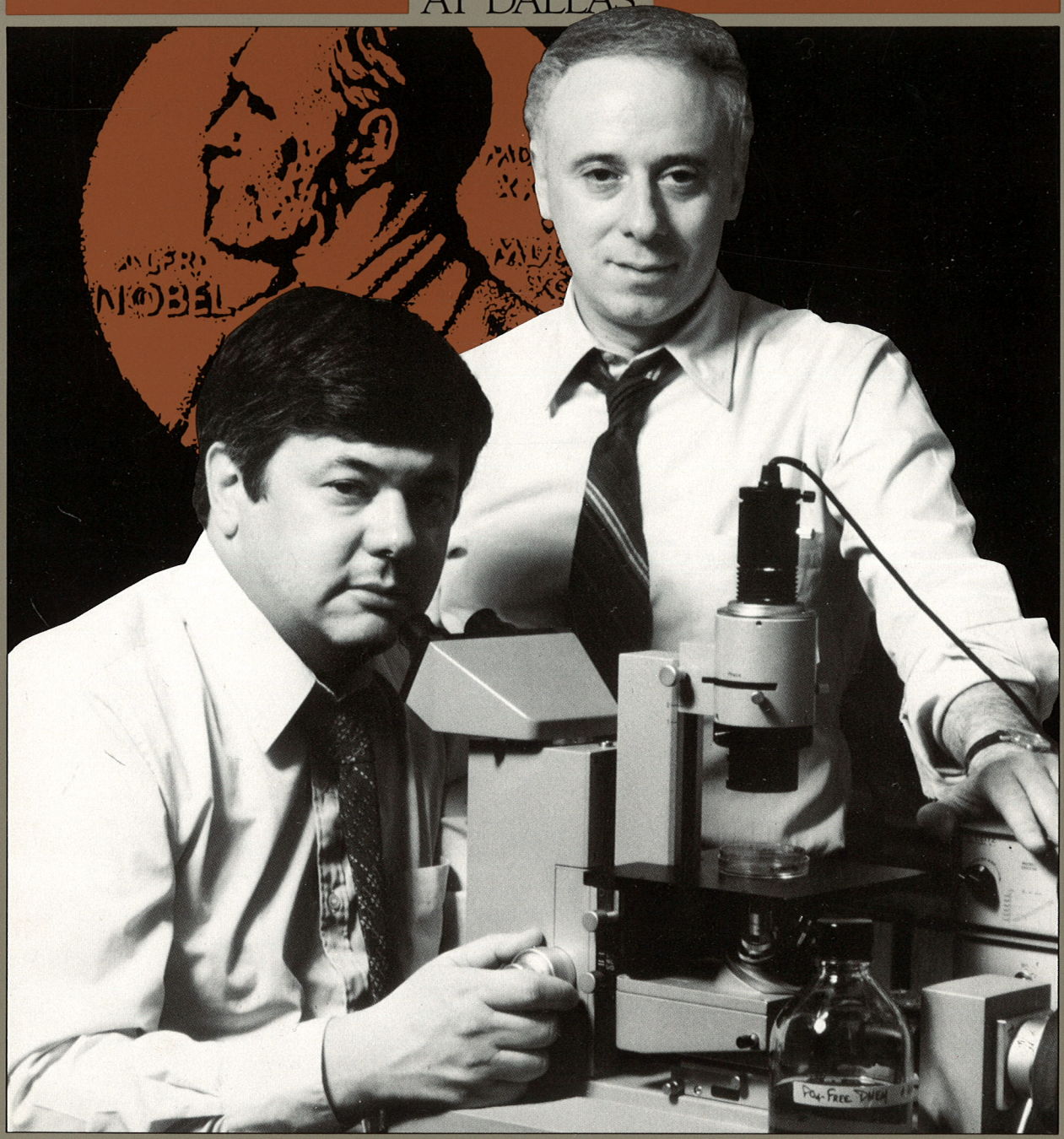
BIOLOGUE

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT DALLAS



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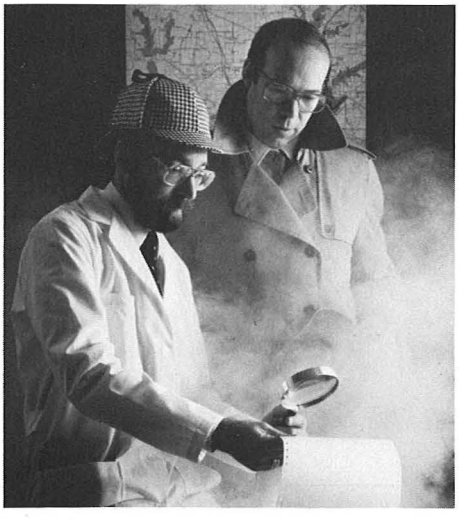

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A Message from the President

It is difficult to express my feelings as I approach retirement after serving the health science center for the past 19 years. Obviously, there are mixed emotions: satisfaction and pleasure because of the successful growth and maturation of the institution to that of a university of the first class, joyfulness and pride because of the achievements and much-deserved recognition on the part of a wide array of faculty members, sadness at the prospect of ending the day-by-day association with the university and anticipation at the opportunity for another career where I could still be of assistance to the school.

The remarkable development of the health science center over a relatively short period of time (43 years) cannot be attributed to any one person or group of persons. But there are certain individuals and organizations that should be recognized as playing major roles. From the inception of the medical school as a proprietary institution created by the Southwestern Medical Foundation, there has been an increasing number of faculty who created a tradition of scholarship and an intellectual environment conducive to attracting and retaining individuals with the potential for making major contributions.

Among that group is Dr. Donald Seldin, chairman of the Department of Internal Medicine. He arrived at the time the school was still in "The Shacks" and for the ensuing 33 years has been the intellectual leader on campus. There are others too numerous to mention who played a similar role, but certainly Dr. Seldin symbolizes that particular group of faculty members.

In addition, the institution has benefited enormously from the Dallas community. This is not to minimize the support the institution has received through the years from The University of Texas System Administration, the Board of Regents and the Legislature. Indeed, without that core support the community support would have meant very little.

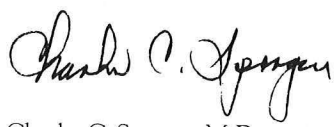
From the inception of the medical school as Southwestern Medical College, the Southwestern Medical Foundation has played a major role. Early in its history, Dr. Ed Cary and Karl Hoblitzelle were particularly important. More recently, George McGregor, James Aston and James Keay have been of critical importance as presidents of the foundation.

In addition to the Southwestern Medical Foundation, there have been other foundations that have made possible the expansion of certain programs to bring them to a world-class status as well as the creation of new programs, which now have that potential.

Also early in my tenure, persons such as the McDermotts, the Greens and the Jonssons played vital roles. Subsequently, an increasing number of individuals have been major players. I shall not attempt to list them, for some of them would wish to remain anonymous. Suffice it to say that private philanthropy has been of enormous value, and, given the present status of state and federal support, it is going to be of even greater value in the future.

Finally, I would like to express my thanks not only to those mentioned above but to the wonderful staff at every level whose loyalty and dedication to their work has permitted the faculty and students to "do their thing."

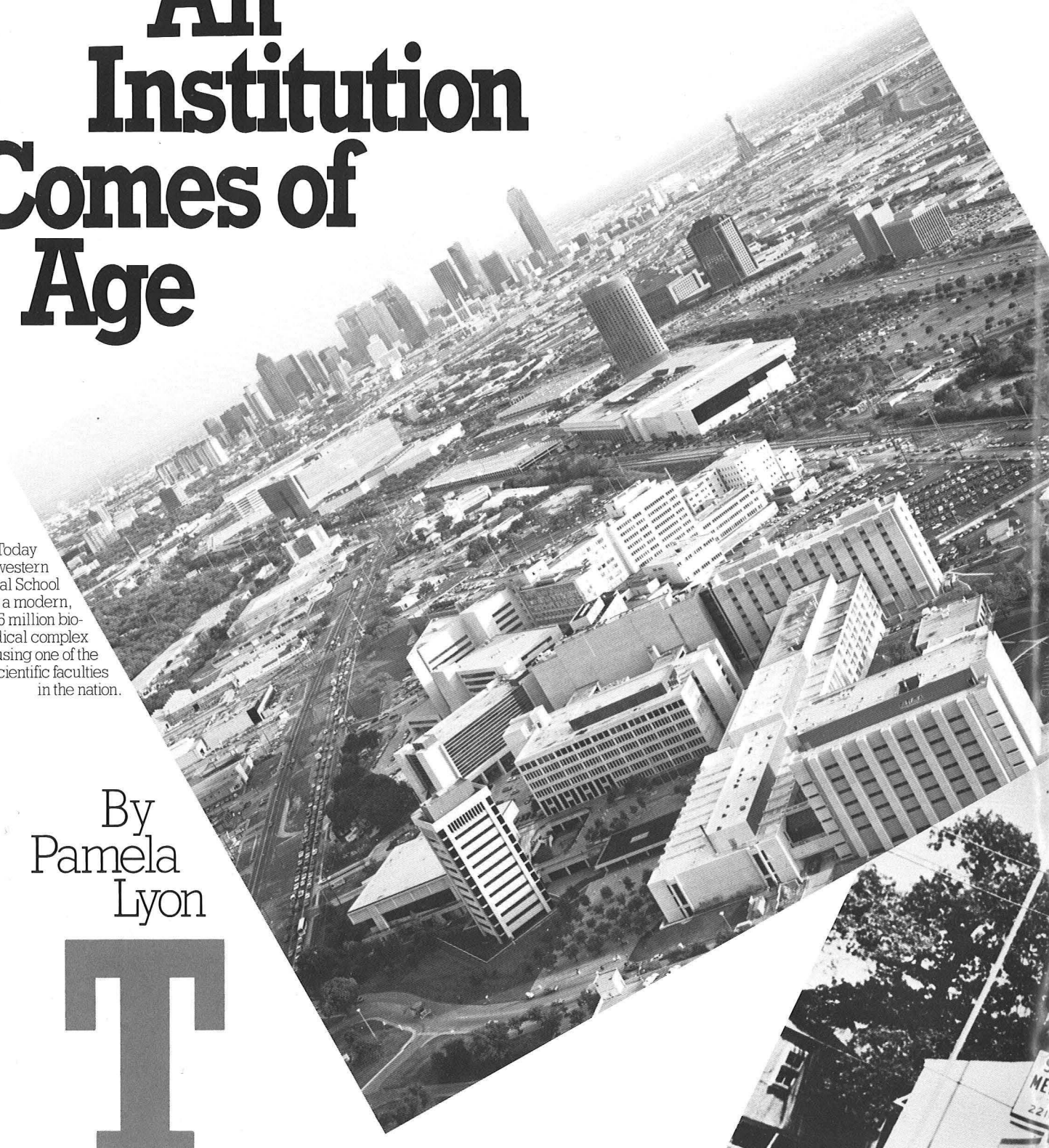
I feel privileged to have had the opportunity to be associated with the health science center over the past 19 years, and I have every confidence that it will continue to grow and prosper in the future. Success, however, is not guaranteed. But with the quality and commitment of the faculty and administration, along with the support of the university and the community, I will be surprised and disappointed if it does not occur.



Charles C. Sprague, M.D.

Photo by Gittings

An Institution Comes of Age



Today Southwestern Medical School is a modern, $125 million biomedical complex housing one of the finest scientific faculties in the nation.

By Pamela Lyon

There aren't many times in the course of a history when a single year stands out as a benchmark before it is even finished. But the 1985-86 academic year clearly is one for The University of Texas Health Science Center at Dallas.

It marks the realization of the shining future hoped for by the administration, faculty and community supporters of Southwestern Medical College 43 years ago, when the fledgling institution opened shop in a ramshackle collection of army barracks to prepare doctors for wartime.

And it is the yardstick against which achievements to come will be measured.

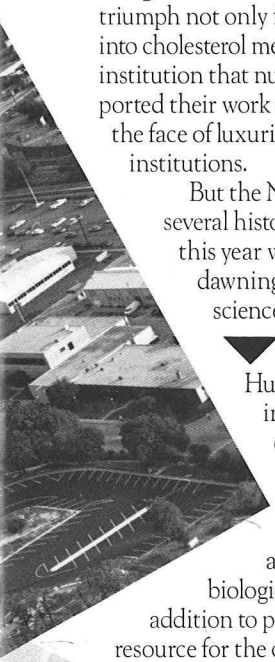
This, of course, was the year of the Nobel

In the early 1940's it was a collection of ramshackle Army barracks dubbed "The Shacks."

Prize — the first for Southwestern and the first Nobel Prize for Physiology or Medicine awarded for research done wholly in Texas.

When Drs. Joseph L. Goldstein and Michael S. Brown received their gold medals and certificates in Stockholm amid the pomp and glitter on December 10, 1985, it was a triumph not only for their landmark research into cholesterol metabolism but also for the institution that nurtured their talent, supported their work and held their loyalty in the face of luxurious offers from other institutions.

But the Nobel Prize is only one of several history-making developments this year which together signal the dawning of a new era at the health science center. Among them:

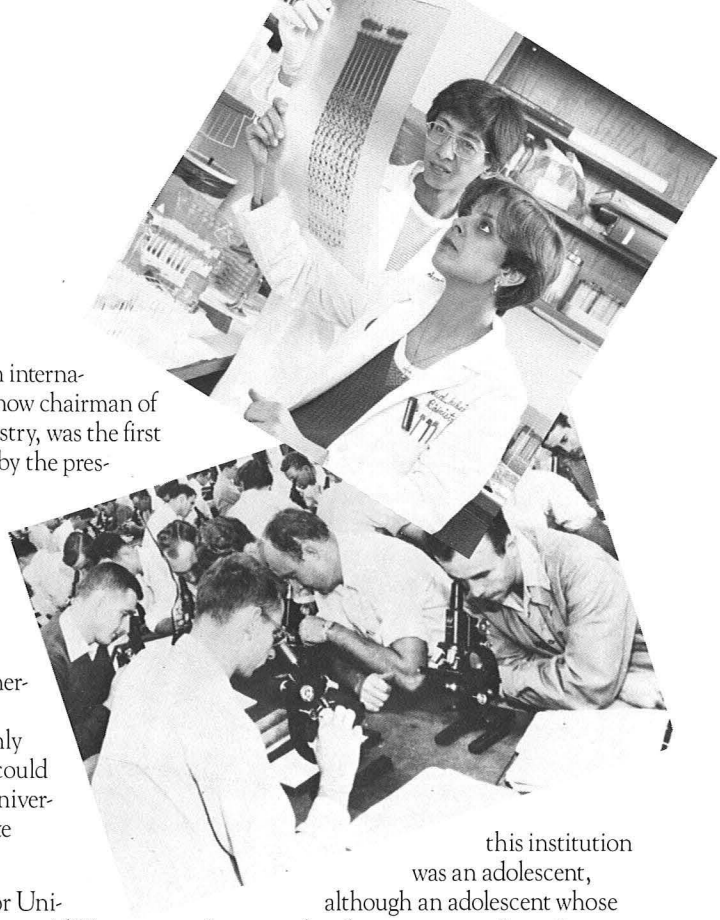


- The arrival of the Howard Hughes Medical Institute, an initial five-year, $28 million commitment by the nation's wealthiest philanthropic organization to develop a center for molecular biological research which, in addition to providing a rich scientific resource for the campus, makes it easier for the university to recruit additional top-caliber faculty.

Dr. Joseph Sambrook, an internationally known scientist and now chairman of the Department of Biochemistry, was the first to be attracted to the faculty by the presence of the Howard Hughes Medical Institute.

- The creation of Dallas Biomedical Corporation, a unique partnership between the university and private business, to hasten the commercial development of research breakthroughs, which not only will benefit humankind but could prove very profitable to the university, researchers and corporate investors.

- The progress of plans for University Medical Center, a proposed $38 million, 159-bed teaching hospital for referred patients that will provide the health science center's clinician-scientists and medical students with a vitally needed "laboratory/classroom" in which to advance hands-on health care for specialty cases not usually seen at Parkland Memorial Hospital, the school's main teaching hospital.



But if this academic year marks the beginning of a new era, it also, sadly, marks the end of another. After 19 years of innovative leadership, Dr. Charles C. Sprague announced his retirement as president of the health science center, effective August 31, 1986. His is the longest tenure of any chief executive of the health science center and certainly among the most influential.

Under Sprague's leadership, the three-building campus of a small, respectable medical school has grown into a modern, $125 million biomedical complex housing one of the finest scientific faculties in the nation, which annually produces not only first-rate physicians and scientists but also world-class research.

Indeed, during Sprague's administration the institution came of age.

"When I arrived here in 1967, this institution was an adolescent, although an adolescent whose character already was apparent," says Sprague. "But what was then a somewhat malnourished child, poorly clothed, is now a vigorous, robust and healthy adult."

Sprague credits generous community support for this transformation. Although state-funded, the health science center could not have grown as it did without the help of private philanthropy. In fact, Southwestern Medical College, the modest seed from which the modern institution grew, was founded and for the first six years entirely supported by the Southwestern Medical Foundation, a group of private citizens who believed — then as now — that the medical school plays a vital role in the life of the city.

But as Dr. Edward H. Cary, the foundation's first president, noted in the school's 1944 annual, it takes more than brick and mortar — or money, for that matter — to build an outstanding medical school: "It is men . . .who really make an institution."

Conditions at Southwestern in the early days assured that, whether student, teacher or administrator, those who stayed were made of strong stuff. The school was a primitive collection of prefabricated barracks on Oak Lawn Avenue, appropriately dubbed "The Shacks," across from the old Parkland Hospital, which students called "The Black Hole of Calcutta." Plumbing lay on the ground, and when the temperature dropped, the school shut down. Buildings leaked when it rained, and on one occasion part of a class fell through a gaping hole in the floor. The school became part of The University of Texas System in 1949, but things didn't

Conditions at Southwestern in the early days assured that, whether student, teacher or administrator, those who stayed were made of strong stuff.

change much, at least not right away.

Dr. Donald Seldin, chairman of the Department of Internal Medicine since 1952, recalls that on a visit in the early fifties Governor Allan Shivers was struck — quite literally -- with the sorry state of the school. "One of the windows, which were fragilely hinged, fell down and hit him," says Seldin. "He became impressed that the school really needed permanent buildings."

The school needed rather more than buildings. Within a year of his arrival at Southwestern from Yale University School of Medicine, Seldin ascended from the position of associate professor in internal medicine to chairman of the department. While his commanding intellect certainly was a factor, so was the fact that he was the only one left in the department. Within a short time, the chairmen of all the other clinical departments also abandoned the school.

The school, understandably, was on probation. Seldin, too, considered jumping ship and, in fact, sent his wife on to New Haven, Conn., where he planned to rejoin the Yale faculty. Fortunately for Southwestern, he changed his mind.

"Despite the rather abysmal physical facil ities and the fact that we had no money, there were certain opportunities," says Seldin.

"First of all, there was no faculty to replace because there was no faculty. Second, there was an opportunity to be innovative, to start new things, to develop new kinds of programs. And third, there was an opportunity to instill a certain sense of style into the program."

The school's limitations, physical and fiscal, ruled out certain approaches to development. There were barely enough funds to attract promising postdoctoral fellows much less a "cosmic figure" for the faculty, Seldin says, so the chairman looked to what was at hand — the students and residents.

Seldin worked closely with his students in an intimate, tutorial setting, a tough, demanding, inspiring and sometimes witheringly critical mentor. He selected his future faculty carefully, directing them into fields he thought would yield the best results for both the school and the professor-to-be. Then he sent them away for training at prestigious institutions and laboratories before bringing them back to Dallas as faculty members.

Dr. John Fordtran, chief of internal medicine at Baylor University Medical Center, remembers Seldin picked him out as a resident to be a gastroenterologist, a specialty he had never heard of. "He said to me, 'I'm going to send you to work with Franz Ingelfinger (then at Boston's Massachusetts Memorial Hospital and later the influential editor of the *New England Journal of Medicine*). He'll make a gastroenterologist of you, and then you'll come back,' " says Fordtran. "I could never figure out how he chose the ones he chose, why he chose me over others I thought were smarter or better suited. I think it's a lot like that professor, Henry Higgins, in the musical 'My Fair Lady.' "

Among those former students and residents who remain at Southwestern are Nobel laureate Goldstein and others who have earned national and international reputations in their respective fields, including: Drs. Jere Mitchell (cardiology/exercise physiology), Norman Kaplan (hypertension), Jean Wilson (endocrinology), Charles Baxter (burn treatment) and Dan Foster (diabetes/metabolic diseases). Another graduate, Dr. Kern Wildenthal, is now dean of Southwestern Medical School. Dr. Charles Mullins, Class of '58, is now chancellor for health affairs for The Univer-

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The Hughes Institute: A Look at the Atomic World

By Pamela Lyon

In addition to a massive infusion of research funds and scientific expertise, the Howard Hughes Medical Institute brings to the health science center an entirely new field of endeavor, although it is hard to know what to call it.

Structural biology, structural biophysics, molecular dynamics — the field is so new there is no clear consensus on its label. What it involves is the adoption by biomedical scientists of techniques and tools developed by physicists to examine matter at the ultra-small level of the atom.

These techniques allow the examination of cell structures, their function and the genetic materials that produce them at a level of resolution of two one-hundred-millionths of a centimeter, far beyond the reach of the most sophisticated electron microscope. At that level, individual atoms and the interactions between them are discernible.

Through such research, scientists hope to speed discoveries in human health and disease and, perhaps, revolutionize treatment with the design of new drugs by altering specific atoms within certain large molecules, such as proteins.

In May, the Hughes Institute launched a $60 million research program into structural biophysics at six of the 22 institutions where Hughes Institute-sponsored research is conducted. The health science center is one of them; it is one of only two selected for the program where no such research currently is conducted.

"This is such an expensive form of basic research that no university can easily put together such an effort without assistance," says Dr. Mary-Jane Gething, an investigator at the Hughes Institute here.

The aim of this new research effort at the health science center will be to unlock the mysteries of protein structure and function. Proteins are complex molecules composed of strings of amino acids that are folded into convoluted, three-dimensional configurations. More than that, they are among the fundamental building blocks of life.

There are tens of thousands of proteins in the human body, each with a highly specialized biochemical function that helps maintain the living organism. Every protein has a different shape, which determines its function. Many of them are enzymes that catalyze chemical reactions.

Scientists have learned quite a lot about proteins. They are able to determine the sequence of amino acids that make up a protein, how it is synthesized within a cell, the location of the gene responsible for its production and even the different parts of the gene that make — or "express" — different parts of the protein. They also can clone the gene and alter specific amino acids to produce new proteins.

What they don't yet know is how the two-dimensional structure of DNA can precisely specify the folded shape of a three-dimensional object, says Dr. Joseph Sambrook, chairman of the Biochemistry Department and an internationally known scientist who has taken major responsibility for recruiting investigators for the Hughes Institute here.

"If the rules that govern protein folding could be established," Sambrook says, "scientists may be able to develop more effective drugs by manipulating protein structure to make proteins that work better — or worse, if that's what you want. It's like designing clothes; you can make things fit exactly what you want."

Among the proteins likely to be studied are the LDL receptor, a cell-surface protein vital to maintaining the body's cholesterol balance whose discovery earned Drs. Joseph L. Goldstein and Michael S. Brown the Nobel Prize last year; HMG CoA reductase, an enzyme that controls the rate at which cells manufacture cholesterol; G Proteins, a class of proteins under study by Pharmacology Department Chairman Dr. Alfred Gilman that play an important role in the formation of some tumors; and plasminogen activator, an enzyme in the bloodstream of mammals that dissolves blood clots and currently is under study by Sambrook and Gething.

The primary tools to be used in this new research effort are X-ray crystallography, to record the atomic structures of proteins; sophisticated computer analysis and graphics display, to determine the three-dimensional shape of the proteins; and protein dynamics and modeling, to help predict what will happen if changes are made in the amino acids that make up the protein.

X-ray crystallography was developed by physicists to determine the arrangement of atoms in metallic crystals. Its use in biomedical research contributed to, among other things, the discovery of the double-helix structure of DNA, the coded message of heredity in cells. The principle behind X-ray crystallography is fairly simple, although the analysis of the data obtained by this technique is staggeringly complex.

A beam of X-rays is shot through a crystal — in this case, a crystallized protein (which in itself is a very tricky thing to make). The X-rays are bent, or diffracted, by the crystal in much the same way light is bent by a prism. The X-rays exit the crystal in a spray, which can be recorded as spots on film or by state-of-the-art electronic "area collectors."

By applying an elaborate series of mathematical manipulations to these diffraction patterns, the three-dimensional configuration of the atoms within the crystal can be deduced, much like retracing the track of a billiard ball based on the angle and speed of its entry into a pocket, taking into consideration the other balls on the table and adding a third dimension.

This process demands extremely powerful computing resources and lots of time. Calculation of the atomic structure of a single protein crystal, which may contain tens of thousands of atoms, may involve tens of millions of numbers. From crystallization of a particular protein to determining its atomic structure usually takes at least two to three years.

The structural biophysics unit will complement the Hughes Institute's broader program of basic research at the health science center into the mechanisms of protein traffic within cells, the interaction between cell-surface receptors and the molecules to which they bind and the transmission of signals within cells from proteins on or near the surface through the cytoplasm to the nucleus, which contains genetic material. ■

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sity of Texas System. And many others have taken high positions in other prestigious institutions, including Fordtran and Dr. Floyd Rector, director of nephrology at the University of California at San Francisco.

Says Seldin: "It turns out that the Texas farm boys, given appropriate stimulation, were as gifted as anybody."

In 1955, Southwestern moved to the clinical sciences building on its current 60-acre site adjoining Parkland; within a few years after that, Seldin had recruited the bulk of his faculty. As a result of community fundraising, at least one figure of the cosmic variety was among them: Dr. Morris Ziff, then a leading rheumatologist, now a world figure in the study of arthritis.

When Sprague arrived in 1967 to take the helm as dean of the medical school, the campus consisted of three buildings and had earned an excellent reputation for scholarship and for solid clinical departments. But there were obvious deficiencies in the school that needed to be corrected if the institution was to fulfill its promise.

First on the list of priorities, says Sprague, was the expansion of the physical plant. Next, but no less important, was the need to develop the basic science departments on a par with the clinical departments. Finally, the clinical departments needed to expand in important areas. These were crying needs recognized by the administration and faculty, and they coincided with an increasing desire within the community to develop the school.

"There was a strong consensus among the leaders of the Dallas community that they wanted to see their school become really an outstanding institution, and the faculty was anxious to see that happen," says Sprague.

