the innermost layer of the capillary wall, is the earliest warning sign of diabetic complications.

Because the organs cannot function without an unimpeded supply of blood, progressive failure of these microscopic blood vessels precedes the failure of the eyes and kidneys, and eventually causes damage to the general nervous and circulatory systems. While the Raskin study addresses only the question of changes in the capillaries of the skeletal muscles, its implications are major.

"In the diabetic patient," Raskin says, "thickening of the basement membrane is the basic pathological lesion found in the eye and kidney. But one problem has been establishing a correlation between the clinical manifestations of eye and kidney disease and the width of the skeletal capillary membrane. This study indicates such a correlation; it shows that the trend is there.

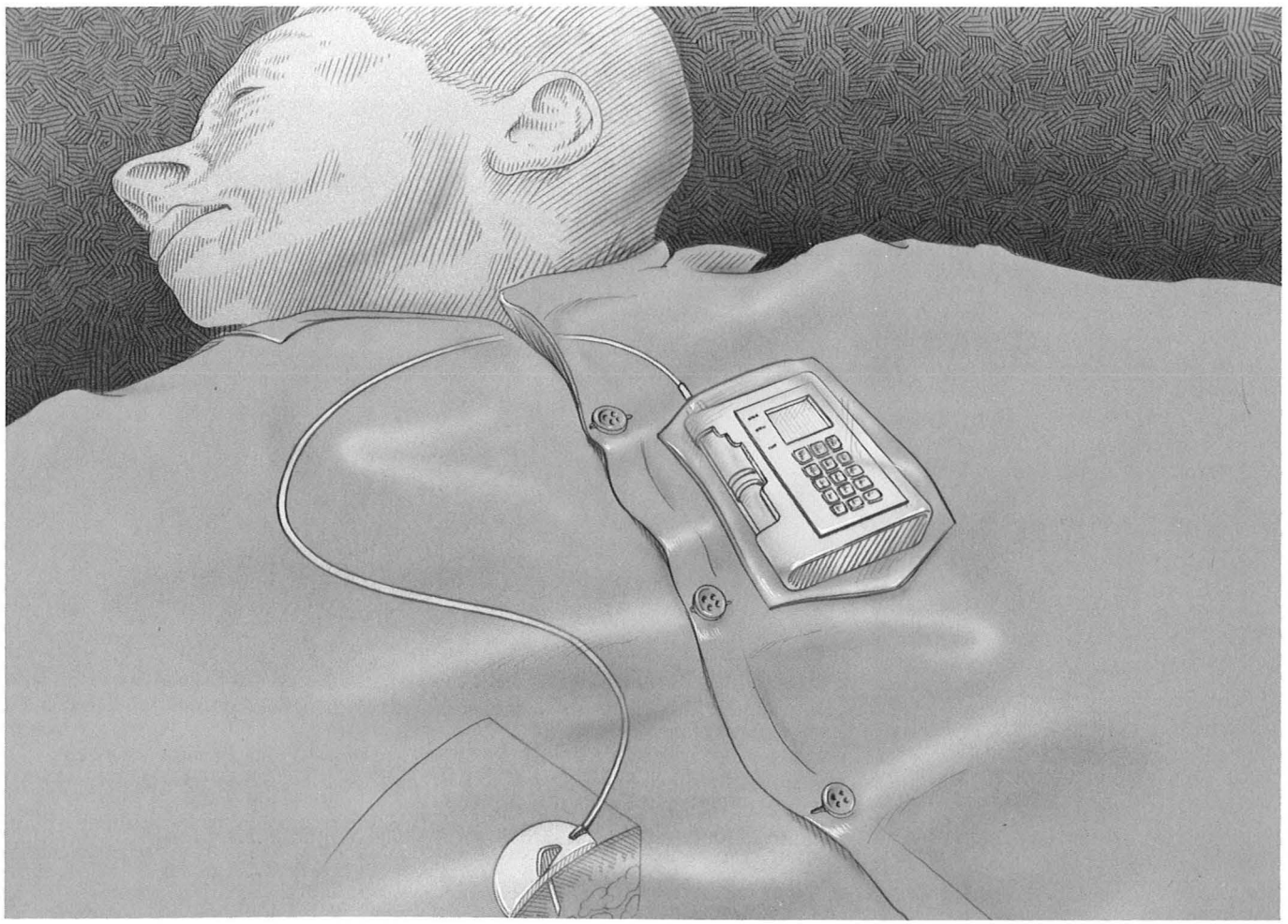
> If the insulin pump program proves efffective in preventing kidney failure, it will have an enormous impact on health care expenditure in America.

"However, what these findings mean to the kidney is not clear as yet. We hope that the same reversal could occur there, since kidney problems cause so many complications in patients. But so far other kidney studies have not shown improvement. Perhaps, however, studies of longer duration may show a parallel tendency.

"If changes in the capillaries in skeletal muscle do in fact parallel those in the capillaries in renal tissue, then meticulous control of blood glucose may be beneficial over a long period of time in preventing the microvascular complications of diabetes," says Raskin.

If the insulin pump program proves to be effective in preventing kidney failure, it would relieve an incalculable amount of suffering. But it would also have an enormous impact on health care expenditure in America.

At present, with no effective preventive treatment, over 12,000 diabetic pa-



The insulin pump at work: the programmable unit can be carried easily in a pocket; the tube carries measured doses of insulin to a tiny needle inserted under the patient's skin, mimicking the body's own distribution of insulin.

tients in the United States develop end-stage renal disease each year. Eventually, some two million diabetic Americans will develop uremia when their dysfunctional kidneys are no longer able to remove toxic impurities from their blood.

Kidney failure requires that the blood impurities be removed mechanically by dialysis. Dialysis costs $35,000 to $40,000 per year per patient: costs paid by the federal government. New cases alone account for over $500 million per year in added dialysis costs.

But the major costs of diabetes cannot be counted in dollars. The disease is the single greatest cause of acquired blindness in American adults. "Our study," says Raskin, "showed that we could at least slow the progression of diabetic eye disease. It also adds credit to the fact that there is a relationship between skeletal-muscle basement membrane changes and the clinical manifestations of eye disease."

Jim Baxley, the pump-slinging patient who so worried the airport guard, was lucky; through the team of experts at UTHSCD that monitors the patients in the pump study, incipient problems with the neovascularization in his eyes were successfully prevented.

"Your eyes grow new blood vessels," explains Baxley, "and sometimes they can be torn and cause hemorrhaging. They caught it with laser surgery.

"I don't think it's over-dramatization to say that being a part of this program saved my eyes."

Nerve damage—neuropathy—is the most pervasive complication of diabetes. It can affect every part of the body and can manifest itself in many ways. It can cause impotence in males. Nerve dysfunction in the bladder can lead to kidney infection. In the gastrointestinal tract, it can cause vomiting and severe diarrhea. Diabetic neuropathy can make it impossible for the heart to speed up in response to exercise, so that the patient can no longer tolerate exertion.

Neuropathy is also a leading cause of amputation. Nerve damage from diabetes can cause patients to lose feeling in their feet; unable to sense injuries from such things as tacks in their shoes, they may develop diabetic foot ulcers and gangrene. Too frequently, the only procedure possible is partial or complete amputation of the foot and lower leg.

The exact cause of diabetic neuropathy is not completely understood. Laboratory tests reveal one feature that seems to be common to all incidents of neuropathy: the failure of the large nerve fibers that conduct impulses quickly. As a result, there is a measurable decrease in the speed with which nerve impulses travel.

"Many patients," says Raskin, "can have this abnormal laboratory test result without having any symptoms of diabetic nerve disease. But people who have symptoms of nerve disease almost always have this slowing in nerve conduction. Clinically, they show symptoms of pain, numbness, tingling, motor changes, weakness, atrophy—all of these symptoms are possible, alone or in combination."

> Nerve damage is the most pervasive complication of diabetes, but control of a specific enzyme may allow control of the process.

This decreased conductivity seems to occur as an effect of high levels of glucose in the blood. Much of the available glucose is metabolized by the body, but some glucose is acted upon by an enzyme, aldose reductase, and converted to sorbitol. When blood glucose levels are high, sorbitol accumulates. And high sorbitol levels have toxic effects on nerve cells.

Researchers targeted aldose reductase, the enzyme that catalyzes the conversion of glucose to sorbitol, for control. The ability to regulate this enzyme would allow control of the entire process.

"You prevent the buildup of sorbitol, and that protects the nerve tissue," explains Raskin. "You can do the same thing by keeping the blood sugar level normal, but it's difficult to do that. If you could give a medication that acts one step further along in the conversion process, you wouldn't have to worry so much about the blood sugar."

One of the most promising aldose-reductase inhibitors is Sorbinil. Raskin is now conducting clinical tests of the drug. "There's a lot of enthusiasm for it," he says, "and certainly in the preliminary animal work, the drug was very successful.

"But our study is masked; half of the patients get Sorbinil, and half get placebo, so we won't know anything specific until it's over. I can say, though, that about half of the patients show an improvement.

"I just hope," he smiles, "that it's the half getting the Sorbinil." ■

—KEVIN ORLIN JOHNSON

TIME IS OF THE ESSENCE

Until a cure is found, insulin-dependent patients need to monitor their blood sugar carefully. This can be difficult enough during the day, but at night there is a significant chance that the patient may not wake up at the onset of hypoglycemia, or may wake up too late to help themselves. One new aid for many of these patients is the Sleep Sentry, a wristwatch-sized device worn during sleep. The unit detects perspiration and drops in skin temperature, two common symptoms of diabetic hypoglycemia, and sounds an audible alarm to awaken the wearer when these symptoms occur. The wearer can then take necessary action to regulate his blood sugar.

The manufacturer, Teledyne Avionics, points out that there are no definitive studies on the frequency of perspiration and skin-temperature drop among insulin-dependent subjects, but the device has been shown reliable in detecting these two symptoms and can be of use to those who exhibit these changes.

