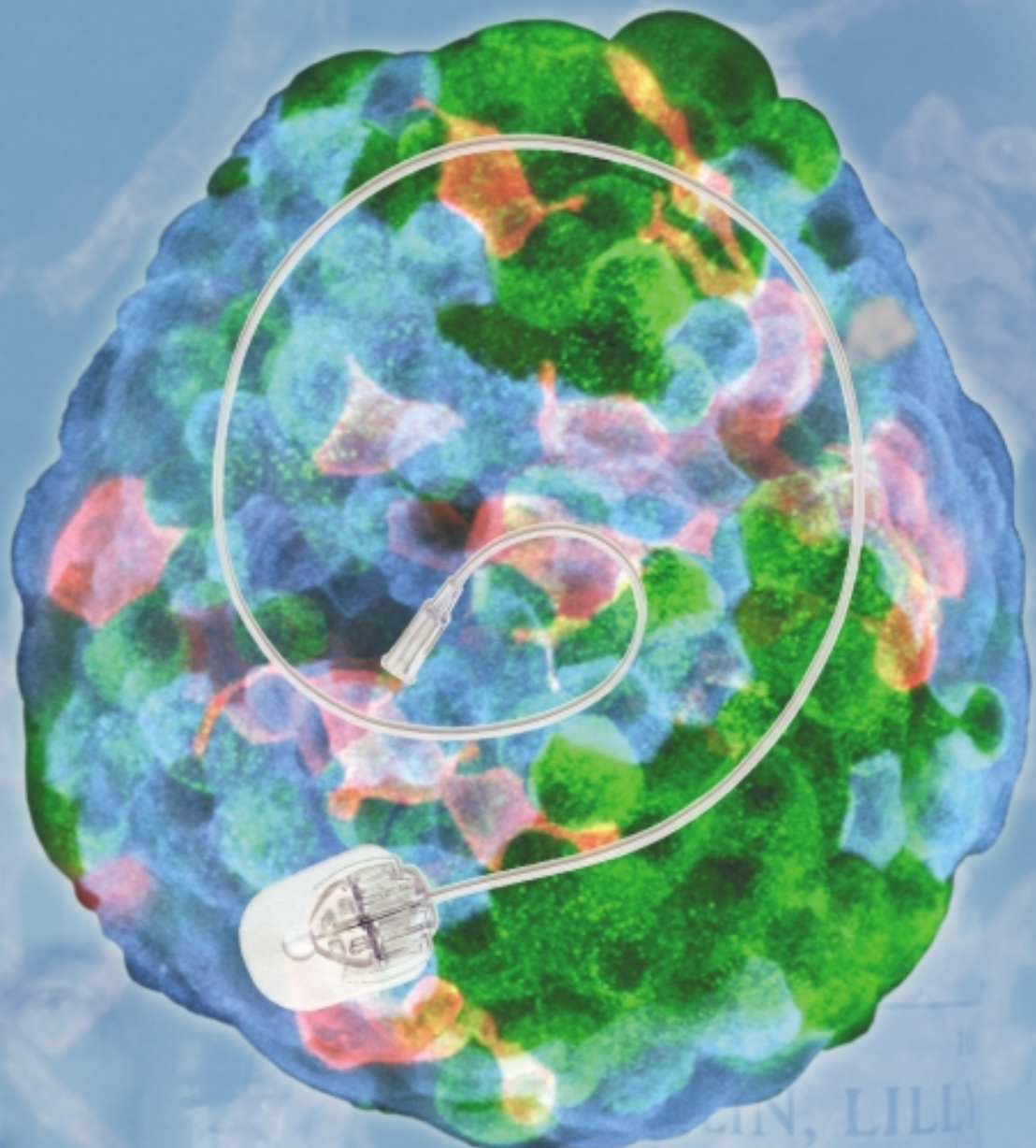
SUMMER 03

Lens

A New Way of Looking at **Science**



Diabetes

Unraveling the mysteries of an ancient disease.

A PUBLICATION OF VANDERBILT UNIVERSITY MEDICAL CENTER

Lens –
A New Way of Looking
at **Science**

SUMMER 2003

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Discovery consists of seeing what everybody has seen, and thinking what nobody has thought.

– ALBERT VON SZENT-GYORGYI

About the cover: A 3-D image of an intact rat pancreatic islet, in which is coiled an insulin pump infusion set, courtesy of SpectRx, is shown against a background of images that suggest the past and future of diabetes research.

In the background: Dr. Frederick Banting (top right) and Charles H. Best (bottom left), co-discoverers of insulin, and early insulin bottles, courtesy of Eli Lilly and Company Archives. Squiggly lines are images of blood vessels in the islet and surrounding tissue, courtesy of Marcela Brissova, Vanderbilt University.

The islet image, visualized with multi-color, laser scanning confocal immunofluorescence microscopy, is courtesy of T.C. Brelje and R.L. Sorenson of the University of Minnesota Medical School. It shows insulin-secreting beta cells in green, glucagon-secreting alpha cells in blue and somatostatin-secreting delta cells in red.

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DEAN DIXON

Steven G. Gabbe, M.D.
Dean
Vanderbilt University School of Medicine

Dr. Gabbe is professor of Obstetrics and Gynecology and Medical Administration, and an expert on treating diabetes during pregnancy.

A rich heritage of diabetes research

One of the pivotal events of the 20th Century was the discovery of insulin in 1921 by researchers at the University of Toronto. Within a year, diabetes had been transformed from a hopeless, wasting disease into one that could be controlled through the injections of a miraculous pancreatic extract.

Daily injections of the hormone saved hundreds of thousands of lives, but it was not the cure for diabetes that many people had hoped it would be. Because glucose control was fairly crude, many patients developed long-term complications of chronic hyperglycemia – blindness, kidney failure, heart disease, neuropathy, and poor circulation requiring amputation of the lower extremities.

When I diagnosed myself to have type 1 diabetes as a medical student in 1968, there were two schools of thought. One of my professors discouraged tight glucose control because of the risk of hypoglycemia, too little glucose in the blood that could lead to coma and death. Others, including my personal physician, urged me to try to keep my glucose level as close to normal as possible.

I chose the latter course because I didn't want to find out at some future time that I had missed an opportunity to prevent the complications of the disease. This was before the Diabetes Control and Complications Trial confirmed the value of tight glucose control. And it was before glucose meters, so I had to guess what my glucose level was by testing my urine.

Thanks to the technological and pharmacological innovations of the past 15 years, I now use an insulin pump that injects a rapid-acting form of the hormone below the skin, and a glucose meter that gives me a reading of my blood glucose level in five seconds.

But we still don't understand why and how diabetes and its complications develop as clearly as we'd like. Obesity and type 2 diabetes have reached epidemic proportions throughout the world, and the incidence of type 1 diabetes also is increasing.

This is where medical research plays a critical role. Following in the footsteps of Dr. Frederick Banting, Charles Best and their colleagues at Toronto, scientists around the world are pursuing avenues of inquiry that are improving understanding of this complex disease and which may lead to better methods of treating, preventing and – perhaps one day – curing it.

Vanderbilt University Medical Center has an especially rich heritage in diabetes-related research. Charles "Rollo" Park, John Exton, Earl Sutherland, Joel Hardman, Oscar Crofford, Daryl Granner and Alan Cherrington, to name only a few, helped pioneer current understanding of how glucose and lipid metabolism is regulated. That tradition and that dedication to deciphering the riddle of diabetes continue today. I consider it to be a privilege to be here, both as a patient and as a faculty member.

This issue of *Lens* provides a glimpse of exciting advances in understanding diabetes: new ways of visualizing the pancreas; decoding the complex interplay of tissues and chemical signals that regulate glucose and body weight; and the prospects for "cell-based therapy" – transplants of insulin-secreting cells that have been created in the laboratory.

I hope our readers will come away with an appreciation for how discoveries in what appear to be unrelated research fields provide important clues to improving diabetes treatment. Interpreting and integrating diverse sources of information is crucial for understanding. That's the scientist's job. That's the nature of science.

Faces of diabetes

Meet Emily Alexander and Ellis Hollerman. They share a workplace and a disease – diabetes.

Mr. Hollerman is principal of Shafer Middle School in Gallatin, Tennessee, about 30 miles northeast of Nashville, where Mrs. Alexander teaches Teen Living – health and wellness – to students in the sixth through eighth grades.

They represent the breadth and complexity of a disease that touches every community in this country and – to an ever-growing extent – throughout the world.

Mrs. Alexander has type 1 diabetes, characterized by an attack by her body's immune system on the insulin-producing beta cells in her pancreas. She wears an insulin pump, which feeds a programmed amount of the vital hormone into her body to keep the amount of glucose in her blood within a normal range, and to reduce the risk of the complications of diabetes, including blindness, kidney failure and heart disease.

Mr. Hollerman also requires insulin. But he has type 2 diabetes, the most common form of the disease, in which his tissues have become "resistant" to insulin and do not absorb glucose like they should. At the same time, his beta cells have lost their ability to produce sufficient levels of the hormone.

In the past 15 years, a plethora of new drugs and devices have been brought to market to aid patients in controlling their disease. Progress continues to be made, thanks to the nation's substantial investment in medical research. The challenge is to bring these advances from the laboratory into the clinic, for the benefit of people like Mrs. Alexander and Mr. Hollerman, and the millions of others who share their disease.

– BILL SNYDER

ANNE RAYNER POLLO

Ellis Hollerman and Emily Alexander

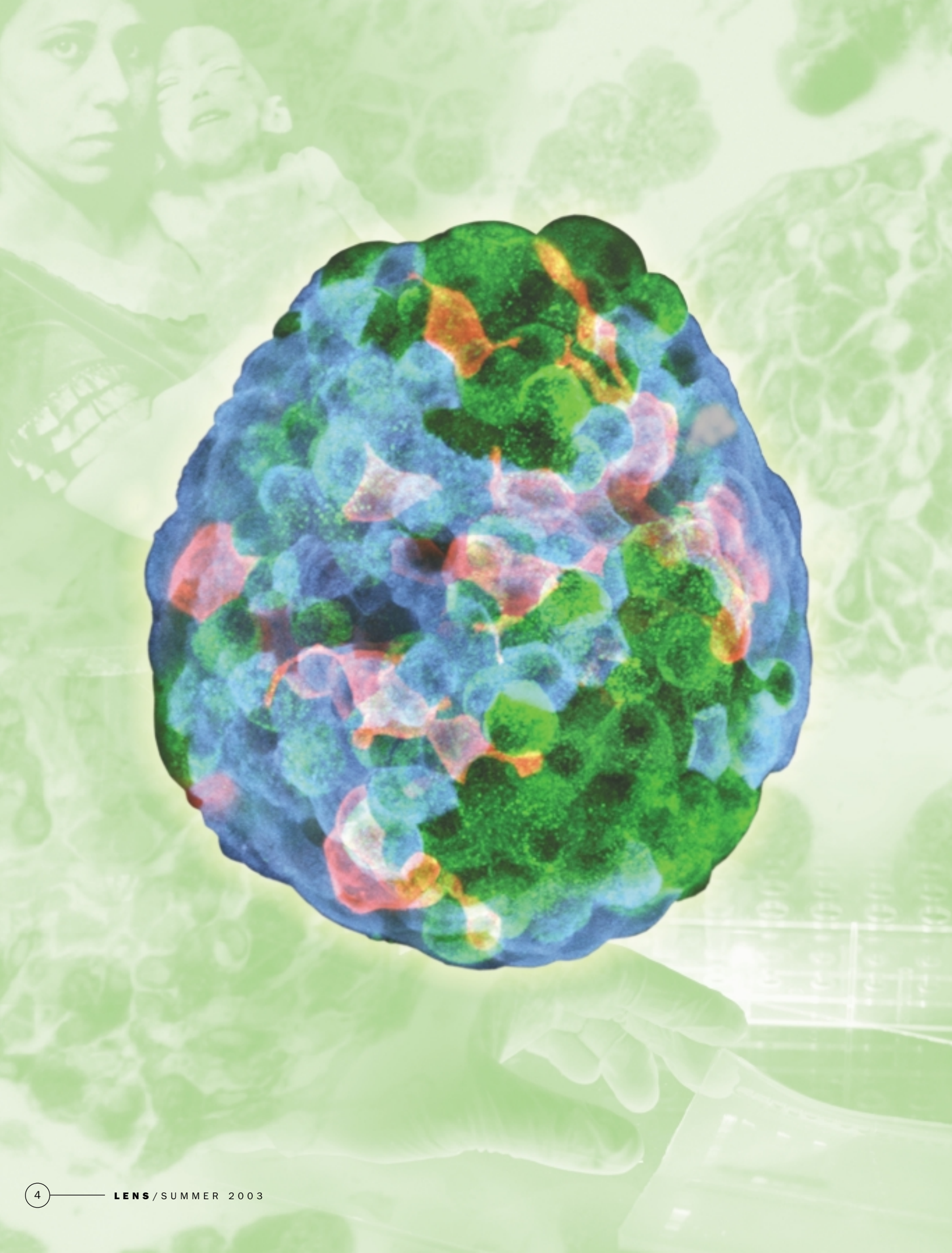
A NEW CLINIC AT VANDERBILT PROMISES "ONE-STOP SHOPPING"

Vanderbilt University Medical Center, site of the nation's first federally funded diabetes research center, is developing plans for a comprehensive program that will more fully integrate diabetes care, training and clinical research.