The time was ripe to make a major move forward: The Texas economy was booming, Dallas was growing and the federal government was providing funds for expanding medical schools to meet the increasing need for physicians. And the personable Sprague was just the man to bring it all together. A former Southern Methodist University football star and son of a former Dallas mayor, Sprague returned to his hometown after supervising a major building program at Tulane University School of Medicine, where he was dean. By the time Sprague was through, the student body and faculty would more than double, and the campus would spread out dramatically.

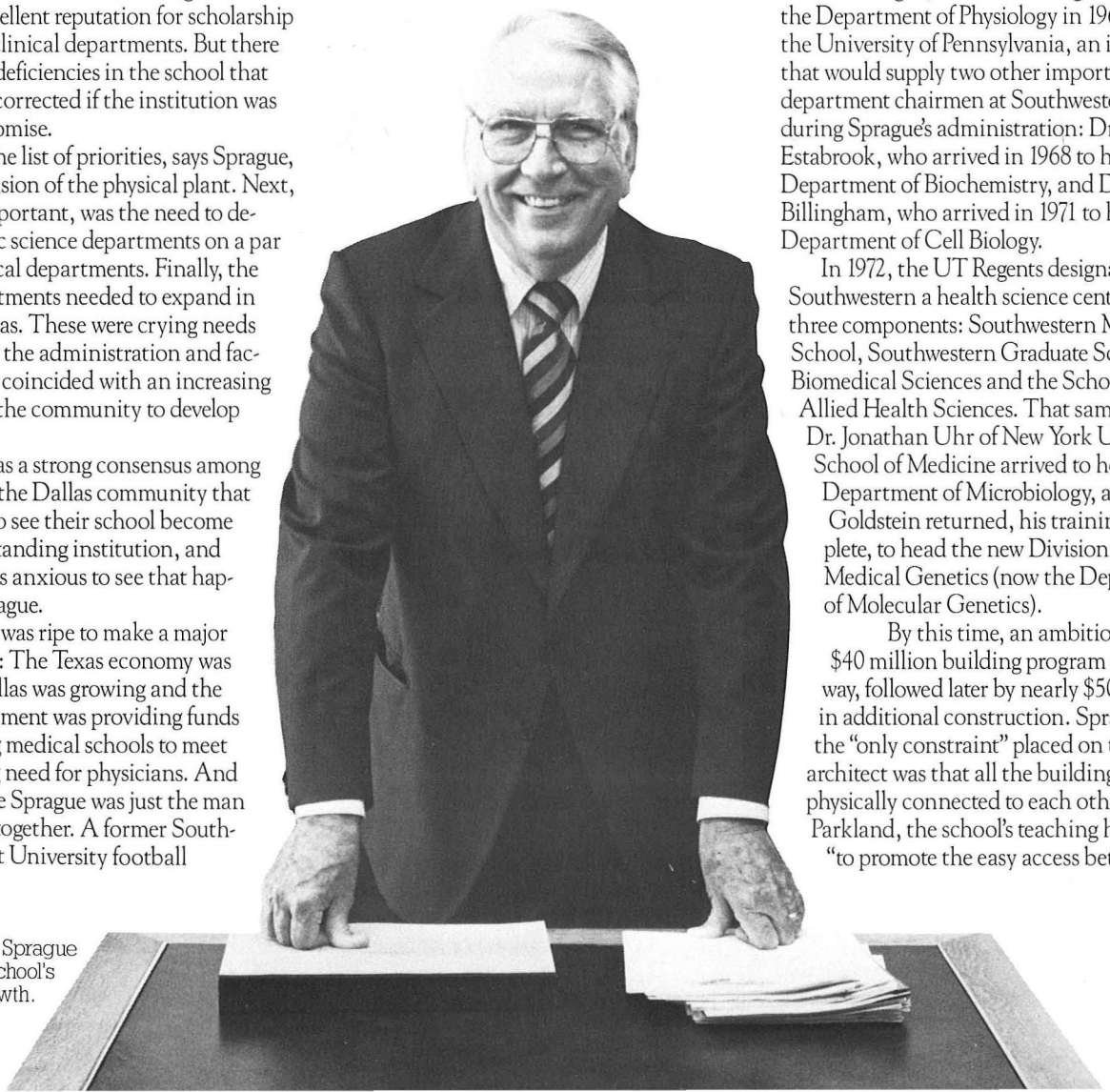
"There was a strong consensus among the leaders of the Dallas community that they wanted to see their school become really an outstanding institution, and the faculty was anxious to see that happen," Sprague says.

Although there was no articulated "strategic plan" for developing the institution, says Sprague, "there was a clear understanding on the part of virtually everyone that the major initial thrust ought to be to strengthen the basic sciences, both in terms of providing additional, much-needed space and also to recruit outstanding people into these departments."

The key was to bring in top chairmen, says Sprague. Dr. Samuel McCann, a neuroendocrinologist, had been brought in to head the Department of Physiology in 1965 from the University of Pennsylvania, an institution that would supply two other important department chairmen at Southwestern during Sprague's administration: Dr. Ronald Estabrook, who arrived in 1968 to head the Department of Biochemistry, and Dr. Rupert Billingham, who arrived in 1971 to head the Department of Cell Biology.

In 1972, the UT Regents designated Southwestern a health science center with three components: Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences and the School of Allied Health Sciences. That same year, Dr. Jonathan Uhr of New York University School of Medicine arrived to head the Department of Microbiology, and Goldstein returned, his training complete, to head the new Division of Medical Genetics (now the Department of Molecular Genetics).

By this time, an ambitious $40 million building program was under way, followed later by nearly $50 million in additional construction. Sprague says the "only constraint" placed on the architect was that all the buildings be physically connected to each other and to Parkland, the school's teaching hospital, "to promote the easy access between



Dr. Charles C. Sprague spurred the school's growth.

different groups and departments."

"Architecture can separate people; it can also draw people together," notes Seldin, who was a vigorous supporter of this unconventional architectural approach.

The result was the evolution of a remarkable esprit de corps in an already stimulating intellectual environment and a pattern of close collaboration, free exchange of information and support across departmental lines.

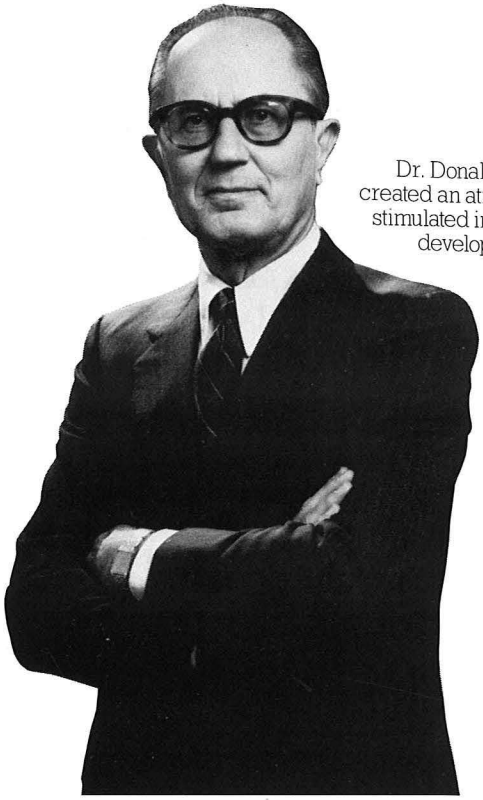
"The degree of mutual support, respect and cooperation between the basic science and clinical departments is, I think, truly remarkable," says Sprague. "This cooperative attitude has evolved into one of the major strengths of the institution."

The intellectual stimulation and collaborative spirit that pervade the health science center are among the factors that have helped keep important investigators, such as Goldstein and Brown, in Dallas. Says Brown: "In many ways, I don't believe the work that Joe and I have done could've been done at any other institution, because no other institution has the combination of assets and people that have made it possible for us to do a kind of research that spans a very broad field of endeavor."

The potential for first-rate scientific collaboration was also an element in the decision of the Howard Hughes Medical Institute to locate here instead of a dozen other top medical schools, says Wildenthal. Competition for these institutes among the leading medical schools in the country has been formidable, and the health science center's selection as the twelfth Howard Hughes Medical Institute put it in elite company.

The health science center will be one of a half-dozen institutions where the Howard Hughes Medical Institute will accelerate research into structural biophysics with laboratories containing the most sophisticated devices performing X-ray crystallography. The thrust of the institute's research will be to understand the genetic continuum from the gene to the protein to the protein's cellular function — the very basic stuff of biology and our understanding of life.

"Obviously, the Howard Hughes Medical Institute enhances the reputation and prestige of our school; but, more importantly, it also provides for us a real opportunity to enrich the school in areas in which we have not yet achieved eminence," says Wildenthal.



Dr. Donald S. Seldin created an atmosphere that stimulated intellectual development.

There were barely enough funds to attract promising postdoctoral fellows, much less a "cosmic figure," for the faculty, so Seldin looked to what was at hand — the students and residents.

In addition to the institute's sizeable monetary commitment — an estimated $28 million over the next five years and probably triple that figure over the following decade — what makes the arrival of the Hughes Institute so overwhelmingly significant is its effect on the university's ability to attract new faculty, says Wildenthal.

"It becomes a mutually enriching thing," says Wildenthal. "The Hughes Institute provides a massive influx of A-plus caliber expertise. Because they are here, we can recruit better people. Because we can recruit better people, they can recruit better people, and it spirals upward."

But this will only accelerate a trend that has been evident for the past decade. The determined commitment to excellence at Southwestern has resulted in impressive gains, and today the medical school is one of only 11 nationwide that rank at the top in seven measurements for assessing the quality of research faculty at U.S. medical schools.

These peer-review mechanisms include a survey of medical school deans; competition for Howard Hughes Medical Institutes, National Institutes of Health medical scientist training programs and NIH grants; faculty members whose papers are "most cited" in the biomedical literature; and faculty membership in the Association of American Physicians and the National Academy of Sciences. Indeed, the health science center is the only Texas medical school with more than one faculty member named to the prestigious National Academy of Sciences. The university has eight NAS members — all selected since 1979 — plus two members of the Royal Society, the British equivalent of the national academy.

"The faculty, students and alumni of this institution and all of the citizens of Dallas who support Southwestern should feel proud of these achievements," says Dr. Daniel Tosteson, dean of the Harvard School of Medicine. "They would be remarkable for any institution but are particularly impressive in a school that was founded only 43 years ago."

The Harvard School of Medicine, probably the No. 1 institution of its kind in the United States, is now in its 204th year, Tosteson notes, adding that during its first century "it was largely a local enterprise." Southwestern, on the other hand, has emerged into the international limelight within a mere four decades.

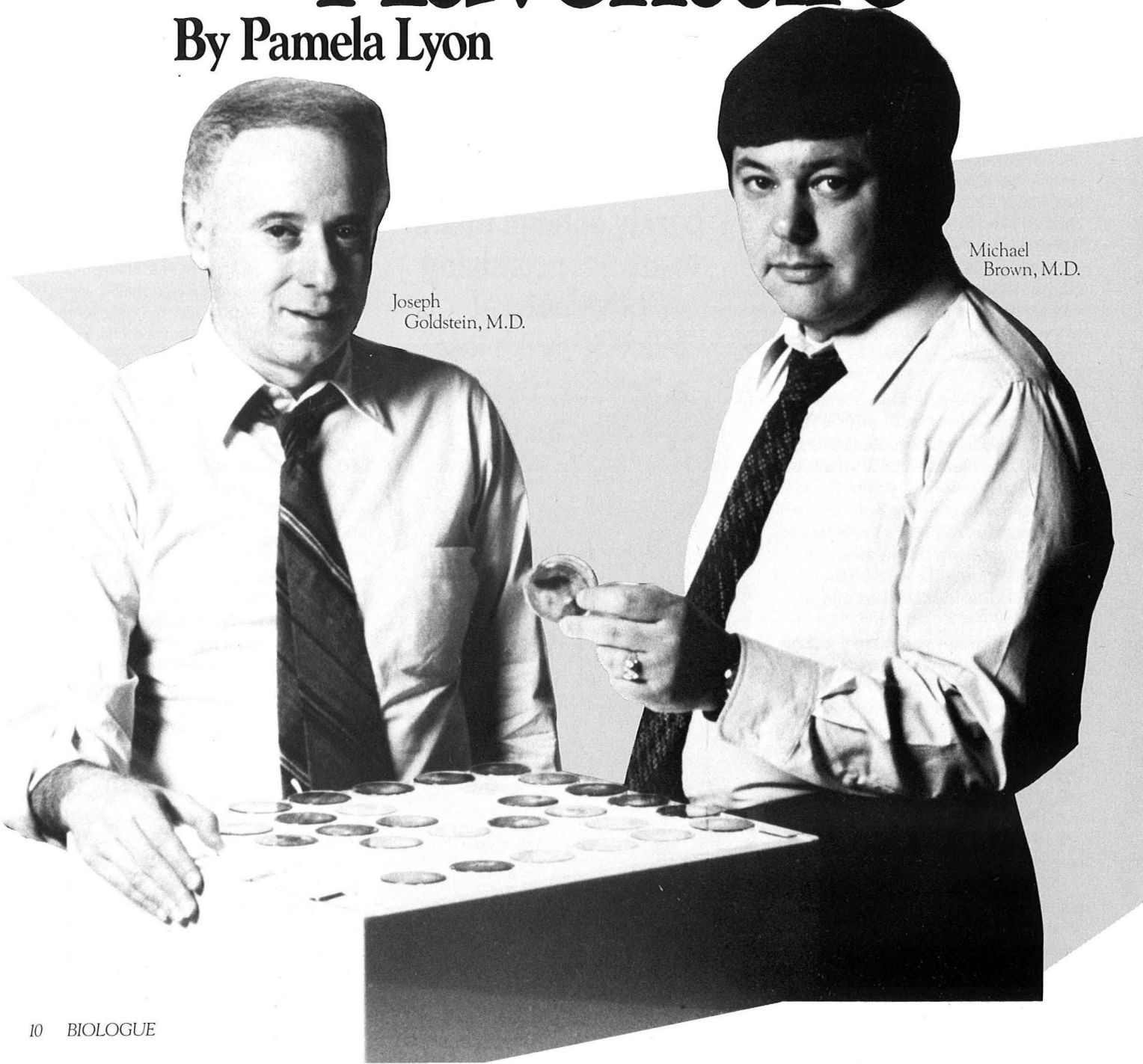
In his 1944 "Message from the President," Cary declared unequivocably Southwestern's intent to build "an institution which would rank with the best." With the achievement of that goal, Sprague has aimed those sights even higher — that by century's end, Southwestern would be named reflexively as one of the very top U.S. medical schools, alongside such renowned institutions as Harvard, Yale and Johns Hopkins University.

This year marks a giant stride in that direction. ■

Their work began with a problem of genetics. It has brought new hope for conquering heart disease and won the highest honor bestowed in medicine. But for Joseph Goldstein and Michael Brown, the continuing quest for knowledge is still

The Great Adventure

By Pamela Lyon



Joseph Goldstein, M.D.

Michael Brown, M.D.

At first glance, they couldn't have been more different. Brown was a dyed-in-the-wool Yankee with an Ivy League education. Goldstein was a resolute Southerner.

"Science is a response to the demand that our experience places upon us, and what we are given in return by science is a new human experience. . ." *Physicist Heinz R. Pagels, from "Perfect Symmetry."*

It is difficult to say what makes a person, two men, choose a path that leads to revolutionary discovery. A problem presents itself. An idea is sparked. A notion takes hold in the mind, and the painstaking quest for an answer begins.

Intuition plays a part. So does luck. Fate, too, perhaps.

In the case of Joseph L. Goldstein and Michael S. Brown, the problem was presented in the late 1960s in the form of two unfortunate children at the National Heart Institute in Bethesda, Md. The cholesterol level in the blood of these children was dangerously high. On their bodies were wartlike globs of waxy yellow fat. Their vessels were clogged with cholesterol, like a middle-aged person with atherosclerosis. Although still children, they had already had heart attacks.

This striking condition had a tongue-twister of a name: familial hypercholesterolemia, inherited high blood cholesterol. Called FH for short, the condition was identified in 1938 as an "inborn error of metabolism," passed from generation to generation, in which the complex chemical process by which cholesterol is handled in the body somehow was deranged, causing high levels of the fatty substance in the blood.

"These children were thought of as a curiosity," Brown recalls. "They were called FH — it was thought to be a severe form of FH — but nobody really thought of this as a serious genetic problem."

Goldstein and Brown, then young scientists-in-training, suspected otherwise. Here, they thought, was a totally different kind of case, a unique opportunity for studying a particular kind of genetic disease that had confounded researchers.

They could not know then, of course, that their search together for the key to understanding this perplexing disease would take them on the greatest adventure of their lives, leading them deeper and deeper into the microscopic clockwork of the body to the lowest biological denominator, the molecule.

They could not foresee that, in the years to follow, their biological sleuthing not only would uncover the defect in these children but also would prove critical to understanding and treating the No. 1 killer of Americans: atherosclerosis and resulting heart disease.

Their detective work, drawing on the talents of half a dozen key collaborators in several different fields, would do this and more. It would uncover how certain large molecules are ushered into cells past the protective barrier of the cell membrane, a basic biological process of fundamental importance not only to understanding cholesterol metabolism but also a number of the body's other chemical pathways.

And in 1985 it would earn Goldstein and Brown the highest accolade in medical science: the Nobel Prize for Physiology or Medicine.

"I don't know if they could have stayed together all these years if they hadn't been friends. They started out as friends; they did well as friends." *Dr. David Bilheimer, Southwestern Medical School's associate dean for clinical affairs and a longtime Goldstein and Brown collaborator.*

Mike Brown didn't quite know what to make of Joe Goldstein that first day of their internship at Boston's Massachusetts General Hospital in 1966. The internship was a prestigious one, and here was this graduate from a medical school he'd never heard of in, of all places, Texas. But it didn't take Brown long to realize what every person who'd ever known Goldstein realized usually sooner than later: Goldstein was special. Recalls Brown: "He was the best intern in the group."

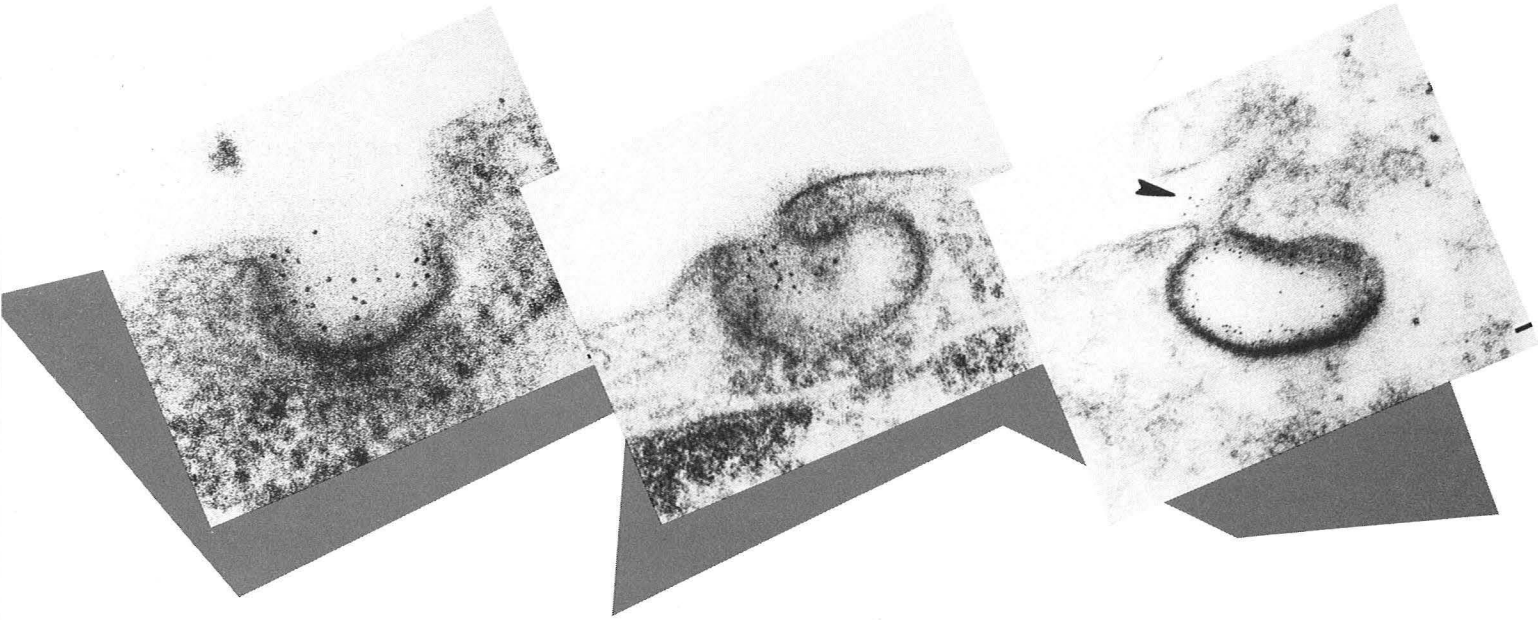
At first glance, they couldn't have been more different. Brown was a dyed-in-the-wool Yankee with an Ivy League education, born in New York, raised in Elkins Park, Pa., and educated at the University of Pennsylvania, where he received both his bachelor's and his medical degrees. Goldstein was a resolute Southerner, born in Sumter, S.C., raised in nearby Kingstree and educated at two Southern schools: Virginia's Washington and Lee University, where he received his B.A., and The University of Texas Southwestern Medical School, where he earned his M.D.

The regional influences were reversed in their personalities. Goldstein, the Southerner, was the fast talker, words and ideas shooting out in machine-gun bursts. Brown, the Northerner, was more laid back and contemplative, renowned for his sense of humor.

Beyond first impression, however, they had much in common: both were stellar academic achievers who also were heavily involved in other activities, including journalism, at all stages of their education. Both were avid bridge players. And both had won the top honors at their respective medical schools: Brown the Frederick L. Packard Prize in Internal Medicine and Goldstein the Ho Din Award.

More importantly, they shared a dynamic, penetrating intellect, a driving curiosity to know the why and how of things, a deep respect for one another's opinions and the ambition to work at the cutting edge of biomedical science — genetics.

The postulation in 1953 by Francis Crick and James Watson of the double helix structure of DNA, the basic stuff of heredity, ignited a revolution in biological study that was switching into high gear by the late 1960s, a revolution fueled by the intoxicating promise that the key to unraveling the



mysteries of life were within man's grasp. On a practical level, that could mean the discovery of ways to "fix" some of the fatal glitches thrown by nature into the human machine.

"It was clear even in the sixties where the excitement was in biomedical research, where the future lay," says Brown.

They would glimpse their future at the National Institutes of Health in Bethesda, Md., where they went for scientific training after their residencies were complete in 1968. Goldstein joined the Laboratory of Biochemical Genetics at the National Heart Institute as a clinical associate, while Brown took the same position at the Digestive and Hereditary Disease Branch of the National Institute of Arthritis and Metabolic Disease. They worked in different laboratories, but the scientific discussions continued, and it was here that their interest in familial hypercholesterolemia was sparked.

There were many gaps to fill in the emerging science of genetics, and Goldstein and Brown saw an opportunity to close a major one with an investigation of the metabolic defect in patients with FH. Of the two broad categories of inherited diseases — dominant and recessive — considerably more was known about disorders of the recessive type, such as phenylketonuria (PKU), a common cause of mental retardation. Recessive diseases don't show up when the defective gene from one parent is offset by a normal gene from the other. The absence of a normal gene makes recessive diseases easier to study because an investigator can determine the defect by comparing an afflicted patient to a normal person.

FH, on the other hand, is a dominantly inherited condition; all it takes is one gene for symptoms to appear. The dominant class of genetic disorders is statistically larger — the probability of getting one bad gene is greater — but not one of these diseases had been cracked at that time because of the interfering presence of the normal gene.

FH "heterozygotes," individuals with only one defective gene, are fairly common, about one in 500 people. In these people, the amount of cholesterol-carrying molecules in the bloodstream — the primary one being low-density lipoprotein, or LDL — is double that of normal folk from the time of birth. The excess cholesterol builds up into greasy plaques in the arteries, ultimately choking off the flow of blood and oxygen to the heart, causing a heart attack. Exacerbated by environmental factors such as smoking and diet, people with the heterozygous form of FH can have heart attacks in their thirties.

What excited the two young researchers about the children at the NIH was the belief that they were FH "homozygotes," one-in-a-million cases in which no normal gene is present to mitigate the effects of the disorder. These people have LDL levels six to 10 times that of normal people, and frequently have heart attacks before age 10. A few clinical articles had been written about the homozygous form of FH but had generated little interest. Goldstein and Brown were fascinated.

"We knew if we could figure this out (the FH defect) we'd have something really different," says Brown. "The fact that it involved cholesterol metabolism was a double bonus because it had implications for atherosclerosis and heart disease."

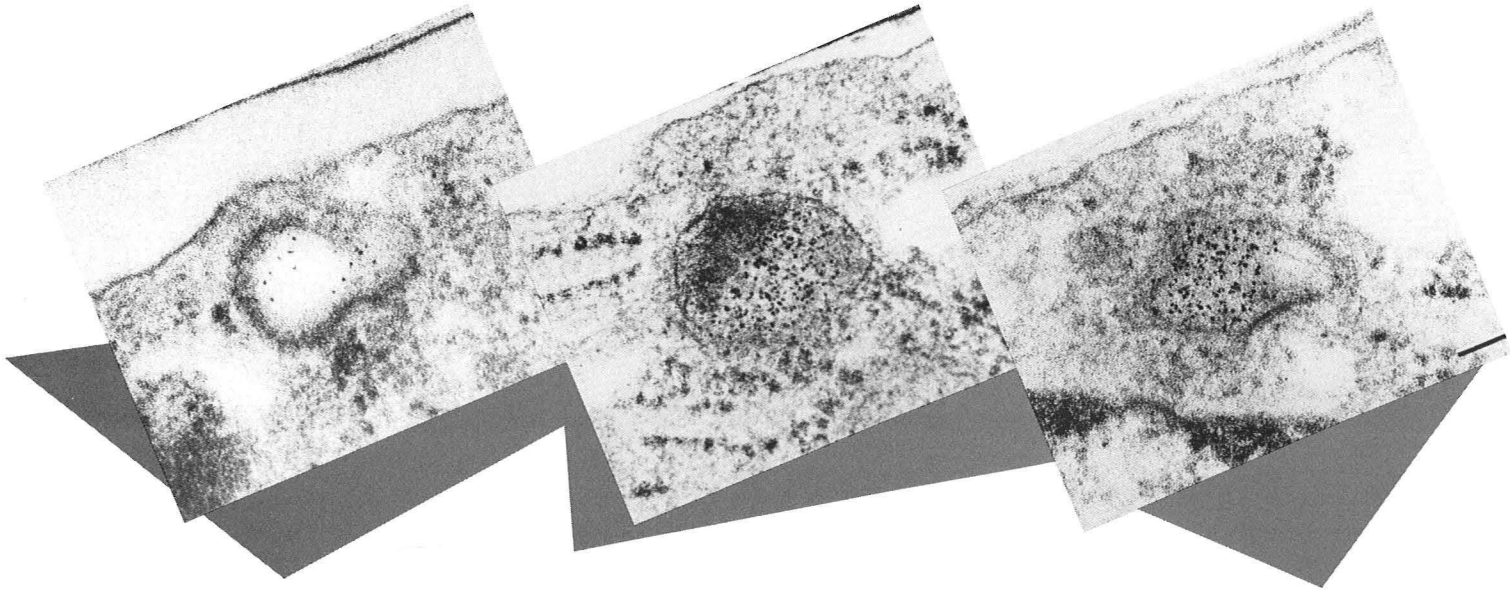
Their scientific training prepared them well for attacking the FH problem. Goldstein worked with biochemist Dr. Marshall W. Nirenberg, who won the Nobel Prize in 1968 for "breaking" the genetic code by determining that the formula for each of the body's 20 amino acids, the building blocks of proteins, is "written" on DNA in a grouping of three chemicals called nucleotides. Brown worked with Dr. Earl Stadtman, a biochemist world-renowned in the study of metabolism-regulating enzymes.