THE NEW BREED

UTHSCD's Dr. Roger Unger changed the way the world sees diabetes—now a new generation of researcher is carrying this work into the future

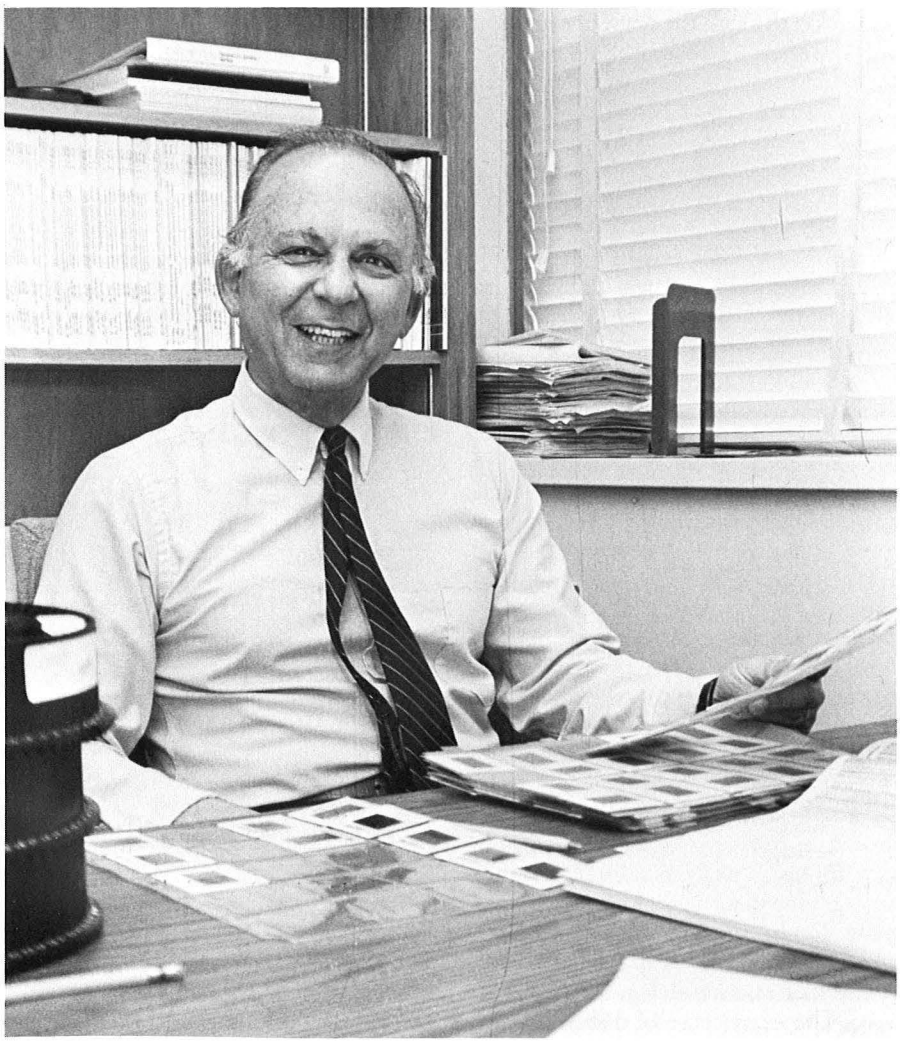
"We may be close to curing or preventing diabetes," says Dr. Roger Unger, UTHSCD Professor of Internal Medicine. With cautious optimism, he estimates that such a breakthrough is possible within the next decade. What is needed at this point, he thinks, is a "new breed" of researcher.

"In this country, the majority of researchers in diabetes are middle-aged or older, and there are too few coming behind them," says Unger. The new breed he's calling for will be trained in the "new sciences"—molecular biology and molecular genetics—in addition to medicine.

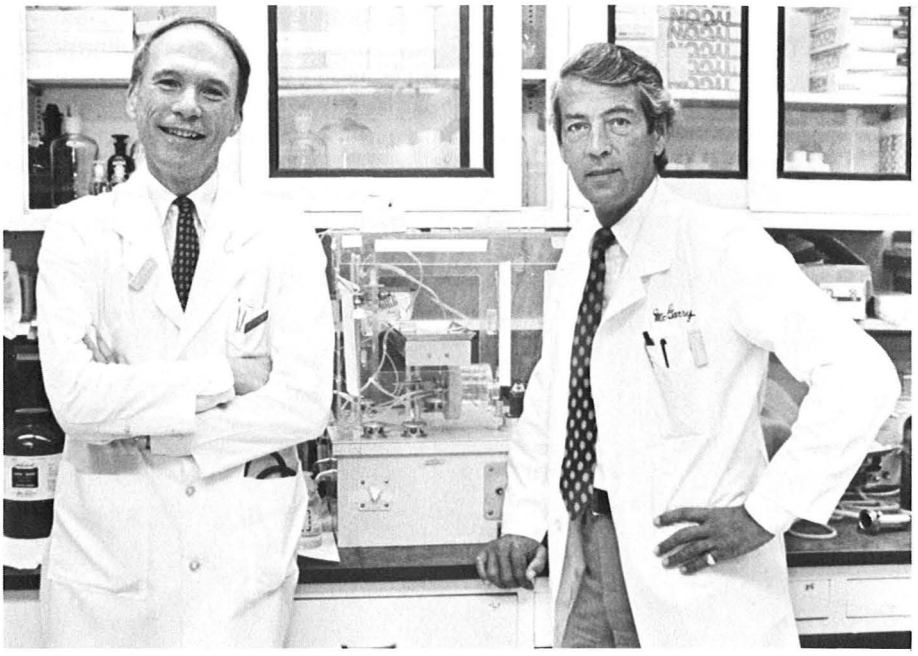
Dr. Unger doesn't say so, but his own work gave modern medicine a new definition of diabetes. It represented the sort of breakthrough that he is now calling for in prevention and treatment of the disease.

Formerly, diabetes was believed to result solely from a lack of insulin. The pancreatic hormone insulin lowers the blood sugar and promotes metabolism in most cells of the body. Insulin deficiency was known to be a cause of the elevated blood sugar that characterizes diabetes; Unger's important contribution was the discovery of another factor that had been overlooked. He investigated another pancreatic hormone, glucagon, which is found during the insulin extraction process but was usually dismissed as a contaminant. In 1959 Unger developed a radioimmunoassay—only the second such test ever developed—for glucagon. By making glucagon radioactive, he was able to track its function in the normal bloodstream and establish that it was, indeed, a hormone.

This discovery sparked a series of further experiments. Unger confirmed that the source of glucagon was the alpha cells of the pancreatic islets, much as insulin is produced by islet beta cells. He also showed that glucagon, like insulin, responded to changes in the level of sugar—glucose—in the bloodstream; it followed that glucagon was involved in glucose regulation. Most interesting, however, was the observation that glucagon and insulin were modulated in exactly opposite ways. When blood glucose was high, Unger noticed, glucagon production was suppressed but insulin release was stimulated; when glucose levels



UTHSCD's Dr. Roger Unger, discoverer of the role of glucagon



Drs. Daniel Foster and Denis McGarry, discoverers or glucagon's role in diabetic coma.

fell, insulin was decreased but glucagon increased. Unger proposed that it was the ratio between the two hormones, and not the absolute amount of either, that controlled blood sugar levels. He perceived that alpha and beta cells work in conjunction, secreting glucagon and insulin by turns to regulate blood sugar levels. This idea explained for the first time how the body was able to maintain relatively stable blood sugar levels under various circumstances: whether it had ample glucose available from a recently eaten meal, was in the midst of a fast, or had exercised strenuously.

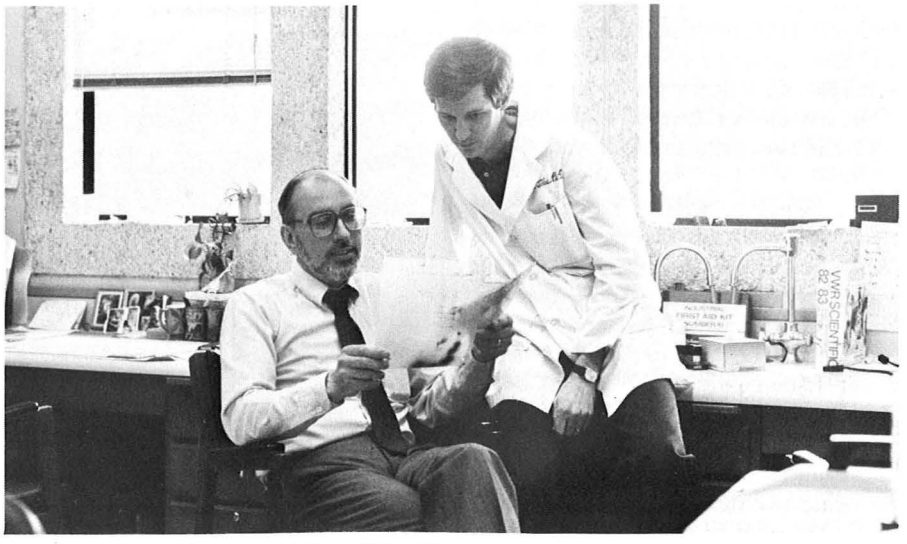
The idea of normal balance between glucagon and insulin was confirmed by further studies. Unger found diabetes to be more than just a matter of too little insulin; glucagon levels were high relative to insulin in every type of diabetes, including that experimentally induced in laboratory animals. Surprisingly, even when the pancreas was entirely removed, experimental animals showed high glucagon levels. This was shown to be due to the presence of alpha cells elsewhere in the body, particularly in the gastrointestinal tract. The alpha cells outside the pancreas stepped up their production of glucagon to compensate for the loss of those in the pancreas.

Unger then repeated the pancreatic experiments of Minkowski and Von Mering (see "Sweet Mystery of Life" earlier in this issue) with one important difference. After excising the experimental animals' pancreases, he blocked the remaining alpha cells' production of glucagon. Such animals were without insulin, but also without glucagon, and not a single animal developed diabetes. In a series of subsequent studies, Unger showed that many of the symptoms of diabetes, such as severe elevation of the blood sugar with its consequence of increased thirst and urine production, appeared only if glucagon was present; they disappeared when glucagon was suppressed.