The Vanderbilt-Eskind Diabetes Clinic will bear the name of Dr. Irwin B. Eskind, a Nashville physician and philanthropist who chairs the board of the existing Vanderbilt Diabetes Center. Patients will be able to see specialists and have all their tests done at one location, starting at childhood and continuing through adult life.

"We want this to be as close to one-stop care as possible," says Dr. Stephen N. Davis, chief of the Division of Diabetes, Endocrinology and Metabolism and Rudolph H. Kampmeier Professor of Medicine.

"Our objective is to have Vanderbilt be a place that affords the best care available and to discover new care that we don't have yet, so that patients consider this as the place to go for their care, and health care professionals consider it as the place to go for their training," adds Dr. Daryl K. Granner, director of the Vanderbilt Diabetes Center and Joe C. Davis Professor of Biomedical Science.



pathway to a cure

Transplantable cells offer hope, but face obstacles

BY LEIGH MACMILLAN

One step into Chris Wright's Vanderbilt office, and it's clear that this guy is fond of frogs. Perched on a long low bookcase are all manner of them – wooden, ceramic, stuffed. The figures join a striking series of models that show, in hand-painted detail, stages of the developing frog embryo.

The décor pays homage to the animal that gave Wright his scientific start. It was in studies of the frog embryo – a system long-favored for developmental biology research – that Wright discovered a gene critical to the development of the pancreas. The findings launched a path of inquiry that has landed Wright in the thick of the push to cure diabetes.

It's not a place he set out to be. The pressure of finding something that will benefit the millions of patients suffering from diabetes can be daunting, says Wright, professor of Cell & Developmental Biology, but "it's also invigorating.

"Our research really has a chance to help people; it's not just an academic question whose answer might be in the textbooks, if you're lucky."

Wright's team and a handful of other laboratories are seeking the set of genes that control the development of the specialized cells of the pancreas. "If we can identify the factors that make a pancreas," Wright says, "we might be able to coerce embryonic stem cells or other cells to turn into pancreas."

Success could mean unlimited supplies of insulin-producing cells for transplantation therapy. And transplantation appears to be as close to a cure for diabetes as we've come.

Only one kind of cell in the body – the pancreatic beta cell – can sense blood glucose and respond by secreting insulin. Destruction of these precious cells by a person's own immune system gives rise to type 1 diabetes.

Although glucose testing and insulin injections can stand in for the lost beta cells, they cannot begin to match the minute-to-minute control of blood glucose normally exerted by these cells. While intensive insulin therapy reduces the long-term complications of diabetes, it does not eliminate these complications and often results in dangerous episodes of hypoglycemia.

So why not simply replace the lost beta cells with new ones? That is the premise of transplantation therapy as a cure for diabetes.

One option is to transplant an entire pancreas, and indeed, pancreas transplantation has proven successful in restoring normal blood glucose levels.

Pictured left: An intact rat pancreatic islet is shown against a background of images: a 3-year-old child held by his mother (upper left), one of the first patients to receive insulin; gels used to identify genes involved in the development of the pancreas (lower right); and the different kinds of cells that make up the newborn mouse pancreas. For more on the islet, see inside front cover. Other images courtesy of Eli Lilly and Company Archives and Chris Wright, Ph.D.

Unfortunately, the procedure carries high morbidity and mortality rates, restricting it as a therapy to those patients with diabetes and significant end-stage organ disease like renal failure.

Most patients with type 1 diabetes need a safer alternative. Perhaps, investigators reasoned, the surgical complications of full pancreas transplants could be avoided by transplanting only the "islets of Langerhans," named for the German pathologist who first described the characteristic cell islands in the pancreas. Islets are home to the insulin-producing beta cells, along with several other hormone-releasing cell types.

The idea showed early promise. In 1972, Paul Lacy at Washington University in St. Louis reported that islet transplantation could cure diabetes in rats. Investigators raced to apply the procedure to human beings. But of the hundreds of attempts made over the next 20-plus years, less than 10 percent resulted in insulin independence.

More encouraging results began to surface in the late 1990s, with groups in Miami, Minneapolis, and Milan achieving longer periods of islet cell survival, higher percentages of insulin independence, and, for those transplant patients who still required insulin, avoidance of dangerous blood glucose extremes.

The breakthrough report came in July 2000 from a group at the University of Alberta in Edmonton, Canada. Dr. James Shapiro and colleagues announced that each of seven islet transplant recipients – patients with type 1 diabetes and a history of severe hypoglycemia – were insulin independent, the longest for 15 months and counting. Their strategy used a novel combination of non-steroid immunosuppressant drugs – ones that were kinder to the fragile islets and that were less likely to induce insulin resistance in the transplant recipients. And it used islets from two, and in one case three, donor pancreases.

The Edmonton group "made a leap forward in terms of immunosuppression and standardization of islet isolation techniques, culminating in a very high success rate," says Dr. Christopher Marsh, chief of the organ transplantation service at the Scripps Clinic in La Jolla, Calif., and co-director of the Organ and Cell Transplantation Center at Scripps Green Hospital.

The approach, now known as the "Edmonton protocol," triggered a surge in interest in islet cell transplantation and prompted the National Institutes of Health and the Juvenile Diabetes Research Foundation (JDRF) to fund larger clinical trials of the protocol and variations of it.

Since the Edmonton group's original publication, more than 150 patients worldwide have received islet transplants as part of these trials, according to the JDRF.

Preliminary results from at least one JDRF-sponsored transplant center support the idea that islets from a single donor pancreas might cure diabetes. Using one cadaveric pancreas per diabetes patient would stretch the islet supply, but not enough to provide islet transplantation to all the patients who could benefit from it.

Last year in the United States, fewer than 2000 pancreases were recovered from donors. More than a million patients have type 1 diabetes.

"What you need is more tissue," says Vanderbilt's Wright. "Where do you get more tissue?"

Islet tissue could potentially come from another species, like pig, an area of research called xenotransplantation. Or insulin-producing cells could be grown in the laboratory, as genetically engineered cells or as the products of stem cells – embryonic or adult.

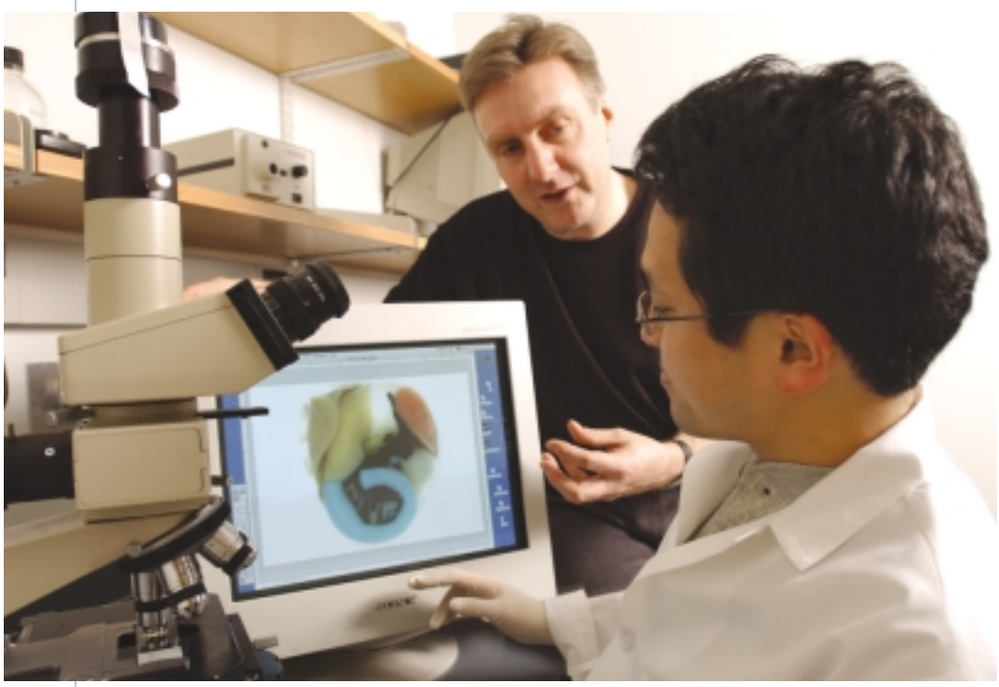
None of these options is clear-cut. Xenotransplantation must overcome concerns that pig-specific pathogens will infect the human recipients and potentially endanger public health. Genetic engineering of cells requires an appropriate cell starting point and knowledge of all the genes that are necessary for glucose-regulated insulin secretion. Likewise, turning stem cells into pancreatic cells requires identification of the complete set of factors that will elicit that conversion.

Securing a plentiful supply of islets or an alternative source of insulin-producing cells is just one of the hurdles looming for islet transplantation. Equally vexing is the long-term immunosuppression required to prevent attack of the transplanted cells.

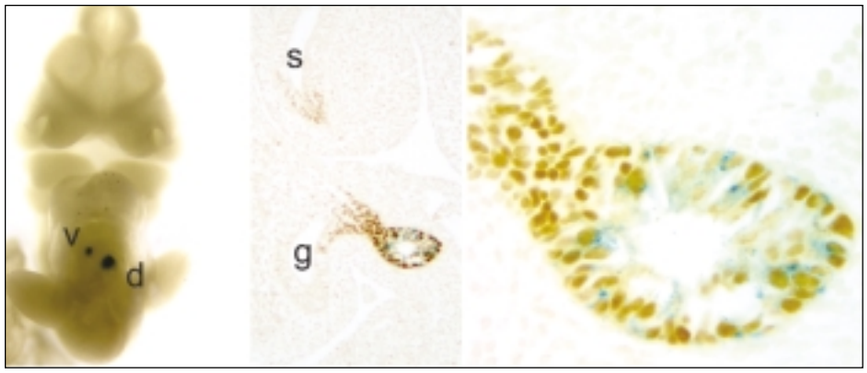
Immunosuppressive drugs can blunt the immune system's attack on transplanted tissues, as well as its attack on beta cells, the hallmark of type 1 diabetes. But even the Edmonton protocol's newer, less toxic drug cocktail has "side effects that are not justified lifelong in juveniles," says Dr. Allen Spiegel, director of the National Institute of Diabetes & Digestive & Kidney Diseases. Immunosuppression puts patients at increased risk for infections of all types, for lymphomas and related malignancies, and for renal toxicity.