In 1970, Goldstein and Brown's paths temporarily diverged. Brown stayed in Bethesda as a guest worker in the National Heart Institute's biochemistry laboratory under Stadtman. Goldstein moved to Seattle as a special NIH fellow in medical genetics at the University of Washington School of Medicine, where under the tutelage of Dr. Arno G. Motulsky, the eminent geneticist, he got his first chance to tackle the problem of hereditary high cholesterol with a study of heart attack victims and their families.

Goldstein and Brown would be reunited again in 1972 at, of all places, the medical school Brown had never heard of — Southwestern. From the start of their friendship, Goldstein had been an effective ambassador for his alma mater, extolling the virtues of Southwestern's creative intellectual environment and especially the inspiring leadership of Dr. Donald Seldin, the razor-sharp chairman of internal medicine who so shaped Goldstein's thinking. After his fellowship in Seattle, Goldstein would be returning to Southwestern to head a new medical genetics division, a position promised him by Seldin in his student days.

From the standpoint of investigating the FH problem, Southwestern had an additional attraction: Dr. Marvin D. Siperstein, a pioneer in the field of cholesterol metabolism. Siperstein, now professor of internal medicine at the University of California at San Francisco, was one of the first to demonstrate that the rate at which cells manufacture cholesterol is regulated by an enzyme called HMG CoA reductase. A defect in the action of this enzyme, Goldstein and Brown supposed, was the root cause of FH.

Brown had a choice: Southwestern or the University of California at San Francisco, his wife Alice's favorite city. Mrs. Brown agreed to sacrifice, and in 1971 Brown joined the



From left: LDL clusters on the protein-lined surface of a coated pit, which pinches off to form a coated vesicle, or sac. This coated sac ferries the LDL to an organ in the cell that removes the cholesterol for storage and later use by the cell.

Southwestern faculty as a postdoctoral fellow in the laboratory of Dr. John M. Dietschy, now chief of gastroenterology. Goldstein returned the next year.

The great adventure had begun.

"... In the process of discovery there comes a unique moment: where great confusion reigned, the shape of the answer springs out — or at least the form of the question." *Horace Freeland Judson, from "The Eighth Day of Creation."*

Investigation of a biological process often begins with the clinical observation of a disorder and a detailed description of its effects. Then, because he can't just start probing people, the investigator tries to induce the disease in an animal to study its effects on tissues and individual cells as well as the whole body.

Goldstein and Brown couldn't do this. There were very few animal models for genetic diseases to begin with, and FH wasn't among them — at least not in 1972. They knew FH was characterized by abnormally high blood cholesterol levels, but what caused this was the puzzle. How to proceed?

A considerable body of science already had been built — and five Nobel Prizes won — based on the study of cholesterol. Cholesterol, despite its potential for harm, is so important to life that the body doesn't rely on the vagaries of diet for its supply. It manufactures its own cholesterol through the action of more than 30 enzymes to build cell membranes and to make bile acids and certain hormones. Goldstein and Brown knew from studies by others that several types of animal cells grown in the laboratory synthesized cholesterol. Why not human cells?

Soon after Goldstein arrived at Southwestern in 1972, he and Brown set about establishing a method for measuring in cultured human cells the activity of the enzyme that determines the rate at which cells make cholesterol: 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase. HMG CoA reductase, for short. The idea was to see if the FH defect showed up in fibroblasts, a kind of skin cell, which could be grown virtually limitlessly in petri dishes. Tissue from foreskins, readily available from nearby Parkland Memorial Hospital, served for their normal cell line.

This was not as simple as it sounds. As new faculty members, Goldstein and Brown not only had extensive teaching and clinical responsibilities, they also were working on other projects with more established investigators: Brown with Siperstein and Goldstein with endocrinologist Dr. Jean Wilson. Their bid to obtain funding for the fibroblast experiments failed when the proposal of which it was a part was uniformly rejected, so they scraped together funds from grants for other projects and bought time when they could, usually nights and weekends.

In addition, the notion was not widely accepted that a single genetic fault in a complex, whole-body process could be demonstrated in cultured cells. And skin cells! Prevailing wisdom had it that in order to learn anything significant about cholesterol metabolism, the liver had to be studied. Studying the livers of FH homozygotes may not have been possible or practical, but in certain scientific quarters what these young investigators were proposing to do was nothing short of heresy.

The tissue culture system was set up, and initial tests with normal cells indicated it might work. What they needed now were some cells from an FH homozygote. Since a one-in-a-million case was involved, a certain amount of luck was, too.

Enter J.P., a very sick 12-year-old girl in Denver, Colo., about to undergo experimental surgery to reduce her skyrocketing cholesterol level. The surgeon, Thomas Starzl, later world-famous for liver transplants, had a call placed to Siperstein to see if he would perform an experiment on the girl. Siperstein was in Switzerland. Brown said he would be glad to fly to Denver. And, oh yes, could he get a bit of skin from the biopsy? No problem.

The second stroke of luck, which they only could appreciate years later, was that J.P. had the "right" kind of FH defect, one that would lead most directly to a breakthrough. Today, Goldstein and Brown have a library of cells from more than 100 FH homozygotes from around the world. Each one has a slightly different genetic mutation, or error, within four broad categories identified to date. Another kind of defect might have delayed their landmark discovery for years — or sent them in another direction entirely.

"There are so many places that it could have easily gone off the track," says Brown. "We sometimes think about how long it would have taken to find out what we did if these things hadn't fallen into place the way

On the black and white images Anderson could see the LDL clustering on dense indentations on the cell membrane. But what was happening he was at a loss to explain.

they did . . .We really needed an all or nothing difference back in the early days." J.P.'s cells gave them just that.

By spring 1973, they had already learned through experiments that the FH defect, whatever it was, appeared in the cultured cells. When normal fibroblasts were mixed with serum containing LDL, cholesterol synthesis — as measured by the activity of the HMG CoA reductase enzyme — was suppressed. When LDL was removed, the enzyme's activity, and the cell's cholesterol factory, cranked up again. But when J.P.'s defective cells were mixed with the LDL-suffused serum, this feedback mechanism didn't work. The cell kept churning out cholesterol and appeared unaffected when LDL was removed.

Goldstein and Brown hypothesized that the FH defect lay in the enzyme. Something must be wrong with the HMG CoA reductase in the defective cells that prevented it from shutting down cholesterol production when LDL cholesterol was present, they reasoned. The next series of experiments disproved this hypothesis; when LDL cholesterol was treated to make it soluble enough to pass easily into the defective cells, the enzyme shut down production just like in the normal cells.

Clearly, LDL cholesterol inhibited the enzyme in some way. Could the FH defect be in the way the cells got cholesterol from the bloodstream? They designed a series of experiments using LDL tagged with radioactive iodine to find out if the molecules somehow bound to the cell. To do this they incubated the cells in a test tube with the "hot" LDL, chemically "washed" the cells to make sure nothing extraneous stuck and then ran them through a scintillation counter, a machine which measures radioactivity.

It was a summer weekend in 1973. Goldstein, Brown and a technician, Suzanna Dana, worked feverishly in a quasi-assembly line fashion, experimenting with the proportions of the chemical wash and other variables, fine-tuning the procedure. They worked in a refrigerated room to slow down whatever biological process was at work in the cells. The experimenting went on for hours; the results looked promising.

In the normal cells, they found that radioactive LDL bound to the cell surface. So far so good. Now for the FH cells. An initial test seemed to indicate that the LDL wasn't sticking to the defective cells, but they couldn't be sure. They needed at least one more result to verify the finding. They made another preparation and put the test tubes into the scintillation counter.

The machine, which was borrowed, jammed. Frustrated, they went home late that Sunday night not knowing what they had.

Recalls Goldstein: "The next day, when I came in to look at the tubes, I couldn't believe what I saw. We had these 50- to 100-fold changes we knew were very important. It wasn't something you needed statistics for."

According to conventional wisdom, cholesterol from lipoproteins passed freely into cells without any special control mechanisms. Goldstein and Brown's experimental evidence now showed that there was something on the surface of normal cells that reached out and grabbed LDL from the bloodstream. In the homozygous FH cells, the molecules didn't stick. This "something" that received the LDL was missing. The LDL "receptor," cholesterol's doorman to the cell, was born.

"From that moment, when we realized these cells had a problem in getting cholesterol from LDL, we knew there was something fundamentally new," says Brown.

"It was so exciting I don't think I could really sleep well for the next several months," says Goldstein.

They would spend the next 13 years working out the details of the LDL receptor discovery, which had profound implications beyond cholesterol metabolism. It turns out there are receptors for all sorts of things, from insulin to vitamin B-12.

At the time, however, there were quite a few people who were critical of the findings, scientists who thought the results were the product of the experimental procedure using cultured tissue and not something "real" that happened in the body. One critic even suggested the promising young researchers might do real damage to their careers if they didn't try a new line of inquiry.

"We had a strong feeling that we had something," says Brown, "but we had to look further." They were going to need help.

"To talk about these discoveries and only mention us is like covering the Dallas Cowboys and only mentioning Danny White without the rest of the team." *Mike Brown.*

To appreciate that discoveries in modern science are not the tortured work of individual scientists laboring alone in isolated laboratories, one need only scan an issue of any respected scientific journal. A research article listing a single author is the exception rather than the rule.

More and more, scientific discovery is the offspring of marriages of multiple disciplines, a paradoxical recognition of increasingly specialized areas of knowledge and an accelerated blurring of the boundaries between disciplines. The cell biologist comes to the aid of the geneticist; both employ the molecular tools of the biochemist. Nowhere is this blending more apparent than in Goldstein and Brown's work.

Dr. David W. Bilheimer was the first of what would be an impressive array of collaborators. A member of Brown's medical fraternity at the University of Pennsylvania, Bilheimer's career developed in parallel fashion, from Mass General to the NIH to a faculty appointment at Southwestern in 1973. Bilheimer's interest was lipoprotein metabolism, especially LDL, and at the NIH he had worked with some of the leading researchers in the field.

In fact, Bilheimer's method was used to prepare the radio-labeled LDL for Goldstein and Brown's initial binding experiments, but his role in the LDL receptor research would be primarily as physician to the FH patients referred to Goldstein and Brown. Bilheimer would confirm in the whole human being the discoveries in cultured cells in the laboratory.

Mary Cheatham was the first FH homozygote to come under Bilheimer's care and the first to provide the clinical proof they needed. Mary entered the health science center's research ward at Parkland in 1974 at age seven, after suffering a heart attack. During the next 10 years, until her death at age 17 in

Knowledge of the LDL receptor and its role in cholesterol metabolism alone would have profound implications for the treatment of atherosclerosis and heart disease, but Goldstein and Brown, the geneticists, had further yet to go.

1985, she would submit to a multitude of tests that would show how the LDL receptor defect interferes with cholesterol metabolism in FH patients and the rate at which LDL is produced and removed from the body. Mary Cheatham's cells are, in fact, still used in experiments.

Meanwhile, Goldstein and Brown were scouting for another collaborator. Now that they knew the receptors were there, they needed a cell biologist skilled in microscopy techniques to "show" them where they were and how they took LDL into the cell. They weren't having much success until they met Dr. Richard Anderson in 1974.

A cell biologist who had come to Southwestern a year earlier from the Oregon Regional Primate Research Center, Anderson had been studying how eggs travel to the womb and had become fascinated with cell membranes. In Anderson, Goldstein and Brown found an independent investigator who not only was versed in the techniques of cell biology but who also understood how cellular systems work. "I thought like cells think," says Anderson, now chairman of the cell and molecular biology graduate program.

Together, the three scientists succeeded in tagging LDL with ferritin, an iron-laden protein that showed up well under an electron microscope. On the black and white images Anderson could see the ferritin-linked LDL clustering on dense indentations on the cell membrane. But what was happening he was at a loss to explain.

Anderson searched the literature for references and found an obscure article published in 1964 about "coated pits," protein-coated indentations on the cell surface, which the author hypothesized might serve to transport substances into the cell. No evidence was provided, and the study languished for 10 years — until Anderson. He would demonstrate, with photographs, that the coated pit is such a vehicle for the LDL receptor. The coated pit is, in fact, vital to cholesterol metabolism. Without it, LDL can't begin its remarkable journey into the cell.

"Receptor-mediated endocytosis" was the name the three Dallas scientists gave this newly found process. As the receptors snag LDL, the coated pit pinches off to form a sac. Then, like a travelling salesman working a backroads circuit, the receptor-carrying sac ferries the LDL to a specialized organ in the cell filled with digestive enzymes called a lysosome. Here, cholesterol is extracted from the LDL, and the protein portion discarded. The receptor then travels on to other destinations in the cell, undergoing subtle changes for its trip back to the surface, where it nestles once again in a coated pit.

During its 20-hour lifetime, a receptor will make several hundred of these round-trips, roughly once every 10 minutes. The Dallas research group used a dazzling array of techniques to confirm each step of this pathway and in a long series of papers described the crucial role of each one in the process by which cells acquire cholesterol.

Nothing like this had ever been described before. Here was an intricate ballet within the cell, a series of delicate movements and complex chemical interactions to maintain the vital balance of a precious yet potentially dangerous substance. When LDL comes into the cell, which has been happily making cholesterol, the incoming cholesterol acts on the gene encoding HMG CoA reductase, causing production of the enzyme and cholesterol to fall. Meanwhile, another enzyme switches on to package cholesterol for storage. As the cell's cholesterol level rises, receptor production drops to prevent an overload of LDL. Balance is achieved.

Knowledge of the LDL receptor and its role in cholesterol metabolism alone would have profound implications for the treatment of atherosclerosis and heart disease, but Goldstein and Brown, the geneticists, had further yet to go. The next logical step was to locate the gene that produced the receptor protein and to determine what exactly was wrong with that gene in people with FH.

To do this, they needed to learn the techniques for identifying and cloning genes, a new technology that arrived on the scene in 1973. Gene cloning theoretically gave scientists the tools to "play God" in a real sense, to reproduce those unimaginably small bits of nucleic acid that instruct the chemicals of the body to make proteins and enzymes. With recombinant DNA techniques, the molecular biologist can identify, out of tens of thousands, not only a single gene that produces a particular protein but also the segment that governs a particular part of that protein.

The groundwork for moving into this area already had been laid. Investigation at the level of the gene required the purification of the LDL receptor, and by 1981 this had been accomplished by Goldstein and Brown in collaboration with Dr. Wolfgang Schneider, a former postdoctoral fellow now at the University of Alberta in Edmonton, Canada. This was not a simple thing to do, since no one had ever actually *seen* a receptor.

Schneider built upon the work of two other postdoctoral fellows, Drs. Sandip Basu and Petri Kovanen, who bravely went through a cow, organ by organ, to determine the richest source of receptors. The purification process involved a series of chemical washes of receptor-rich tissue to strip away everything except the receptor, something on the order of purifying a pinch of salt from a bowl of stew by removing all the meat, vegetables, stock and other flavorings. Technician Richard Gibson became a regular patron of the slaughterhouse, and after three years of painstaking work, Schneider finally completed the task.

By 1982, the first molecular clone in the receptor research — of HMG CoA reductase — was obtained by Dr. Kenneth Luskey, a postdoctoral fellow and now assistant professor with a long history with Goldstein and Brown. While still a medical student at Southwestern in 1973, Luskey had gone to work for Goldstein and Brown as a lab assistant "because," Goldstein jokes, "he was tired of selling boots," at his family's Fort Worth-based Western wear stores. After his clinical training, Luskey returned to Southwestern in 1980 for a fellowship. With advice from biochemist Dr. Raymond MacDonald and assistance from Dr. Daniel Chin, another postdoctoral fellow, Luskey isolated the gene for HMG CoA reductase.

But isolating the gene for the enzyme had been relatively easy because Goldstein and Brown had used a clever trick to develop a clone of cultured cells that contained 30 copies of the gene; normal cells have only two copies. Isolating the LDL receptor gene would be much trickier. Help was needed. So, on a trip to Toronto to collect one of the team's

Continued on page 25

Trail of Discovery

How one breakthrough begets a chain of others.

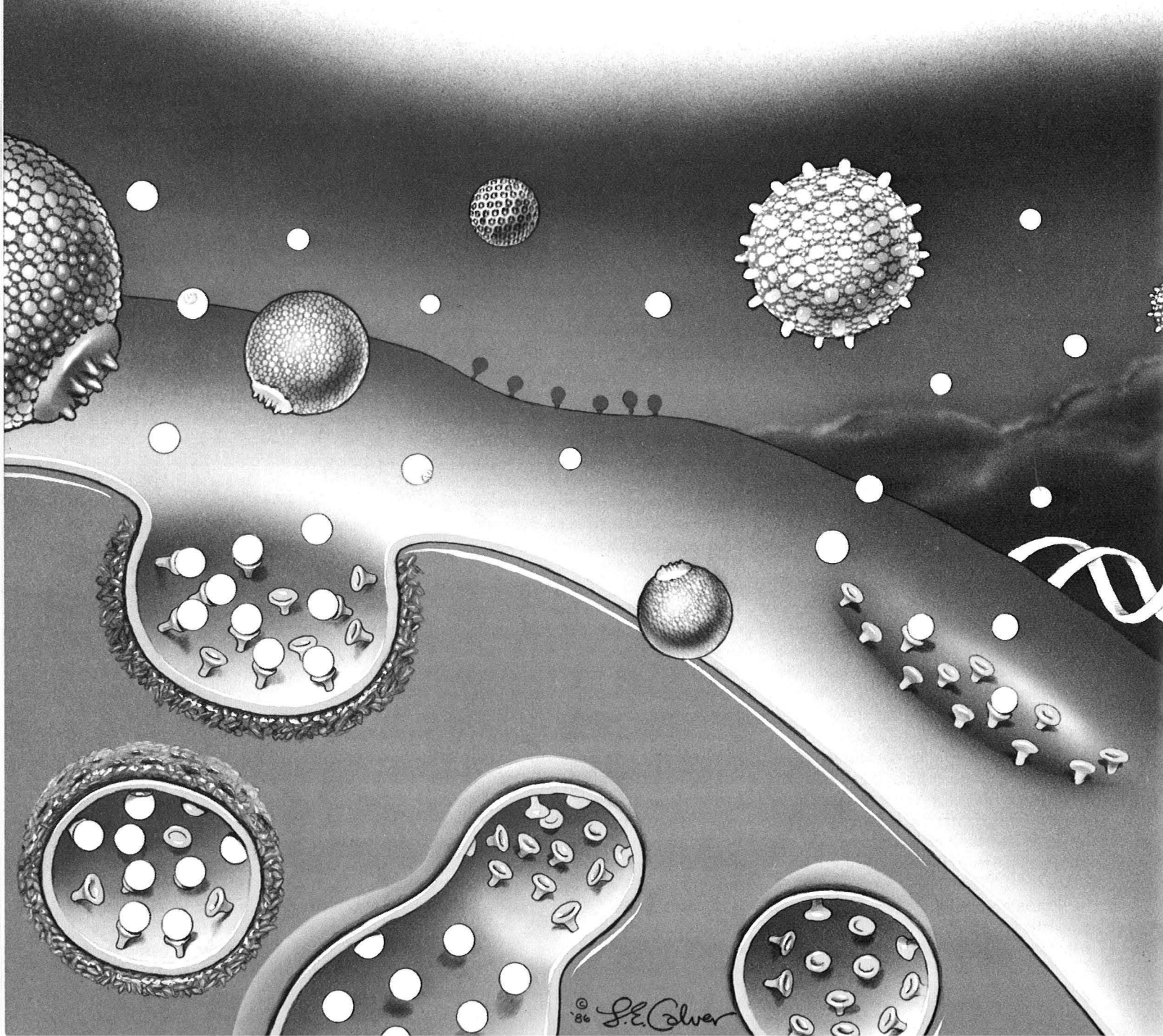
By Bob Fenley

paradigm (par'a-dim), n. 1. An example, model or pattern.

Johannes Kepler stumbled backwards into his. Some say the rap of an apple startled Isaac Newton into his. Albert Michelson and Edward Morley walked around a strange machine made of mercury and mirrors for years and never found theirs.

Each had searched in his own way for a paradigm, a pattern of the way things work so accurate and basic that it becomes a stepping stone for man's climb toward knowledge.

For Newton, it was gravity. For Kepler, it was a series of equations to describe planetary motion, which even today are written into the computers at Cape Canaveral. For Michelson and Morley, it would have been the speed of the Earth's drift through the "aether" deter-



mined by the effects of this invisible substance on a beam of light split at right angles. They would not see it, but the null result they obtained later would form the bedrock of a revolutionary paradigm — the constancy of the speed of light expounded by Albert Einstein in the theory of relativity.

Although perhaps on a less cosmic scale, scientists and academicians now are using the word "paradigm" to describe the Nobel Prize-winning work of Drs. Michael S. Brown and Joseph L. Goldstein at The University of Texas Health Science Center at Dallas. The foundation of this work was the discovery that cells have receptors on their surfaces that trap cholesterol-carrying molecules called low-density lipoprotein (LDL) in the bloodstream and then internalize them for cellular use.

"Knowledge of the LDL receptor as worked out by Brown and Goldstein has revolutionized our understanding of cholesterol and lipoprotein metabolism," writes Dr. Arno G. Motulsky, professor of medicine and genetics at the University of Washington in Seattle, in the Jan. 10 issue of *Science*. ". . .Scientists working on lipoprotein physiology and pathology had a new paradigm, and all research in this area had to pay attention to these findings."

The Dallas work opened new avenues of research in cholesterol metabolism and led the way to development of new therapies for people with dangerously high blood cholesterol levels, but its ultimate clinical impact — a possible cure for atherosclerosis and heart disease —may not be known for decades.

Nevertheless, it already is clear that their elucidation of "receptor-mediated endocytosis" — the process by which molecules are bound by receptors and taken into cells for various uses — provided a paradigm that has guided science into new realms of discovery at the most basic level. Their work illuminated a fundamental biological pathway that appears to apply to many metabolic processes and disease states, the number of which continues to rise.

The trail of discovery that began with the landmark work of Goldstein and Brown in cholesterol metabolism may lead to the understanding and conquest of many medical scourges, possibly even AIDS.

When Brown and Goldstein started their work, the existence of "receptors" — or certain areas on the surfaces of cells that appeared to have an affinity for binding certain substances — already had been postulated. What exactly these receptors did, how they worked and how common they were was not known, however. That these receptors might play a vital part in certain metabolic functions, such as the regulation of cholesterol in the bloodstream, was a quantum leap that could not even have been guessed at — until Goldstein and Brown.

If you could shrink to microscopic size to observe the process of receptor-mediated endocytosis, you might see on the cell surface what appeared to be a patch of dandelions waving in a small vale over a carpet of geometrically formed undergrowth. As the bulbous shapes of LDL float by, they are ensnared or bound by the heads of the dandelion-like receptors. Then, when enough LDL has been bound, the carpet in the vale changes, its lattice turning into pentagons

Illustration by Lewis Calver

and hexagons as the pit grows deeper and deeper, finally vanishing as the hole closes over itself.

The coated pit invaginates into the cell and pinches off, beginning a series of events in which the cholesterol is removed from the LDL and sent to build cell membrane walls or make hormones, at the same time suppressing the cell's internal cholesterol synthesis. To complete the cycle, the LDL receptor is reprocessed and returned to the surface of the cell to bind more LDL.

Since this process was discovered, studies by other investigators have shown that cells have receptors for such diverse substances as transferrin, which shuttles iron around the body, vitamin B-12, insulin, epidermal growth factor and some immune complexes.

Dr. Ari H. Helenius, an eminent professor of cell biology at Yale University School of Medicine, says that receptor-mediated endocytosis "seems to be rather a rule than an exception." Helenius says there are "at least a hundred known" substances that enter cells with the assistance of receptors.

These findings may have important implications for the development of new therapies. For example, if a drug could be developed to increase the efficiency or number of insulin receptors on cells, the regulation of blood sugar in patients with diabetes mellitus might be more easily managed.

Indeed, receptor defects may be responsible for a whole host of disorders. In some, for example Huntington's chorea, researchers know receptors are involved but they don't know the nature of them. In others, scientists only suspect the involvement of receptors.

Receptors also may be the unwitting doormen to disease, says Helenius. The Yale researcher has found that viruses can enter cells by attaching to receptors for other substances. In a kind of microscopic version of the Trojan Horse, the viruses masquerade as other substances — fats, for example — to enter the cell and do their damage, Helenius says. Diptheria, cholera toxin, rabies and retroviruses such as AIDS apparently enter cells this way.

"It doesn't make sense for cells to have virus receptors. The viruses are using someone else's," says Helenius. "The virus attaches to the receptor and the cell makes the mistake of internalizing it."

The AIDS virus, HTLV III, probably enters the cells through a receptor used by the immune system, the T-4 antigen, which is present on a small group of lymphocytes, says Helenius. This knocks out the T-cell helpers, which play an important role in the body's ability to combat foreign substances. Once inside the cell, the virus is released by a natural acidifying mechanism. Attempts have been made to block this mechanism, but the acidifying process is necessary for other cellular functions and those are blocked as well.

The LDL receptor work also has had a significant effect on research into hormones, chemical messengers secreted by the endocrine glands which regulate the rate of chemical reactions in the body. Some hormones apparently enter cells via receptors to do their work, but the LDL receptor has particular relevance to a special class of hormones — steroids.