Later, elevated glucagon levels were shown to be a key in the development of diabetic coma—ketoacidosis—by Dr. Denis McGarry, Professor of Internal Medicine and Biochemistry, and Dr. Daniel Foster, Professor of Internal Medicine. Ketoacidosis is the accumulation of very strong acids called ketone bodies in the blood because of uncontrolled diabetes. In the blood of normal persons, ketone bodies appear after a fast of around 24 hours. They are a very effective energy source for the brain; therefore, during a fast when the blood sugar is expected to fall, the body provides ketones as a backup energy source for the brain, which cannot burn fat for energy as most tissues of the body can. So during a fast, fatty acids are released from the body's fat stores and pass to the liver for conversion into ketone bodies. The liver does not carry out this conversion efficiently in the fed condition. McGarry and Foster discovered that it is glucagon that changes liver metabolism so that fatty acids can be changed into ketone bodies.

"In normal people during a fast," Foster said, "ketone concentrations in the blood never reach dangerous levels because of the balance between insulin and glucagon. If ketones approach such dangerous concentrations, insulin is released, and glucagon is lowered; the progression to ketoacidosis is prevented. In the insulin-dependent diabetic subject, where there is no insulin, this protective mechanism is missing. Therefore, if the patient does not take insulin or if the effectiveness of insulin is overcome by the stress of some other illness like pneumonia, uncontrolled production of ketone bodies occurs, and diabetic coma results."

Since the mechanisms by which a deficiency of insulin and elevation of glucagon lead to the symptoms and acute complications of diabetes are now



J. Donald Capra, M.D., and Robert Giles, Ph.D., discuss the genetics of diabetes.

well understood, current research is focusing on the possibility of preventing or curing the disease. It is this work that will require young investigators trained in the new science. Unger points out that both genetics and immunology are involved in the development of Type I diabetes, the more serious of the two major forms of diabetes. Some children—Unger estimates as many as one in two hundred—are genetically programmed to get Type I diabetes. However, this genetic predisposition is not, by itself, enough to cause the disease. The genetic program has to be activated by "something in the environment," says Unger. "Everybody thinks it's a virus, but it could be a toxic substance."

It is now thought that this environmental agent, whatever it may be, alters the insulin-producing beta cells of the pancreas so that they are perceived by the body as being foreign—the scientist would say that they have been transformed from "self" to "non-self." The immune system of the body is designed to reject or destroy all foreign invaders; for example, a kidney or other organ can be transplanted into the body only if the immune system has been paralyzed with immunosuppressant drugs. In the case of Type I diabetes, the immune system is activated to attack beta cells because the environmental agent has caused beta cells to be recognized as "non-self."

"The destruction takes place little by little," explains Unger, "over a matter of years. For a while the surviving beta cells can produce enough insulin to avoid trouble, but then symptoms come on suddenly. Some event may increase the need for insulin, and the body has no functional reserve. This could happen with a viral infection, a cold, emotional trauma, an auto accident—any kind of stress will do it." It is remarkable that the glucagon-producing alpha cells are not damaged in this process: only the beta cells are destroyed.

Research to prevent Type I diabetes will focus on two areas. First, attempts will be made to identify the virus or viruses that trigger the disease so that a vaccine might be produced. Second, attempts will be made to modulate the immune system early in the process before significant numbers of beta cells are destroyed.

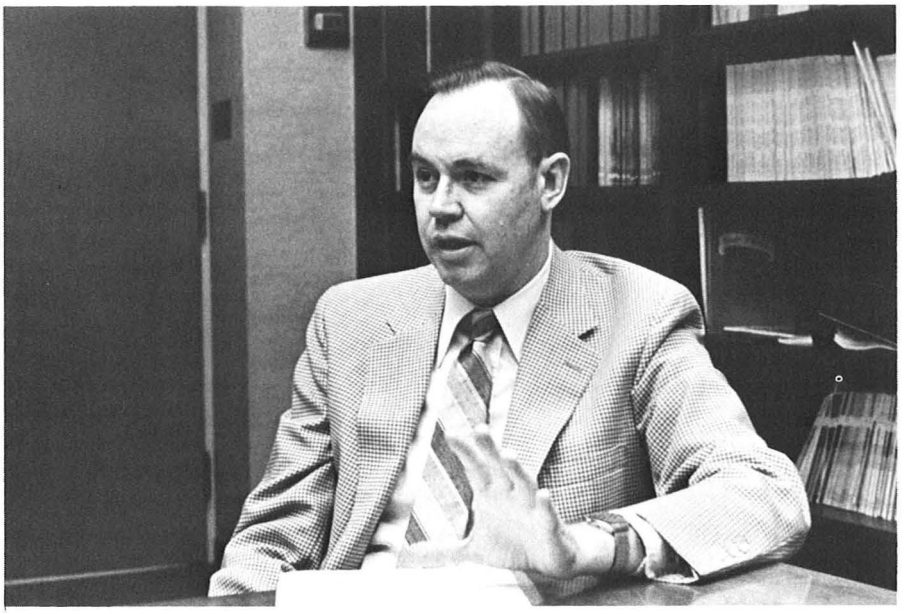
Immunological aspects of diabetes are being investigated by J. Donald Capra, M.D., Professor of Microbiology and Internal Medicine. "Many diseases," Capra notes, "are associated with a specific histocompatibility or transplantation antigen. It's the antigens that are involved in the recognition of an invading pathogen like a virus as foreign, and they trigger the body's defenses against it. Diabetes is unusual in that there are two antigens, encoded by the genes DR-3 and DR-4. A person having the DR-3 gene is more than three times as likely as the population at large to get Type I diabetes; the DR-4 gene indicates a risk factor six times greater than normal. But a heterozygous person—one who receives a DR-3 gene from one parent and a DR-4 from the other—is more than 30 times as likely to get diabetes.

"These risk factors just don't add up, and there was no obvious explanation for the great increase in risk when the two genes occurred together until Robert Giles, who's here on a post-doctoral fellowship from the Arthritis Foundation, made an observation that makes sense out of these facts."

Giles, who will be joining the UTHSCD faculty in July as Assistant Professor at the Harold C. Simmons Arthritis Center, knew that the DR genes are made up of two molecular chains, an alpha chain that never varies and a polymorphic beta chain that can be of one of several types. The type of beta chain determines the type of DR gene.

"The fact that the DR alpha chain doesn't vary means that something other than the DR molecule must be responsible for diabetes," Giles explains. "That is, a heterozygous person who is DR-3,4 should have no greater risk than a DR-4 person." Giles observed that the DQ genes found next to the DR genes are different; both the DQ-alpha and the DQ-beta chains are variable. Therefore, in a person genetically disposed to diabetes, a DQ-3 alpha chain can combine with a DQ-4 beta chain, producing a "neoantigen," a molecule unlike any found in either parent.

"This means," says Giles, "that a child can be DQ-3,4—carrying both genes—and have a high risk of diabetes although there is no sign of the disease and, conceivably, no family history of diabetes. A virus may then attack, and the neoantigen may cause an inappropriate response. Either the response to this viral infection may be too strong or too weak, or it may be absent. This may explain why a viral infection can trigger Type I diabetes."



Scott M. Grundy, M.D., Ph.D., researches the use of controlled diet to ameliorate diabetes.

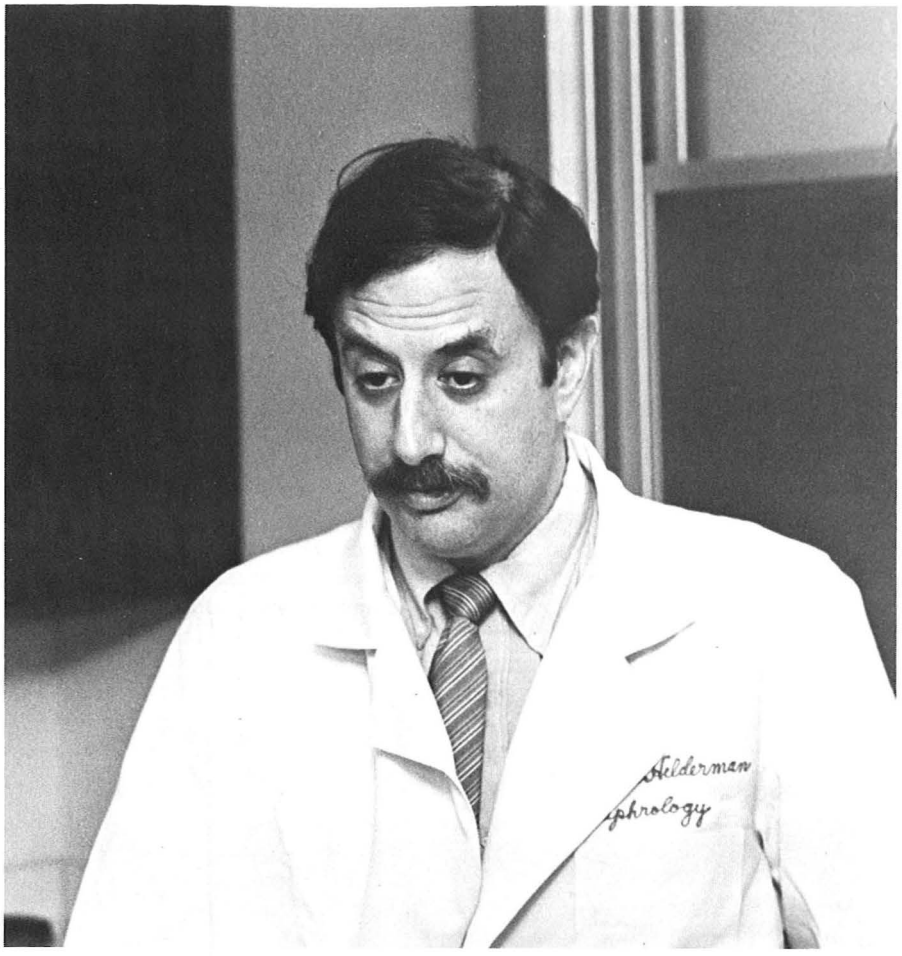
Perhaps 80% of patients with Type II diabetes would be cured if they lost enough weight.

The causes if Type II, or "insulin resistant" diabetes, remain somewhat more mysterious. In this condition, there is not an absolute deficiency

of insulin, but the body is resistant to its own insulin. Beta cells remain in the pancreas and produce insulin at maximum capacity. Despite this, they are unable to overcome the resistance, and diabetes results.