One appealing way to leap over this obstacle, Spiegel says, would be to induce "tolerance" of the transplanted cells, without requiring chronic drugs and without suppressing immunity overall. The

Pictured below: Chris Wright (left) and Yoshio Fujitani, senior post-doctoral fellow, discuss their mouse embryo research. They have used genetic manipulations to introduce an inherited marker – a blue color that can be followed in cells that turn on the *p48* gene and form the pancreas (shown on computer screen).



ANNE RAYNER POLLO



Images of a developing mouse embryo show the ventral (v) and dorsal (d) pancreatic buds as two blue spots (left panel). A section through one of the buds (middle and right panels) shows blue color only in cells that will go on to form the pancreas. Brown color marks cells that not only will form the future pancreas, by also the stomach (s) and gut (g). See story, page 8.

Courtesy of Chris Wright, Ph.D. and colleagues, and *Nature Genetics.*

Immune Tolerance Network, a $144 million project co-funded by the National Institute of Allergy and Infectious Diseases, the NIDDK and the JDRF, is working toward this goal. "There are some encouraging results, but a lot of work remains to be done," Spiegel says.

It might also be possible to sheathe islets, or cell clusters, in materials that protect them from immune system attack but that allow passage of nutrients, glucose and insulin. Encapsulation strategies include ultrathin polymer membranes – microencapsulation – and porous matrixes with cells or islets dispersed inside – macroencapsulation.

"What we like about encapsulation is that it will eliminate the need for long-term immunosuppressive drug therapy," says Taylor Wang, Centennial Professor of Mechanical Engineering and Applied Physics at Vanderbilt, and a former astronaut whose 1985 space shuttle experiments involving water and oil droplets turned out to have implications for encapsulating islets.

Wang and colleagues developed an encapsulation method – materials and bioreactor system – and successfully reversed diabetes in a mouse model by transplanting encapsulated rat or pig islets. But their capsules failed in dogs. The investigators have since worked through nearly 20 different engineering parameters, adjusting each in order to optimize performance.

Now, bolstered by a new grant from NASA, they are preparing to test the improved capsules in larger animals and, assuming success, in human beings. "We are starting to see the light at the end of the tunnel," says Wang, who directs the Vanderbilt Center for Microgravity Research and Applications. "You can get a little bit edgy though. Is it really the light, or a train coming at me?"

As investigators make progress in shielding transplanted cells from host immune attack, islet transplantation will become all the more desirable as a treatment and cure for diabetes. Translating it into a widespread option, however, will depend on securing a suitable and plentiful source of insulin-producing tissue.

Even if xenotransplantation proves workable, the number of donor animals required to meet patient demand for islets would likely be excessive. Insulin-releasing cells that could be produced in unlimited quantities in the laboratory – or pharmaceutical factory – are a more desirable option.

Toward that end, an international group of scientists, assembled together as the NIH-supported Beta Cell Biology Consortium, are working toward the ultimate goal of converting human stem cells into functional beta-like cells or complete pancreatic islets.

Stem cells, the basic building blocks of the body's many different tissues, offer promise for a variety of ills. They come in two types: embryonic, which normally populate the early embryo and give rise to all the tissues of the body, and adult, which are found in and serve to replenish "mature" tissues – the best known are the bone marrow-residing cells that renew the blood supply. Embryonic stem cells are considered more versatile than their adult stem cell relatives, in terms of the cell types they can become, but they are more controversial.

That controversy might be avoided by identifying human adult pancreatic stem cells – cells that spin off renewed pancreatic cells, including beta cells. Evidence from several laboratories suggests that these adult stem cells exist, but no one has yet isolated the actual cells.

"In the next couple of years, one may unequivocally identify the adult pancreatic stem cell," says Douglas Melton, a Harvard investigator studying the development of the pancreas. "The problem is whether it can be replicated to any appreciable extent, to be useful in a clinical context. Can you coax it to grow outside the body, to make a pile of cells?"

More promising, Melton says, is the embryonic stem cell. "Here, two of the problems have already been solved. This cell is available, and it grows like a weed. You can make virtually an infinite amount.

"That leaves one big problem: how do you direct differentiation into pancreatic cells?"

This is where studies of pancreas development come in – finding the gene switches that turn an undefined bit of embryonic tissue into the specialized cells

(continued on next page)

INTERNATIONAL GROUP CHANGES THE WAY SCIENCE IS DONE

Based at Vanderbilt University Medical Center, the Beta Cell Biology Consortium includes researchers from more than a dozen universities around the world and from the National Institute of Diabetes and Digestive and Kidney Diseases, which funds the effort.

When the consortium was created two years ago, Vanderbilt was chosen to be the coordinating center because, at the time, "we had the only program project (funded by the institute) that was focused entirely on the pancreatic beta cell," says Dr. Mark A. Magnuson, assistant vice chancellor for research at Vanderbilt who chairs the consortium's steering committee.

Other Vanderbilt faculty who participate in the consortium include Chris Wright, Roland Stein, Jason Moore, David Piston and Maureen Gannon.

Magnuson is optimistic that this coordinated effort will lead to the identification of factors necessary to convert stem cells into pancreatic islet cells. "These mega-organizations are really changing the way that we approach doing science," he says.

For more information, visit the consortium's Web site at www.betacell.org.

As investigators make progress in shielding transplanted cells from host immune attack, islet transplantation will become all the more desirable as a treatment and cure for diabetes.

of the pancreas. Wright's observations in the frog embryo identified one of the first.

In the mid-1980s, Wright was plugging away as a postdoctoral fellow at UCLA, looking for new members of the "homeobox" gene family – genes that had just been identified as being critical for proper pattern formation in the fruit fly. Of the several he identified, one had an interesting pattern of expression in the developing frog embryo; it was turned on in the area that would give rise to the pancreas and part of the intestines.

Wright launched his Vanderbilt laboratory with the intention of studying the function of the gene, now called *pdx1*, in mammals, specifically mice. "I was sure it would be exciting," he recalls. He was right. Mice without the *pdx1* gene failed to develop a pancreas.

The *pdx1* gene is a transcription factor – it turns on other genes, a cascade of which eventually turns undifferentiated embryonic tissue into the pancreas.

In recent studies, Wright and colleagues have characterized the action of another transcription factor, a gene called *PTF1p48* (*p48* for short).

The group reported last summer in *Nature Genetics* a novel and powerful cell marking method that they used to track cells in the mouse that express the *p48* gene, starting very early in embryonic pancreas formation. The method relied on genetic manipulations to introduce an inherited marker – a blue color that could be followed in cells that turned on the *p48* gene, and in all the cells that came from those cells.

A simple way to think about the technique, Wright says, is to picture the crowd at a football stadium and to imagine that somewhere in the stadium, for a limited time, a man gave away unique blue hats and asked people to wear them. "Now we can follow the people who got hats, no matter where they go," Wright says. "Whether they go to get a hot dog or leave the stadium entirely, we can find them."

Wright and colleagues found that cells expressing the *p48* gene, blue hat-wearing cells, formed the pancreas. When the investigators knocked out the *p48* gene, they found that cells, which would have normally formed the pancreas, became intestinal cells instead.

"The really important point is that these cells without *p48* don't just die; they go on to behave as a different tissue," Wright says. "That is very powerful information when you are thinking about manipulating stem cells in the laboratory. Because you know now – at least for some genes – that you can put them in or take them away and you don't kill the cells; you manipulate what they're going to become. And that's exactly what we want to do therapeutically."

The next step, he says, is to see whether introducing the *p48* gene into cells that would normally become intestinal cells changes their fate and causes them to become pancreas cells instead.

"If we can do that," Wright says, "we're a big step further towards knowing that *p48* is one of the gene triggers that you might want to put into an embryonic or other stem cell to make pancreas."

But one of how many? Wright wonders. "We're just sort of clutching and still trying to get some basic understanding. It's like climbing an ice wall with ice picks: you'd better have a good hold before you start going up too high."

Even knowing the complete set of factors that will convert stem cells into pancreas doesn't address the logistical problems of applying that information on a large scale to generate products for human transplantation. Simple manipulation of laboratory growth conditions, for example, may not be sufficiently rigorous to pass FDA muster.

"We have to understand very deeply the physiological behavior of those cells," Wright says. "How long do we spend characterizing those cell types before we say it's appropriate to put them into people? I don't know the answer to that."

At the end of the day, it is the fundamental academic question that drives Wright's quest for answers. Relaxing in his office of frog companions, he ponders the intricacies of pancreas development. "I'm still fascinated by how a piece of tissue buds out, goes through a branching process, makes the right numbers of cells of different types, and generates an organ that works so beautifully," he says. "It's an amazing thing." **LENS**

Political "chill" slows scientific progress

Their very name raises hackles – ***embryonic*** stem cells. These are the cells that populate the early embryo and give rise to all of the body's tissues. These are the cells that can be grown in virtually limitless quantities in the laboratory. And these are the cells that scientists hope will someday provide replacements for cells damaged in diabetes and other disease states.

Embryonic stem cells come from human embryos – those created by in vitro fertilization and donated to research in lieu of being discarded – landing the cells squarely at the center of political debate. Should the federal government support embryonic stem cell research?

Congress has repeatedly passed legislation barring federal funding for any research that involves the creation or destruction of human embryos. Private funding supported isolation of the first human embryonic stem cells in 1998 by investigators at the University of Wisconsin and Johns Hopkins University. In 2001, President Bush decided that federal funds could support embryonic stem cell research, but only using stem cell lines that existed as of August 9 that year.

The controversy and "political chill" have hindered stem cell research in the United States, says Douglas Melton, a Howard Hughes Medical Institute investigator at Harvard University. "One can imagine in another circumstance, the best and brightest young people would be very much attracted to the area of stem cell research. We don't see that happening," he says.

"Scientifically, it doesn't make sense to only have access to these particular cell lines when people are just now discovering how best to grow human embryonic stem cells," adds Christopher Wright, a developmental biologist at Vanderbilt University.

The research is proceeding in the United States, but not as rapidly as in countries with fewer restrictions. Some universities, including Harvard and Stanford, have established private foundations to support human embryonic stem cell research. Relieving the "chill" and boosting stem cell research in the United States requires a public better informed about the issues, Melton says.

"These are complex issues about when life begins, and there may not be universal answers," he says. "But we shouldn't shy away from this discussion."

– LEIGH MACMILLAN

A normal life

New technologies help patients avoid the "highs" and "lows" of diabetes

by Bill Snyder

ANNE RAYNER POLLO

Katie Rush (right) participates in sports year round, thanks to her insulin pump. She's pictured at home with her parents, Drs. Charlie and Meg Rush, and her younger sister, Libby.

Two years ago, Katie Rush was having frequent and unsettling episodes of hypoglycemia – low blood glucose.

"I'd just feel really sleepy and hungry," says the active Nashville seventh grader, now 12, who's had type 1 diabetes since she was 3. "I wouldn't remember anything that happened before I got low. I just felt really bad."

Fortunately, at that time, insulin pumps were beginning to be used more frequently in children, and Katie was fitted with one in the summer of 2001. Since then, "we've only had five or six of the kind of spells we'd been having twice a week," says her mother, Dr. Meg Rush, assistant professor of Pediatrics at Vanderbilt.

Insulin pumps are among the recent technological and pharmaceutical marvels that are improving the lives of people with type 1 diabetes.

The battery-powered device, which is a little larger than a pager, contains a cartridge of rapid-acting insulin that is pumped through a plastic catheter inserted under the skin. With the help of a miniature computer, the pump can deliver precise amounts of insulin throughout the day, even when the patient is asleep.

Rapid-acting forms of insulin help improve blood glucose control because they more closely mimic the body's normal insulin response after eating a meal. There are also long-acting forms of the hormone, designed for people who can control their blood glucose with once-a-day injections.

Patients still must test their blood glucose frequently, but they can program their pumps to deliver an additional dose of insulin before snacks and mealtimes to help avoid the "highs" and "lows" of blood glucose that can occur with traditional insulin therapy.

"You have to be aware of how you feel," Katie Rush says. "You have to monitor it closely."