Steroid hormones, such as testosterone, estrogen and progesterone, are synthesized from cholesterol. Cells in some steroidogenic tissues, the testes for example, apparently are sufficiently sluggish in their production of steroid hormones that uptake of LDL from the bloodstream is not essential, says Dr. Evan Simpson, associate director of the Green Center for Reproductive Biology Sciences at the health science center. For other tissues, however, LDL is required to supply adequate amounts of cholesterol. Fetal adrenal glands, for example, have more LDL receptors per milligram of protein than any other organ. The placenta and corpus luteum, which synthesize progesterone, also depend on LDL uptake for vital cholesterol.

Not surprisingly, the receptor discovery also has opened up intriguing new avenues for investigation in the area of cholesterol metabolism, says Dr. John M. Dietschy, chief of gastroenterology at Southwestern Medical School who has collaborated with Goldstein and Brown and expanded on their work.

It is known, for instance, that all mammals have receptors, says Dietschy, but comparative biology has not yet been done "to the extent of, say, determining whether alligators have them." Dietschy himself is now working on comparing the numbers of receptors in animals and humans, which may provide clues to the difference in blood cholesterol levels between animals and man and possibly redefine "normal" human cholesterol levels.

"I take the point of view that what we call normal levels (of LDL in the bloodstream) are actually way too high," says Dietschy. "That's radical because no one wants to treat a 'well' population."

Dietschy says that animals generally have about 25 milligrams of LDL cholesterol per deciliter of blood, whereas a young, healthy Western man has 75 mg/dL. Studies of some populations in Africa, South America and the Old World show bloodlevels of 25-50 mg/dL and very little atherosclerosis. (The difference, Dietschy believes, is attributable to diet.)

The current thrust of Goldstein and Brown's work is at the level of the gene, exploring how the genetic set of instructions that produce LDL receptors is turned on and turned off. The LDL receptor gene is one of less than 100 — among the more than 100,000 genes estimated to be in the human body — that have been cloned and mapped.

While the Dallas team has concentrated on the study of familial hypercholesterolemia (FH), a specific inherited condition in which a genetic defect in the LDL receptor produces high blood cholesterol levels, researchers in other parts of the country — notably the University of Utah — are building on this work to determine if variations in other genetic structures related to cholesterol metabolism might also predispose individuals without FH to high blood cholesterol.

One of the more fascinating offshoots of Goldstein and Brown's molecular work has been the discovery of similarities in the genetic coding for the structures of the LDL receptor protein and those of other proteins with unrelated functions, such as epidermal growth factor, which regulates skin growth.

Results of experiments reported last year appear to support a theory proposed by Nobel laureate Dr. Walter Gilbert of Yale University that in the course of evolution new structures with increasingly diversified jobs were built by borrowing segments of genes, called exons, from older structures. This process is called "exon shuffling." Thus the LDL receptor and epidermal skin growth factor seem to share portions of their genetic codes that may have been derived from a common ancestor. Some scientists suggest that these findings constitute strong proof at the molecular level for the process of evolution.

As a result of continued probing at the genetic level, it may be possible, in the distant future, to introduce cloned, normal genes into the cells of individuals with defective genes to produce LDL or other kinds of receptors. "Gene therapy" is currently only a tantalizing promise, however.

"The technology is simply not available to put a gene into, say, a liver cell," says Dr. Richard Anderson, chairman of the cell and molecular biology graduate program and a key Goldstein and Brown collaborator. "Gross introduction of normal genes to replace defective ones is theoretically possible but will not be technically feasible for a long time."

In summing up the impact of Goldstein and Brown's work, Dr. George E. Palade, Yale University cell biologist and winner of the 1974 Nobel Prize in medicine, says it is "a beautiful example of research that leads from discovery to understanding of biomedical problems at different levels — from that of a given molecule to that of single cells and finally to that of a whole human organism.

"The final result," says Palade. "is knowledge that will live for a long time, if not forever."■

WHAT DIET CAN DO, AND WHAT IT CAN'T

GETTING A GRIP ON CHOLESTEROL

BY
TOMMY JOY BOSLER

If you love your heart as much as you love your steak, you'll eat less steak. But you know that, don't you?

For 20 years, a number of health agencies, including the National Institutes of Health and the American Heart Association, have been trying to convince us to moderate the amount of fat and cholesterol in our diet to lower the risk of heart attack — to cut out the fried foods, cut off the visible fat, replace butter with polyunsaturated margarine and eat no more than three egg yolks a week.

For 20 years, we've been listening with one ear. After decades of increase, the death rate from coronary heart disease — mainly heart attacks — suddenly began to go down in 1968. During the next eight years, it fell 21 percent and may still be declining. An NIH panel concluded that reducing blood cholesterol levels accounted for 30 percent of the drop in coronary heart disease between 1968 and 1976.

We *are* more aware of a relationship between diet and heart disease and have changed our eating habits to some extent. We eat less beef, eggs and butter than we did two decades ago. Still, heart attacks remain the leading cause of death in the United States, and too much cholesterol circulating in the blood is still the primary culprit.

Cholesterol tends to deposit on artery walls in places where vessels branch or where the lining is roughened for some reason. As coronary artery walls are thickened by the deposits, a condition called atherosclerosis, the supply of blood to the heart muscle is gradually choked off, causing angina, or heart pain. These deposits also attract calcium and fibrinogen, forming a hard plaque that may break off as a clot and cut off the blood supply abruptly, causing a heart attack.

The link between atherosclerosis and cholesterol in the blood is well-established, and research shows that above-normal levels of a form of cholesterol known as low-density lipoprotein (LDL) appears to do the most damage. The LDL molecule combines a high proportion of cholesterol with smaller amounts of other fats and protein. LDL directly enters the arterial wall, and these particles can be identified in plaques.

Two other forms of cholesterol circulating in the blood — very low density lipoprotein (VLDL) and high-density lipoprotein (HDL) — do not appear to have the same harmful effect. VLDL is made up of a small amount of cholesterol and protein and a larger amount of a different type of fat, triglyceride. HDL has a larger protein component, and actually seems to transport cholesterol for removal from the blood.

When your doctor has a full spectrum of blood tests made during a checkup, the tests usually include a total cholesterol count. All three lipoproteins — LDL, VLDL and HDL — are accounted for in this reading, although LDL is of most significance for coronary heart disease. The reading also probably includes a total triglyceride count. Your physician can calculate your LDL count from the total cholesterol if your triglyceride level is normal. If triglycerides are high, the LDL needs to be measured in a specialized laboratory.

Most people in Western societies have far more cholesterol circulating in their blood than their bodies need. The body uses only 25 milligrams per deciliter (mg/dL) of LDL daily to make cell membranes, bile acids and certain hormones.. This is roughly one-fifth the amount of LDL in the bloodstream of an average person living in these countries.

At what level does circulating cholesterol become a clear risk factor for heart disease? According to Dr. Scott Grundy, director of the Center for Human Nutrition at The University of Texas Health Science Center at Dallas, there seems to be a threshold above which the chance of coronary heart disease rises sharply. When total cholesterol levels are below 170 mg/dL, a figure corresponding roughly to 100 mg/dL of LDL, heart attacks are rare — assuming a person doesn't smoke or have high blood pressure.

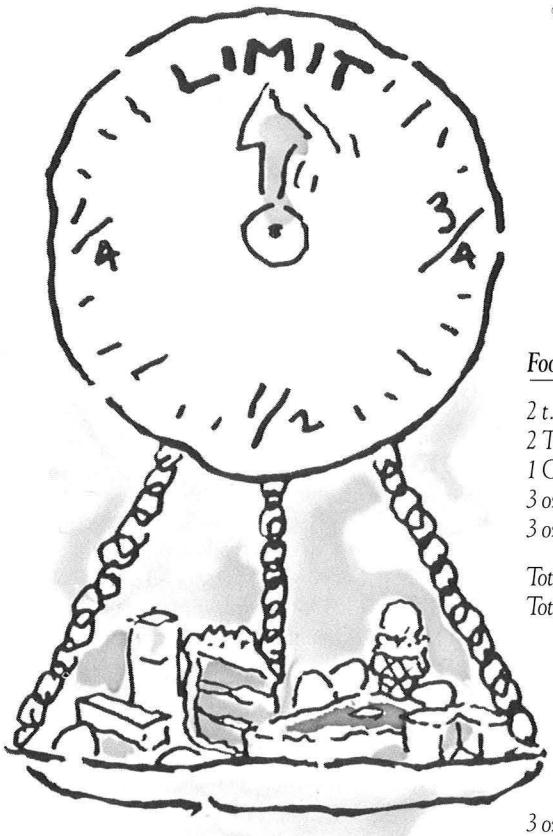
"The risk appears to increase at a steady rate until the total cholesterol reaches 200 mg/dL; then there's a curve upward," says Grundy. "A person with a total cholesterol of 250 mg/dL has about two times the risk of developing coronary heart disease as the person at 200."

Grundy defines high blood cholesterol, or hypercholesterolemia, as any blood cholesterol level associated with an accelerated risk of developing coronary heart disease. Grundy uses this rule of thumb:

Mild hypercholesterolemia — total cholesterol of 200-250 mg/dL, LDL concentrations between 125 and 175 mg/dL.

Moderate hypercholesterolemia — total

EATING FOR A HEALTHY HEART



A moderately active man maintaining his weight on 2,200 calories a day wants to follow the low-fat diet. He'll have to limit his total fat intake to 660 calories. All fats equal nine calories per gram, so he can eat 72 grams of fat in equal parts of saturated, monounsaturated and polyunsaturated fats. Fruits, vegetables and grains contain negligible amounts of fats, so only meats and dairy products need be counted. Here's what a typical day's fat intake might include:

Food	Grams/ Saturated	Grams/ Mono	Grams/ Poly
2 t. margarine	1.2	3.4	3.0
2 T. Italian dressing	2.8	8.6	6.8
1 C. milk (2% fat)	2.9	1.6	0.2
3 oz. tuna	5.0	4.0	8.0
3 oz. lean beef steak	8.6	7.0	0.8
Total grams	20.5	24.6	18.8
Total calories	185	221.4	169.2

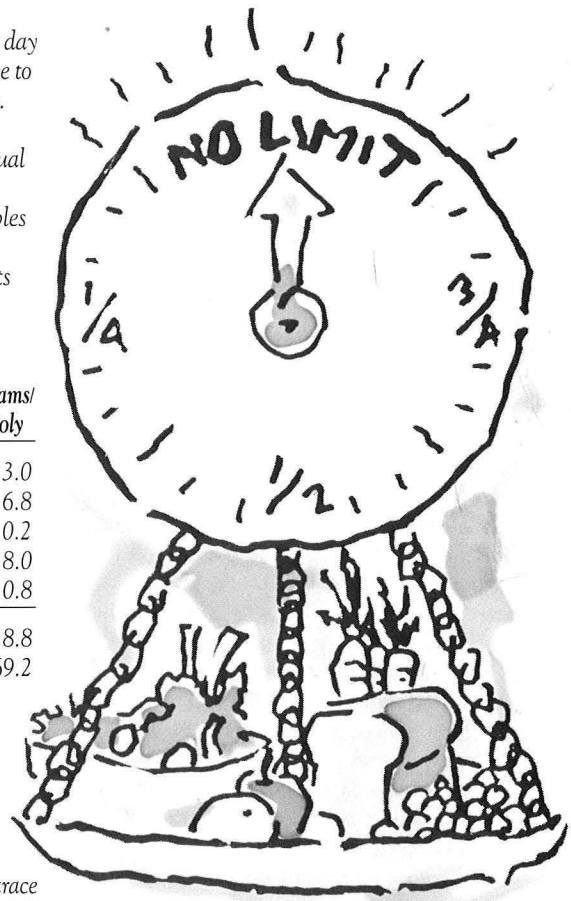
If he wants to save some fat calories for dessert, he might substitute one of the following for steak:

3 oz. salmon	5	4	trace
3 oz. chicken	2.2	2.2	1.6
1 T. peanut butter	1.5	4.1	4.1

But that won't make up for dessert if Häagen-Dazs is the choice:

1 C. rich ice cream	14.7	8.1	0.9

Information courtesy of Marjorie Whelan, clinical coordinator of the Center for Human Nutrition.



cholesterol of 250-300 mg/dL, LDL at 175-225 mg/dL.

Severe hypercholesterolemia — total cholesterol over 300 mg/dL.

Using these figures, about half of the U.S. population has some form of high blood cholesterol: 40 percent has the mild form, 8 to 10 percent has the moderate form and less than 1 percent has a severe problem.

Diet is still a valid way, generally to control high blood cholesterol, but the severity and cause of each individual case dictates specific treatment. One in 500 people, for example, has a hereditary flaw that predisposes him or her to hypercholesterolemia. Diet alone may not be enough to lower cholesterol levels to the desirable range in many of these people.

In the typical American diet, about 40 percent of calories come from fat, providing about 400 milligrams of cholesterol per day. These fat calories include 17 percent saturated fats from animal and dairy products, 17 percent monounsaturated fats, such as olive oil, and 5 percent polyunsaturated fats, or oils from vegetables and other plant sources. Cholesterol usually goes hand-in-hand with saturated fats but is especially high in organ meats and egg yolks.

You could cut your cholesterol level by as much as 40 points — a reduction worth achieving for anyone with high blood cholesterol — by following this simple recommendation of the American Heart Association: Reduce total fats to 30 percent of calories, with 10 percent each coming from saturated, monounsaturated and polyunsaturated fats. (See Chart). Cholesterol intake should not exceed 300 milligrams daily. With these diet modifications, a total cholesterol level that was 240 mg/dL — a point of increased risk for heart attack — could be reduced to the safer threshold of 200 mg/dL.

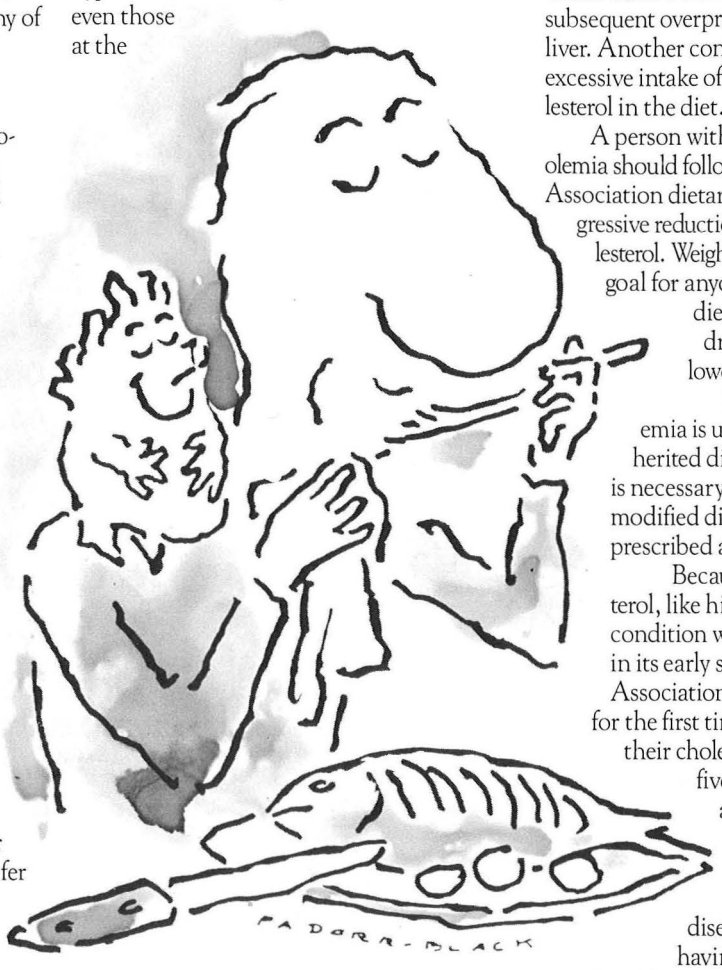
"Dietary factors seem to be the major cause of mild hypercholesterolemia, so it is only reasonable that diet should be employed in its reversal," says Grundy.

In fact, modifying the diet should "cure" most cases of mild hypercholesterolemia, says Grundy. Avoiding obesity and decreasing saturated fats and cholesterol in the diet generally can bring cholesterol levels near the 200 mg/dL level or below.

There are at least three alternatives for lowering cholesterol: a diet low in total fat calories, a diet rich in polyunsaturates and a diet rich in monounsaturates. All three reduce the intake of saturated fatty acids and cholesterol; they differ in the way fatty acids are replaced to maintain caloric balance. Regardless of choice, it is important to reduce caloric intake to achieve the desired weight.

A low-fat diet should have no more than 30 percent of calories provided by fat. The 10 percent reduction this represents from an average diet should be replaced by carbohydrates. Total fat calories should be divided equally among saturated, polyunsaturated and monounsaturated fats.

The American Heart Association further recommends a regimen that progressively reduces the total fat intake to about 20 percent of calories and dietary cholesterol to 150 milligrams a day, if necessary. Such a diet should lower cholesterol levels to the desirable range for almost all patients with mild hypercholesterolemia, even those at the higher end of the spectrum.



A diet rich in polyunsaturates is the second dietary strategy to control mild high blood cholesterol. Such a diet could retain total fat intake at 40 percent of calories, a level palatable to most Americans, but half would be polyunsaturated fats and half would be split equally between monounsaturates and saturates. This diet should reduce cholesterol levels nearly as well as a low-fat one, but animal studies have suggested that a polyunsaturate-rich diet may increase the risk of cancer. Prudence is recommended in adopting this alternative, although it may be the only one acceptable for some severe cases under medical supervision.

A diet featuring the same percentages but substituting monounsaturates as the predominant fat category should lower cholesterol levels to about the same extent. Such diets include large amounts of olive oil and are followed in many areas of the Mediterranean, including Crete, Greece and southern Italy. These diets have been used for hundreds of years in large populations with no untoward health effects.

Moderate high blood cholesterol is associated with a striking increase in risk for coronary heart disease and should not be ignored. Many cases involve a genetic defect in the removal of LDL from the bloodstream, which can be exacerbated by obesity and the subsequent overproduction of LDL by the liver. Another contributing factor may be the excessive intake of saturated fats and cholesterol in the diet.

A person with moderate hypercholesterolemia should follow the new American Heart Association dietary plan that calls for a progressive reduction of saturated fats and cholesterol. Weight loss also should be a major goal for anyone overweight. Although dietary therapy is indicated, drugs may be necessary to lower cholesterol to a safe level.

Severe hypercholesterolemia is usually the result of an inherited disorder. Drug therapy is necessary at this level, although a modified diet probably would be prescribed as well.

Because high blood cholesterol, like high blood pressure, is a condition with no obvious symptoms in its early stages, the American Heart Association recently recommended for the first time that all adults have their cholesterol levels checked every five years, beginning at age 20. Younger people with family histories of hypercholesterolemia or coronary heart disease also should consider having these tests done.

Should everyone in the United States go on a low-saturated fat, low-cholesterol diet? Grundy makes a fairly good case for most people. Obviously, those with elevated cholesterol levels should waste no time, as should people with other risk factors for coronary heart disease, including smoking, high blood pressure, diabetes, obesity or a family history of heart disease. Young and middle-aged people with cholesterol levels below the threshold can't relax. Cholesterol levels tend to increase with age.

Says Grundy: "About the only people for whom I wouldn't recommend a change in diet is an older person with a cholesterol level below 200 who has no other risk factors." ■

WHEN Diet ISN'T ENOUGH

Promising new cholesterol-lowering drugs may offer hope for many.

By Susan Rutherford

For the person suffering from hardening of the arteries, or atherosclerosis, there are now only a few drugs available to reduce dangerous levels of cholesterol in the bloodstream, and those only work to a modest degree in some people. For the one in three Americans who will die of heart attacks resulting from the critical clogging of coronary arteries, this is not reassuring.

Fortunately, the picture is rapidly changing.

Researchers at The University of Texas Health Science Center at Dallas are investigating a new generation of drugs that have proven effective in lowering the level of cholesterol in the blood, which in turn lowers the risk of developing—or worsening—the fatty plaques in the vessels that choke off blood flow.

Clinical trials are in progress to study the drugs' total effects on the body, including toxicity. If all goes well, these drugs soon may be available to reduce high blood cholesterol levels in many patients at risk of dying due to an overabundance of the fatty substance.

To date, however, no drugs have been designed specifically to remedy high blood cholesterol. Those drugs that have succeeded in doing so generally were used to treat other conditions or were discovered through a process of hit or miss. Drug researchers at the health science center are at the forefront of designing compounds specifically tailored to affect cholesterol metabolism in certain tissues.

"We are moving from an era of having no rational basis for designing cholesterol-lowering drugs to an era in which we can design drugs that will act on specific tissues with predictable outcomes," says Dr. John M. Dietschy, chief of gastroenterology, who currently is working with pharmaceutical companies to produce new drugs. "You can tell a good organic chemist what a drug should look like, and he can make it for you."

Research into cholesterol-lowering drugs at the health science center has been built largely on the Nobel Prize-winning discoveries of Drs. Joseph L. Goldstein and Michael S. Brown and their collaborators as well as investigations related to that work. Among the key scientists in the drug research are Dietschy; Dr. Scott Grundy, director of the Center for Human Nutrition; and Dr. David W. Bilheimer, Southwestern Medical School's associate dean for clinical affairs.

The foundation of this work was Goldstein and Brown's pioneering discovery that certain proteins on the surface of cells, called receptors, play a crucial role in controlling cholesterol balance. These receptors pull cholesterol-rich molecules, called low-density lipoproteins (LDL), out of the bloodstream. The more LDL is removed from the blood, the lower the cholesterol level.

Cholesterol is a two-faced molecule that, while dangerous in excessive amounts, is vitally necessary to the body. It's so important that, in addition to taking it in through receptors, cells can synthesize cholesterol themselves. Cells need it to build protective membranes, among other things.

Because cholesterol metabolism is a complex, multifaceted biological process, a combination of drugs is necessary to significantly reduce high blood cholesterol levels. Health science center researchers have succeeded in obtaining impressive results with two drugs: cholestyramine (or colestipol), a drug first used to combat the intense itching associated with elevated bile acid levels, and compactin (or mevinolin), an experimental drug developed a decade ago in Japan.

Goldstein and Brown's studies have shown that when cells need cholesterol, the number of receptors increases. Health science center drug researchers theorized that it might be possible to create a cholesterol deficiency and thereby stimulate the production of receptors to remove cholesterol from the blood.

Studies performed by Dietschy, Dr. David Spady, an assistant professor of internal medicine at Southwestern, and others showed that the liver takes up and degrades more cholesterol than any other organ in the body. The liver contains approximately 70 percent of the body's LDL receptors. Normally, cholesterol is used by the liver to produce bile acids, which are secreted into the upper intestine to emulsify dietary fats. Conversion of cholesterol into bile acids and the secretion of bile acids from the liver is the major route by which cholesterol leaves the body.

A major portion of bile acids is not excreted from the body but instead is reabsorbed by the intestine and returned to the liver to be reused. If the recycling of these bile acids could be interrupted by drug therapy, blocking their re-entry into the liver, it seemed reasonable that a beneficial cholesterol deficiency might result. The liver would convert still more cholesterol into bile acids, and more receptors would be produced to fuel this manufacture by pulling additional LDL from the bloodstream. Cholesterol levels ultimately would fall.

ecause cholesterol metabolism is a complex, multifaceted biological process, a combination of drugs is necessary to significantly reduce dangerously high blood cholesterol levels.

A class of drugs, gritty polymers or resins, was known to interrupt the recycling of bile acids by binding to these acids in the intestine. Because the resins can't be absorbed by the intestine, they are excreted from the body. These "bile acid sequestrants," among them cholestyramine and Colestipol, lower blood cholesterol levels about 15 to 20 percent.

The bile acid sequestrants were a welcome addition to a meager arsenal of modest cholesterol-lowering drugs, which included nicotinic acid, or niacin, a B-complex vitamin. Together with diet modification, these therapies were reasonably successful in treating some patients with moderately high cholesterol levels. But a more powerful drug therapy was needed for patients with severe cholesterol problems.

Mitigating the success of the bile acid sequestrants is the body's ability to gear up its own cholesterol production when a deficiency is perceived. Even as more receptors are produced, cholesterol is synthesized at a greater rate. In a delicate, see-saw process, just as the amount of LDL coming in from the bloodstream suppresses this internal synthesis, the synthesis of cholesterol puts a lid on receptor production. For the receptors to work to their top potential, the cell's internal cholesterol factory also had to be shut down.

The research team took advantage of another cholesterol-lowering drug called Compactin, which was developed in 1976 by Akira Endo at the Sankyo Drug Company in Japan. Endo was looking for an inhibitor of cholesterol synthesis, and Compactin was discovered only after screening more than 10,000 compounds. A fungal metabolite, compactin works by inhibiting the action of an enzyme that regulates cholesterol synthesis within cells. Turning off this enzyme—HMG CoA reductase—shuts down the cholesterol-making process, stimulating the formation of receptors.

Soon after Compactin's discovery, an American company—Merck, Sharp and Dohme Research Laboratories—replicated the drug in almost identical form, calling it Mevinolin. FDA approval of this drug is expected as early as 1987.

Studies by Bilheimer, Grundy, Goldstein and Brown showed that Mevinolin works to shut down cholesterol synthesis and promotes the removal of cholesterol from the bloodstream by stimulating receptors. In patients with high plasma LDL levels, Mevinolin can reduce blood cholesterol by as much as 30 percent.

As with the bile acid sequestrants, the action of Mevinolin alone is insufficient to bring cholesterol levels into the desirable range. By administering it with a bile acid sequestrant, Mevinolin's effectiveness is dramatically improved. In patients with inherited high blood cholesterol, the combined drug therapy has reduced LDL plasma levels by an average of 52 percent, bringing them within the normal range.

While the benefits of the combined drug treatment are clear, the dangers are not. Therefore, clinical tests to gauge their toxicity are continuing. If Mevinolin and related compounds prove to be nontoxic, they will provide a crucial weapon in the fight against coronary heart disease by lowering blood cholesterol levels.

There are some patients for whom these drugs are not the solution, however, the one-in-a-million cases of severe inherited high blood cholesterol in whom there are no functional receptors to stimulate. For these patients, who often have heart attacks before age 10 and usually die by age 20, the options are limited and difficult: plasmapheresis and liver transplants.

In plasmapheresis, blood is removed from the body, substances filtered out (in this case, LDL) and then returned to the body. The process must be repeated every several weeks and is very taxing for the doctor as well as the patient.

Liver transplantation has proven an effective method of providing functioning receptors that can be stimulated by drugs, thereby dramatically reducing plasma cholesterol levels. But recipients of liver transplants must continue to take drugs, such as cyclosporin, to prevent rejection of the organ, and the long-term effects of these drugs are not known.