Insulin resistance is associated with obesity; most often, the victim of Type II has been obese for a number of years before the onset of symptoms. The vast majority of patients with Type II diabetes—probably about 80 percent—would be cured of their disease if they lost enough weight to return to normal size.

Dr. Scott Grundy, Professor of Internal Medicine and Biochemistry and Director of the Center for Human Nutrition at UTHSCD, and Unger have predicted that preventing high blood sugar in Type II patients may prevent destruction of insulin-secreting pancreatic cells. Grundy is testing two different diets to determine which is better for curtailing high blood sugar. One of the diets is a high-carbohydrate, low-fat diet currently recommended by the American Diabetes Association for diabetic patients. The other, a diet high in fat and low in carbohydrates, contains mainly monounsaturated fats, which Grundy recently showed to be effective in lowering cholesterol levels. In preliminary studies, the diet high in monounsaturated fats produced lower levels of blood sugar as well as a favorable response in the blood lipids. If these results can be confirmed, they may lead to a change in the recommended diets for diabetic patients.



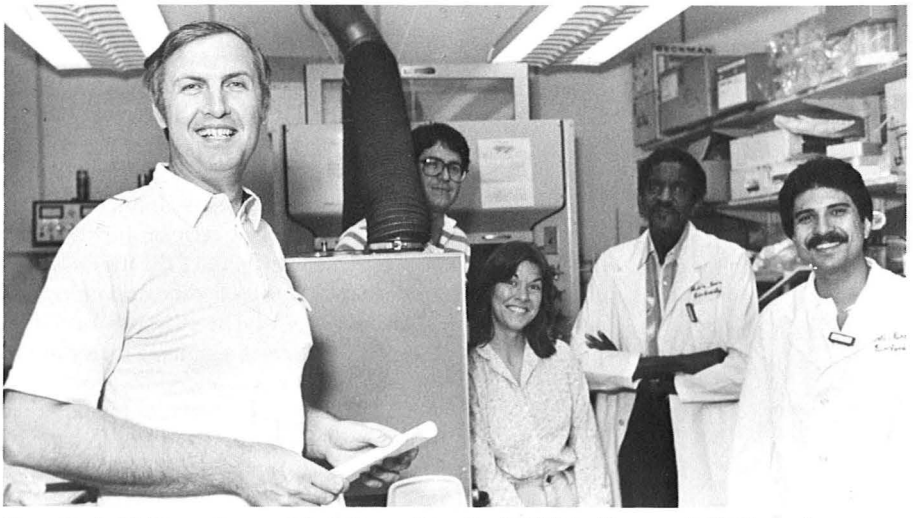
Dr. Harold Helderman explains the way insulin instructs the immune system

The body's reduced response to its own insulin in Type II diabetes may be at least partially because of decreased numbers of insulin receptors on the cells' surfaces. Brent Reed, Ph.D., Assistant Professor of Biochemistry, is studying this possibility. The receptors are generated inside the cell and move to the cell surface to lock onto an insulin molecule. The insulin-receptor unit moves to a special location on the cell surface and reenters the cell.

Then the insulin is separated from the receptor, and the receptor is sent back to the surface.

"Basically," Reed explains, "we're doing research on a molecular level to find out what controls the number of receptors that are on the cell's surface. The manner in which a cell regulates these processes—the rates of receptor synthesis, receptor internalization, receptor recycling and degradation—could obviously affect the number of total cellular receptors and ultimately the extent to which receptors reside on the cell surface. The level of cell-surface receptor established by the interplay of these processes, in turn, can control the cell's sensitivity to insulin.

"We feel now that the number of receptors inside the cell controls the rate of receptor degradation in some cell types. One thing you see in the tissue samples of a high-insulin-level diabetic patient is a suppressed number of surface receptors and total receptors, in many cases. And the cells are not very responsive to insulin. Now, it isn't just because they have



Brent Reed, Ph.D., and crew: Mark Fraga, Kim Reed, Melvin Dews and Ali Bagheri

lowered numbers of receptors; there are other factors, possibly more important, that affect this too. But a suppressed receptor level does contribute.

"So, in connection with diabetes, our research is aimed at trying to understand more about what's going on in terms of controlling these processes. But we are also interested on a basic level in what controls this receptor. The more we understand about this receptor, and about its synthesis and metabolism, the better we understand the whole process."

In addition to its metabolic role, the insulin-receptor unit plays an important part in regulating other cellular functions. "Our research with the insulin receptor," says Dr. Harold Helderman, Associate Professor of Internal Medicine, "has gone on for about 10 years. We have shown that the lymphocyte has such receptors, at certain unique times. The lymphocyte, of course, is the cell that helps the body fight infection, and it's also the cell that makes the body reject transplants. We have shown, some years ago, that it obtains an insulin receptor that it didn't have before when it is stimulated by an antigen, as happens in infection.

"When the receptor appears on the surface of a lymphocyte, the provision of insulin to the receptor instructs the cell to function better as an immune cell. That much we knew from animal studies, and we knew it was true for normal humans. The question later came up as to whether the various kinds of carbohydrate metabolic disorders, like Type I and Type II diabetes and obesity, could alter the way the receptor appeared on the cell.

"Working in collaboration with Philip Raskin, we demonstrated that, in fact, they do. This shows that the type of disease you have could regulate differently the number and function of these receptors, and now we are asking whether there is an immunological correlate to the regulation of the receptor in the function of immune cells.

"There are three major clinical implications of this basic research. One has to do with transplant biology; we are now looking at a number of kinds of transplant to alter the life of the patient who already has diabetes—a kidney transplant, for instance, for what used to be the most common cause of death in these patients, or a pancreas or islet-cell transplant to repair the glucose-regulatory defect. There are some suggestions from animal work that the diabetic animal is less susceptible to transplant rejection. Regulation of the lymphocyte receptor may give us a way to manipulate the rejection process.

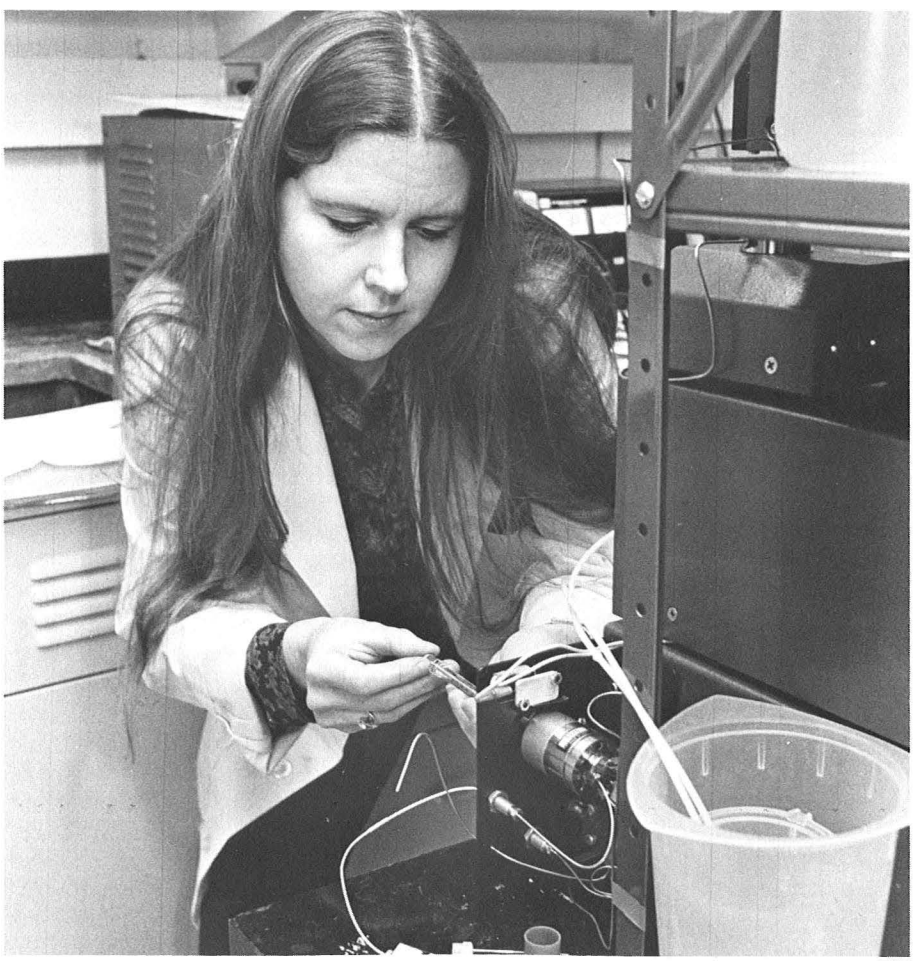
"The second clinical benefit may be that working on the lymphocyte receptor may be a way to alter the known susceptibility of the diabetic patient to infection. A third implication may be less clinical, but we know that the appearance of the insulin receptor during cell activation by an antigen occurs at a certain precise moment in the cell cycle. Several labs have studied the appearance of this and other cell-activation molecules, which advanced information about what lymphocyte activation is all about. This has shown us a new road to modulation of the cell cycle using drugs like Cyclosporin A, which interrupts the cell cycle at a unique point after some of the activator molecules appear but before certain others can appear. There may be a host of drugs that allow us to take advantage of what we have learned about the insulin receptors on lymphocytes, as well as about other activation molecules on cells' surfaces."

"We know that insulin binds to cell-surface receptors," says Melanie Cobb, Ph.D., Assistant Professor of Pharmacology. "But recently it has been discovered that insulin receptors have an enzymatic activity that is triggered when the receptor binds to insulin. We assume that the enzymatic activity is involved in control of cell growth and in cell differentiation, because similar activities that are regulated by other hormones and viruses have been implicated in control of these processes."

Cobb's goal is to establish a "cell-free" system to investigate these processes of growth and differentiation. "The evidence indicating a relationship between the enzymatic activity of the insulin receptor and control of differentiation and growth is large," she says. "I'm trying to find out if that enzyme activity is important to what insulin does, and if so, how.