Of all the complications of diabetes treatment, hypoglycemia is perhaps the most frightening. "Often (patients) will prefer to have their blood glucose values running a little bit high in order to prevent hypoglycemia," says Dr. Stephen N. Davis, chief of the Division of Diabetes, Endocrinology and Metabolism and Rudolph H. Kampmeier Professor of Medicine at Vanderbilt.

Davis is trying to figure out why the body doesn't compensate for insulin-induced drops in blood glucose, for example, by boosting secretion of glucagon, another pancreatic hormone that can stimulate glucose release by the liver.

A clue is cortisol, a stress hormone that appears to blunt the body's ability to compensate for low blood glucose. Drugs that may block the cortisol effect are now being tested in humans.

In the meantime, new forms of insulin are being tested, including a form that could be inhaled, and efforts are underway to develop an insulin "pill." Also in the pipeline: devices that can "read" blood glucose levels by shining infrared light on the skin.

The "holy grail," of course, is the restoration of normal beta cell function. Whether or not that day ever comes, "we have spent the last eight years really encouraging her to know she can live a normal life," Meg Rush says of Katie.

"This does make her different, but it doesn't have to change her dreams." **LENS**

A disparate burden

Genes, culture and the challenge of prevention

By Mary Beth Gardiner

When 19-year-old Ron Reid went to the doctor's office he knew something was seriously wrong. It took his falling into a hyperglycemia-induced coma, however, before the problem was nailed as diabetes.

The week or two before that day, Reid had been feeling pretty bad. Normally active and athletic, he was dragging, his glands swollen and his vision blurred. He battled cottonmouth, awaking each morning with a thickly coated tongue. An unusual craving for Butterfinger candy bars had him baffled. "I had never had a taste for sweets, even as a kid," he says.

Scared and fearing the worst – it was the early '90s and AIDS was escalating – he finally headed to a clinic. As the staff plied him with juice, chocolate milk, and soda pop to quench his bottomless thirst, he made trip after trip to the restroom, what seemed to Reid "every three seconds." When he began vomiting, the fruity alcoholic odor raised suspicious eyebrows. "They thought I was drunk," Reid laughs. As they continued trying to make him comfortable, Reid lapsed into a coma. Finally, they checked his blood glucose level. It measured a whopping 1244 milligrams per deciliter of blood, over 10 times the normal value.

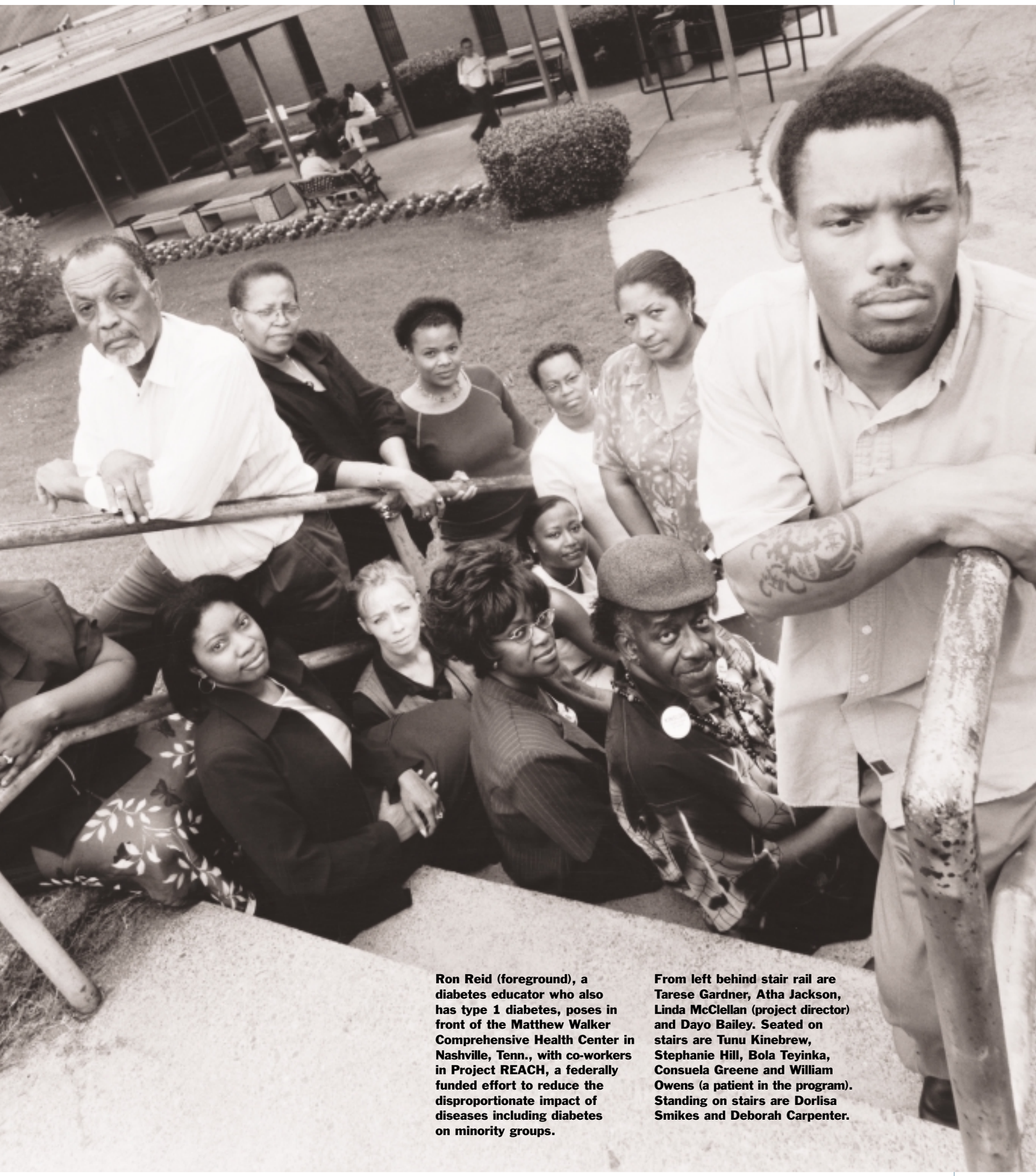
Now 28 years old, Reid works as a diabetes educator in Nashville, Tenn., determined, he says, to ensure that others not reach the point he did before learning they have the disease. Reid heads out each day into his own community where he and other African Americans like him are disproportionately at risk, not only for developing diabetes but also for the long-term complications that come with advanced disease.

This disparity isn't limited to African Americans. That population is joined by other racial and ethnic minority groups, including Hispanics, Native Americans, Asians and Pacific Islanders, in experiencing some of the highest incidences of diabetes and its complications, particularly type 2 diabetes. Though there is little doubt that genetics plays a part in this inequity, there is mounting evidence that lifestyle, cultural factors, and access to healthcare also strongly contribute to what is now a growing tsunami of new cases.

Reid has type 1 diabetes, which has an abrupt onset of characteristic symptoms, frequent urination and terrific thirst being two of them. Type 2 diabetes, on the other hand, comes on more quietly. Often, by the time it's diagnosed, the disease is advanced.

Reid's disease, which is much less common, typically develops at a younger age and results from destruction of the insulin-secreting cells of the pancreas. Insulin, a hormone key to converting food

DEAN DIXON



Ron Reid (foreground), a diabetes educator who also has type 1 diabetes, poses in front of the Matthew Walker Comprehensive Health Center in Nashville, Tenn., with co-workers in Project REACH, a federally funded effort to reduce the disproportionate impact of diseases including diabetes on minority groups.

From left behind stair rail are Tarese Gardner, Atha Jackson, Linda McClellan (project director) and Dayo Bailey. Seated on stairs are Tunu Kinebrew, Stephanie Hill, Bola Teyinka, Consuela Greene and William Owens (a patient in the program). Standing on stairs are Dorlisa Smikes and Deborah Carpenter.

ANNE RAYNER POLLO

Having become a diabetes expert out of necessity, Reid knows that the tighter he controls his blood sugar – through watching what he eats and keeping active, as well as through judicious insulin supplementation – the more likely it is he will avoid health complications down the road.

into energy, must be injected to restore normal function.

Making the case

Type 2 diabetes differs in that it usually develops later in life and results from, essentially, an overworked pancreas. Insulin resistance in predisposed individuals causes the pancreas to pump out larger and larger amounts of the hormone each time food is eaten. Eventually, the insulin-secreting cells die a premature death, forcing the need for insulin injections.

Diabetes currently affects 17 million Americans, with about 90 percent of cases being type 2. An estimated one-third are unaware they have the disease. Since World War II, type 2 diabetes has mushroomed in this country, becoming one of the costliest and most devastating diseases in recent history. While Caucasians suffer from the disease in high numbers, the disease is most ruthless in its attack on those whose ancestors came from places other than Europe.

African Americans are at especially high risk for diabetes. The rate of type 2 diabetes in that population is 60 to 70 percent higher than that seen in Caucasian Americans, a tripling of the rate seen in 1963. Complications from diabetes are greater, too. African Americans suffer a two-fold higher rate of blindness and lower limb amputation, and a three- to five-fold higher rate of end stage kidney disease.

Hispanic Americans, the second largest and fastest growing minority group in the United States, are twice as likely as non-Hispanic whites to develop type 2 diabetes and, like African Americans, Hispanics also see higher rates of long-term complications.

Native Americans are the population in this country most disproportionately affected by diabetes, especially type 2 diabetes. The Pima Indians of the desert Southwest have one of the highest incidences known worldwide. The disease is so common – more than 50 percent of adults develop type 2 diabetes – that public restrooms on reservations are equipped with hazardous waste bins for safe disposal of insulin needles and lancets. Most Pimas grow up assuming it is their destiny.

The prevalence of type 2 diabetes is estimated to be about two to four times greater in Asians living in the U.S. than in those living in their native country, though that may be changing. Recent reports suggest a wave of obesity is sweeping through Asia as populations throng into burgeoning cities emulating the Western bent for fatty fast foods and urban conveniences.

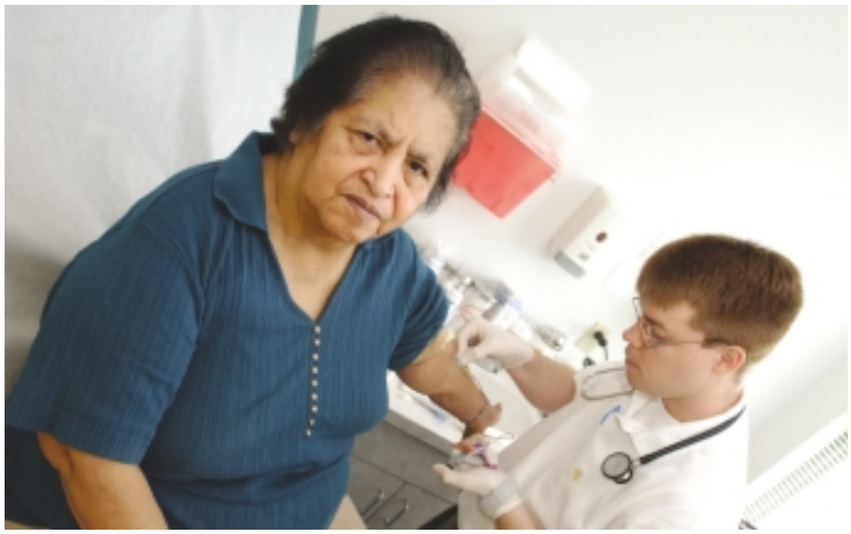
It is this modern Western lifestyle of too much food and too little exercise that many are concluding is behind the explosion of type 2 diabetes in this country. While genes may set us up for diabetes, it appears to be behavior that tips the scale.