In addition, in many individuals high blood cholesterol is exacerbated by overproduction of LDL by the liver, says Dietschy. Just how much LDL overproduction contributes to high blood cholesterol has not been fully appreciated, he says, and what causes this is still not entirely understood.

With the accumulation of detailed knowledge of how the body produces LDL and clears it from the bloodstream—both by receptors and by another method that is not as clearly understood—Dietschy foresees the evolution of a whole new class of drugs, which scientists can target to slow down production of LDL as well as speed up its removal from the bloodstream.

Perhaps the biggest question mark of all is whether the combined drug therapy, by reducing blood cholesterol levels, also will lead to the dissolution of atherosclerotic plaques already built up in vessels. Researchers say there is some indication that it may, but much investigation remains to be done. Unfortunately, there are no proven pharmaceutical remedies to unclog vessels choked with cholesterol from years of accumulation.

Currently, the only procedures available to deal with cholesterol deposits are used only in emergencies to rescue those with critical, life-threatening accumulations. Coronary arteries closed off by plaque sometimes can be opened surgically. Drugs are available in some major hospitals to dissolve clots and keep blood flowing as arteries narrow and close. Lasers are even being tested to cut away plaque deposits.

In this regard, drug testing has an additional benefit, says Bilheimer, because it provides important information about the physiological system upon which the drugs act. "The research with Mevinolin, for example, has taught us much about how the body metabolizes cholesterol, demonstrating in the whole human body findings made in the laboratory and adding valuable new information," says Bilheimer.

And every piece of new information brings us closer to a more complete response to the challenge of cholesterol.■

Taking The Guesswork Out Of Drug Design

By Pamela Lyon

Niacin, a B-complex vitamin, was long used as a treatment for pellagra before doctors discovered in 1955 that in large doses it also happened to lower cholesterol in the bloodstream. Another drug, cholestyramine, was used to relieve the intense itching associated with elevated bile acid levels in the blood before, strictly by accident, it was shown to reduce plasma cholesterol.

"If you look at the history of every one of the four or five drugs we currently have available to lower cholesterol, they were discovered by accident," says Dr. John Dietschy, chief of gastroenterology at Southwestern Medical School. "And, except for cholestyramine, we don't know how any of them works. This has been the primitive state of drug development."

Dietschy hopes to take much of the guesswork out of designing cholesterol-lowering drugs with the help of a special computer program he has developed with Southwestern researchers Dr. David Spady, an assistant professor of internal medicine, and Dr. Jonathan Meddings, a fellow in internal medicine.

The computer program is based on an exhaustive and complex series of measurements that weigh the rate at which cholesterol-carrying low-density lipoprotein (LDL) is produced by the liver against the rate at which it is removed from the blood by all the organs, especially the liver and intestine, and various other body tissues, such as skeletal muscle, skin and fat.

The program takes into account two different ways LDL is cleared from the blood: by receptors on the surface of cells — the primary pathway — and through a second process, independent of receptors, which is not as clearly understood. The program also takes into consideration how cholesterol levels in the blood affect receptor activity.

Using this new computer program, drug companies should be able to tell how plasma cholesterol will be affected if a particular drug does a certain thing. For example, a pharmaceutical house using this computer model should be able to determine how much more cholesterol would be removed from the blood if the number of LDL receptors in the liver or intestine were increased, say, five-fold.

"For the first time, we'll be able to determine how new drugs or new diets — anything that affects plasma cholesterol — will work in the body and how effective they will be," says Dietschy.

It took Spady more than a year of painstaking work, but Dietschy says LDL removal curves have been drawn for every organ in several different experimental animals, including the rat and the hamster, and it is now possible to make these predictions in man. If the curves for every organ are added up, a picture emerges of how the whole animal will behave with a given treatment.

"With this data you can now ask the question, 'What are the things that affect plasma cholesterol?' " says Dietschy. "You can break it down and ask what happens if you change the rate of LDL production in the liver or the number of receptors in a specific organ. The computer will do anything you want it to do."

The development of such extensive data on a single biological process for the purpose of designing a regulating therapy is unusual and may be unique, says Dietschy. But its value certainly has been perceived by some drug and food-processing companies, which are eager to set up the computer models "right now," he says.

"This is a major breakthrough," the scientist says. "For any company that wants to develop cholesterol-lowering drugs or diets, this is the way to go, I suspect."

While the laboratory investigators pursued answers at the molecular level, Bilheimer had been treating a new patient that would thrust Goldstein and Brown's work into international headlines. Her name was Stormie Jones.

Great Adventure

Continued from page 15

many awards, Goldstein asked molecular geneticist Dr. Michael Smith of the University of British Columbia a question which, by Brown's reckoning, was most "perspicacious" — did Smith know any molecular biologists looking for work?

As it happened, a talented postdoctoral fellow under Smith's supervision, Dr. David Russell, was completing his fellowship in the biochemistry department. He was Texan to boot, a Dallas native who had earned his bachelor's degree at UT Austin and his Ph.D. in chemistry from the University of North Carolina.

Russell started work as an assistant professor at Southwestern on July 1, 1982, and immediately began a series of experiments aimed at isolating and duplicating the gene for the LDL receptor. One year later to the day, Russell succeeded in cloning the bovine LDL receptor gene with the aid of Dr. Tokuo Yamamoto, a postdoctoral fellow from Japan.

Things moved quickly in all quarters of the department. By September, the first piece of human DNA corresponding to the cloned bovine gene was identified. The domains of the receptor gene were mapped, and the chemical sequence of the HMG CoA reductase gene was determined. By March 1984, the first human genetic mutation was located.

While the laboratory investigators pursued answers at the molecular level, Bilheimer had been treating a new patient who would dramatically thrust Goldstein and Brown's work from the world of scientific appreciation to international headlines. Her name was Stormie Jones. Bilheimer had been seeing Stormie since summer 1983, and was planning to start her on an experimental combination of cholesterol-lowering drugs to reduce a cholesterol level more than six times above normal. Then, in October, she suffered a severe heart attack. After two by-pass operations and a mitral valve replacement failed to improve the child's condition, the doctors decided to try something radical.

"Stormie was a stroke of luck in some ways," says Bilheimer. "She got so sick so fast we were forced to start thinking in a heroic way: What can we do to save this child's life?"

Studies in several laboratories around the world, including Dietschy's, had shown that two-thirds of the LDL cleared from the bloodstream was removed by receptors and that 70 percent of the LDL receptors in the body were in the liver. It made theoretical sense that replacing Stormie's liver with a normal person's would dramatically reduce her alarming cholesterol level. Transplant experiments in animals, in particular a special rabbit developed in Japan that had inherited high cholesterol, had not been promising, however. None of the rabbits had survived the liver transplants, and Stormie's heart also would have to be replaced because it was so damaged.

On Valentine's Day 1984, at age six, Stormie became the first recipient of a heart and liver transplant. The operation was performed by Thomas Starzl, the surgeon who years before had operated on J.P., and his colleagues. The results were impressive. Stormie's cholesterol level dropped 75 percent, and she now responded to drugs that reduced it further to the normal range. Stormie's future is far from assured, however, since she must continue to take drugs to prevent her body from rejecting the transplanted organs.

"You have all these theories, and you think you know what's going to happen, but you don't," says Brown. "When a theory is put into practice, that's a magic moment in science. That's really special."

"From discovery to understanding the logic of a system one studies . . . is a very long way; this makes the difference between everyday science and great science — science that outlives for centuries, if not forever, the men and women who dug it out of the darkness of the unknown." *Dr. George E. Palade, Nobel laureate, at a dinner for Goldstein and Brown.*

Two and a half years have passed since Stormie Jones' landmark surgery, and the discoveries haven't stopped. In fact, they are coming at an even greater pace. From the original team of two scientists and a technician, the LDL receptor research has grown into a collaborative effort involving three departments and an estimated 30 faculty members, postdoctoral fellows, technicians and administrative support personnel.

While these days they find themselves acting as administrators as often as scientists — Goldstein is chairman of the Department of Molecular Genetics and Brown is director of the Center for Genetic Diseases — the excitement of that first series of experiments has not abated. In the hallways and at the Wednesday lunchtime conferences are ever-challenging discussions of problems to be overcome and new findings to be developed.

The "practical" result of Goldstein and Brown's revolutionary work may well be — as the Karolinska Institute noted in announcing the Nobel Prize — that we someday may be able to have our steak and eat it, too. At this writing, promising clinical trials continue of cholesterol-lowering drugs, and diets to reduce plasma cholesterol levels, such as those recommended by the American Heart Association, are being refined based on scientific research.

Whether their work leads to a "cure" for atherosclerosis or heart disease is "the $64,000 question," says Goldstein.

But the real prize is enlightenment, knowledge upon which more will be built that will change forever the way we know the world. The work for which Goldstein and Brown were honored with the Nobel Prize has laid the foundation necessary to tackle the problem they originally set out to solve — the genetic mechanisms of FH, this time at the ultra-small level of the gene. What they have learned so far has allowed them to craft the questions: How is the inherited message written on an individual's DNA translated into the labyrinthine string of amino acids that make up the receptor protein? What signals the receptor gene to turn on or shut off the manufacture of that protein? How does a substance entering a cell regulate an enzyme?

These questions, and others like them, are the fundamental issues now bedevilling molecular geneticists and biochemists in laboratories all over the world (indeed, in other departments at Southwestern). The answers, when they are found, may have implications every bit as profound as the discovery by Watson and Crick that sparked this passion.

This chapter in the scientific odyssey of Goldstein and Brown may now be one for the history books, but the great adventure is far from over. ■

ON THE WINGS OF DISCOVERY

BY LORI WAGGONER

Thirty years ago, Drs. Cyril Clarke and Philip Sheppard didn't know their fascination with the color patterns on butterfly wings would eventually save thousands of newborn babies each year or make safe blood transfusions possible. But it was their determination to find out what controlled the inheritance of repetitive designs on butterfly wings that led them to discover the similarities between these patterns and blood groups in man.

Their research uncovered Rh factor in human blood, without which advanced medical procedures such as artificial implants and organ transplants — or even simple blood transfusions — would not be possible. Yet it was not a deliberate attempt to unravel the mystery of what makes the blood of one person incompatible with that of another which led to this breakthrough. It was, rather, a concern for a fundamental question of science.

The case for basic biomedical research is not a new one. Without it, there can be no medical breakthroughs. At The University of Texas Health Science Center at Dallas, research strategy focuses on significant health issues, but investigation often proceeds at a very basic level. Bridging the gap between the laboratory and the marketplace, however, has been problematic.

"When exploring basic questions that can eventually lead to the level of practicality, it's hard to convince Congress or lay people that, hey, we're studying something serious here," says Dr. Don Capra, professor of internal medicine and microbiology. "The guy who is studying butterfly wings is just as important in understanding where science is going as the guy who is trying a new drug to treat brain tumors. They're just different ends of the spectrum of what research is all about."

Recently, however, business has begun to perceive the profit potential in biotechnology, the catch-all term used to describe a rapidly expanding field built on basic science that involves everything from producing trees that bear more fruit to finding cures for cancer to the genetic engineering of hormones such as insulin.

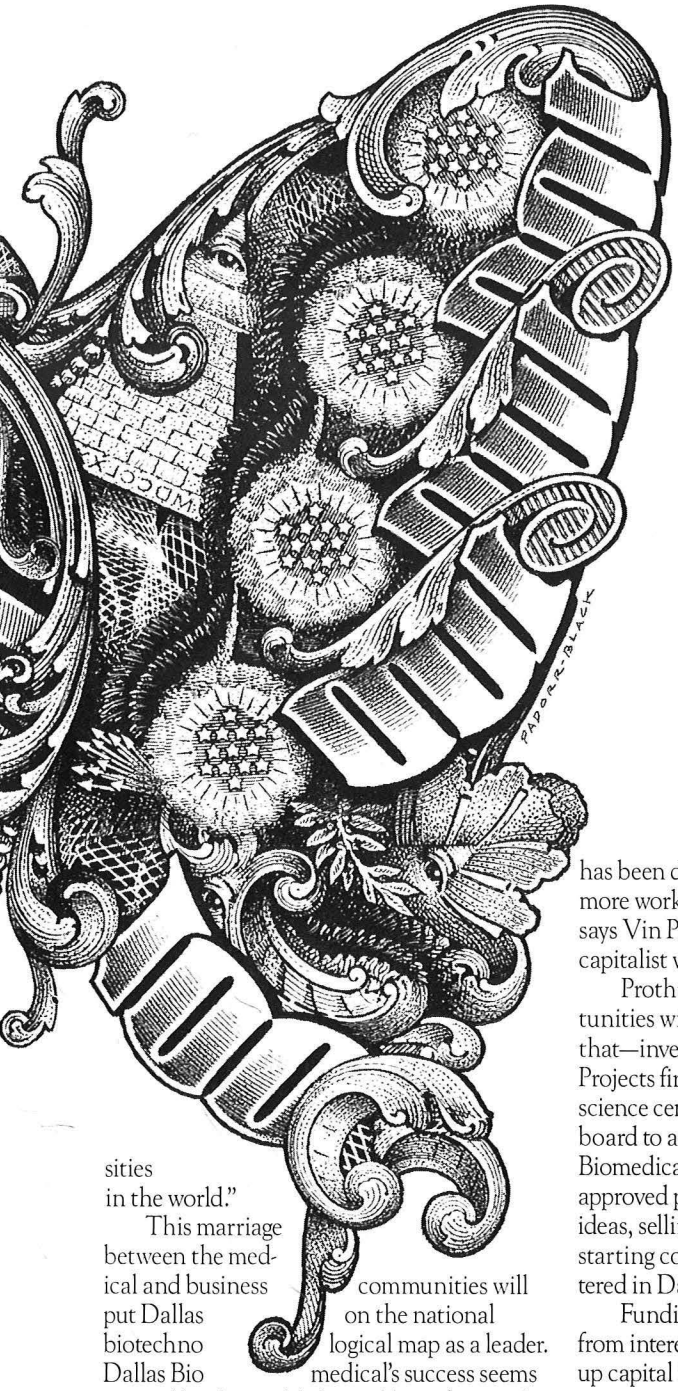
A new kind of partnership between the scientist and the commercial investor is emerging, and in Dallas a new corporation has been formed to turn biomedical research into profits.

Dallas Biomedical Corporation, created in the fall of 1985, is the first organization of its kind in the country. Designed as a private corporation independent of the health science center, Dallas Biomedical will spot promising research at the university and develop its commercial potential.

"The benefit of Dallas Biomedical is that it will identify these projects earlier in their development and accelerate the process of commercialization so that the public doesn't have to wait so long for the results of basic medical research," says Dr. William Neaves, dean of the Southwestern Graduate School of Biomedical Sciences. "This unique structure differs from existing and medical pharmaceutical products companies, which normally contract for the continuation of a project only after its commercial potential is clear."

Dallas Biomedical's beginnings promise great success. Investors already have put $12 million into the corporation, exceeding by $2 million the original capitalization goal. Taking the corporate helm as president will be Devon Giacalone, former director of commercial development for Biogen, Inc., a successful commercial biotechnology firm based in Cambridge, Mass.

Dallas Biomedical is the result of a special task force created by Mayor A. Starke Taylor to investigate ways of commercializing biotechnical research at local universities and attracting related industries to Dallas. The group recommended a partnership with the health science center, describing it as "one of the outstanding biomedical research univer-



A new kind of partnership between the scientist and the commercial investor is emerging, and in Dallas a new corporation has been formed to turn biomedical research in profits.

sities in the world."

This marriage between the medical and business communities will put Dallas on the national biotechnological map as a leader. Dallas Biomedical's success seems assured by the world-class caliber of research at the health science center, but the university also will benefit from the financial and marketing expertise of the corporation, which will help fill the funding gap between basic research and commercialization of university-developed technology.

Last year, the university received competitive outside funding of $46 million for more than 700 different research projects, a figure that should grow to more than $50 million this year, Neaves says. But very few research projects are developed commercially. Of the 700 projects in progress, only 10 currently have contracts with for-profit corporations.

This is where Dallas Biomedical will help. "We will fund ideas where the basic science has been demonstrated and needs just a little more work to come to the commercial sector," says Vin Prothro, the Dallas-area venture capitalist who headed the task force.

Prothro stresses that investment opportunities with Dallas Biomedical are just that—investments, not contributions. Projects first will be reviewed by the health science center's six-member scientific advisory board to assure their scientific merit. Dallas Biomedical then will commercially develop approved projects, which includes licensing ideas, selling ideas to other companies or starting companies that could be headquartered in Dallas.

Funding for commercialization will come from interest earned on $12 million in start-up capital from investors. Among the invited investors who have put their money and faith in Dallas Biomedical are: Diamond Shamrock Corp., LTV Corp. Retirement Trust, Lomas & Nettleton Financial Corp., Gaylord Broadcasting Co., Equitable Securities, a subsidiary of MCorp., InterFirst Securities Co. and Republic Investment Co., Inc.

While risk always accompanies investment, Prothro says that if Dallas Biomedical has only one successful project, "the return to investors could theoretically yield a profit of up to 10 times the initial investment."

Dallas Biomedical plans to fund between 15 and 20 projects at the health science center during the first five years, according to Prothro. Profits will be split 50-50 by Dallas Biomedical and the university, since both parties will equally contribute to each project's funding.

The health science center's portion will come from a $3 million grant awarded by the John A. Hartford Foundation that will serve as an investment pool to be replenished by the university's share of income from successful ventures. Dallas Biomedical was chosen to receive these funds from among 12 proposals submitted by leading U.S. research universities.

Says Hartford Foundation Chairman Leonard Dalsemer: "We anticipate that (Dallas Biomedical) may serve as a model for other universities nationwide."

Dallas Biomedical certainly has the potential for doing just that, considering the quality and quantity of medically relevant research being conducted at the health science center. Several projects already have been singled out for possible development by the corporation.

▼ Under the direction of Dr. Joseph Sambrook, chairman of the Department of Biochemistry, research into the rules governing protein structure is under way that may lead to improved drug design.

Proteins are complex molecules composed of strings of amino acids that are folded into convoluted, three-dimensional configurations. Every protein has a different shape; many of them are enzymes that catalyze chemical reactions on their surfaces and in their nooks and crannies. While scientists can fairly easily determine the sequence of amino acids in a particular protein, they

don't yet know how the rather boring two-dimensional structure of DNA can precisely specify the shape of a three-dimensional object.

If the rules that govern protein folding could be established, Sambrook says scientists may be able to develop more effective therapies by manipulating protein structures. For example, the bloodstream of mammals contains small quantities of an enzyme, plasminogen activator, whose function is to dissolve blood clots. Plasminogen activator has tremendous potential as a drug to get rid of clots that form in the coronary arteries and cause heart attacks and to prevent the formation of thromboses in the veins of people confined to bed.

The gene for this enzyme has been identified, cloned and expressed at several commercial genetic engineering companies as well as in Sambrook's laboratory. Sambrook would like to understand the three-dimensional shape of the protein, so that he can use the power of recombinant DNA technology to design a better plasminogen activator — for example, one that dissolves clots faster or acts for a longer time.

▼ Dr. Robert Eberhart and his colleagues in the graduate bioengineering program have patented a method of making plastic more compatible with blood. The process has far-reaching applications in procedures involving artificial implants and devices, which often fail because of the body's tendency to reject foreign "invaders."

In the past, the major barriers to successful implantation have been the rapid buildup of fibrinogen on the surface of the implants, which causes clots to form, and activation of the immune system, which manufactures white blood cells to attack foreign substances. Eberhart's new process prevents both problems by using a combination of chemicals and albumin — one of the body's own proteins — to coat medical plastics.

The coating "tricks" albumin in the bloodstream into perceiving the implant as free fatty acids. Since one of the functions of albumin is to bind these fatty acids and carry them out of the blood, the protein sticks to it. Fibrinogen can't collect on the plastic surface, and clots don't form. Because albumin isn't foreign, the immune system doesn't perceive the implant as a danger.

A number of plastics used in artificial hearts, vascular prostheses, dialysis and oxygenator membranes, catheters and chemical sensors in the bloodstream have been successfully coated by this process.

▼ When foreign substances enter the body, white blood cells produce tailor-made antibodies to combat each one. Dr. Richard

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Magnetic Resonance Imaging

▼ *Safer than an X-ray, keener than a CAT-scan, it's becoming the diagnostic tool for the 21st century.*

By Susan Rutherford

Magnetism, a basic force of life, holds a strange fascination for us all, like some naturally occurring magic trick. The mysterious allure of magnetism has produced such concepts as "animal magnetism" and "magnetic personality," each with connotations of an exotic, uncontrollable power.

Today medical scientists are harnessing that universal force to peer inside the living body. Powerful cylindrical magnets, large enough to position a human body within their cores, are being used to take "pictures" without X-rays. The resulting images are cross-sections of the head or body recorded with remarkable clarity and a level of detail never before achieved.

This high-quality imaging of human anatomy is called magnetic resonance imaging (MRI) or nuclear magnetic resonance imaging. It is allowing doctors at the health science center to see the thinning of heart walls after a heart attack, tumors growing inside bone and fetal disorders inside a mother's womb.

The precision of detail in these images is so improved over other imaging techniques that many scientists believe the technique may even someday replace the now-commonplace computerized X-rays known as CAT scans. In fact, for imaging of the head and spine, MRI is currently the method of choice in some hospitals.

"Most imagers believe that CAT scanning has plateaued, while MRI has just barely scratched the surface of its potential," says Dr. Kenneth Maravilla, a health science center radiologist and MRI authority.

With its scientific uses rapidly expanding, MRI is becoming a new must-have diagnostic device for high-tech hospitals. Even the most basic MRI units provide improved imaging of the brain, spinal column and pelvis, and they can be adapted to keep up with the latest advances through added computer software. CAT scanners, on the other hand, have to be totally replaced every few years to stay abreast of new developments.

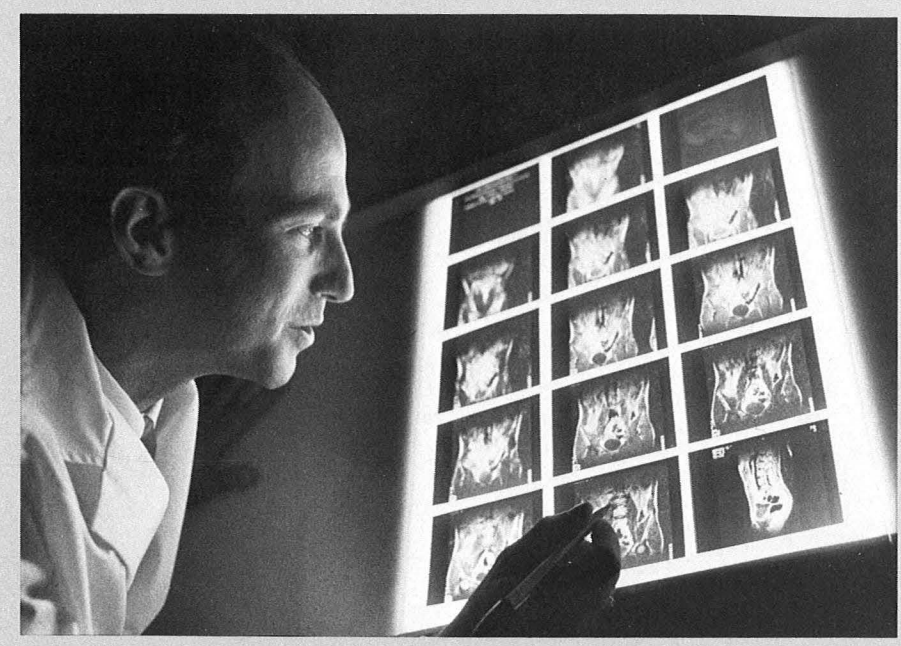
Across the nation MRI sales have risen dramatically — from 90 machines sold in 1984 to about 200 in 1985 — and manufacturers predict that in five years 1,500 will have been sold for a total of $3 billion.

Still, the average cost of an MRI unit — at least twice that of a CAT scanner — is more than most hospitals can bear. The race is on to increase the number of practical uses of magnetic resonance imaging, and the health science center is at the forefront of that research.

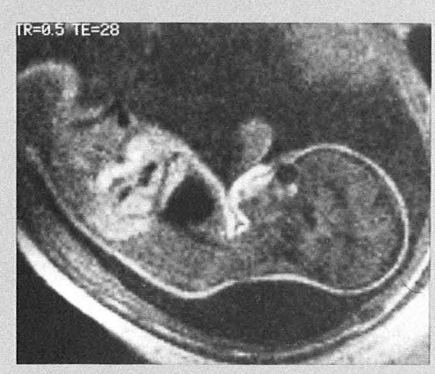
Last fall, the university's Biomedical Magnetic Resonance Center received a five-year, $2.7 million grant from the National Institutes of Health to become a regional biotechnology resource, to which investigators from Texas and surrounding states will have access. The grant will enable the center to purchase a truly state-of-the-art MRI unit that will operate at a magnetic field more than double that of other whole-body MRI machines. The center will be one of only nine such federally funded facilities for MRI research in the United States.

Scientists at the health science center are among a handful of researchers worldwide who are improving magnetic resonance imaging while also developing a new class of technology called "MR spectroscopy." This technology involves the use of even more powerful magnets to measure amounts of chemicals within a given tissue. Scientists can monitor intricate metabolic, or chemical, changes within cells by knowing what constitutes normal amounts of these chemicals.

Whereas magnetic resonance *imaging* produces CAT scan-like pictures, in MR spectroscopy results appear as graphs composed of peaks and valleys. The MRI



Above: Dr. Jeffrey Weinreb reviews MRI images. Right: MRI — safe enough to reveal a fetus in the womb.



machine's radio pulse is changed to a different frequency to detect specific chemical elements, which appear as spikes or dips in a graph according to their quantities in a particular tissue. These graphs can be visualized on a television screen or printed out on paper.

MR spectroscopy is now being used experimentally at the health science center to determine how drugs are metabolized in unhealthy tissue and how diseases can be detected early for preventive treatment. For example, researchers are investigating ways of using spectroscopy to assess the amount of injury to the heart after a heart attack.

Indeed, it was to further cardiac research that Drs. James Willerson, director of the Ischemic Heart Center, and Robert Parkey, chairman of the Department of Radiology, decided to purchase the health science center's first research magnet in 1978.

Willerson — together with Parkey and Drs. Ron Peshock and Craig Malloy in the Department of Internal Medicine — continues to pursue an extensive program of heart research using MR spectroscopy as well as imaging techniques. He is particularly hopeful about the prophylactic potential of MR spectroscopy.

"MRI may allow us to identify patients at risk of having heart attacks so that we can subsequently prevent heart attacks from happening in the future," says Willerson. "This may be done by non-invasive evaluation of changes in coronary blood flow and metabolism and serve as a warning of blood vessel narrowing."