"The greatest promise for potential treatment," Cobb says, "is to figure out how insulin works and—maybe—intervene."■

—KEVIN ORLIN JOHNSON



Melanie Cobb, Ph.D., studys insulin's role in cell growth and differentiation

CHILDREN OF HOPE

Children's Medical Center offers help for youngsters suffering from cancer, hemophilia and sickle-cell anemia

Nine-year-old Brett Brown is off to a football game, cleats in hand and a big smile on his face.

Travis Roop, four years old, is listening to his sister tell a story about a family camping trip in the wilderness of Colorado—and dreaming about the first time his family will let him go, too.

Teenagers George and Carla Sanders are getting ready for another day at school.

To all outward appearances, these are ordinary children following day-by-day routines. But there is one big difference in their lives: all have serious blood diseases or tumors. All are patients at the Hematology/Oncology Program conducted jointly by The University of Texas Health Science Center at Dallas and Children's Medical Center. And all are working to lead normal, happy lives.

Dr. George Buchanan, pediatric hematologist/oncologist, is director of the program. An Assistant Professor of Pediatrics at UTHSCD, he has been involved in patient care and research in these areas for over 10 years.

Patients seeing Buchanan and his associates range generally from infants to teenagers and even include a few young adults. They may have such disorders as hemophilia, sickle-cell anemia, leukemia or solid-tumor cancers. In addition, he says, "We see a whole bunch of 'rare birds'—that is, patients with extreme, unusual anemias, from whom we learn a lot that's important about pathophysiology."

Children from all over Texas and the Southwest are referred to Children's Medical Center for treatment; in turn the research done here benefits children throughout the region and, indeed, throughout the country. The Hematology/Oncology Program at Children's is part of the Pediatric Oncology Group, an association of the 35 top cancer treatment institutions in the United States.

At Children's, the focus is always on the child. The oncology team, for instance, meets several times a week to consider cases on an individual basis. Buchanan believes in a multidisciplinary approach combining the specific chemotherapy, surgery, drugs and radiation appropriate to the type of disease. But besides fighting the illness, Buchanan and his team also fight the negative effects that the disease has on the lives of the patients.

The physician is excited about the progress that has been made over the last few years in treating children's blood disorders and cancer. Buchanan points out

that, as research brings more answers, health-care teams are able to provide more successful treatments. And the UTHSCD Hematology/Oncology Program has done more than make remarkable progress against pediatric cancer, hemophilia and sickle-cell anemia.

It has brought back hope.

Brett Brown (not his real name) was only two when his leukemia was diagnosed at Children's. He was a very sick little boy who suddenly refused to walk because of the pain in his legs and who kept wiping at the continuous trickle of blood coming from his nose. Brett's parents took him to his pediatrician but were unprepared for the shock they received when the doctor undressed him for an examination. On the baby's back were three large, dark splotches.

"How long has he had these bruises?" he asked.

Her voice shaking, Leslie Brown replied, "They weren't there when we left home."

The spontaneous bruises, the toddler's refusal to walk, his constant nosebleed and his elevated white-blood cell count added up to major danger signals. Brett's pediatrician sent him immediately to Children's Medical Center for a bone-marrow test.

"It was frightening," says Mike Brown, Brett's father. "I think Leslie had an idea what might be wrong, but I didn't want to believe it might be leukemia."

Because leukemia has its own special name, most people do not realize that the disease is a form of cancer. The name is descriptive of the disease, in which the growth and proliferation of white blood cells—leukocytes—are distorted. About 80 percent of the leukemia patients have acute lymphoblastic leukemia (ALL), a disorder of the white blood cells, while the remaining 20 percent suffer from acute myeloblastic leukemia (AML), in which the blood-producing tissues of the bone marrow are involved.

While the mortality rate for adults with these and other kinds of disseminated cancer—cancer spread throughout the body—is sobering, the outlook for children is much more hopeful, especially because of advances in pediatric treatment made over the past 10 to 15 years. Currently, says Buchanan, nearly 60 percent of pediatric cancer patients are cured; that is, their cancers are in remission for five years or more.

Most of the cancers seen in children, in fact, are not seen in adults. And although children do not have most of the common adult cancers, such as lung, breast, skin and esophagus cancers, there are about 10 different cancers that occur in children. Forty percent of pediatric cancer cases are leukemia-related, like Brett's. Sixty percent involve solid tumors; tumors of the brain are the most common type. In fact, recently the Oncology Program at Children's has started a monthly Brain Tumor Clinic in cooperation with the neurology, radiology and neurosurgery areas.

The outlook for children is hopeful, especially because of advances in treatment made over the past 10 years.

Lymphomas (abnormal growth of lymphoid tissue), which include Hodgkin's disease, are also often seen at Children's Medical Center. Children are also frequent patients for Wilms' tumor, which occurs in the kidney, and neuroblastoma, a tumor of the nerve tissue in the chest or abdomen.

A major aim of research at Children's is more effective treatment plans for children like Brett. "For years," says Buchanan, "we have been treating cancers very intensively, that is, with long-term doses of chemotherapy and/or radiation. The cost to the patient was also intensive; extreme nausea, hair loss and the danger of potential future malignancies are some of the prices they have to pay. Because of these painful and unpleasant side effects, some well-meaning parents are hesitant to put their children through a cancer-treatment program. They usually know someone whose child went through agony during this period and then died 'anyway.' "

However, Buchanan points out, they should think of the numbers of children who are being saved today because of the progress that has been made in recent years. And, of course, no matter how sick the treatment makes the patient, most of the side effects are temporary.

Currently, the investigators are studying whether less treatment can cut side effects without compromising medical care. "For example," says Buchanan, "it has now been recognized that limited-stage lymphoma may have a good prognosis even without radiation therapy. We'd also like to find a less harsh treatment regimen for Wilms' tumor."

The philosophy of the medical team is to treat the child as an out-patient whenever possible. Unless surgery is involved, the initial hospital stay is from one to two weeks. Then the patient usually comes back for testing and medications once a week for about two or two and a half years. If the child does well on treatment and is lucky, another hospitalization might not be required. Re-hospitalization, however, is a common occurrence because drugs and radiation suppress the child's immune system, thereby allowing other infections a chance to take over.

Nor do all stories have happy endings. When a young patient is terminal, the team believes that the best place for the child to be is usually at home. "As long as the pain can be managed and the child is comfortable, that's what the child and the family usually prefer, " says Buchanan.

Brett Brown was lucky. He began treatment at Children's immediately upon diagnosis. Today, seven years later, his leukemia remains in remission.

Four-year-old Travis Roop is lucky to be living in a city where he can receive comprehensive care for his hemophilia. So far, Travis hasn't had so many bleeding incidents that his family would need training for home infusions, a major way to keep children with hemophilia out of the hospital. But Gloria Roop, Travis' mother, fears that the "bleeds" could be-

come more of a problem as Travis grows older. At that time, both parents will take lessons at the Children's Medical Center Hemophilia Clinic on how to properly infuse Travis at home. Then, she says, the family will feel freer to go camping together in the Colorado wilderness. When she and her husband can render emergency aid to Travis, they won't have to worry about backpacking to civilization before he could receive help.

Buchanan and his team are also concerned with treating children suffering from hemophilia—the genetic, life-long chronic condition that prevents blood from clotting normally. Buchanan explains that many people think that hemophiliacs are people who can bleed to death from any little cut, but this is not the case. The hemophiliac doesn't bleed at a greater or faster rate than the normal person. However, because his blood lacks the plasma proteins needed to form the clots that normally plug torn blood vessels, the hemophiliac will continue to bleed for prolonged periods of time.

It takes only a few hours of spontaneous or injury-induced bleeding in a hemophiliac to cause severe blood loss. Internal bleeding from slight injuries is not a problem for one whose blood clots readily, but hemophiliac bleeding into the joints, particularly the elbows, ankles and knees, can lead to a pain-ridden existence or even to permanent crippling.

These internal bleeds may cause a painful type of arthritis, aggravated by the weakening of muscles around the joints. Sometimes the resultant nerve pressure causes numbness and temporary paralysis around the joint. Severe problems may necessitate joint replacement or other types of extensive rehabilitative surgery—surgery that the patient's lack of a clotting ability only complicates.

But modern methods of treatment have certainly led to lengthening the lifespan of hemophiliac patients. Most forms of hemophilia are usually treated with blood products from normal donors or with plasma extracts. These products are given by infusion into the patient's bloodstream, either at the doctor's office or at home if family members are properly trained.

In addition to teaching appropriate treatment for hemophiliac patients, the comprehensive care programs offered at Children's are making a distinctive contribution to the quality of patient life. Physical therapists are on hand to help head off possible crippling, and an orthopedic surgeon routinely monitors patients for permanent damage. In addition, there are the services of nurse/educators and of dentists specially trained to handle oral surgery for hemophiliacs.

Another important role is played by the social worker. Serious hemophilia is often responsible for keeping young patients out of school for long periods of time; there may be learning problems or a tendency for the hemophiliac to drop out. Apart from the feeling of futility that any hemophiliac patient can develop, the young male hemophiliac, restricted from potentially dangerous school athletics, may develop uncertainties about his masculinity. Buchanan thinks that this kind of problem is both detrimental and unnecessary, and the team's philosophy is directed at achieving a full life for each child. One clinic patient even skis and goes scuba diving, and others play soccer or baseball.

Modern methods of treatment have led to lengthening the lifespan of hemophiliac patients.

Nearly all victims of hemophilia, in fact, are male. The disorder is transmitted on a gene of the X chromosome. Since women have two X chromosomes, at least one of her chromosomes will probably not carry the defective hemophilia gene. However, there is a 50/50 chance that a mother who carries the defective gene in one of her X chromosomes will pass it on to her sons. Since males carry one Y chromosome and only one X chromosome, transmission of a hemophilia-carrying X chromosome from a carrier mother to a male offspring gives him hemophilia.

Similarly, there is a 50/50 chance that a carrier mother's daughters may be carriers. The appearance of this pattern of transmission among the descendants of Queen Victoria, most notably in the only son of Czar Nicholas II of Russia, has given hemophilia its nickname, "the royal disease."

Tests for carriers, according to Buchanan, are unfortuantely only about 80 percent accurate. When there is no record of hemophilia in the family of a newly-diagnosed case, it may be because of incomplete family history, or, more rarely, the occurrence of hemophilia may represent a mutation.