And tipping the scales is literally what we're doing, from all evidence. Obesity among adults has doubled since 1980, while overweight among adolescents has tripled, according to former U.S. Surgeon General Dr. David Satcher's 2001 report "Call to Action." Especially at peril are children, where obesity and type 2 diabetes – formerly known as "adult-onset" – are increasing hand-in-hand at an alarming pace, leaving them vulnerable for years to come.

So is it genetics or is it environment at the heart of the epidemic? And why are certain people at particular risk for what Dr. James R. Gavin III, president of Morehouse School of Medicine in Atlanta, Ga., and chair of the National Diabetes Education Program, calls "diabesity"?

One of the most durable theories as to why so many humans are poorly suited for our modern lifestyle, is a notion first posed three decades ago by genetics pioneer Dr. James V. Neel, that of the so-called "thrifty genes." Neel proposed that certain genes allowed ancestral

Pictured at right:
Susana Solano has blood drawn by Vanderbilt nurse practitioner Jason Jean at the Vine Hill Community Clinic in Nashville. Her blood will be tested to see how well she has controlled her glucose over the past several months.



MARY DONALDSON

hunter-gatherers to store fat during times of feast to survive times of famine. Today, with our easy access to caloric abundance, those genes that were designed to protect us from starvation are now a major handicap.

The anatomy of change

Some experts say it is this heritable penchant for high-energy foods that makes diabetes so hard to beat. The current wisdom for diabetes prevention and control – weight loss through sensible diet and moderate exercise – is good advice for anyone. Making those changes, however, can be difficult for many people.

Fast food is everywhere, it's cheap, and it tastes good. When money is tight, it's hard to argue when a hungry family can be satisfied for just a few dollars.

But food can be more than mere sustenance. Holidays, reunions, weddings, funerals. Saturday picnics and Sunday dinners. Gatherings of family and friends often revolve around special meals, rich with tradition and steeped in cultural meaning.

"A meal is often a cultural event," says Marilyn Skaff, Ph.D., associate adjunct professor of Family and Community Medicine at the University of California, San Francisco. "Within the Chinese American population, for instance, the family gathers and eats from one big pot, making it very difficult to measure amounts eaten and calories consumed."

African Americans in her community also talk of how tough it is to stick to a diet when they go to family gatherings, she says. "Convincing people to change this part of their life is very difficult."

Physician Patricia Weaver agrees. Weaver is medical director of the Matthew Walker Comprehensive Health Center in Nashville, where 90 percent of those treated for diabetes are African American. Adding physical activity to her patients' lives is just as challenging, she says. "We have a lot of patients who I think, to the best of their ability, are making some changes in terms of diet, but they don't have the exercise component. That, without a doubt is the most difficult part to change."

Reid, whose job is based out of the federally funded health center, knows first-hand how much difference physical activity can make in regulating blood glucose. Reid walks, rather than drives, as much as he can during his daily neighborhood rounds, and at his second job at a car lot. In the evening, the insulin pump plugged into his torso comes off for his nightly game of basketball.

All this activity makes it so that Reid programs his pump to deliver additional insulin usually only once a day, before his evening meal. He's become so attuned to his body, he's learned that the mile-long walk to Burger King and back is enough to reduce by half or more the insulin needed to take care of the burger and fries he will consume there.

Having become a diabetes expert out of necessity, Reid knows that the tighter he controls his blood glucose – through watching what he eats and keeping active, as well as through judicious insulin supplementation – the more likely it is he will avoid health complications down the road. The same complications that took the legs and eventually the life of his diabetic grandfather.

Breaking barriers

On the frontline of diabetes care, the barriers to success are daunting. In for her quarterly check-up at Nashville's Vine Hill Community Clinic, Susana Solano epitomizes the challenges faced by those with advanced diabetes. Solano contends with heart disease, which commonly accompanies diabetes, as well as searing leg pain caused by neuropathy. She moves slowly these days, with the aid of a cane.

"She gets very tired and also light-headed," explains daughter Maria Ramirez. "She just wants to stay in her chair a lot, because if she's up after a few minutes her head spins. My husband and I go to work during the day…so it's very, very hard."

Solano moved to this country from Mexico a decade ago to live with her daughter. Insulin-dependent for twenty years, she administers her own injections, before each meal and at bedtime, but doesn't monitor her blood glucose. Finger pricks are just too painful – and too expensive.

Although glucometers, instruments for measuring blood glucose, are commonly donated by manufacturers and made available at no cost to the largely impoverished clientele seen at Vine Hill, the test strips are expensive. At 75 cents apiece, the costs add up quickly.

"It's not blue ribbon care, but we do the best we can under the circumstances," says nurse practitioner Jason Jean. Solano will have blood drawn by Jean today for testing her hemoglobin A1c level. Hemoglobin A1c is a form of the oxygen-

African Americans are at especially high risk for diabetes. The rate of type 2 diabetes in that population is 60 to 70 percent higher than that seen in Caucasian Americans, a tripling of the rate seen in 1963.

carrying blood protein that also binds to glucose, and thus can give a measure of how well Solano has been controlling her blood glucose over the past few months.

About half of his client visits at Vine Hill, a clinic founded and staffed by Vanderbilt's School of Nursing, involve diabetes in some form or fashion, Jean says. "Every diabetic patient I see gets pounded on three things: diet, exercise, and stopping smoking. Whether or not they follow that regimen is another matter."

"It is a tough, tough disease to live with," says nurse practitioner Anne Brown. "I can't think of any other disease where we ask people to do so much to take care of themselves."

Brown sees referral patients in her endocrinology practice as part of the Diabetes Improvement Program, one element of Vanderbilt's NIH-funded Diabetes Research and Training Center. The nurse practitioner-run program aims to help patients fine-tune their glucose control.

With the help of dietitians, the advanced care nurses intensively counsel patients over a three-month period, meeting weekly to adjust medication regimens and facilitate lifestyle changes. Once glycemic targets are achieved, patients return to the care of their primary physicians.

A similar program, conceived through an alliance between Nashville's historically black Meharry Medical College and Vanderbilt University, exists at local "safety net" clinics to ensure that every diabetic patient receives a recommended standard of care, which includes annual measurement of hemoglobin A1c, cholesterol, weight, and blood pressure, in addition to a kidney function test and eye and foot exams.

"There is no aspect of these patients' lives that diabetes does not touch and that they don't have to make adjustments for," says Brown.

The demands of the disease can cause frustration and anxiety in patient and family, leading to marital strife and other stresses. Feelings of helplessness can overwhelm, and depression is common, especially at diagnosis and later, at the onset of long-term complications.

Addressing patients' expectations of being disabled by diabetes and how those feelings affect self-care is the research focus of Dr. Kathleen Figaro, assistant professor of Medicine at Vanderbilt.

"In my practice I had noticed that my black patients felt overwhelmed and isolated by coping with the disease," says Figaro, "that diabetes was a curse and there was nothing they could do about it."

The patients not only didn't trust their medical system, she says, but they also didn't believe that their own behavior could affect outcome. "I thought that might have something to do with the disparities and outcomes between whites and blacks, because self-care is so important in diabetes."

With funding from a Robert Wood Johnson Career Development Award, Figaro plans to create a scale for measuring patients' expectations. She hopes the tool will help tailor interventions aimed at empowering patients.

Raising awareness

Putting the brakes on escalating diabetes incidence in disadvantaged and minority populations will not be easy, but most agree that the greatest impact will come from education, both at a local community level and on a broader national scale.

"Certainly, community outreach and intervention is critical to the control of this problem," says Satcher, who is now director of the National Center for

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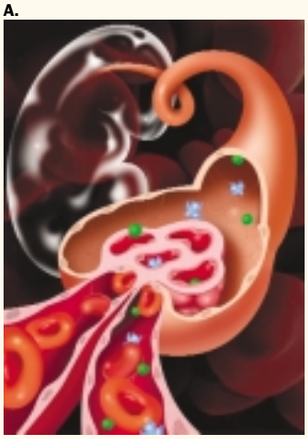

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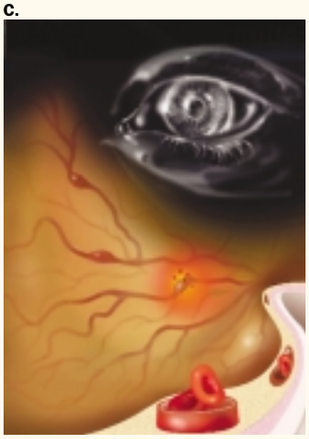

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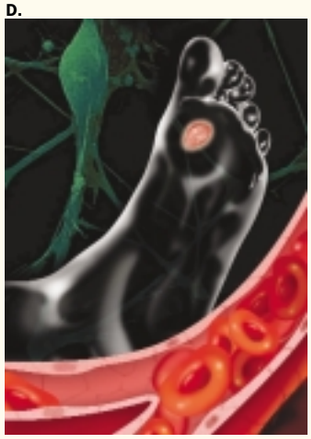


Complications of diabetes

ILLUSTRATIONS BY DOMINIC DOYLE

A: Kidney disease
Diabetes can damage the glomeruli, the blood-filtering units of the kidneys (shown here). As a result, protein (green) is lost in the urine, and the kidneys gradually lose their ability to remove waste products (blue) from the bloodstream. Ultimately, the kidneys may fail and patients will require artificial kidney dialysis.

B: Heart disease
Most adults with diabetes have high blood pressure and high blood levels of triglycerides and low-density lipoprotein (LDL) cholesterol. Elevated cholesterol can lead to atherosclerosis, the build-up of fatty deposits in artery walls (shown here). Both high blood pressure and atherosclerosis, if untreated, can lead to heart attack or stroke.

C: Retinopathy
Diabetes can damage tiny blood vessels in the retina at the back of the eyeball. The damaged vessels can leak fluid into the retina, blurring vision. Fragile new blood vessels also may grow into the retina and leak blood (shown here) ultimately destroying the retina and causing blindness.

D: Nerve damage
Diabetes can damage nerves throughout the body, causing numbness. Sores may appear on numb areas of the foot because pressure or injury goes unnoticed. Poor circulation (shown here) may inhibit healing. If the injury is not treated and infection spreads to the bone, the foot may have to be amputated.

Primary Care at Morehouse School of Medicine. "There isn't any substitute for it, really. It's going to get more people into care early. It's going to, in some cases, prevent onset in people who are at high risk. And when people get into care…it will help them stay in care."

Community outreach is precisely the goal of the Nashville REACH Coalition, a group of the city's academic institutions – including Meharry, Fisk University, Tennessee State University, and Vanderbilt University – working with local, county, and state healthcare agencies and providers to address area racial and ethnic health disparities.

A primary focus of the coalition is Project REACH 2010, a multi-center, Centers for Disease Control and Prevention funded effort to end disparities in a number of diseases. Nashville's arm targets a pocket north of the city where African Americans are particularly hard-hit by diabetes and heart disease when compared to Caucasians in the same area, and when compared to African Americans in other parts of the country. The goal of the seven-year project is this: to better understand why the disparity exists and to work within the community to stem the tide.

As an educator with Project REACH, Ron Reid spends his days spreading the gospel of diabetes prevention to at-risk neighbors, often working through community centers and churches. Reid is on one of four teams who fan out into the community of 43,000, 85 percent of whom are African American, with the goals of screening for undiagnosed cases, increasing access to quality healthcare, decreasing tobacco use, and teaching the benefits of nutrition and physical activity.

A lot of what he sees, Reid says, is fear and mistrust. Fearing the worst, many diabetes patients either don't go to the doctor or when they go, they try to slip by with as limited an exam as possible.

"People are afraid to talk to physicians," says Reid. "Usually, they won't take their shoes off, because they want to keep their feet as long as they can. A blind patient I know put off telling her doctor for six months (about her feet), because they are so important to her independence."

Trust in a healthcare provider makes a big difference in how effective treatment is, according to Jason Jean. "I think patients are interested in a community-based practice where they can sit down with a provider and talk about the disease process or their family life or whatever else is impacting their care."