Development of magnetic resonance imaging and spectroscopy is proceeding at such an impressive rate at the health science center that San Francisco-based Diasonics, Inc., a leading manufacturer of MRI hardware and software, has entered into a five-year, $1 million contract with the institution to develop marketable technology.

Through cooperative agreements with Diasonics, researchers at the university's Biomedical Magnetic Resonance Center already have developed the first MRI surface coil to be approved by the U.S. Food and Drug Administration. The surface coil, an enhancing device, is the primary technique for imaging the lumbar and thoracic spine. As a result of the FDA approval, Medicare is expected to begin reimbursing costs for MRI using the spinal surface coil sometime this year.

Under the five-year Diasonics contract, health science center researchers are working on a unique combination of MR spectroscopy and imaging that can be applied to clinical use. The basic idea is that imaging and spectroscopy can be made to complement each other: MR imaging can be used to define a particular tissue area while spectroscopy provides detailed chemical information.

Dr. Ray Nunnally, the MRI center's research director and leader of the team working with Diasonics, says the project involves streamlining an imaging/spectroscopic process to provide the two forms of information faster and better. Only a few research centers are currently able to acquire MR imaging and spectroscopic information simultaneously, says Nunnally, and the process has never been refined for fast data retrieval and high-quality spatial resolution.

The radiology department has benefited from several relationships with industry through the years, says Parkey. "Cooperative agreements with industry have enabled us to purchase expensive state-of-the-art equipment for research and clinical use at reasonable prices," he says.

The Diasonics agreement centers around a new MR imaging and spectroscopy hardware system with a high-strength magnet made in Oxford, England. It is the center's second large magnet. In 1983, the first unit large enough for human body imaging (several smaller units are used for animal research) was purchased from Diasonics with private funds.

This original unit is now being used to capacity for both clinical diagnosis and research. While it is technically an "off the shelf" model, the technology for its use is still evolving. Special techniques developed here for enhancing images and for extracting more information from images are continuing to improve results.

The new magnet to be purchased with the NIH grant will be the health science center's most powerful to date. The new MRI unit, expected to be delivered by late 1986 or early 1987, will be a very powerful tool for research but is too small for most clinical applications.

The university's diagnostic imaging team is composed of five staff physicians and four postdoctoral fellows along with a support staff of biochemists, physicists, engineers and technicians.

Dr. Jeffrey Weinreb, director of MR body imaging, cites several projects in his

area now receiving national attention. Among the most exciting are those using MRI in pregnant women for diagnosis of growth retardation, lung immaturity and congenital abnormalities in the fetus. Because it doesn't involve radiation exposure or injections, MRI also holds great promise as a routine method of safely imaging children with chronic illnesses, such as cancer, who must be monitored over an extended period. Indeed, Weinreb says that no hazards of MRI use have yet been demonstrated "at any level of exposure."

So far, MRI's primary function has been as a problem solver, Weinreb says, and the more the physician knows about what he or she is looking for — a tumor or other abnormality, for instance — the easier it is to find it by setting up the machine properly.

MR imaging of the brain has many advantages over other techniques, says Maravilla, director of neurological MRI. Head injuries and neurologic disorders involving anatomical abnormalities can be seen with greater clarity than with CAT scans, making diagnosis more accurate and at times eliminating the need for surgery.

Today, however, CAT scanning equipment leads in affordability and availability. Patients suspected of having a brain disorder routinely get a CAT scan first and then MRI if the diagnosis remains unclear, says Maravilla.

As MRI research at the health science center gains momentum, funding agreements fortunately are keeping pace with the progress of scientific investigation. In addition to the Diasonics agreement and the NIH grant, The University of Texas System has tentatively approved a grant to the magnetic resonance center for the construction of a special building to house the MRI research team and equipment, which currently are scattered among several locations. Additional research support also will be provided to the MRI center.

"The new funds, together with previous generous community contributions and an existing NIH research grant, will place the health science center at the forefront of MRI research technology," says Parkey. "We look forward to a future of exciting developments, with our researchers remaining on the leading edge of change."■

Wings of Discovery

continued from page 28

L. Wasserman, assistant professor of pediatrics and microbiology, and his research group are creating specific antibodies to provide protection to people whose own white blood cells either can't make them or can't make enough.

By combining white blood cells from the spleen or tonsils with tumor cells adapted to grow indefinitely in the laboratory, the researchers have developed "human hybridomas" with the characteristics of both. The new cells have the immortality of the tumor cells and the antibody-producing ability of the white blood cells. Although this technology is about 10 years old, Wasserman's lab is one of the first to use all human cells to produce human antibodies.

Several hundred hybridomas have been developed that recognize group B streptococcus, the major cause of infection among newborn infants in the United States. About one-third of pregnant women have this bacteria in their vaginas, but some can't make protective antibodies against it. Consequently, their babies are at high risk for contracting this infection at birth, and 10 to 50 percent of the newborns who do so die.

The monoclonal antibodies developed in Wasserman's lab could help provide infants with the protection their mothers can't give them. In addition, Wasserman says a "cocktail" of several antibodies active against up to 90 percent of the infections contracted by newborns could be developed, providing physicians with one preparation to cover all bases.

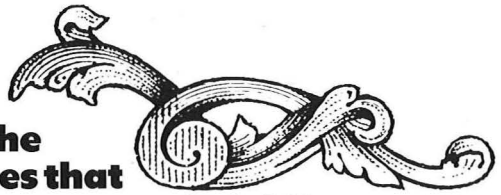
▼ Dr. David Ranney, assistant professor of pathology, has developed an array of magnetic spheres about 2,000 times smaller than the head of a pin for targeting toxic drugs through the bloodstream to tissues with tumors. In gauging the efficiency of these microspheres with magnetic resonance imaging (MRI), which takes pictures of the body with magnets instead of X-rays, Ranney and his colleagues discovered ways of enhancing the images to allow earlier detection of tumors.

Ranney's group has redesigned a simple MRI enhancing agent to improve abdominal and cardiovascular imaging. The first commercially developed enhancing agent cleared too quickly from target tissues for radiologists to complete a long series of images. Ranney's new chemical, carried in the tiny spheres, circulates longer in the bloodstream and stays in tumors longer so radiologists have several hours to complete a series of images. In addition, the new agent is less toxic, produces a sharper contrast and, in animals, has allowed the detection of tumors early enough to be removed by surgery or treated with drugs.

The new agent also shows promise for improving imaging of blood flow by MRI, which is less invasive than current techniques for evaluating the effects of ischemia, heart attacks, aneurysms and embolism of the lungs, brain and limb vessels. The new enhancing agent has the potential for use by hospitals and MRI centers worldwide in the early detection of abdominal cancers and for the non-invasive evaluation of cardiovascular diseases.

▼ For an organ transplant to be successful, tissue from the donor and recipient must match. Until now, tissue typing has been extremely expensive and difficult, but researchers in the lab of microbiologist Dr. Don Capra have developed a method of genetic typing with DNA that could be done as quickly and inexpensively as routine blood-typing.

Current tissue-typing methods rely on the use of serum from women who have been pregnant many times; pregnancy is the only circumstance in which immunization against other human tissue occurs naturally. The serum is usually obtained from Third World



If the rules that govern protein folding could be established, scientists may be able to develop more effective therapies by manipulating protein structures.

Dr. William Neaves (left) and Vin Prothro: A new partnership between science and business.

It will only take one breakthrough for the millions invested in Dallas Biomedical to pay off—for the medical community, for investors and, ultimately, for the consumer.

countries where it is not unusual for women to give birth to as many as 20 children. This procedure is extremely costly, and supplies must be replenished continually.

Capra's tissue-typing method involves isolating DNA from cells taken from drawn blood and making a "genetic fingerprint." Not only would this be useful for determining tissue types for transplants, it also could allow physicians to determine an individual's genetic susceptibility to disease. In addition, researchers could study the childhood influences of those with genetic susceptibility to certain problems and determine the environmental factors contributing to the development of these diseases.

Capra's genetic fingerprinting method currently involves radioactive materials, and the scientist says a non-radioactive approach would have to be developed for commercialization and widespread acceptance of the procedure. But the benefits would be worth it.

"We're at the point right now where we can practically predict, about 50-50, who is going to get certain diseases," Capra says. "Anybody who is poised to jump on this project commercially will do very well."

And it will only take one breakthrough for the millions invested in Dallas Biomedical to pay off — for the medical community, for investors and, ultimately, for the consumer.

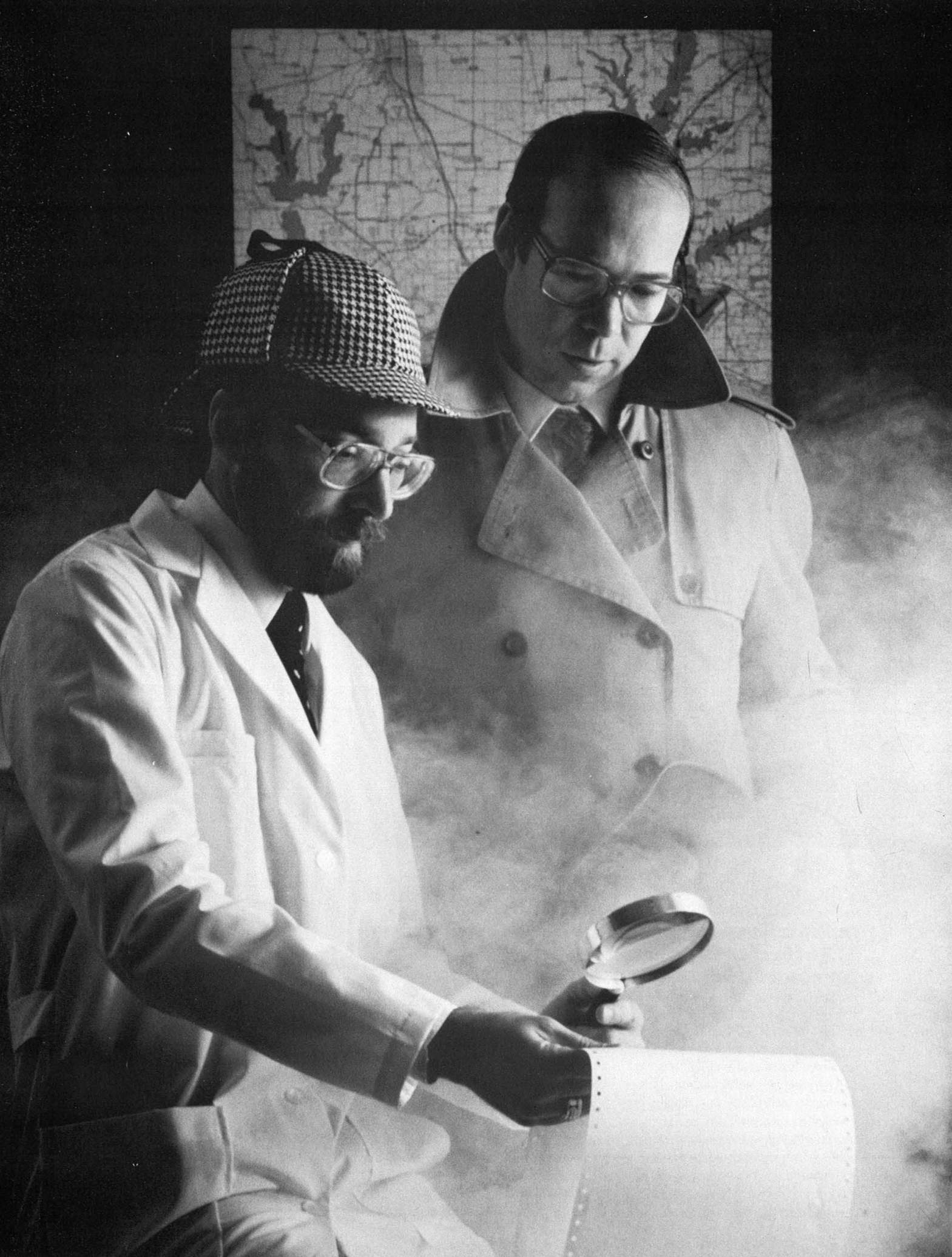
The best example of a "biomedical payoff," according to Neaves, is the polio vaccine. At the time the vaccine was developed in 1954, there were about 25,000 new cases of paralytic polio in the United States each year. Had the vaccine not been introduced, there would have been more than 500,000 additional cases by 1984. The medical cost of caring for these patients would have been about $400 billion — or 10,000 times the $40 million it cost to research and develop the vaccine, which reduced the number of new cases to fewer than 10 per year. In its entire history, the United States has spent only about $200 billion on medical research — total.

"One medical breakthrough has paid for, two-fold, all the investments in medical research in the history of the country," he says. "If anyone doubts the cost-effectiveness of medical research, they need look no further than polio, and polio was a relatively minor disease in terms of the number of people it affected each year."

Heart disease is a much more serious problem, Neaves notes. About 700,000 Americans have heart attacks each year. The annual death toll from heart and blood vessel disease together is more than one million. More than $4 billion is spent every year on coronary by-pass surgery alone — including only hospital costs and doctors' fees — and the procedure doesn't cure the disorder. It only provides symptomatic relief.

The Nobel Prize-winning research of Drs. Michael Brown and Joseph Goldstein and related investigations in other laboratories at the health science center hold the promise of correcting the major cause of heart disease: high blood cholesterol that results in clogged arteries, Neaves says.

"Their work, costing only a few million dollars since its inception in 1972, has the potential for saving society the expenses associated with coronary by-pass surgery," says Neaves. "More importantly, it may alleviate much human suffering."■



Infection Detection

By Vicki Cason

Disease sleuths devise a new scheme for collaring a surprising killer — hospital-acquired infection.

When Dr. Robert Haley arrived in Dallas in 1983 from the Centers for Disease Control in Atlanta, he immediately was faced with a life-threatening problem that would require all his skills as a detective and consume his first summer as chief of epidemiology at The University of Texas Health Science Center.

A staph infection was popping up all over the place at Parkland Memorial Hospital, the health science center's main teaching hospital. Standard infection control measures had failed to eradicate the infection. No one knew how it was spreading.

The problem was a virulent strain of bacteria called methicillin-resistant *Staphylococcus aureus*, or MRSA. It was an infection the hospital staff had first seen in 1978, after a patient was transferred to Parkland from another large hospital where MRSA had been a problem. After several months, the outbreak was brought under control and the patients who contracted it were treated and discharged.

MRSA reappeared in 1981. This time it was more potent and resistant to treatment — and more elusive — than ever. By the time Haley arrived, Parkland staff were seeing more than 30 new cases of MRSA per month. More than 500 patients would be infected, and 25 patients would die before the infection would be brought under control.

The MRSA epidemic at Parkland demonstrates one of the cruelest ironies and one of the most pressing needs of modern medicine: As medical technology and patient care advance to save more and more lives, the door is opened to the oldest scourge of human health — infection — and the need to develop effective systems to control infection becomes more acute.

Hospital-acquired infections are, in fact, one of the leading causes of death in the United States, says Haley. Each year about 20,000 inpatient deaths directly result from infections acquired while in the hospital. In an additional 60,000 deaths, these infections contribute to death but are not the only cause. Together these figures rank hospital-acquired infections among the top 10 causes of death behind heart disease, cancer and stroke.

Deaths from hospital-acquired infections remain an invisible statistic, Haley says, because death certificates usually list the illness the patient was hospitalized for as the cause of death. As a result, hospital administrators are sometimes slow to institute infection control programs that may have no readily apparent benefit.

Parkland was one of the first hospitals in the country to appreciate what a costly mistake such thinking can be, and at the time the MRSA outbreak occurred, Parkland already had an infection control program in place, says Dr. Ron Anderson, Parkland's chief executive officer and president. Parkland also has probably the best wound surveillance system in the country. Even so, Anderson says, the hospital was tested by MRSA.

"We need to understand that hospitals are dangerous places to be. There are people who are vulnerable here," says Anderson. "They certainly need the hospital, so we have to make it the safest possible environment we can for them."

In an effort to do just that, Parkland is putting into effect an intensified infection control system, which was developed at the Centers for Disease Control, tested by Haley and used by him during the MRSA epidemic in 1983.

Haley's system involves the dedication of specific, trained personnel to the infection control effort, the use of a computer to track patient surveillance records and a mechanism to feed back results to the clinical staff to effectively eradicate problems. It has been favorably received by the Joint Commission on Accreditation of Hospitals, a physicians' organization responsible for monitoring hospital compliance with national standards.

The MRSA outbreak is an example of how the system works. Using patient surveillance records Haley tracked the infection from room to room with the help of his brother, Charles, who then had a fellowship in infectious diseases and is now the medical epidemiologist for Dallas County. In all, the Haley brothers collected more than two million records. A computer analysis of the information revealed the path of the contagious disease as it spread from patient to patient. By the end of the summer the doctors were able to explain 80 percent of the MRSA cases.

The brothers took this information to the medical staff and hospital administration. They outlined a 12-point plan to bring the infection under control, including strict enforcement of hand-washing practices, intensive environmental disinfection and repair of an air conditioner.

Photo by Jon Gnass

Drs. Charles (left) and Robert Haley

Under the direction of Dr. John Weigelt, the surgeon on the infection control committee, heroic efforts by nurses and other medical staff put the new intensive infection control measures into effect within a week. The next monthly surveillance report showed the most serious type of MRSA bloodstream infections had dropped from six per month to one per month. Parkland has managed to keep its MRSA infection rate at a low level since then.

Managing infection in hospitals has become more and more difficult with the increasing use of sophisticated and invasive medical devices and techniques. "Medical technology is absolutely fabulous — but the miracle is bought at the price of infection," Haley says.

Twenty years ago, a child with leukemia was expected to die. Now, more than half of these children can expect to live normal lives. But the powerful chemotherapy that kills cancer cells also paralyzes the immune system. If a nurse touches someone who has an infection and then touches the leukemia patient without thoroughly washing her hands, that patient may contract the infection and die.

Today we have more burn units, more intensive care units, more catheters, more respirators. But even as more lives are being saved, Haley notes, "every piece of equipment and every invasive technique provides the opportunity for infection to develop."

For example, several years ago a new device was marketed to monitor blood pressure in the arteries of patients in intensive care. A catheter is inserted into the artery of the patient. The blood flows up a tube and pumps against a membrane in a transducer that registers blood pressure as an electrical signal.

The manufacturer's instructions for use of this device said to discard the membrane after each patient. But, in an effort to save money, the medical staffs of many hospitals decided it would be safe to clean and reuse the membranes. As a result, the membranes developed microscopic holes that allowed bacteria to pass from the device into the patient's bloodstream. Several patients contracted blood poisoning. Some died. But the medical staffs never realized the infection was coming from the device until a thorough epidemiological investigation was conducted.

Haley says that part of the problem in spotting nosocomial, or hospital-acquired, infections is that physicians are trained to focus on patients as individuals. In a hospital where there are hundreds of patients, doctors may not see that several have the same symptoms.

A young doctor in the early 1800s uncovered a gruesome example of how physicians

Promoting the use of computers to track hospital-borne infections has become a personal crusade for Haley.

can miss "the big picture" in a patient population. Ignaz Semmelweis was an assistant professor at the Royal Lying-In Hospital of Vienna in the late 1840s. When he first assumed his position as head of the obstetrical service, nearly one of every 10 women died in the postpartum period of streptococcal endometritis, an infection of the uterine wall.

The faculty, though concerned with the high maternal mortality rate, had resigned themselves to the situation after blaming unavoidable overcrowding in the wards, poor ventilation and seasonal and climatic factors. Some blamed the preponderance of unmarried and/or hard-working mothers of low social status in the hospital. Another popular theory held that the women were so afraid of dying from the well-known hospital contagion they became sick to death from fear itself.

Semmelweis could not accept these theories, and, in what was probably the first epidemiological study in a hospital, disproved them all. He analyzed the hospital's maternal mortality statistics from the previous 60 years and found that the mortality rates had not always been so high, but had risen from 2 percent to the 8 to 10 percent range in the 1820s. This increase coincided with the advent of the new Anatomical School of Pathology, in which cadavers were used routinely to teach medical students.

Semmelweis' investigation ultimately revealed that the infection was being transmitted from cadavers to women in labor by medical students who went from morgue to labor room without washing their hands. After instituting a strict policy of washing hands in a chlorine solution before examining women in labor, the maternal mortality rates immediately fell below 3 percent.

Unfortunately, Semmelweis' colleagues, unable to directly observe the effect of hand washing in any single patient, refused to accept his explanation. After only two years on the staff, Semmelweis' appointment was terminated. His successor allowed the hand-washing practice to deteriorate, and within another year the mortality rates resumed epidemic levels. This situation continued unchanged for another generation.

Inadequate hand-washing practices and overcrowding contribute to the spread of infection even in modern hospitals. In December 1985, a bacterial infection in the newborn intensive care unit of a Houston hospital killed one premature baby and infected 25 others. Officials blamed the spread of infection to overworked doctors and nurses not washing their hands in the overcrowded unit.

In addition to the cost in lives, hospital-borne infections exact a heavy toll in health care costs — almost $4 billion a year. Hospitals generally do not recover costs for nosocomial infections under prospective payment by diagnosis-related groups (DRGs), the categories used by insurance companies and government programs such as Medicare to designate how much they will pay for each illness.

Many hospital administrators and doctors have thrown up their hands and decided nosocomial infections are something they'll have to live with. But Haley says new information and technology are bringing about a revolution in the battle against hospital-acquired infections. Powering this revolution, says Haley, are the drive to contain costs, the scientific evidence that infection control makes a difference and his own comprehensive system for preventing and containing nosocomial infections.

DRGs have provided a financial incentive for the prevention of nosocomial infections, Haley says. In the past, insurance companies paid the additional cost for these infections. Now, in most cases, the hospital pays. The average hospital with 250 beds can prevent 168 infections and save about $260,000 each year by establishing an effec-

tive infection control program, Haley says. Preventing these infections would save 640 extra hospital days, worth about $320,000, while the cost of implementing the infection control program is about $60,000. In addition, Haley says the infection control program is an effective tool in reducing malpractice losses.

The Centers for Disease Control in Atlanta provided the scientific evidence that infection control works. In 1974, the CDC initiated a four-year study to find out how these programs were working in hospitals across the country. Of the 338 hospitals canvassed at random, half had infection control programs and half did not. Researchers found that the hospitals with infection control programs reduced nosocomial infections by roughly one-third, while hospitals without such programs showed an increase.

Haley's own system, which can be tailored to fit the needs of any hospital, is the third element in the drive for quality hospital care through infection control. The most effective infection control program, Haley says, involves dedicated infection control staff: one full-time infection control coordinator for every 250 beds and a physician trained in infection control who can spend part of his or her time on the infection control program. An active program is necessary to intervene when an epidemic is discovered, and systems to gather data on infections must include a mechanism to feed back results to clinical staff in a way that will influence practice.

Many hospitals have had problems in establishing effective infection control programs because of the volume of statistical analysis involved. Computerization is providing a solution. Haley says microcomputer software recently has been developed so that hospital staffs can use personal computers to keep track of these statistics.

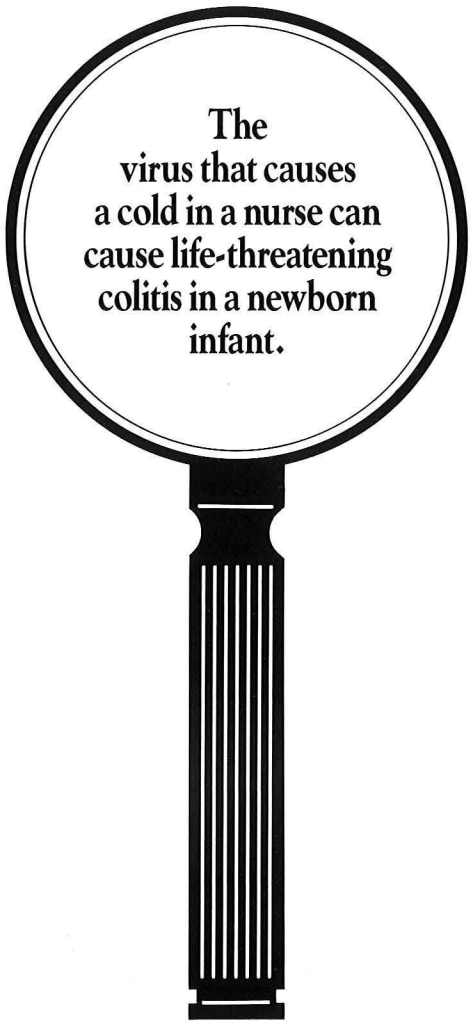
Promoting the use of computers to track hospital-borne infections has become a personal crusade for Haley, who would like to see all hospitals use his system as an integral part of infection control programs. In preparation for taking his revolution to hospital administrators, Haley took an intensive two-year course in finance and management, and he also has published a book. Within the first two months of its release, "Managing Hospital Infections for Cost Effectiveness" was number three on the American Hospital Association's best-selling list.

Parkland's Anderson is among those convinced that computerized surveillance and infection control can both cut costs and improve the quality of patient care. Anderson says Parkland will be setting the stage for a world-class infection control system by implementing Haley's recommendations in addition to funding the salaries of an epidemiologist and two additional registered nurses.

"We want to be a leader, we don't want to follow everybody else in this regard," Anderson says.

Parkland has been a pioneer in infection control since the 1960s when Dr. J.P. Sanford, former chief of infectious diseases at Southwestern Medical School, started one of the first active programs at the hospital. After only five years in practice, Parkland's wound surveillance program is now considered one of the best in the country, says Dr. James Luby, chief of infectious diseases at the health science center.

The complexity of infection control in a 940-bed hospital such as Parkland is mind-boggling. Building renovation can uncover organisms in the soil and walls that are not a problem for a normal, healthy person but can create serious complications in a kidney transplant patient. The use of antibiotics may produce new strains of drug-resistant organisms. Hospital staff can spread disease if they aren't properly immunized or if they aren't sent home to recover when they become ill. The virus that causes a cold in a nurse can cause life-threatening colitis in a newborn infant.



Infection control nurses are the first line of defense against infection. A team approach is important, but sometimes the job requires the tact of a diplomat, says Donna Dryer, who began nursing at Parkland 25 years ago and became Dallas' first infection control nurse in 1969.

"Once people know you're not there to point fingers, you'll get cooperation," says Dryer, adding that the hardest thing to make people understand is that infections are caused by people. "It's easier to blame an inanimate object like the air-conditioning system," she says.