Although these facts sound fairly grim, today more than ever before there is hope for the hemophilia patient. Buchanan and members of the hemophilia team at Children's are working with Parkland Memorial Hospital for blood-product support and care of adults in cooperation with the Hematology/Oncology Division of the UTHSCD Department of Internal Medicine. They are also involved in cooperative programs, such as summer camp, with the Texas Central Chapter of the National Hemophilia Foundation to combat the disease and its effects.

The only complaints that George and Carla Sanders make about being sickle-cell victims is that they're always going to the doctor. And when they're there, they always get "stuck."

George and Carla are happy, normal students. Their sister Rhonda, also a teenager, is not so lucky: she is confined to a nursing home, a victim of the same disease.

Sickle-cell anemia is an inherited chronic blood disorder that primarily affects people of African descent. About one in 12 are carriers of the sickle-cell trait and can transmit the disease to their children.

Normal red blood cells, Buchanan points out, are round, almost hollow, and doughnut-shaped. In persons whose genetic code is garbled by the sickle-cell trait, these cells have a tendency to twist into the crescent shape of a sickle. These sick-

led cells cannot function as normal red blood cells do, and therefore the patient shows the symptoms of anemia. More dangerously, these cells stick together and block the normal flow of blood in the small veins. These blockages result in pain in the abdomen, chest, arms and legs—the so-called "sickle-cell crisis"—or in extensive damage to the internal organs that are deprived of normal blood flow.

There is no cure for sickle-cell anemia, but treatment is possible. Under Buchanan's direction, the Sickle-Cell Clinic at Children's has grown to be one of the 10 largest treatment programs in the United States. Nearly every child in the North Texas region who is afflicted with sickle-cell anemia is treated at the Clinic. Because the Clinic sees so many patients, and because it can take advantage of the UTHSCD faculty's expertise, it is the ideal place for research into the disease.

No one knows why patients like George and Carla are able to control the manifestation of their disease while victims like their sister Rhonda are devastated by them. "However," says Buchanan, "each year brings new gains in treating the sickle-cell patient. And each research advance brings us closer to solving these complex problems." Diagnosis and prevention of infection, as well as control of pain and "iron overload," are current topics of research at the Sickle-Cell Clinic.

Iron overload is a problem faced by the sickle-cell patient who suffers strokes from the blockage caused by clumps of defective cells. Iron from transfused blood is retained by the patient's body and eventually builds up to toxic levels. At present, some patients are being given medicine to release the retained iron and expel it. The medication is administered through a small infusion pump, not unlike the insulin pumps now used in the treatment of diabetes (see "A Better Life Now" in this issue).

The pain of sickle-cell anemia is "severe, acute and intermittent," according to Buchanan, but often the young patient is not given sufficient drugs for pain control, either because of the risk of "hooking" the patient or because the doctor does not realize the extent of the pain. Buchanan therefore spends a great deal of his time researching the problem and educating other doctors about the need for adequate intravenous infusions of pain relievers. Addiction, he points out, is not usually a problem in the young patients seen at the Clinic because they do not have the "addictive" personalities and other problems that can be associated with adult patients and because they need heavy medications only occasionally, during crisis periods.

Although sickle-cell patients are susceptible to infection, their higher-than-normal white-blood-cell count makes the usual diagnostic methods useless. Researchers on the Buchanan team are currently looking for other indicators of infections in their patients. Infections are particularly dangerous to sickle-cell patients; sepsis, or blood poisoning, kills 20 percent of untreated infants with sickle-cell anemia. Buchanan and his team have demonstrated the effectiveness of pediatric vaccines against germs that cause the most blood poisoning and pneumonia, and in addition they have been involved in continuing research on the prophylactic use of penicillin. This method of combating infection has been used successfully for some time, and now researchers are trying to determine just how long the preventive doses should be given.

Buchanan's "right arms" in working with patients are sickle-cell team members Dr. Robert Sprinkle, Assistant Professor of Pediatrics and Family Practice, and Susan Smith, Pediatric Nurse Practitioner. Smith's role includes evaluating sick patients with the house staff, evaluating them at interval check-ups and providing education for parents of sickle-cell patients.

"Too many people think of patient education as simply giving the patients information to satisfy their curiosity. What we really need to give them is information to help them prevent fatal complications and to handle other problems," says Smith. The nurse/educator has produced educational materials on the disease for both the area program and for the state of Texas. Smith is also a member of the state advisory commission on newborn screening for the disease.

Buchanan believes that newborn screening for the disease—a procedure common in many states for a number of years but new in Texas—will do much to reduce early morbidity and mortality from sickle-cell. The sooner parents know that their child has sickle-cell, the sooner they can enroll him in the program for medical monitoring. In addition, they can begin to receive parent education about the disease and its symptoms, and learn when to seek medical help. ■

—ANN HARRELL

The Sickle-Cell Clinic at Children's has grown to be one of the 10 largest treatment programs in the United States.

A GIFT TO THE FUTURE

The new Cecil H. and Ida Green Biomedical Research Building will help consolidate and coordinate campus growth at UTHSCD

When the newest building on campus opens, everyone at The University of Texas Health Science Center at Dallas will join in thanking Cecil H. and Ida Green for their generosity. Again. And well they should, because the Cecil H. and Ida Green Biomedical Research Building will adjoin the Green Science Building and house, among other facilities, the Green Center for Reproductive Biology Sciences.

The Greens, in fact, are among a dozen or more Texas philanthropists who believe that a gift to medical research is a gift of better life for this and future generations. A roster of the research centers that will move into the new building indicates some others who have shared their point of view: the Harry S. Moss Heart Center, the Eugene McDermott Center for Human Growth and Development, the Cecil H. and Ida Green Center for Reproductive Biology Sciences, the Center for Human Nutrition, the Cancer Center and the Harold C. Simmons Arthritis Research Center. The new Howard Hughes Institute will be located in the Green Biomedical Research Building, as will laboratories and offices for the new Robert A. Welch Chair in Chemistry. In addition, the Animal Resources Center will make a major expansion into the Green Biomedical Research Building.

Cecil H. and Ida Green

However, the building represents more than much-needed extra space. It represents a purposeful coming together of researchers in different fields who will share a centrally located core of state-of-the-art biotechnical equipment. With these new core facilities, procedures in electron microscopy, DNA sequencing and sophisticated computer graphics will be available to some researchers for the first time—and available to everyone more readily. Dr. Kern Wildenthal, Dean of Southwestern Medical School, notes, "This equipment may well be of use to any department on campus. There are an infinite number of projects that will need it." Such core facilities, says Dean Wildenthal, are becoming one of the standard tools of biomedical science.

Bordering Butler Street on its north side and connected to the Green Science Building on the east, the Cecil H. and Ida Green Biomedical Research Building has been designed by Harper, Kemp, Clutts and Parker Architecture/Planning of Dallas. The architects combined aesthetic and practical considations into a structure of great flexibility.

The design is dominated by strongly articulated verticals spaced at regular intervals around the exterior. These elements are an integral part of the building's function: they contain multiple vertical rises of utilities. Organizing the utilities in this way, and providing a walk-in utility chase in the center of the building, mean that either a laboratory or an office can be located at any point in the building, and future remodeling will be simplified. Visually, too, the building's exterior of precast concrete panels blends with the main campus quadrangle. Between the square vertical projections, horizontal bronzed glass windows echo the design of the McDermott Administration Building.

The dramatic focal point of the building's interior will be a two-level glass-capped commons area with a skybridge, joining the fourth and fifth levels to the Green Science Building. On the fourth level, a 45-foot wide student lounge will

be decorated in a warm-toned color scheme against a background of precast concrete walls, glass panels and tile floors, with carpeted seating areas. At the fifth level the walls become all glass, and a pedestrian bridge suspended above the lounge joins the two buildings. The entire commons area is capped with a glass-and-metal greenhouse roof, flooding the lounge and skybridge with natural light.

The Cecil H. and Ida Green Biomedical Research Building contains nearly a quarter-million square feet on 10 levels. The first level is a half-basement containing mechanical support service equipment for the floors above; levels two through seven are being finished to accommodate the special needs of the research centers and support services; levels eight and nine will be reserved as shells for future growth; and the tenth level is a penthouse for climate control equipment. Completion of the $18.5 million project is scheduled for the 1985-1986 academic year.

The building's concept and design will nurture the major biomedical research taking place within its walls. The research centers and support services moving into it will profit both from the space to enlarge their programs and from access to the core equipment.

The Cecil H. and Ida Green Biomedical Research Building

The Center for Human Nutrition

The Center for Human Nutrition was founded "to place the entire field of human nutrition on a firm scientific foundation." In a field in which everyone has an interest and an opinion, there are a superabundance of myths and fads to put to rest. The Center investigates the roles of nutrition in the prevention of disease, in the treatment of disease and in optimizing mental and physical health. In addition to research, the Center promotes teaching of nutrition at all levels within the Health Science Center and cooperative efforts within the community.

Originally funded jointly by UTHSCD and the Southwestern Medical Foundation, the Center has received generous additional support from an anonymous donor. The director, Scott M. Grundy, M.D., Ph.D., is Professor of Internal Medicine and Biochemistry and holds the Distinguished Chair in Human Nutrition.

The Center conducts clinical investigation into human nutritional problems at metabolic units in the Veterans Administration Medical Centers in Dallas and Bonham, Texas, and in the General Clinical Research Center at Parkland Memorial Hospital.

A major research goal of the Center has been to discover nutritional approaches to the prevention of atherosclerosis and coronary heart disease by controlling high cholesterol levels through diet combined with the experimental drug Mevinolin, exploring the role of triglycerides, and comparing polyunsaturated and mono-unsaturated fats in the diet.

Cooperative research with other departments has included studies of the effects of diet in the treatment of diabetics, of the relationship between dietary fat and predisposition to cancer and of nutritional needs of burn patients.

Larger facilities for the Center will allow new avenues of clinical research, beginning with nutrition in pediatric and aging patients.