No medical "home"

Far too many Hispanics and African Americans don't have a medical home, says Satcher. "A lot of them go to emergency rooms for their care," he says, where cultural issues, such as language barriers or racial stereotyping, often make for a less than satisfactory experience.

Satcher points to a 2002 Institute of Medicine report on racial and ethnic bias in health care – *Unequal Treatment* – as "pivotal in increasing sensitivity" among providers, especially in its potential to affect training of future physicians and nurses. "There is, for example, a program here at Morehouse School of Medicine that attracts people from around the country to a course on cultural competence."

Increased cultural sensitivity in providers is a major feature of the National Diabetes Education Program, according to its chairman. The NDEP has a special populations work group, says Gavin, that is "heavily invested in looking at approaches to help bridge the cultural chasms that make it difficult for some of these cross-cultural encounters to be successful."

As to raising consciousness about the disease within minority populations, Gavin believes that the success of diabetes education efforts will hinge on repetition of message, not just isolated, one-hit attempts.

"There has been this tendency to think that…as long as content is accurate and the message is compelling, it shouldn't take much exposure to drive the point home," he says. "I think consistency of message will be required, and that means often and it means early."

Gavin advocates setting up educational programs in schools and in worksites, through public service announcements, and through working with healthcare-oriented cultural organizations – such as Indian Health Services, the National Council of La Raza, and the Association of Asian Pacific Community Health Organizations – to accomplish his goals.

"I hope that the national conversation on diabetes is one that will rise to the same level as the one we saw in the national conversation on cholesterol. Everyone knew it was important; everyone knew their number," he says. "When we see penetration of that level of awareness among our at-risk and affected populations, then we'll know that we're really beginning to move the needle and gain some traction." **LENS**

Meharry, Vanderbilt host national meeting on diabetes disparities

"Overcoming Diabetes Health Disparities" is the subject of a conference sponsored by the Meharry-Vanderbilt Alliance Nov. 13-15, 2003, at the Loews Vanderbilt Hotel in Nashville, Tenn.

Dr. James Gavin III, president of Morehouse School of Medicine in Atlanta, Ga. and chair of the National Diabetes Education Program, will be the keynote speaker.

Other speakers include:

Dr. Ralph DeFronzo, chief of the division of diabetes at the University of Texas Health Science Center at San Antonio;

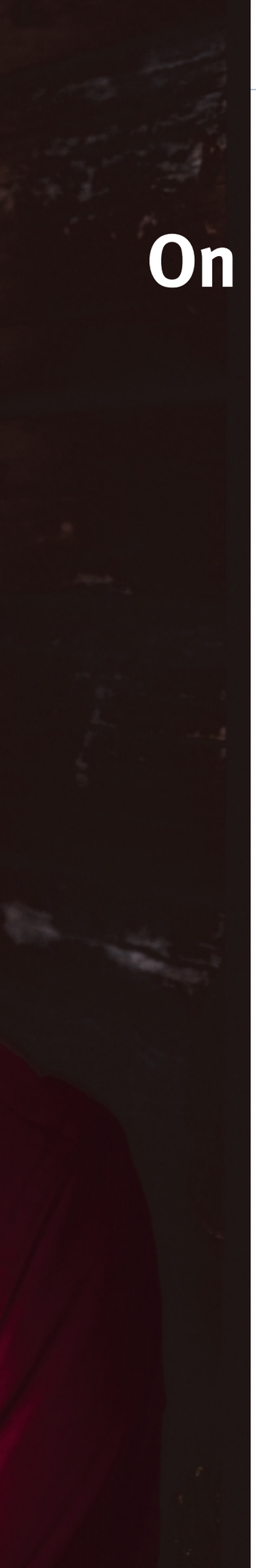
Dr. William Dietz, director of the division of nutrition and physical activity at the U.S. Centers for Disease Control and Prevention in Atlanta; and

Dr. Griffin Rodgers, deputy director of the National Institute of Diabetes, Digestive and Kidney Diseases.

The Meharry-Vanderbilt Alliance is a four-year-old collaboration between historically black Meharry Medical College and Vanderbilt University Medical Center to advance patient care, medical education and research in Nashville.

For more information about the conference or the Alliance, contact Diana Marver, Ph.D., director of Biomedical Research and Research Training for the Alliance, at 615-936-0854 or diana.marver@vanderbilt.edu.

Dr. James Gavin III, longtime diabetes researcher and chair of the National Diabetes Education Program.



DEAN DIXON

On the horns of a revolution

Oscar Crofford and the landmark trial that changed diabetes forever

BY BILL SNYDER

To some of his former colleagues in the world of diabetes research, Dr. Oscar B. Crofford is now living the life of Riley, tooling around the bucolic hills of his Arkansas farm on his four-wheeler, checking on his herd of Black Angus cattle.

What they may not realize is that the retired Vanderbilt University professor approaches his new passion with the same intensity and humor with which he led a landmark study that established the value of rigorous blood glucose control a decade ago.

"I've learned more about labor and delivery and care of the newborn from these cows than I ever did in medical school," he says with a chuckle, his sky-blue eyes twinkling under a shock of white hair.

The tale of the study, called the Diabetes Control and Complications Trial (DCCT), is worth repeating, for it revolutionized the treatment of the disease. Crofford's life story is equally compelling, for it illustrates how an adventurous spirit can achieve a breakthrough in understanding that dramatically improves the lives of patients.

Born in Chickasha, Okla., in 1930, Crofford attended high school in Memphis, and after graduation, decided to go to Vanderbilt. Because of the post-war shortage of physicians, he was able to enroll in an accelerated program, and earned both his bachelor's and medical degrees in seven years. He and the former Jane Long, a recent Vanderbilt nursing school graduate, married during his residency in 1957.

After a two-year stint as a medical officer in the Navy to fulfill his military obligation, Crofford returned to Vanderbilt for a fellowship in clinical physiology under the late Dr. Elliott V. Newman, a pioneering physician-scientist who established Vanderbilt's federally funded Clinical Research Center – one of the first in the nation.

Newman "was really one of the first of a new breed of physicians who bridged the gap between clinical medicine and basic science," Crofford recalls. "He told me, 'Here's your lab. Go in there and discover something.' It was sort of the sink-or-swim philosophy of science."

Newman also became a trusted advisor and counselor. "He was a wonderful scientist and a wonderful human being," Crofford said. "I'd say my character and sense of how to work with people I've learned mostly from Elliott Newman … I probably modeled my life to a large extent after (him) and the way he treated me."

Vanderbilt in the early 1960s was brimming with scientific excitement, in large part because of the "brain trust" in metabolism research attracted by the trail-blazing physiology professor Charles "Rollo" Park. "Those were the grandest years ever of medical science," Crofford maintains. "We were just in the forefront of the technological revolution in medicine, the scientific revolution, things that were never possible in the past … That's where the excitement was. That's where the fun was."

In 1963, Crofford went to the University of Geneva to continue his studies under the late Albert Renold, a renowned diabetes expert who discovered the role of insulin in fat metabolism.

After returning to Nashville in 1965, Crofford became Vanderbilt's first full-time diabetes specialist. He knew more about insulin action than diabetes care, but fortunately he was able to learn on the job under the direction of the late Dr. Addison B. Scoville Jr., a member of Vanderbilt's clinical faculty who ran the Vanderbilt diabetes clinic.

"Virtually everything I learned about caring for people with diabetes I learned from 'Ad' Scoville," he says.

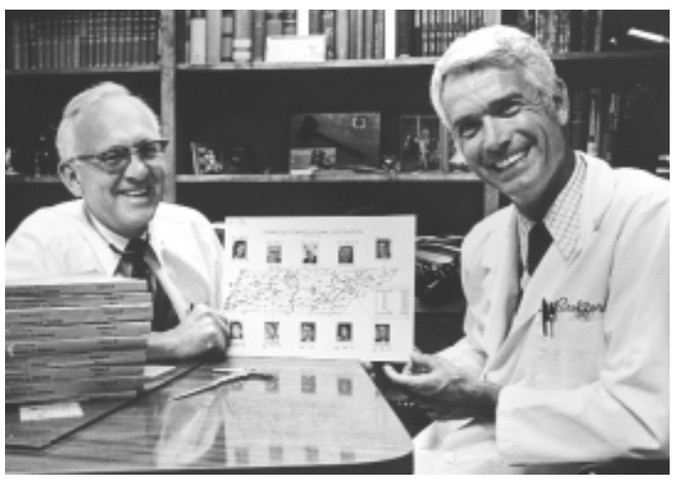
Crofford also expanded his administrative skills. He established the Division of Diabetes, and helped bring the nation's first federally funded diabetes research center to Vanderbilt in 1973.

"The person who sent in the application (to the National Institutes of Health) had to be a physician … so I served as the principal investigator (for the center)," Crofford says. "But it was really capitalizing on work done by … a whole slew of outstanding basic scientists."

At the time, Scoville was president of the American Diabetes Association, and introduced his protégé to the potential

Pictured below: At left, Dr. Oscar Crofford (at microphone) testifies in 1973 for increased federal funding for diabetes research. At right, he and Dr. Addison B. Scoville Jr. (left) hold a chart showing unanimous support for a national diabetes plan by Tennessee's congressional delegation.

Photos courtesy of Dr. Oscar B. Crofford



ANNE RAYNER POLLO

Ellis Hollerman, principal of Shafer Middle School in Gallatin, Tenn., demonstrates to students in a Teen Living class how he uses a portable glucose monitor to check his blood glucose. Frequent "finger pricks" to check blood glucose are essential for controlling diabetes. Portable monitors, introduced in the 1970s, enable people with diabetes to check their glucose levels more conveniently and accurately.

and power of the non-profit organization. Soon Crofford was serving as vice chairman of its research committee, and he was called to Washington, D.C., to testify on behalf of a bill to increase federal funding for diabetes research.

"I had no earthly idea what to do," he recalls. "I didn't even know what you called your congressman or senator – Your Honor, or what?" So Crofford went to the Vanderbilt library, and taught himself the art of testifying by poring over transcripts of previous hearings.

The hearing before Sen. Ted Kennedy's health subcommittee, and subsequent lobbying by the diabetes community ultimately were successful, and in 1974, President Richard Nixon signed what the ADA describes as the first diabetes law in U.S. history. Among other things, it mandated establishment of a National Commission on Diabetes to formulate a "long-range plan to combat diabetes."

Crofford was appointed to the commission and elected chairman. "We involved virtually every scientist and diabetes specialist in the nation, and over the course of nine months … laid out the strategy for what should be done in the future to deal with diabetes at the clinical level, at the research level, at the public information level," he says.

The report was delivered to Congress in December 1975. "I spent a lot of time as a health lobbyist at that point," Crofford recalls, trying to get the recommendations implemented.

Crofford and Scoville approached the Tennessee congressional delegation, and convinced every member to support additional diabetes legislation. They took a group photo of the now-unanimous delegation, displayed it at the ADA national meeting, and urged other state chapters to do the same thing.

"It worked," Crofford says. Thanks to their efforts, those of the Juvenile Diabetes Foundation (now the Juvenile Diabetes Research Foundation) and medical institutions like the Joslin Diabetes Center in Boston, "virtually all of the legislative things that had to be done in order for the diabetes plan to be completed (were) passed," he says.

In 1977, Congress appropriated $5 million to open five more diabetes centers, and to expand their mission to include the training of diabetes specialists. They are now called Diabetes Research and Training Centers.

The commission also recommended that a study be conducted to determine whether strict control of blood glucose could prevent the disabling and life-threatening complications of diabetes, including blindness, kidney failure, amputation and heart disease.

The NIH asked Crofford to help get it started. "This was a new endeavor for me," he recalls. "I had never run what we now call clinical trials." So back to the library he went.

A clinical trial attempts to determine the effectiveness of a drug or other treatment, by comparing one group of patients who receive the treatment to a closely matched group that is not given the treatment and which serves as the "control."

What made the diabetes study so difficult was that it would require the participation of more than 1,000 patients at multiple research centers over the course of several years.