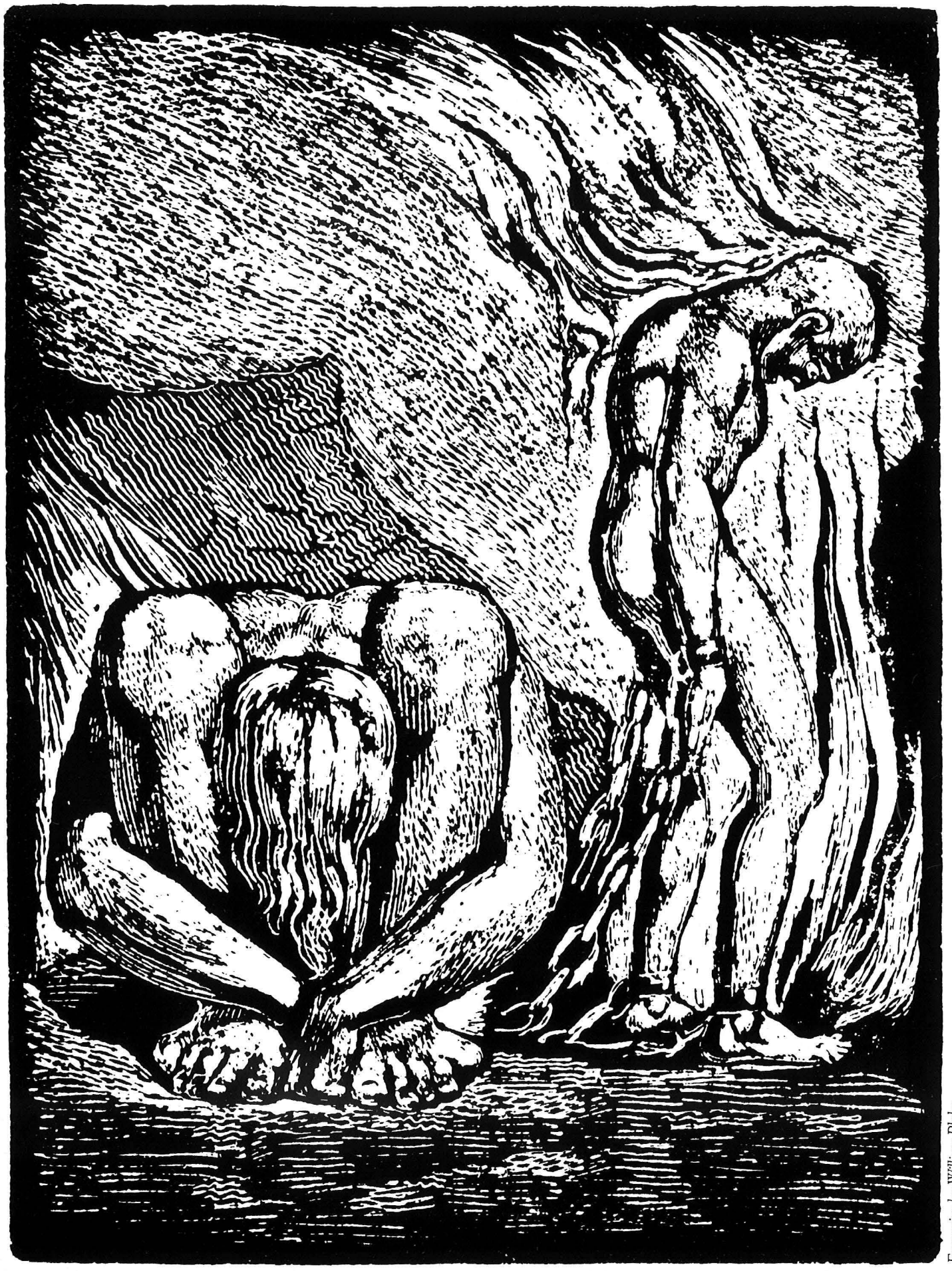
Dryer says she believes that Haley's recommendations for infection control will be heeded by infection control specialists, but she doesn't know how much support they will get from hospital administrators. "In a small hospital, where there is a money crunch and positions have to be eliminated, they eliminate infection control because it's hard to put a dollar sign on what we do," she says.

Anderson agrees. Under the DRG system, the drive is to cut existing costs and avoid new ones. "Many hospital administrators aren't going to invest in anything that costs new dollars that they don't see revenue attached to," says Anderson. So instead of instituting a quality infection control program, a hospital may open up a day surgery unit or spend money to market plastic surgery.

Anderson believes the way to win under the DRG payment system is to provide high quality care at the best possible price by using Haley's infection control system. Anderson plans to encourage the State Board of Health to set up seminars around the state for smaller rural hospitals.

But resistance to change is ever present, Anderson admits. Hospital administrators and staffs may prefer to stick with their own methods of infection control even if they aren't the most effective. "People have been dutifully running around culturing the floor and culturing the windows and culturing the curtains and culturing all kinds of things. They have their whole jobs built around this," Anderson says. The result of hit-or-miss efforts may be worthless from the standpoint of identifying the source of a spreading infection.

"Many people just blindly assume that if I do the best I can, it must be good. That's just not going to be acceptable," says Anderson. "I want to be in a hospital that's measuring these things and is on top of what happens instead of one that assumes that it's doing a good job."■



Engraving by William Blake

BY LORI WAGGONER

FROM HELL TO HERE

The road to recovery from a serious burn is a long and torturous one. Researchers now are studying how burn victims adjust.

"My whole life changed in two hours," says Debbie Davidson, a beautiful, 30-year-old blonde, of the accident that burned 76 percent of her body. Although it happened six years ago, the memory remains fresh.

She was taking a hot shower late one night and had an epileptic seizure. When she woke up two hours later, she touched the faucet to turn off the water and felt a thousand needles pierce through her body. She knew something was wrong. She looked down at her throbbing, beet-red legs but still didn't know what had happened to her. She ran to the kitchen, climbed onto the counter, put her legs into the sink and ran cold water on them. The water felt warm. Debbie decided to call an ambulance.

The first time Debbie knew she had been burned was when she heard the ambulance attendant radio Parkland Memorial Hospital to alert them to the arrival of a young woman with second- and possibly third-degree burns. "What's happened to me?" she screamed. The emergency room team rushed about her and asked for next of kin. The nurse's expression was Debbie's first clue to the severity of her condition.

"Am I going to die?" she asked.

"You might," came the reply.

Today, Debbie lives a "normal" life. She has a job as a marketing assistant that she loves; she enjoys volunteering her time to visit burn patients in the hospital; and she speaks with excitement about her coming wedding.

More and more victims of serious burns, like Debbie, are surviving because of advances in burn treatment. Nearly three million Americans are burned each year. About 11,500 of them die, but the survival rate has improved roughly 20 percent in the last 20 years. Patients with burns as severe as 90 percent or more are surviving life-threatening infections, fluid loss, respiratory failure and malnutrition because of continued research and new techniques.

But living through the nightmare of the accident itself is only the beginning of a long road to recovery, a road traveled with hours of excruciating pain, months of rehabilitation and a lifetime of horrifying memories.

"Surviving is only the start," says Dr. Charles Baxter, medical director of the Skin Transplant Center for Burns and the Lions Sight and Tissue Foundation at The University of Texas Health Science Center at Dallas. "Patients must face months, even years, of watching their bodies change — seeing scars develop and feeling the tightening and restricted movement of their injuries.

"Many face years of additional reconstructive surgery. And treatment can involve prolonged periods of separation from family, friends, job — all the comforts and security of everyday life. This produces extreme psychological stress on top of learning to accept and live with extreme physical deformity."

Not all burn patients adjust as well as Debbie. Most who survive have a lifetime of medical and psychological complications. But little has been documented about the long-term effects of burn injuries, so a team of doctors and researchers at the health science center has started a two-year study to see how burn victims adjust physically, emotionally and socially to lives radically altered by freak accidents.

"Nobody really knows what happens to burn patients five, 10, 20 years later," says Baxter. "Are they back to normal mentally, physically, emotionally? After cosmetic surgery they may appear almost normal on the outside, but on the inside they may have problems with their own personal image. And we don't know how they're functioning physically. Do they have any chronic diseases, or do they just convince themselves that they're always going to be sick?"

Baxter, Dr. Phala A. Helm, chairman of physical medicine and rehabilitation, and Dr. Fred Cromes, chairman of rehabilitation psychology, will head the team, which will take patients who were burned several years ago through a two-day series of tests that includes cardiovascular, neurological and psycho-social evaluation. During the next two years, the researchers hope to test 50 to 100 patients and collect enough data to indicate how a severe burn affects a person later in life.

"To our knowledge, nothing has been published specifically for this purpose," says Cromes. "What we know about what happens to patients long after they've left medical care is based on speculation, not data."

Once published, the study can help doctors more accurately inform their patients about potential health problems that often result from severe burns, such as arthritis, weight fluctuation and impaired immune defenses. Initial burn treatment also may be improved.

The information gained from the study also will help burn patients work with insurance companies and employers toward resolving workman's compensation claims and returning to work.

But why, with all the recent advances in burn care, have studies such as this not been conducted? "No one has ever had the patient population to bring back like we have," says Helm, who sees more than 1,000 outpatients each year.

The highly respected Parkland Burn Center, run by Southwestern Medical School, has developed an enormous patient population during the last 25 years as its reputation for top-quality patient care and research has grown. In 1973, the burn unit became one of four federally designated "centers" of the National Institutes of Health. (A unit only treats patients; a center also conducts extensive research and offers comprehensive treatment and rehabilitation.) Today, the Parkland center is one of the largest burn facilities in the country in patient volume.

Through the years, the burn team at Parkland has developed new approaches to handling burn complications, innovations for which the center is respected nationwide. The "Parkland formula" for fluid resuscitation developed by Baxter is widely used, and health science center researchers have led the way in what is probably the most significant accomplishment in burn care — the use of human skin for covering large wounds. The Dallas skin bank, headed by Baxter, routinely receives between one-third and one-half of the donated skin in the United States and was the first to supply skin to other centers on an emergency basis.

The long-term burn study is a logical outgrowth of the health science center's pioneering burn research. "Long term," for purposes of the study, includes patients who were burned at least two years ago, but the doctors also hope to test patients who were burned as many as 10 to 15 years ago. Past studies of burn recovery have been limited to hospitalization or the immediate post-discharge period.

Burn victims to be tested in the study have all suffered burns to more than 30 percent of their total body surface. These will include severe facial and hand burns, burns to the pelvic area and electrical burn injuries. Participants in the study will be tested by Baxter and Helm for physiological functioning and by Cromes for psycho-social adjustment. These different areas of interest and expertise, when combined, will cover all aspects of the patients' physical and psycho-social well-being.

Dr. Baxter is looking at normal physical capabilities. Strength tests will give an indication of muscle deconditioning, which is quite common among burn patients, he says. Many burn patients complain of tiring easily.

"Before his accident, Marvin was in excellent physical condition," says Bill Pinney of his 46-year-old brother, who suffered burns over 70 percent of his body in an electrical accident. "He ran two miles every day and worked out at the gym; he worked most younger men under the table. There's just no comparison to the condition he's in now. He can walk a short distance and immediately be tired and out of breath."

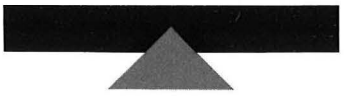
Baxter plans to monitor patients' responses to cardiac stress and isometric exercise. Both stress and blood testing will allow researchers to determine changes in the fatty deposits on artery walls and cholesterol levels that may indicate future cardiac problems. Doctors already have noticed similarities between burn patients and patients with hardening of the arteries.

The team also will conduct nutritional assessments. Baxter says it is not unusual for post-burn patients to crave certain types of foods that include excessive amounts of oils, fats and carbohydrates. It's not unusual for a skinny patient to become extremely overweight due to this insatiable appetite. The study hopes to determine whether this nutritional imbalance is the result of depression and eating "binges" or metabolic changes resulting from a burn injury, Baxter says.

Patients also will be tested for hearing and vision loss. Burn patients often must take large dosages of antibiotics for extended periods, which can cause progressive hearing loss. And electrical injuries often lead to cataracts and other eye impairments.

Hormones also can be affected by a severe burn injury. Testosterone production in men is halted in the acute phase and may not return to normal for up to three years, says

Thanks to advances in treatment, more and more burn victims survive. But nobody knows what happens to burn patients — physically and emotionally — five, 10, 20 years later. "Surviving is only the start," says Baxter.



Baxter. The pituitary gland, which secretes hormones that regulate many bodily processes, also may be affected.

Finally, Baxter is concerned with the burn patient's reduced immunological responses. Before his burn accident Marvin Pinney was always healthy; now infections are commonplace — everything from eye infections to respiratory infections. Infection in the burn wound itself can pose problems, says Baxter, so tests will be done on blood flow to the burn and the actual healing of the wound. In many burn patients, the wound may be chronically open, he says.

Helm's primary area of interest is studying neurological complications. Electrical injuries, for example, often damage the spinal cord, which can lead to paralysis. While doctors know the possibility for such damage is ever-present, they don't know exactly when paralysis will occur or if the condition will get progressively better or worse. Helm says this problem often is complicated by the absence of early signs or symptoms.

Helm also plans to study how a burn injury affects muscles and bones. Severe burns can cause bone and joint changes that may trouble the patient throughout his or her lifetime. Contractures in the joints can severely limit movement, as in Debbie Davidson's case. Scald burns critically damaged the joints and tendons in her left hand, of which she still has not regained full use. Doctors have told her to watch for signs of arthritis, a condition many burn patients develop.

In some cases, bone spurs occur in tissues that normally do not ossify, which restricts a patient's range of motion, while in other cases bones decalcify. Osteoporosis, or a severe thinning of bone, has been reported in about 36 percent of severely burned patients.

Since burn patients also may lose feeling in their grafted or scarred areas, Helm says she will monitor sensory return. Heat and/or cold tolerance may be a significant problem for many patients. Those with deep burns often lose their sweat glands, which gives them an extremely high intolerance for heat.

But physical disability is only a small part of the adjustment process. Once the patient's life is saved, a long process of psycho-social adjustment lies ahead. "Life is a continuous adjustment process — with or without disability," says Cromes. "And there is no precise point at which a patient is completely adjusted."

Cromes says many people assume that a burn patient is completely "adjusted" once he is back at work. This assumption is erroneous, although it is used frequently by medical professionals as a recovery criterion, says Cromes. Nevertheless, vocational rehabilitation is an important aspect of treatment that is often ignored, especially in a hospital atmosphere.

In his part of the study, Cromes will research return-to-work patterns among burn patients — how soon they return to work and how many return to the same jobs. Many burn patients injured at work find it psychologically impossible to return to their jobs, even though they are physically capable. Cromes would like to learn, for example, what the chances are of an injured electrician returning to the job compared to someone accidentally burned in a restaurant kitchen fire.

In addition to work issues, Cromes says sexual relationships are of major concern to burn patients: An attractive, middle-aged woman suffers a major burn injury and faces years of cosmetic surgery. She fears her husband will no longer be attracted to her and that her marriage will dissolve. Indeed, the worst nightmare of a burn for many patients is learning to cope with a distorted appearance.

"We have the capacity to scare ourselves to death," says Cromes. "Many patients have the tendency to create the worst possible scenarios while lying in the hospital wondering if they will ever be socially accepted, and this fear is likely to continue after they've left the hospital."

How well a burn patient learns to adjust depends to a significant extent on the strength and stability of his or her family life. Role reversal sometimes is inevitable: A wife may have to assume bread-winning responsibilities, a husband may have to assume household duties. Cromes will study how families have or have not altered their patterns of behavior to compensate for the injury of a loved one. While some familes are torn apart by crisis, Cromes says he has seen many brought closer together.

Sometimes, families of burn victims aren't able to make rational decisions. A case in point: The husband of a young bride expecting her first baby suffers severe electrical burns. He remains unconscious in intensive care for nearly four months; his chances of full recovery are dim. Doctors suggest he be placed in a home where he can be cared for, yet his wife is determined to bring him home to be with her and the new baby.

Fluctuating emotions can tear individual lives apart. Cromes says many victims report experiencing chronic depression, unusual dreams or nightmares or frightening thoughts and feelings. He recalls one male patient who had always believed that men were not supposed to cry, that they were not to show any type of emotion. Faced with the trauma of a horrible burn accident, the patient no longer could contain the emotions raging inside him, so he screamed and cried. He thought he was going crazy, says Cromes, but he wasn't. He was releasing his emotions, a crucial part of recovery.

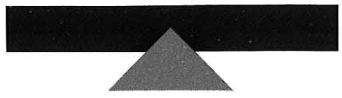
While the road to recovery for burn victims is a long and painful one, health science center researchers are hoping their findings will shed new light on initial treatment and ultimately improve the burn rehabilitation process.

"By looking at the results of the study," says Baxter, "we hope to see things that can be done in the acute stages to prevent the conditions that often result from a serious burn. Also, we might be able to design a rehabilitation period that is much more meaningful in helping a recovering burn patient lead a satisfying life."

Debbie Davidson says she's forgotten a lot of the pain of her burn, but sometimes it's still hard for her.

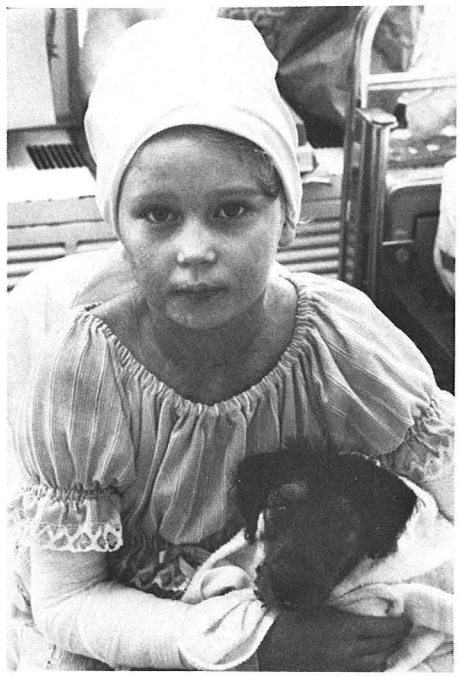
"That accident was the worst experience of my life," she says. "But I told myself that when I got out of the hospital I'd never let anything depress me again — and it hasn't. I've realized that at least I still have my life."■

"We have the capacity to scare ourselves to death," says Cromes. "Many patients tend to create the worst possible scenarios while lying in the hospital, and this fear is likely to continue after they've left the hospital."



SHERRY

PORTRAIT OF A SURVIVOR



**Her survival 13 years ago made medical history.
Her life today is a triumph of the spirit.**

The first time I heard of Sherry, she had no name. She was not a person but a medical case.

In late July 1973, the Office of Medical Information received a call from Dr. Charles Baxter, professor of surgery at The University of Texas Health Science Center at Dallas and attending physician at Parkland Memorial Hospital. There was a little girl in the burn unit who had been burned over more that 92 percent of her body, he announced, and "she was going to make it." Until that time no one ever had.

As the new kid on the block, I was excited to be given the assignment. I would be the one to tell the world about the culmination of research advances and the almost superhuman team effort leading to this major breakthrough. Baxter patiently explained the basics to me: the importance of restoring fluid balance to the burn victim's body, the need to remove charred tissue, even though the procedure left huge gaping wounds in the flesh, and the technique of covering these wounds with skin — the patient's own skin, that of a close relative or from tissue donors. In this case, the donor was Sherry's mother.

I was heady with science, intoxicated by the tales of this eminent burn pioneer and dizzy with the realization that this little girl might pull through. Patients burned over 50 percent of their bodies rarely did. I raced down the connecting corridors that join the school and the hospital to see the "case."

But instead of a "case," I saw Sherry.

Surrounded by the icy swirls of hospital linens and cartoon-like stuffed toys was a tiny girl in gauze dressings and a frilly nightgown. Her body curled inward as if seeking the comfort of the womb. Big blue-green eyes peered up at me from beneath a lock of blond hair. A triangular scarf covered her baldness beneath the one curl. She whimpered softly to herself in pain and bewilderment. She acknowledged our introduction with a weak smile.

Suddenly, I was sick to my stomach. I wanted to run back down the halls to the safety of my writer's cubicle and back to the security of writing about a "case" instead of an eight-year-old who had gone through the hell of incineration and who was starting the descent into another — recovery and return to the world.

At that moment, I couldn't see the core of iron in that ravaged little girl, the woman she would become. Today, Sherry is a mother. Her son, David, nicknamed Boo, is three and resembles her, all bright, almond-shaped eyes and bouncy, blond curls. Sherry has passed a high-school equivalency examination and is excited about starting one of the community colleges soon. Her return and recovery are complete.

It has been a long and tortuous journey from that blistering, late spring afternoon 13 years ago.

Photo by Walter Pfrogner

By Ann Harrell

"There was this explosion," says Sherry. "It blew me back from the door — almost to another room. I started running out and crying and asking God not to let me die."

On May 10, 1973, Sherry White skipped home with her little sister, Beanie. It was a hot day, and the White sisters couldn't resist the temptation to shed their shoes and pop bubbles in the asphalt with their toes. "We used to do it all the time," Sherry recalls, "but it really made a mess."

The girls' father took them to the bathtub one at a time to clean the tar from their feet. William Alton White opened the bathroom window, checked the kitchen to make sure the burners were off, then scrubbed their feet with gasoline. Although her father had cleaned the tar from the tub, Sherry returned for one more look to see if further cleaning was needed before her mother came home from work.

"As soon as I came back to the bathroom, there was this explosion," says Sherry. "It blew me back from the door — almost into another room. I started running out and crying and asking God to not let me die."

At this point Sherry's memory of what actually happened mixes with memories of hearing other people talk about that tragic day and the days that followed. Days of delusion and hallucinations, times of confused waking and sleeping. And always the doctors and nurses, the pain and longing to go home.

"They told me Sherry was going to die," says her mother, Loretta White. "But I didn't believe it. I couldn't believe it. There was no way God was going to let her die. The doctors wanted me to prepare the other children, but I wouldn't do it."

Dr. Baxter, who is devoted to finding new ways of saving the badly burned, also was determined Sherry would live. In the previous two years, the burn expert and his team had lost five or six severely burned patients they had hoped to save because there simply was not enough donor skin available. The skin was needed as "human bandages" to cover the patients' massive wounds during the healing process and to protect them from infection.

At the time Sherry was burned, the health science center's skin bank was about six months old. Miraculously, there was enough skin.

Sherry's burns covered the whole of her body except the sole of her right foot and the upper part of her face, which was spared by the thick, unruly curls that formed a shield around her eyes. Her wounds were excised with scissors, a knife and an air-pressure needle that separates the burned flesh from the underlying tissue. Massive blood transfusions were given during multiple surgeries, and daily soaks in saltwater were used to soften any remaining burned tissue so it could be stripped away.

"Because the body that has suffered burn trauma develops a metabolism that races out of control, Sherry was encouraged to take in several times her normal amount of calories per day," says Baxter. She needed to consume 4,500 calories per day to maintain her 73-pound weight.

Baxter says burn patients who lose more than a third of their body weight die, so eating is vital. Sherry herself recalls how hard she tried to please Baxter by eating. "I remember eating and throwing up, and eating and throwing up again," she says. "I was so sick.

"Mom would get me anything I wanted. She'd bring me tacos, pizza, stuffed animals, anything. I was getting so much that I felt sorry for some of the kids there who weren't getting as much attention, so I'd tell Mom to get them some toys, too. And she would.

"Baxter got in on the spoiling, too," says Sherry. When the little girl was too ill to eat, the burn physician told her he would get her anything she wanted if she would finish her meals and eat the snacks her mother would bring.

"How did I know she'd want a dog?" he asks, still amazed.

Baxter brought Sherry an Airedale pup, which she named Charly in his honor. Having a dog in the strictly controlled environment of the burn center was certainly unorthodox, but Baxter is not one to let rules get in the way of what he considers important. He had Sherry's mother bathe Charly, wrap him in a clean blanket and smuggle him in.

"Yes, Dr. Baxter spoiled me, too," says Sherry, reminiscing about her hospital stay. "He bribed me to walk, too, you know."

Rehabilitation begins as soon as the burn patient is stabilized. Painful and slow, exercises are a vital part of the medical program for each patient. Because the scar tissue tightens inflexibly around the body and joints, the whole body begins an inward curl. Constant stretching and bending, moving and flexing are necessary to keep the patient from becoming crippled.

Sherry's right foot was badly burned, and her left was raw from the skin taken for transplant. She was like the Little Mermaid in the children's tale whose every step was like walking on ground glass. "So Dr. Baxter would stuff a dollar into my St. Bernard dog bank every time I took a step for him," she says. "I just loved him."

But Sherry didn't love the burn doctor all the time.

One day someone had carelessly removed the towel from a mirror near Sherry's bed. It had been placed there so she would not learn that her head had been shaved in order to use the skin for transplant. Because the head was swathed in bandages and the mirror always covered, she did not realize she was no longer "Goldilocks." As the little girl sat up in bed to eat her lunch, suddenly her eyes caught her own reflection in the mirror. She let out a

scream and hurled her bowl of soup at Baxter, who was standing beside the bed.

Comfort was a long time in coming.

At last the ordeal of hospitalization was over, and Sherry went home after long months of treatment. Still, she was a patient and returned daily to the hospital gym for paraffin baths to soften the scar tissue, followed by exercise sessions with physical therapists. She also visited her doctors as an outpatient and was fitted by occupational therapists for the elastic, form-fitting pressure garments — much like a girdle — she had to wear over her entire body.

But at least she was home. Her friends, whose visits to the burn unit had consisted of peeping in a hallway window, could come to see her. School was starting, and Sherry could soon go back to the life she had known. Looking back, Sherry speaks fondly of her friends who never made her feel "different." Some of them, like Mary Price, a Dallas community college student, are still close today.

"Sherry wasn't different," says Mary. "She always had a strong personality. She's always been a part of things and participated in all the activities. She was just like anybody else."

Sometimes people's staring made Sherry feel awkward, but Sherry says most people were "really okay," just curious. Her burns hardly affected her life at school, either. "The kids were really nice," she says. "They accepted me."

She admits she was self-conscious about the scars that covered her body, though, and would wear long-sleeved shirts to hide her arms. "I loved swimming and didn't want to be seen in a bathing suit," she recalls.

The teen years are tough for anyone, and Sherry had her share of ups and downs. Suddenly, school wasn't fun any more, and she let her grades drop. Fights with her mother made her want to move out on her own, causing arguments. Boys. Staying out late. Buying new clothes. Dropping out of school. All were fodder for their battles.

How much of Sherry's teen rebellion can be traced to her injury no one will ever know. Sherry thinks not much, and Mary agrees. "It's the area," she says, referring to West Dallas. "In the area we lived in, most of the parents didn't finish school themselves. Lots of them married early."

Sherry nods her head. "My mom didn't finish school, either. I wanted to get a job, have my own apartment, have my own life."

Loretta finally let Sherry drop out of school. Eventually she got a job as a receptionist and did well. Then she met David Hilliard through one of her cousins. They married six months later.