The Howard Hughes Medical Institute

The Howard Hughes Medical Institute is a private research institute formed in 1953 for the promotion of human knowledge within the field of basic sciences (principally the fields of medical research and medical education) and the effective application of this knowledge for the benefit of mankind. Twenty-two years later, the Institute has widened its medical research program into disorders arising in three major areas: genetics, immunology and metabolic regulation.

The Hughes Institute's facilities at UTHSCD will be located on the fourth and fifth levels of the Green Biomedical Research Building, contiguous with existing basic science departments in the Green Science Building. A sizable proportion of the fourth level will be allotted to core equipment and facilities to which the entire UTHSCD faculty will have access. Hughes investigators and laboratories will occupy the remainder of the two floors.

The Institute employs investigators at 11 major university medical centers throughout the country: Harvard, Johns Hopkins, Yale, Duke, Vanderbilt, Baylor, Washington University in St. Louis, University of Washington-Seattle, University of California-San Francisco, University of Utah-Salt Lake City and Stanford.

Two UTHSCD faculty members are on the Institute's Scientific Review Board: Dr. Jonathan W. Uhr, Professor and Chairman of the Department of Microbiology, and Dr. Joseph L. Goldstein, Paul J. Thomas Professor of Genetics and Chairman of the Department of Molecular Genetics.

The Cecil H. and Ida Green Center for Reproductive Biology Sciences

Scheduled to occupy the sixth floor of the Cecil H. and Ida Green Biomedical Research Building, the Green Center

for Reproductive Biology Sciences has a 10-year history of basic and clinical research on human reproductive processes and has established an international reputation for excellence in this field.

Begun with a gift of $600,000 from Cecil and Ida Green in 1973, the Center is now endowed with a total commitment of $5 million, primarily as a result of the continued support of the Greens. The staff includes 14 full-time UTHSCD faculty members working on a score of projects.

Directing the Center from its inception has been Paul C. MacDonald, M.D., who also holds the Cecil H. and Ida Green Chair in Reproductive Biology Sciences. MacDonald, formerly chairman of UT Southwestern Medical School's Department of Obstetrics and Gynecology, brought to the Center a wealth of basic research into the mechanisms of reproductive processes, as well as many years of effort to reduce infant deaths and illness through careful management of pregnancy and childbirth. This experience provided the impetus and direction for the work of the Center.

Currently, numerous research projects underway in the Center are aimed at a better understanding of the mechanics of parturition, which may also lead to the prevention of prematurity and to an understanding of the control of fertility.

Research on the regulation of the biosynthesis of pulmonary surfactant, a lipoprotein which lowers the surface tension of the lungs allowing them to expand and take in air, may lead to means of treating hyaline membrane disease in premature infants.

Other research involves several aspects of the aging process, including changes in the pattern of secretion of hormones by the brain and pituitary as well as the role of estrogens in the etiology of endometrial cancer. The Center is also conducting basic and clinical research into the causes of pregnancy-induced high blood pressure.

Most of this research is funded by grants from the National Institutes of Health and the March of Dimes, attracted by the personnel and facilities made possible by the Center's endowment.

The Harry S. Moss Heart Center

Dallas oilman and philanthropist Harry S. Moss established the Harry S. Moss Trust for the Prevention and Cure of Heart Disease because, as he stated in his will, "I could not pursue any course which potentially could be of greater service to the community."

Jere Mitchell, M.D., Professor of Internal Medicine and Physiology, is Director of the Moss Center. Mitchell is also Director of the Weinberger Laboratory for Cardiopulmonary Research and is the Frank Ryburn Jr. Professor of Heart Research.

The Harry S. Moss Heart Center cuts across department lines to support cardiac research projects in internal medicine—including cardiology and medical genetics—as well as in physiology, cell biology, pharmacology, radiology and surgery.

> The building represents a purposeful coming together of researchers in many different fields.

Current research sponsored by the Center focuses on the response and adaptation of the heart and circulatory system to exercise. Much of this research currently takes place in the Moss Center, using two laboratories in the Harry S. Moss Clinical Science Building and on two floors of the Dan Danciger Research Building in the Pauline and Adolph Weinberger Laboratory for Cardiopulmonary Research. Many sophisticated and highly complex techniques are used to study the function of the heart and circulation during exercise.

Expansion into the Green Biomedical Research Building will give the Moss Heart Center four additional laboratories and offices.

The Robert A. Welch Chair in Chemistry

A new chair to enhance the quality of chemical research has been endowed by the Robert Alonzo Welch Foundation. Laboratories and offices will be located in the Green Biomedical Research Building.

The Eugene McDermott Center for Human Growth and Development

In 1972 Eugene McDermott, one of the founders of Texas Instruments Inc. and a major benefactor of the university, endowed an academic chair for the Eugene McDermott Center for the Study of Human Growth and Development.

The overall purpose of the Center is to study various structures and functions of the human body, with particular emphasis on their relationship to growth and development. It was intended that a study of growth patterns, beginning at birth and extending over a long period of time, could be monitored and correlated with intelligence and other tests related to the maturing process. The resulting body of knowledge would serve as a measure of the norm and as a basis of predicting pathologies.

New research facilities in the Green Biomedical Research Building and the appointment of a new director for the Eugene McDermott Center for the Study of Human Growth and Development are expected to revitalize these research efforts.

The Cancer Center

The Cancer Center serves as an administrative focus for the coordination of cancer programs in research, teaching and patient care for the campus. The new facilities for the Cancer Center in the Green Biomedical Research Building will provide a core unit to expand the coordinative role of the Center as well as provide support core laboratory space for research and education, according to Center director Eugene P. Frenkel, M.D., Professor of Internal Medicine and Radiology and Emma Freeman Professor of Radiation Research.

The current research activities coordinated by the Cancer Center cover a variety of areas, but major programs relate to cancers of the lymph node system and leukemia, as well as cancers in the brain, breast and lung. With the new facility, core support will be available; a cell analysis laboratory will bring together currently functioning fluorescence-activated cell sorting equipment, presently scattered on the campus, into a functioning, coordinated unit. These instruments provide highly sensitive analyses of a variety of changes on and within cancer cells. In addition, the cell sorting equipment can be used to examine the pattern of cell replication in cancer.

Near these cell analytic instruments will be a resource for cell culture, for development of antitumor antibodies by hybridoma technology and a laboratory to examine chemotherapy and responsiveness to drug sensitivity for human tumors. Finally, laboratory core support will be available for radioimmunoassay of cancer chemotherapeutic drugs and correlated pharmacological distribution studies.

In addition to providing the core laboratory unit, the Center will expand its role in teaching students, house staff and community clinicians, as well as in helping to coordinate patient care and cancer control research programs.

The Harold C. Simmons Arthritis Research Center

When Dallas philanthropist Harold Simmons underwrote the Arthritis Research Center in 1983 with one of the largest endowments ever received by the Health Science Center, he said, "Obviously we'd all like a cure, but I'd be happy with any progress toward curing any part of arthritis—any small cure or medication to alleviate symptoms."

One year later, the Simmons Arthritis Research Center was in operation under the direction of Peter Lipsky, M.D., Professor of Internal Medicine and Microbiology, with six other M.D.'s and Ph.D.'s involved in research and two more staff professionals to be added.

"Our focus," said Lipsky, "is basic research on the genetic and immunological aspects of inflammatory arthritis." Several aspects are being studied—a genetic link in arthritis; arthritis as an auto-immune disease; and a group of bacterial pathogens that appear to trigger inflammatory arthritis in genetically susceptible individuals.

The move from quarters in the Danciger Building to the seventh floor of the Green Biomedical Research Building will be a very positive one for the Simmons Arthritis Research Center, according to Lipsky. "In the first place, it will contain new equipment that will advance our research—a fluorescence-activated cell sorter, advanced electron microscopy equipment and the DNA lab. Second, we look forward to the interaction with the other research centers and the Hughes Institute. That should be a major benefit."

The Animal Resources Center

The UTHSCD Animal Resources Center, which orders or supplies all experimental animals for university research, already runs the equivalent of a one-acre animal farm—50,000 square feet of space in buildings throughout the campus. However, the Center has outgrown its space for conventional animal housing and needs specialized environments that are not available now, according to Steven Pakes, D.V.M., Ph.D., Director of the Animal Resources Center and Professor and Chairman of Comparative Medicine.

Those needs will be met when the Center moves into the second and third levels of the Green Biomedical Research Building, expanding available facilities by almost 50 percent and making it possible, thanks to careful planning with the architects, to provide two much-needed specialized animal laboratories.

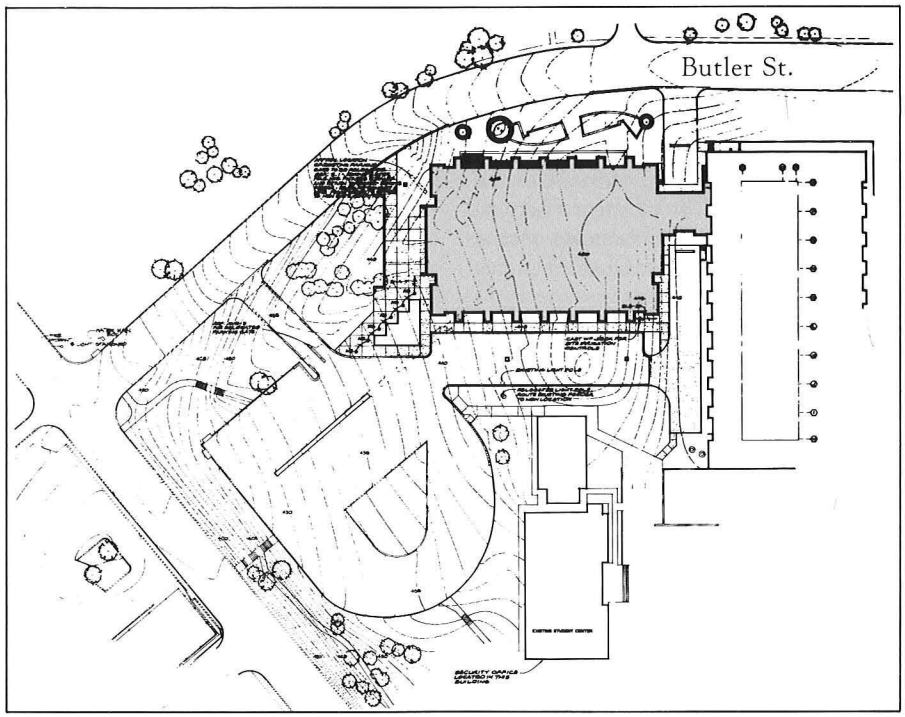
The Center will allot 6,000 feet on the second level to barrier facilities where inbred strains of mice, rats and other rodents can be maintained in a disease-free state over a long period of time. Experimental animals can be brought into the barrier facility clean and kept clean through an elaborate physical setup similar to those devised for people working with radioactive materials. Workers will pass through a three-part barrier to avoid contamination of the laboratory. In the first room, they will remove and store their conventional clothing; in the second room, they will shower; in the third room, they will don sterile clothing before entering the laboratory. The animals' food and supplies will also be sterilized, and there will be a special antibacterial water supply.