Despite his relative inexperience, Crofford was a natural to lead the study, his colleagues say. He had continued to advise the NIH on the direction of diabetes research and, in 1981-1982, he served as ADA president. "He was on the ground floor, both from the scientific and public policy aspects," says Dr. Phillip Gorden, who directed the National Institute of Diabetes and Digestive and Kidney Diseases from 1986 to 1999.

In addition to scientific curiosity, Crofford was motivated by empathy for the plight of his patients. "He saw people having terribly devastating complications from diabetes," says Vanderbilt research nurse Janie Lipps, who worked with him on the trial and who continues to follow some of the participants. "He wanted to know the truth. Does (controlling blood glucose) really matter?"

This was not the first time that scientists had tried to answer the question.

In 1970 another U.S. study, the University Group Diabetes Program, found no benefit in controlling blood glucose in type 2 diabetics. But it was hampered by the lack of a reliable method for measuring chronic high blood glucose. The hemoglobin A1c test would not become available for several years.

Hemoglobin is the protein in red blood cells that transports oxygen to body tissues. A form of the protein also can bind to glucose, and carry it around for several weeks. Measuring hemoglobin A1c, then, is a way of determining a person's average blood glucose level over a two- to three-month period.

"That was a very important tool for the clinical trial," says Dr. David M. Nathan, who, as a young investigator at Harvard Medical School, had helped develop the hemoglobin A1c test. "It gave you this wonderful … timed window on average blood sugar control in a single measurement."

Two other developments in the 1970s made the study possible: portable glucose monitors, which enabled patients to check their blood glucose conveniently and accurately; and new forms of insulin and insulin pumps, which made it easier for patients

Pictured below:
Starting with 12 cattle seven years ago, Oscar and Jane Crofford now have about 40 head on their Arkansas farm. Mornings and evenings will find them feeding and checking on the livestock with their five dogs in tow.

to keep their blood glucose within the normal range.

By the early 1980s, the pieces "were all falling into place," says Nathan, now a professor of Medicine at Harvard and director of the Diabetes Center at Massachusetts General Hospital.

Nathan's center was one of 29 across the United States and Canada that participated in the study, which focused on patients with type 1 diabetes who had not yet developed complications of the disease, or who had only mild retinopathy, the overgrowth of blood vessels in the retina of the eye that can cause blindness.

Between 1983 and 1989, more than 1,400 participants were enrolled, making the Diabetes Control and Complications Trial (DCCT) one of the largest studies of diabetes ever undertaken.

It was also one of the most difficult. Participants were randomly assigned to a "treatment group" or a "control group," as is the case in most clinical trials, but those in the treatment group required an unprecedented amount of monitoring by health professionals.

These participants used an insulin pump or gave themselves three or more insulin injections every day, monitored their blood glucose at least four times a day, and adjusted their insulin dose accordingly. They also visited their study center once a month and were in frequent phone contact with the researchers to review and adjust their regimens.

In comparison, participants in the control group gave themselves one or two insulin injections a day, at the time the standard treatment for type 1 diabetes. They did not adjust their insulin dose as frequently, and they were examined once every three months.

While the study was being designed and throughout the entire trial, Crofford took great pains to listen to the ideas expressed by the physician investigators, and by the dietitians and research nurses. "It's the well trained, highly motivated nurse who really does most of the work … in terms of caring for people with diabetes," he explains. "Their role in this is critically important."

Smooth as a United Nations diplomat, Crofford worked to reach consensus and to resolve disputes that could have stopped the study in its tracks.

"I'd say Oscar masterfully allowed, fostered, stimulated, directed and finally concluded those discussions in a way that we had a sound protocol," says Dr. Saul Genuth, professor of Medicine at Case Western Reserve University in Cleveland, Ohio, who was vice chair of the DCCT and chaired its planning committee. "Oscar pushed us when we needed to be pushed, and he pulled us when we needed to be pulled."

Just as important to the study's success were the participants themselves. "They weren't human guinea pigs," Crofford says. "They were partners in doing the most important study in diabetes that had ever been done since the discovery of insulin. If they dropped out, they were not only hurting themselves but they might blow the whole study ... So they had to be part of the team."

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Oscar Crofford may look like a man of leisure, but breeding and selling Black Angus bulls on his family's farm in north central Arkansas has become nearly a full-time occupation for him and his wife Jane.

Drawing on his experiences in the ADA and Congress, Crofford visited each of the 29 research centers, attending banquets, speaking to participants and encouraging them "to hang in there."

The team approach seemed to work. Better than 99 percent of participants completed the study, which lasted for most of them an average of six-and-a-half years. Because of the high "adherence" rate, the study was able to end a year early.

The results, reported in 1993, showed that strict control of blood glucose dramatically delayed the onset and slowed the progression of three common complications of diabetes – retinopathy, kidney problems and nerve damage.

There was a downside: Participants in the treatment group were more likely to experience severe hypoglycemia, episodes of low blood glucose that can be life threatening. They also gained more weight on average than those in the control group, a side effect of the more aggressive insulin therapy.

But for Emily Alexander, a Gallatin, Tenn., schoolteacher who has been followed for nearly 20 years by the DCCT and a follow-up study, participation has meant a life essentially free of diabetes complications. "Research certainly makes life easier," she says.

The DCCT was not the only study to demonstrate the benefits of blood glucose control, nor was it the largest. But it set the standard for how a comprehensive and complicated clinical trial should be run, Genuth says.

At Crofford's insistence, "we made extraordinary attempts to collect good, verifiable, high-quality data, to analyze it by the best bio-statistical means we could, and then to publish our conclusions in a non-speculative, straightforward manner," he says.

At the same time, Crofford worked with the NIDDK to ensure the study was within its budget, and met federal data management and safety requirements.

"He was astride four horses, if you will," Genuth says, like Charlton Heston in the movie *Ben-Hur*. "Oscar was the key person in this whole trial in getting all these horses to pull in the same direction."

The challenge now is to continue to educate health care providers and their patients about the importance of aggressive blood glucose control, and, through advances in technology, make it easier for patients to keep their disease in check.

Many patients don't have the opportunity to be monitored by nurses and dietitians in the way that study participants were. "The issue is not whether it works or not, but how hard it is to do," Crofford says. "And believe me, … it's very difficult for patients to follow a regimen of strict glucose control. It will take technological advances that we do not have today in order for the average person to be able to do that.

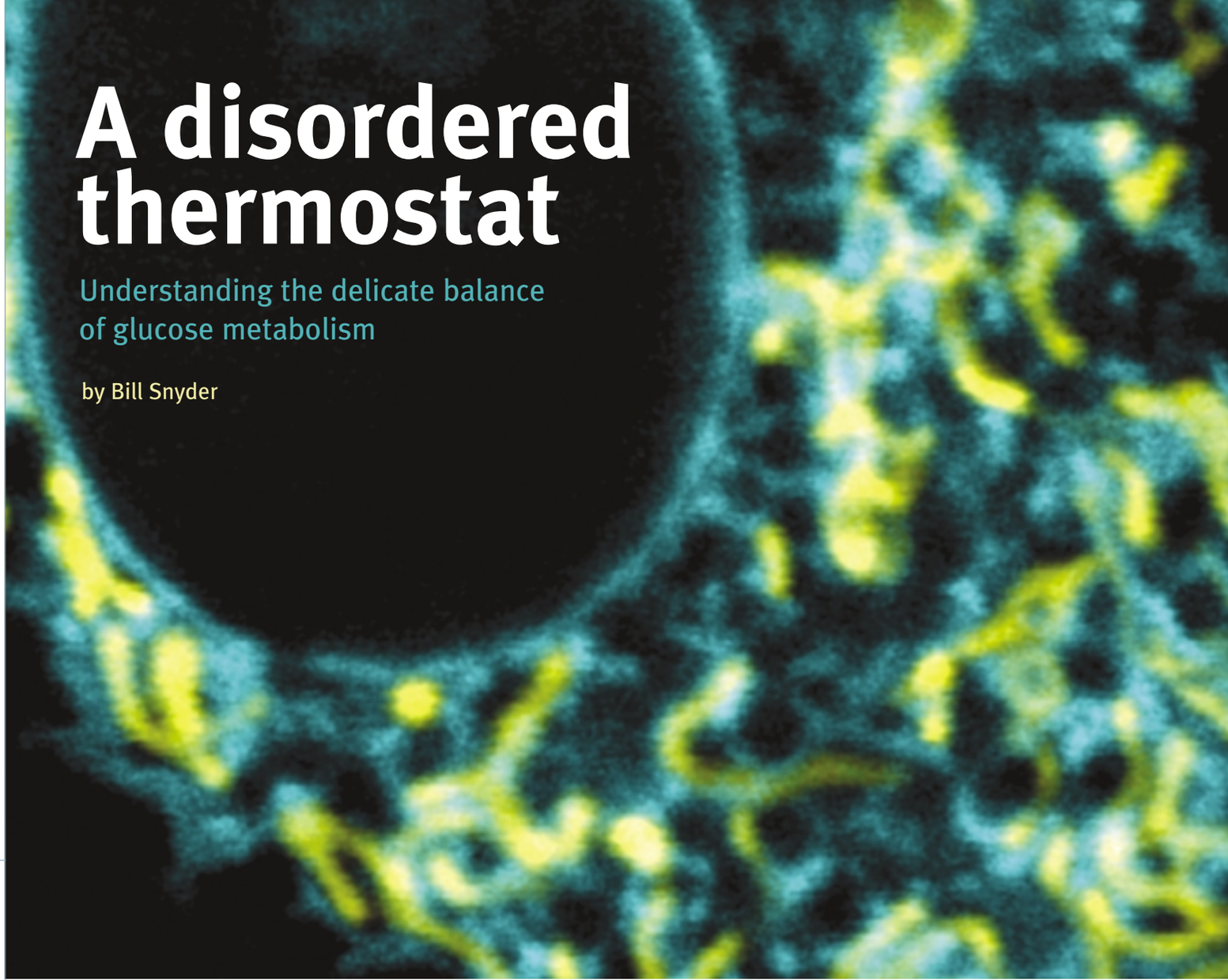
"The good news is that even if you're not perfect, if you make a little bit of improvement, you get a little bit of benefit," he adds.

Two years after the DCCT ended, Crofford began a new chapter in his life. He and Jane "retired" to his family's 700-acre spread in the Ozark Mountains to raise Black Angus bulls.

Starting with 12 cattle seven years ago, the Croffords now have about 40 head on their Rocky Bayou Angus Farm, named for the creeks running through it. Mornings and evenings will find them navigating their pastures aboard the four-wheeler and a golf cart, feeding and checking on the livestock with their five dogs in tow.

Crofford hasn't retired completely from diabetes research. He attends scientific meetings, keeps up with his journals and e-mail, and recently chaired a committee that monitored the progress of another clinical trial.

But he doesn't spend much time dwelling on the achievements of the past, or brooding over tasks left undone. He's too busy for that. There are too many new things to learn. **LENS**



A disordered thermostat

Understanding the delicate balance of glucose metabolism

by Bill Snyder

Four years ago this month, Gary Webb's body was in trouble.

"I was doing a lot of sitting and eating," says the 56-year-old Nashville man, who was carrying 256 pounds on his 6-foot, 2-inch frame. His triglycerides were high, a major risk factor for heart disease, and he had developed type 2 diabetes.

Dr. MacRae Linton, who directs the Vanderbilt Lipid Clinic, prescribed drugs to lower Webb's triglyceride and blood glucose levels, referred him to a dietitian to help him change his eating habits, and recommended that he begin a program of regular aerobic exercise

Scared and depressed by his diagnosis, Webb responded immediately. "I started eating veggie burgers on high fiber/low carbohydrate bread, and a lot of salad," he says.