The job made Sherry feel good about herself. So did David, and later, their son David Jr. Gradually, Sherry lost her self-consciousness about her scars. "At first, I just wore short-sleeved shirts when we were at home alone together," says Sherry. "David just laughed at me, so then I started wearing them when we went out together. Now, I don't think anything about it. I even wear a bikini."

Says Mary: "David, by accepting her, has made her more relaxed around other people."

Happy with her own child, Sherry has become close again to her mother. Always pretty, poised and well-dressed, Sherry thinks of herself as attractive, and she is. When she was young, she wanted to be a model; today, she has the carriage of one. She still loves fashionable clothes as well as grooming her nails and hair. Her scarred body no longer requires countless hours of tiring and painful therapy to combat crippling, but Sherry, who loves dancing, swimming and riding her bicycle, is naturally active.

Surgery is still a part of her life, though. After years of reconstructive procedures and tissue "releases" to permit natural growth and freedom of motion, Sherry recently decided to volunteer as a teaching case for Baxter. Although the work being done for Sherry today is not necessary to her survival, she believes it is important to the quality of her life — reshaping the bust area, removing scar tissue around the mouth. Baxter also plans to work on the thickness of some of the scar tissue with a new technique in which a balloon is placed under the tissue to stretch it into a thinner layer. Sherry was so excited about the first operation that she went out and bought a new robe and gown for the hospital.

Baxter is excited about working with Sherry again, too. "We work on patients to save their lives all the time," he says, "but the important thing about Sherry is for the surgery residents and medical students to see that it's worth it to save these badly burned patients, for them to see what good results can be and what good things can happen after we save their lives."

Does Sherry ever ask herself, "Why me?"

"I used to," she says. "But I've accepted it. I'm still me, and I don't let anything stop me when I want to do something — I just do it. I know I gave my parents a lot of problems. After I was burned, I was very spoiled, and I learned how to get my way by telling them I wished I had died. But I really didn't; it was just an easy way to get what I wanted.

"It happened. I can't change it. But I have a strong personality, and I've noticed that the burn patients with strong personalities and the more outgoing ones get on with their lives better than the ones who just sit in a corner."

Watching Sherry grow and bloom into womanhood has been a hymn to life for me.

She is the bravest person I have ever known. ■

"Sherry always had a strong personality," says Mary. "She's always been a part of things and participated in all the activities, just like anybody else."

Vital Signs

Hospital Plans Move Ahead

Plans for University Medical Center — the major new element in the health science center's teaching and research complex — take a significant step forward this year with the drawing up of architectural designs for the new teaching hospital.

The 159-bed University Medical Center, to be located near the corner of Harry Hines Boulevard and Motor Street, will function as a referred-patient teaching hospital for the faculty and students of Southwestern Medical School and will be an integral part of the medical complex composed of the university, Parkland Memorial Hospital and Children's Medical Center.

A worldwide referral center for patients requiring specialized care, UMC will provide medical students with diagnostic and treatment opportunities rarely found in public hospitals but which are an important part of private practice; it will further provide the clinical environment necessary for faculty to fully develop their medical research.

University Medical Center, Inc., a nonprofit organization formed to raise funds for the hospital, has approved a total construction and equipment budget of $37,910,423 for the 191,607-square-foot hospital. Ralph Rogers, chairman of the UMC board, says construction should start by the end of the year and take 30 to 36 months to complete. Henry C. Beck & Co., the largest general contractor in the Dallas area, will manage construction.

The hospital will be designed jointly by The Oglesby Group, Dallas, and Page Southerland Page, Austin. Dr. Philip O'Bryan Montgomery Jr., chairman of the building committee, says an architect with a reputation for excellence in design and considerable experience in building hospitals was needed, but finding both qualities in one firm was difficult.

"The architects know we are looking to The Oglesby Group for interior and exterior design excellence and to Page Southerland Page to make the nuts and bolts work," says Montgomery, a professor of pathology who also helped plan the health science center's $40 million expansion program.

The Oglesby Group designed the Eugene McDermott Academic Administration Building on campus. Page Southerland Page is ranked second in the United States in terms of numbers of hospitals designed.

Planning for the new hospital has involved extensive consultations with the heads of every clinical department and every professional and nonprofessional group that will use the hospital, says Montgomery.

"We asked them what they needed to make the hospital work well for them, whether they represented a medical or surgical specialty, a nursing service, communications, records, maintenance or security," Montgomery says. "The results of those consultations form the basis for the building committee's final recommendations," upon which the design will be based.

University Medical Center will not provide emergency care nor will it provide maternity or pediatric care. A heart attack victim, however, might be brought by ambulance to the emergency room at Parkland, stabilized and then transferred to the UMC cardiac intensive care unit upon request.

Because of the close interaction among UMC, Parkland and the Aston Ambulatory Care Center, a special communications system is being planned that will allow transfer of patient information by computer among the three locations.

Says Montgomery: "University Medical Center is not an ordinary hospital, so it is receiving extraordinary care in planning and design."■

"Magic Bullet" On Target

After six years of promising animal experiments and 18 months of preparation, the cancer-fighting "magic bullet" developed by Drs. Jonathan Uhr and Ellen Vitetta has moved from the laboratory to the clinic, and the first signs from the clinical tests are encouraging.

At press time, three terminal leukemia patients had undergone transplants with bone marrow treated with the immunotoxin developed by the Dallas team. In the first two cases, the marrow had engrafted, and the

patients showed no sign of acute graft vs. host disease (GVHD), a deadly side-effect of bone marrow transplants which occurs within three months in about 50 percent of patients. It was still too early to evaluate the third patient, but so far things had gone smoothly.

The immunotoxin weds a monoclonal antibody with ricin, a powerful poison derived from the castor bean, to kill specific cells. Because ricin is dangerous to work with, Uhr and Vitetta removed the toxic portion of the molecule, the A-chain, and discarded the portion that binds the molecule to all cells in the body, the B-chain.

When the A-chain is linked with a monoclonal antibody the result is a poison that will bind only to certain cells. In this case, the target cell is a T-cell in matched donor bone marrow that could cause GVHD. The tests, which began in December, are being conducted at the Fred Hutchinson

Cancer Research Center in Seattle.

Uhr, chairman of the Department of Microbiology, and Vitetta, co-director of the immunology graduate program, are among a handful of pioneering investigators worldwide who have harnessed the killing power of ricin to targeted antibodies to create what they hope will prove a powerful weapon against certain cancers.

Bone marrow transplantation is still considered an experimental treatment for cancer, and the prognosis for the first leukemia patients in the immunotoxin trials was that they would be dead within weeks. Preparation for a bone marrow transplant is itself lethal: one week of combined radiotherapy and chemotherapy. The patient is then rescued from death by the injection of healthy bone marrow from a matched donor, usually a close relative. The immunotoxin is used to cleanse the donor marrow of T-cells to prevent GVHD.

It is much too soon to tell how successful the immunotoxin treatment will be. Chronic GVHD and graft rejection can occur many months after the transplant. But acute GVHD has not occurred in the first two patients, and the Seattle group plans to treat a total of 20 this year.

Meanwhile, clinical trials involving direct injection of immunotoxin in patients with far-advanced lymphoma are planned in Dallas. By this method, the team hopes to kill tumor cells in the body that may be missed by chemotherapy and radiotherapy to prevent relapses. These tests are designed only to gauge the toxicity and therapeutic dosage of the "magic bullet." They do not expect to cure these terminal patients.

Whether the A-chain immunotoxin holds out hope for a cure for certain types of cancer is far from certain. The tests in Seattle and Dallas will be only the first in an exhaustive series that must be conducted before the treatment is considered for addition to the anti-cancer arsenal. The "magic bullet" then may be used as a conditioning agent in conjunction with chemotherapy and radiotherapy to rid the body of all tumor cells and as a cleansing agent for bone marrow.

Right now the immunotoxin is being tested against relatively rare cancers: leukemia and lymphoma. If it is successful, the more difficult to treat solid tumors, such as melanoma and breast cancer, may be the next targets.■

Kidney Stone Risk Kit

A new kit developed at the health science center is now available to aid the nation's estimated half million chronic kidney stone sufferers in assessing their risks for forming new stones and to help them avoid repeated surgery for kidney stone removal.

Called the "StoneRisk Patient Profile," the unique diagnostic test kit is intended to assist physicians in determining what form of medical treatment is most appropriate for individual patients and to allow for accurate monitoring of a patient's response to drug treatment.

The kit was developed by kidney stone expert Dr. Charles Y.C. Pak, chief of mineral metabolism at Southwestern Medical School, and is being marketed by Mission Pharmacal Company of San Antonio. Pak also has developed two FDA-approved drugs for kidney stone prevention.

"It is now known that kidney stones form from a variety of metabolic and environmental disturbances that occur in urine," says Pak. "These disturbances are referred to as risk factors, which are responsible for or contribute to kidney stone formation."

It is now possible to identify these risk factors and their role in kidney stone formation, Pak says. This important information can be obtained from one 24-hour urine collection test, which is included in the StoneRisk Patient Profile.

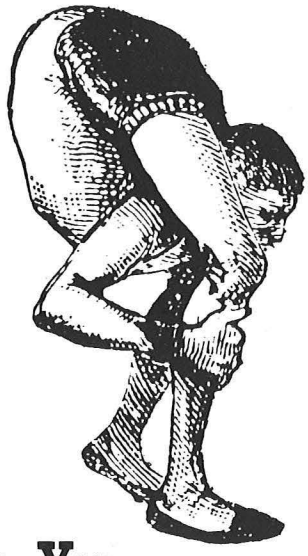
The kit contains a 24-hour urine collection bottle with a preservative-treated sponge inside, two urine sample vials, a patient data card and a pre-addressed, mail-back box. Patients collect a 24-hour urine sample and then send the two vials with small amounts of urine to a laboratory for analysis. The results come back to the physician in the form of a computerized graph showing a patient's risk for various kidney stone-forming disorders.

The graphic display of stone-forming risks permits easy identification of metabolic disturbances, such as high urinary calcium and decreased levels of citrate, a substance that inhibits kidney stone formation. Environmental influences that may cause kidney stones — such as too little fluid intake or increased sodium, sulfate, phosphorous and magnesium in the diet — also can be detected. From this data the physician can identify the kind of kidney stones the patient has a tendency to form, which may help in determining treatment.

The test kit overcomes problems of urine preservation for laboratory analysis, the requirements for which differ according to the test method. With StoneRisk Patient Profile, the various tests can be accomplished from a single specimen without refrigeration.

In addition, the cost of using the kit to test for a group of body chemicals is substantially less than testing for each chemical individually, which was necessary before the kit was developed, Pak says.

While the StoneRisk Patient Profile is not designed to diagnose kidney stone disease, Pak says it should help define risks for future stone development and aid physicians in assessing stone disease.■



Oh, Your Aching Back

Next to the common cold, low back pain is the greatest cause of lost work time in the United States. But when is a patient who has suffered back injury ready to go back to work?

Until recently, such decisions have been judgment calls made by doctors based on the review of a patient's medical records or, sometimes, nothing more substantial than a patient's reports of pain.

Vital Signs

Now, a new line of trunk-testing equipment is able to provide doctors and physical therapists with accurate measures of a patient's back strength. The machines are being marketed by the Cybex Corporation and evaluated by a team of researchers from the health science center.

Dr. Vert Mooney, professor and chairman of orthopedic surgery at Southwestern Medical School, predicts the new testing and treatment system will have a significant impact on determining disability cases, screening athletes and job applicants and prescribing treatment for back-pain patients. Medical and legal decisions involving a patient's condition now can be based on scientific fact.

The health science center research team, which includes orthopedic surgeons, physical therapists and psychologists, has led the way in research on the new equipment by collecting data that will be a standard measure by which all Cybex trunk-tester users will measure their patients' strength and progress.

Psychological studies have measured the differences between how a patient thinks he can perform and his actual physical ability as measured by the machines. Studies on the heart's demand for oxygen when patients use the equipment have led the researchers to prescribe safe limits for treating back patients with a history of heart trouble. Other work with the trunk-testing equipment involves the evaluation of patients who have had surgery or polio.

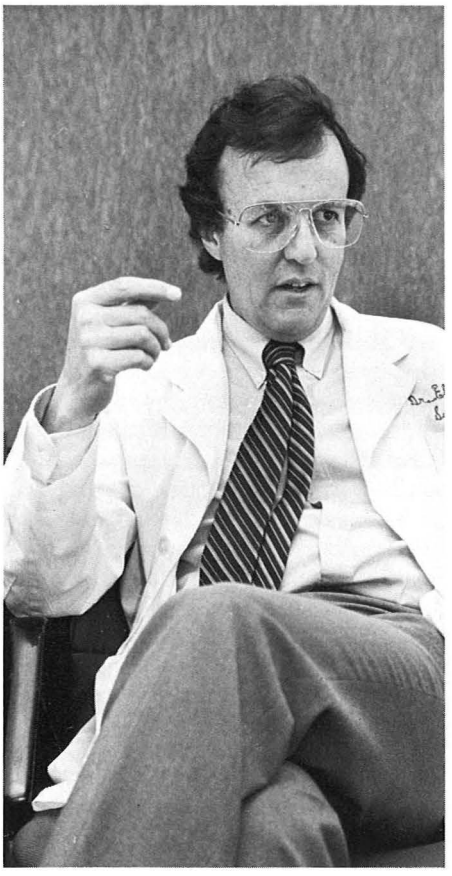
Sue Smith, assistant professor of physical therapy, is testing Southern Methodist University dancers for trunk strength as part of a long-term study designed to measure the machines' predictive abilities. Smith also hopes to test various groups of workers — such as construction workers — to determine how much and what type of back strength is needed to perform specific jobs.

The extensive research at the health science center is largely responsible for the Cybex Corporation's decision to locate its new training and research center in Dallas, says Tom Mayer, clinical assistant professor of orthopedic surgery. The center will be used commercially by Cybex for seminars and training demonstrations for new purchasers of the equipment. The university will have access to the center for continuing medical education, functional testing and data collection.■

Compatible Plastics

Most surgical implant procedures use drugs to suppress the body's tendency to reject any foreign material. Now health science center researchers have found a way to harness one of the body's own substances to make plastic more compatible with blood.

Dr. Robert Eberhart, chairman of the biomedical engineering program at the Southwestern Graduate School of Biomedical Sciences, and some of his students last year were issued a patent for their process of coating medical plastics with albumin, the most abundant protein in the blood. It was the first patent of this kind ever issued.



Robert Eberhart, Ph.D.

The main problem with procedures involving artificial organs, blood vessels and heart valves; heart-lung machines; catheters and other surgical aids has been the body's tendency to reject foreign "invaders." The new process of coating plastic implants with albumin may eliminate, naturally, the main causes of rejection.

"The philosophy that underlies this whole procedure is to turn natural substances in the body to our advantage rather than always trying to put in drugs or substances that turn off otherwise beneficial defenses of the body," says Eberhart.

Eberhart and his research team developed the process in an attempt to prevent the large blood clots that often form on the external circuits of heart-lung machines. The clots threaten to block arteries, which could result in strokes, heart attacks and kidney failure.

Two main obstacles to previous attempts to improve the biocompatibility of medical plastics are the rapid buildup of fibrinogen on the surface of the implants, which causes clots to form, and activation of the immune system, which sends white blood cells on search-and-destroy missions when foreign invaders are detected. Procedures that bring large amounts of foreign material in contact with blood, such as hemodialysis and heart bypass surgery, can cause white blood cells to collect in the lungs, causing pulmonary problems.

Eberhart had heard that soaking implants and heart-lung circuits in an albumin solution reduced complications associated with clotting and bleeding, but these reports had received scant attention because the procedure didn't always work, and the reasons for failure were unknown.

Instead of merely soaking the implants in albumin, Mark Munro, a student of Eberhart's, suggested treating the implant surface with chemicals to trick the albumin into perceiving the device as free fatty acids. One of the functions of albumin is to bind these fatty acids and carry them out of the bloodstream. The treatment results in a dense protein coating on the plastic that is continually renewed; even as the bound albumin decays and is swept away in the blood, the treated plastic continues to attract the protein.

While the albumin clings to the plastic surface, fibrinogen can't collect and clots don't form. The plastic is protected from

the immune system because albumin isn't "foreign." Eberhart says preliminary studies have shown that 65 to 85 percent of the immune response to plastic implants could be prevented with the albumin coating process.

Several plastics, including Dacron polyester, nylon, polyurethane, cellulose-acetate and Cuprophan have been coated successfully with albumin. These plastics are used in artificial hearts, vascular prostheses, dialysis and oxygenator membranes, catheters and chemical sensors in the bloodstream. Methods of treating other medically important plastics also have been successfully developed.■

Insensitive Feet

Chances are good that you or someone you know is affected by diabetes. One out of every 20 Americans suffers from diabetes, and among the complications that make this disease the third leading cause of death in the United States is nerve damage.

Nerve damage, or neuropathy, can occur in every part of the body, but it most often affects the lower extremities. There are hundreds of thousands of people in the United States with neuropathic, or insensitive, feet. And because their feet cannot feel pain, whether it be from fatigue or a wound, they are at high risk of developing an infection that, without attention, could reach to a bone or tendon.

Dr. Phala A. Helm, chairman of the Department of Physical Medicine and Rehabilitation at the university and director of the Problem Foot Clinic at Parkland Memorial Hospital, says one of the greatest fears of diabetics — and a well-founded one — is the loss of a lower extremity. Annually, half of all amputations are due to complications of diabetes. More than 40,000 foot and leg amputations occur each year as a result of diabetes complications.

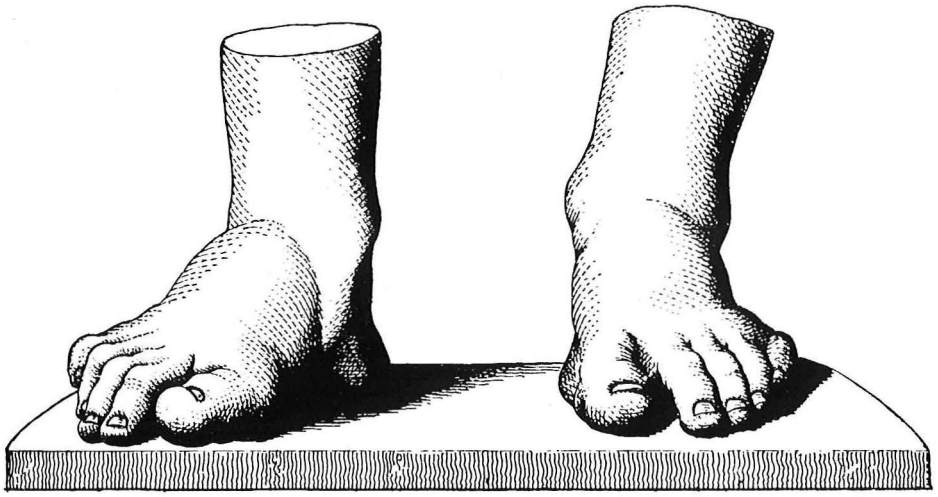
But Helm and other clinicians at the health science center are reducing the risks of amputation with an old technique for treating lepers that has been modified for treatment of patients with insensitive feet.

In Helm's treatment method — total contact casting — a cast is molded to the leg and foot like a second skin. A rocker bottom is applied that evenly distributes body weight as the patient walks on the foot. Research shows that the treatment method is effective because it protects the wound, promotes fluid exchange in the limb and allows the patient to continue his or her daily routine, for the most part. Patients are then seen on an outpatient basis.

The results have been impressive. In a study of 77 patients during a 21-month period, 74 percent of the foot wounds were healed in an average of 36 days, compared to a recovery period of between one and five years with traditional treatment methods such as bedrest and topical medications.

Taken from a practice developed by Dr. Paul Brand, who originally used total contact casting for treating lepers, this method has had, until now, only limited application among diabetics with neuropathies, says Helm.

But news of Helm's successes with this method is rapidly spreading across the country. More than 200 patients with insensitive feet were cast last year, and Helm says she receives calls every week from patients all over the country who want referrals to doctors using the contact cast treatment method.■



Infant Lung Problems

You'd probably expect a four-pound premature baby to have problems. But a 10-pound, full-term baby should be off to a good start toward a career in professional football, right?

Not necessarily. Diabetic mothers frequently give birth to high-birthweight babies who develop respiratory distress syndrome, the leading cause of death among premature, low-birthweight newborns. These infants are in trouble because their lungs collapse completely after each breath, and it requires enormous effort to reinflate the lungs. Consequently, these babies cannot maintain adequate breathing, and they suffer from lack of oxygen.

A substance known as surfactant is often deficient in the lungs of infants born prematurely. Surfactant, a milky liquid, covers the inner surface of the lung, reducing surface tension of the alveolar sacs where the exchange of oxygen takes place. The babies of diabetic mothers usually produce adequate amounts of surfactant. It just doesn't function as it should.

Researchers at the health science center's Green Center for Reproductive Biology Sciences have been working to explain the regulation of surfactant synthesis in the fetal lung. Two of these investigators, Drs. Jeanne M. Snyder and Carole R. Mendelson, have uncovered a possible cause of the increased incidence of respiratory distress syndrome in infants of diabetic mothers.

Surfactant is a lipoprotein composed of 80 percent phospholipid, a fatty substance not unlike the non-stick Pam you spray on cooking utensils, and 10 percent protein. The

surfactant apoprotein appears to be essential for the normal function of surfactant in the lung.

Babies born to diabetic mothers usually produce surfactant in normal quantities; however, the apoprotein concentration in the surfactant may be reduced.

The fetus of a diabetic mother produces an unusually high amount of insulin in response to excess blood sugar, which passes into the fetal circulation through the placenta. Snyder's and Mendelson's investigations have shown that excess insulin inhibits the production of the surfactant apoprotein by fetal lung tissue.

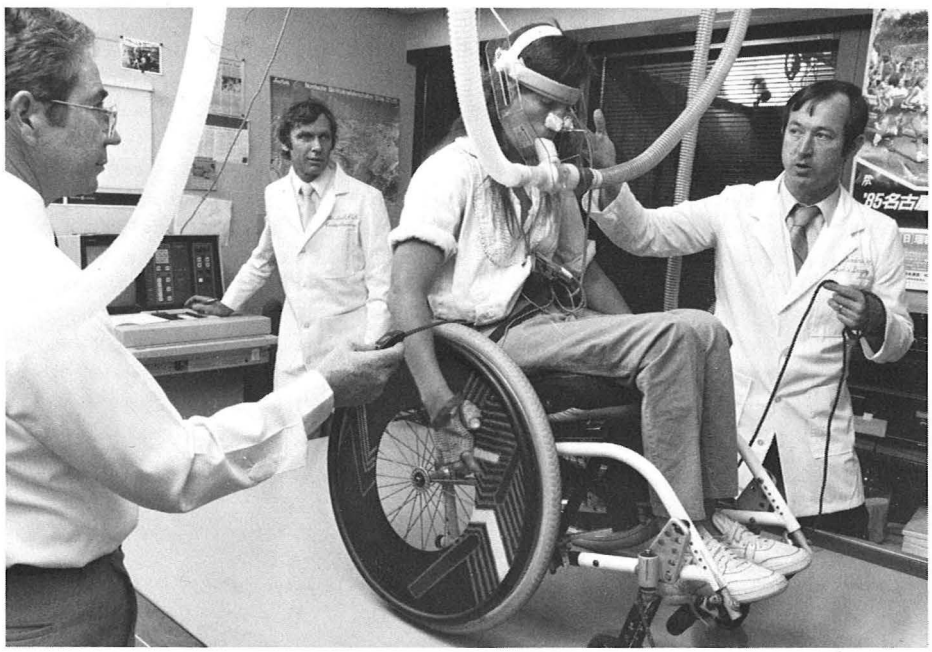
The presence of surfactant apoprotein in the amniotic fluid of diabetic mothers near term can be evaluated by means of certain tests. If the concentration of this protein is found to be low, the physician can anticipate possible development of respiratory distress syndrome in the newborn infant and initiate appropriate treatment at the time of birth.

The Green Center for Reproductive Biology Sciences in the Department of Obstetrics and Gynecology received a five-year grant from the National Institutes of Health in 1980 to investigate fetal lung maturation and the prevention of respiratory distress syndrome. The grant was renewed in 1985 for three years, and the researchers continue to make progress in discovering the basic cellular processes by which fetal lungs produce and utilize surfactant.■

Human Performance

A strange assortment of volunteers pass through the doors of the St. Paul/UTHSCD Human Performance Center and head for tough workouts on a giant, custom-made treadmill.

They include skiers with rollers on the bottoms of their practice skis, cyclists, runners and wheelchair travelers who are taking part in research that hopes to answer questions ranging from what makes an athlete a world-class contender to how the body and heart respond to exercise to how the proper kinds of exercise can contribute to the well-being of people in everyday life.



Researchers in the Human Performance Laboratory study the effects of aerobic exercises on different groups of volunteers.

The project is a joint venture between faculty researchers at the health science center and St. Paul Medical Center under the direction of Drs. Peter Snell, three-time Olympic gold medalist, and James Stray-Gundersen, sports medicine coordinator for the U.S. Nordic ski team. The work is overseen by Dr. Jere Mitchell, a world authority on exercise physiology and director of the university's Moss Heart Center.

The laboratory has twin goals, say its co-directors. First is the commitment to research physiology with projects as diverse as long-term studies of the development of young cross-country skiers as they reach competitive maturity and research into whether a regular aerobics program using stationary bicycles for exercise will improve the fitness of paraplegics. Studies of overtraining in athletes and the use of oxygen as a means of quick recovery in competitive sports are among other projects.

In addition to research, the doctors also provide assessments for both competitive athletes and individuals interested in beginning exercise programs as a way to healthier living — for a fee. A group of "elite athletes," including members of the U.S. Nordic ski team, the Dallas Sidekicks soccer team and the Southern Methodist University swim team, already have been tested at the lab.

Among the individual athletes who have undergone laboratory trials are Ben Husaby, the national junior champion cross-country skier; Keith Connor, Olympic gold medalist in the triple jump; Mary Knisley, U.S. track and field star; Randy Snow, Special Olympics silver medalist in the 1,500-meter wheelchair race; August Wolf, one of America's leading shot put contenders; and Francie Larrieu-Smith, one of this country's top women runners.

The general public should be educated about fitness and the many misconceptions about it, Snell says. For example, many regular runners believe they are in top shape but in reality may be in danger of injuring themselves if they overindulge in another kind of exercise, such as tennis or even gardening.

Snell and Stray-Gundersen hope to expand the program at the human performance laboratory to explore many of the unanswered questions in human physiology, particularly as they apply to sports medicine. Says Stray-Gundersen: "It makes sense that academic centers and community hospitals should become the leaders in answering these questions."■