Another 6,000 square feet will be set aside for research using hazardous biological agents, such as carcinogenic viruses or infectious agents. Located on the north side of the third level, this specialized area will be protected by changing rooms and showers like the barrier area on level two. Isolating this type of research will protect both the personnel and other research animals.

Support labs, procedural rooms and cage-washing facilities will use 4,000 square feet. An additional 5,000 square feet are allotted to conventional animal housing, designed to support the highest levels of humane care of research animals. All told, the Animal Resources Center will add 21,000 square feet of much-needed space in the Green Building.

The association of researchers from different but related fields of inquiry is expected to foster interdisciplinary thinking and encourage the expansion of research across traditional boundaries. Already, the Moss Heart Center, the Center for Human Nutrition and the Cancer Center integrate research from many departments. Core facilities being made available by the Hughes Institute will increase research possibilities. "Many breakthroughs here at the Health Science Center and at other research institutions of note have come, and will continue to come, from interaction of scientists with different training, backgrounds and perspectives," remarked Dean Wildenthal. "Our Green Biomedical Research Building is designed to facilitate this process of bringing together basic and clinical sciences in an atmosphere of collaboration and cooperation," he added. If the anticipated synergism develops, the results will be a gift to the future.■

—TOMMY JOY BOSLER



Site plan of the new building (shaded) and its connection to the Cecil H. and Ida Green Science Building (right).

THE DRAMA OF A HEART ATTACK

Chemical actors given new roles to play

Researchers at UTHSCD's Southwestern Medical School may soon be able to help write the script for those whose clogged arteries lead them toward sudden death or heart attack.

Guided by Dr. James Willerson, head of the UTHSCD Ischemic Heart Center, and by Dr. William Campbell, Associate Professor of Pharmacology, the group is making steady progress in identifying the saga's chemical players and is successfully altering their roles. Of particular interest are those players called "prostaglandins," a family of hormones produced from fatty acids that are part of the lipids of cell membranes. Prostaglandins are at center stage in the drama of ischemia, the progressive narrowing of arteries that reduces blood flow to the heart, bringing on heart pain (angina), heart attack and sudden death.

One of the hormones, a prostaglandin called "thromboxane," triggers the accumulation of platelets, small blood cells that normally gather at injury points to seal off internal bleeding. When a blood vessel is damaged by trauma, this function is beneficial; but when platelets generate thromboxane in an artery narrowed and injured by cholesterol plaque, it only further reduces blood flow to the heart. "We have found," says Willerson, "following arterial injury and narrowing resulting from atherosclerosis, that platelets are attracted to the site of the narrowing and they, in turn, release thromboxane. Thromboxane acts to shrink the artery and to attract more platelets, thereby aggravating the condition.

"We have shown in laboratory models that drugs that inhibit thromboxane synthesis prevent blockage of the artery and acute progression of the narrowing process," Willerson says. The scene is now set for a series of definitive trials of these drugs in humans, which, if successful, may lead to improved control. In some instances, it may be possible to prevent rapid blocking of coronary arteries and its disastrous consequences.

Dr. James Willerson

"We have shown in laboratory models that drugs that inhibit thromboxane synthesis prevent blockage of the artery and acute progression of the narrowing process."

Another prostaglandin, prostacyclin, is cast in a role opposite that of thromboxane. Prostacyclin is released from the lining of blood vessels to keep blood flowing during times of injury. It causes vascular smooth muscles to relax, and it is the most potent known inhibitor of platelet aggregation.

Together, thromboxane and prostacyclin establish a balance in the healthy person. In persons with atherosclerosis, however, the prostaglandins may be thrown off balance. At sites of atherosclerotic plaques, thromboxane can increase, while prostacyclin decreases.

Risk factors may play a part in altering the prostaglandin balance, says Campbell. While there is no conclusive evidence, it appears that risk factors for heart disease may exert some of their effects through alterations in the production and actions of prostaglandins. These risk factors include atherosclerosis and high cholesterol levels, diabetes, smoking, hypertension, age, heredity, emotional stress and diet.

Through ongoing experiments with laboratory animals, the researchers have come closer to understanding the cause-and-effect relationships between prostaglandins and circulatory disorders. "If we can understand the processes in well-controlled animal models," says Willerson, "it will improve our general understanding and lead to further well focused diagnostic studies and, ultimately, therapeutic efforts in man." One such animal study involves looking directly at those ischemic phenomena called "cyclic flow reductions" or "CFR's."

CFR's are characterized by reduction

in coronary blood flow followed usually by abrupt and spontaneous restorations in blood flow. During CFR's, aggregates of platelets and red blood cells form in severely narrowed, or "stenosed," coronary arteries, further reducing blood flow. The aggregates break loose and are carried along by the bloodstream. Blood flow is increased when the clot breaks free, but the clots released after CFR's can cause stroke or other arterial blockage in humans.

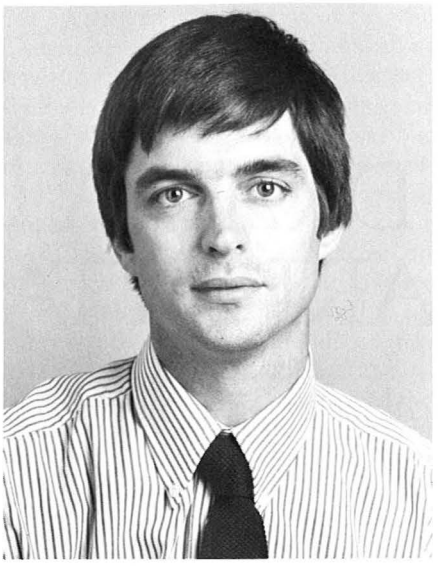
By selectively preventing the release of thromboxane in the severely narrowed arteries of laboratory animals, Willerson's team was able to completely prevent CFR's in most cases.

"This," says Willerson, "supports the view that platelet aggregation and local thromboxane accumulation are important causes of stenosis-induced CFR's."

If prostaglandins prove to be as important as they seem to be in vascular disease, attention can be directed at the correction of pathological imbalance. This may be accomplished by altering one's diet, as well as by the administration of drugs that can alter the hormones' interactions with body cells.

> "If we can understand the processes in well-controlled animal models, it will improve our general understanding and lead to further well focused diagnostic studies and, ultimately, therapeutic efforts in man."

One such drug has been on the market for nearly a hundred years, although its role in the prostaglandin story has only recently been recognized—aspirin. Dr. Thomas Smitherton, Chief of the Cardiac Unit at the Veterans Administration Medical Center and an investigator with Willerson's research team, and his associates, recently showed that the equivalent of one aspirin per day reduces the risk of heart attack and death in patients with unstable ischemic heart disease.



Dr. Michael Winniford

Aspirin in low doses appears to interfere significantly with thromboxane synthesis, somewhat less with prostacyclin synthesis; this too lends support to the hypothesis that platelet clumping and thromboxane release are important factors in unstable ischemia, and indicates that it may well be possible to prevent the death and damage wrought by obstructions of the bloodstream.

While these preventive methods are waiting in the wings, two new players are being tried out to see how well they can lessen the damage done by a heart attack in progress.

Dr. Michael Winniford, Assistant Professor of Internal Medicine at UTHSCD, is participating in a study of two drugs, streptokinase and "tissue plasminogen activator" (TPA), two thrombolic agents that work to dissolve blood clots and restore blood circulation. Streptokinase, an enzyme produced by the streptococcus bacterium, can be injected into a blocked coronary artery to help dissolve the clot, but in so doing it suppresses the blood's clotting factors. The patient is therefore unable to form even a beneficial clot anywhere in his body. During the 24 to 48 hours after injection of streptokinase, Winniford says, "It takes heroic effort to stop bleeding during treatment with streptokinase. We are looking at TPA in hopes that it will be safer and more effective."

TPA acts upon the plasminogen protein that, with blood fibrin, makes up a blood clot. The tissue plasminogen activator changes the plasminogen into plasmin, the body's own fibrin-dissolving agent. The fibrin dissolves and the clot disappears.

"The nice thing about TPA is that it works only at the site of the clot. It doesn't destroy the body's ability to make clots after the drug has been administered. If the patient bleeds from an ulcer, we can stop TPA and the blood clots quickly."

Winniford, along with Drs. George Revtyak, James Willerson and David Hillis, is now testing both drugs as part of a National Institute of Health study. But whichever is accepted for general use, development of these new drugs marks a definite shift in the philosophy of heart attack management.

Only recently, the standard treatment for heart attack was bed rest, analgesics to relieve pain, oxygen and regularization of erratic heartbeats —treatment of the consequences of the blood clot. Many patients, Winniford believes, felt that nothing could be done medically to stop the process and often considered it useless to rush to the hospital during an attack.

> "Now it has become clear that we have the ability to treat the underlying problem of the heart attack by dissolving the clot, provided that the clot can be dissolved in a timely way before the heart attack is finished."

"Now," says Winniford, "it has become clear that we have the ability to treat the underlying problem of the heart attack by dissolving the clot, provided that the clot can be dissolved in a timely way before the heart attack is finished. Ideally, drugs should be administered within the first two to three hours after the beginning of the heart attack. At the latest, a patient must come into the hospital within three to four hours after the onset of severe heart-attack pain in order to limit the amount of heart damage." ■

—SUSAN RUTHERFORD