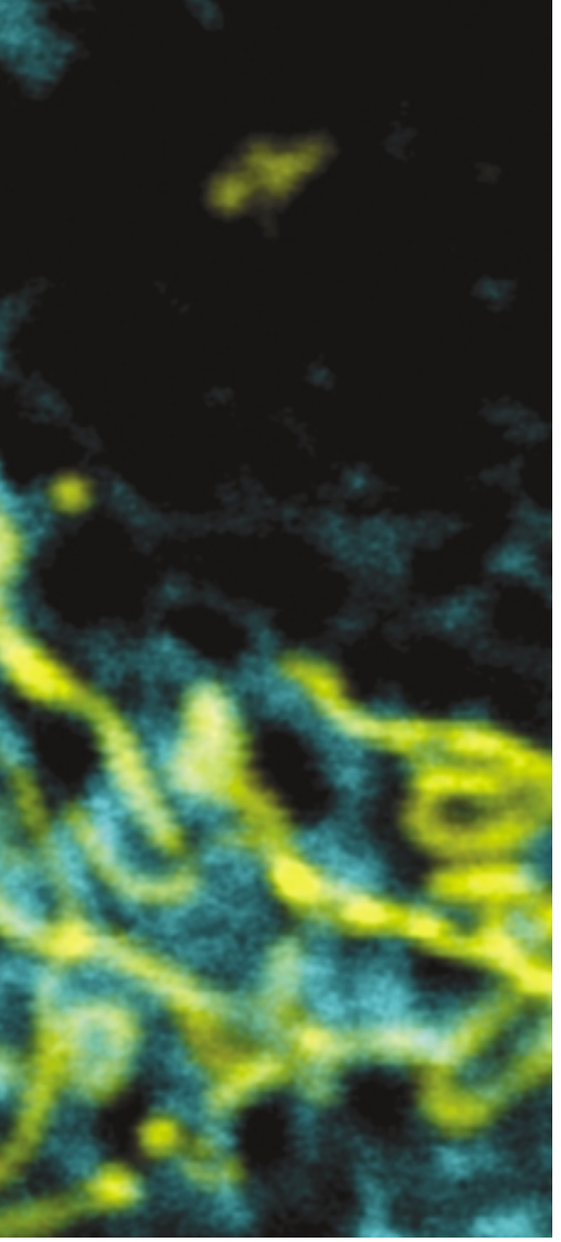
He also started exercising for the first time in a very long time. "That first day, I walked a mile. I thought I was going to pass out," he recalls. "My feet hurt, my knees hurt. But I kept it up."

A month later, Webb was walking three to four miles a day. In September, he started running, two to three miles a day, then up to eight miles a day.

By March 2000, Webb was down to 194 pounds, a better-than 60 pound weight loss in eight months. His triglyceride, cholesterol and glucose levels were all normal, and he no longer needed medication to control them. He no longer had diabetes.

Pictured above: An image taken with a confocal microscope shows the inside of a insulin-producing beta cell in remarkable detail. The nucleus is the dark spot, upper left. Stained with green fluorescent protein, the mitochondria, which are involved in generating energy for the cell, are yellow, while the Golgi vesicles, which help direct secretory proteins to their proper locations in the cell, are blue.

Courtesy of David Piston, Ph.D.
Vanderbilt University



Gary Webb runs about 15 miles a week, a regimen that has helped him reverse high blood triglycerides and glucose levels – and type 2 diabetes. "I feel like I'm a recovering diabetic," Webb says. "If I were to gain 50 pounds and stop exercising, I don't know what would happen."

Today, more than three years later, Webb has kept most of the weight off, and his blood chemistry is in check. His diet has relaxed a bit, but he still runs about 15 miles a week.

"He responded amazingly well," says Linton, professor of Medicine and Pharmacology. "It makes the point, which I think is so powerful, that you can change your metabolism through lifestyle changes."

That was the lesson of the Diabetes Prevention Program, a landmark study that showed that moderate exercise and weight loss reduced by 58 percent the incidence of type 2 diabetes in people at high risk for developing the disease.

The problem is that few people have access to the intensive diabetes management provided to the study participants.

There also is growing evidence that some people are genetically susceptible to becoming obese and developing type 2 diabetes, and no matter how hard they try to lose weight, their bodies are working against them. "It's extraordinarily difficult," says Dr. Rudolph Leibel, who co-discovered the fat hormone leptin.

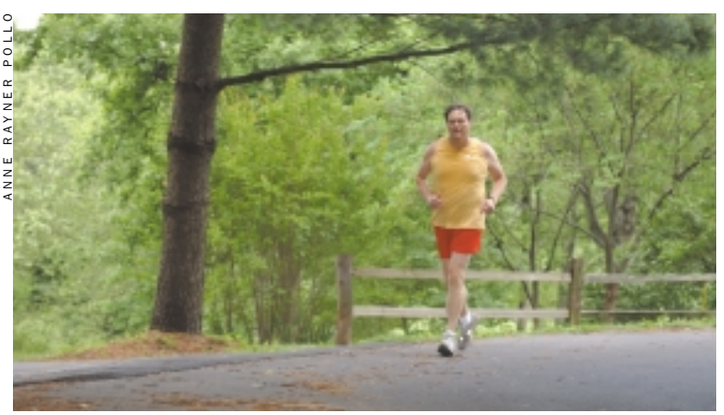
A variety of medications, including those used to treat heart disease and lower cholesterol, can help prevent diabetes. But many of these drugs have side effects, and they don't work in all patients.

Thanks in large part to the genetic and computer revolutions of the past 30 years, there has been a flood of new information about diabetes and obesity. Much of it at this point is incomplete. But progress is definitely being made.

First, a few definitions:

Glucose, a form of sugar primarily supplied by the diet, is a major fuel for the body and virtually the only source of energy for the brain. Because it's so vital, extra glucose is stored in the liver and muscle in the form of glycogen. The liver also can make glucose from raw materials if an emergency supply is needed.

ANNE RAYNER POLLO



Insulin is secreted by "beta" cells, one of four types of cells that are clumped together in "islets" in the pancreas. One of its main jobs is to activate a pathway of biochemical signals that ultimately moves glucose from the bloodstream into muscle.

In the late 1970s, Dr. Daryl K. Granner and his colleagues at the University of Iowa showed that insulin also turns down glucose production in the liver – another way of lowering blood glucose levels – by inhibiting the gene for an enzyme called PEPCK.

"This was the first example of insulin affecting a specific gene," says Granner, now director of the Vanderbilt Diabetes Center and Joe C. Davis Professor of Biomedical Science. "There are probably now 200 of those examples." For instance, there is evidence that insulin acts on the brain to inhibit appetite and help regulate weight.

Other hormones are involved in the control of blood glucose. Glucagon, which is secreted by "alpha" cells in the islet, opposes the action of insulin and stimulates glucose production by the liver. So does cortisol, a stress hormone secreted by the adrenal glands on top of the kidneys.

This push-pull system is designed to keep blood glucose levels in balance, even after a feast, a fast or a flight from a predator.

Not enough blood glucose, a condition called hypoglycemia, can cause uncomfortable symptoms, including dizziness, confusion, heart palpitations and fatigue. It can lead to coma and death unless the glucose supply is replenished.

Too much blood glucose, the hallmark of diabetes, can damage the delicate inner lining of blood vessels, eventually leading to some of the major complications of diabetes – heart disease, kidney failure and blindness, caused by an overgrowth and leakage of tiny blood vessels in the retina of the eye.

"In type 2 diabetes there is an overproduction of glucose because these signals don't work right," says Alan D. Cherrington, Ph.D., chairman of the Department of Molecular Physiology and Biophysics and Charles H. Best Professor of Diabetes Research at Vanderbilt who helped discover what glucagon does.

How do the beta cells know when to secrete insulin? Here's part of the answer: They contain an enzyme called glucokinase, which puts a phosphate group on the glucose molecule. In the process, the enzyme stimulates the beta cell to secrete insulin.

Dr. Mark A. Magnuson, professor of Molecular Physiology and Biophysics at Vanderbilt, helped identify the role of

DEAN DIXON

"With mouse models, we've been able to understand the action of insulin and the role of each of these particular tissues a little bit more than we have any time in the past."

Dr. Mark A. Magnuson, professor of Molecular Physiology and Biophysics at Vanderbilt.

glucokinase in insulin secretion. He compares it to a "thermostat." Depending upon whether it is blocked or activated, blood glucose rises or falls.

Maturity-onset Diabetes of the Young or MODY, a rare form of diabetes, can result from mutations in any one of at least six different genes that play a role in the ability of the beta cell to sense the presence of high levels of glucose, including the gene for glucokinase.

"Type 2 diabetes … may actually be a disease of a disordered thermostat," Magnuson says.

The challenge is to develop drugs or other treatments that can adjust the thermostat without causing serious side effects. "That's why (diabetes), despite all the investment of money, intellect and resources, is still getting worse," says Cherrington, president-elect of the American Diabetes Association. "As yet we don't understand the complexity of the disease."

As an example of that complexity, an estimated 17 million Americans have diabetes, but nearly four times that number may have metabolic syndrome, also called insulin resistance, a constellation of symptoms that places them at high risk for developing type 2 diabetes and heart disease.

Symptoms include abdominal obesity, high blood pressure, high blood glucose, high levels of trigylcerides and low levels of high-density lipoproteins (HDL). Trigylcerides are a form of fat that contribute to atherosclerosis, the build-up of fatty deposits in blood vessels, whereas HDL is a type of cholesterol that seems to protect against it.

Fat cells, also called adipocytes, also can build up in the liver and pancreas, affecting their ability to function properly. In addition, recently discovered hormones released by adipose tissue, including leptin, resistin and adiponectin, can influence glucose metabolism in one way or another, some by opposing or complementing the effects of insulin, others by signaling the brain to suppress appetite. So can hormones released the digestive tract, such as ghrelin, PYY and GLP-1.

"You cannot study the beta cell in isolation," explains Christopher B. Newgard, Ph.D., director of the Sarah W. Stedman Nutrition and Metabolism Center at Duke University. "There is a remarkable interplay and dovetailing of these regulatory circuits."

How are scientists able to tease out the elements of this complex network of interactions? Here are some of the ways:

The recent sequencing of the human genome and the genomes of other animals is just the latest in a series of critical advances during the past quarter century that have enabled scientists to identify specific genes, map their location and determine what they do.

Gene microarrays

The recent sequencing of the human genome and the genomes of other animals is just the latest in a series of critical advances during the past quarter century that have enabled scientists to identify specific genes, map their location and determine what they do.

In just the past three or four years, researchers have figured out how to monitor the expression of thousands of genes simultaneously by spreading complementary bits of genetic material across a glass slide, called a microarray. Active genes will bind to the array in a way that can be detected by fluorescence or other tagging techniques.

"We're not after single genes anymore," explains Leibel, head of the Division of Molecular Genetics and co-director of the Naomi Berrie Diabetes Center at Columbia University. "We're after the interaction of multiple genes … We're trying to study the whole biology."

Thanks to a recent initiative supported by the National Institute of Diabetes and Digestive and Kidney Diseases, researchers at Vanderbilt and elsewhere are creating pancreas-specific microarrays – chips the size of a saltine cracker that contain all of the genes expressed over the life span of the beta cell in mice and humans. This method allows scientists to determine which genes are turned "on" or "off" in pancreatic cells, and it has aided the discovery of previously unidentified genes that play a role in the development of pancreatic islets, Magnuson says.

In vivo imaging

The secret life of the beta cell is being revealed. Recent advances in laser microscopy have enabled scientists to study the "behavior" of beta cells in pancreatic islets grown in the laboratory, and even in animals.

At Vanderbilt, for example, David W. Piston, Ph.D., has helped pioneer the use of fluorescence imaging methods to trace the sequence of events, beginning with the entry of glucose into beta cells, that ultimately leads to insulin secretion.

A goal is to figure out why, in type 2 diabetes, beta cells are unable to respond normally to blood glucose, and what might be done to "fix" that problem. "It's hard to learn these things without looking in the intact animal," says Piston, professor of Molecular Physiology & Biophysics and Physics.

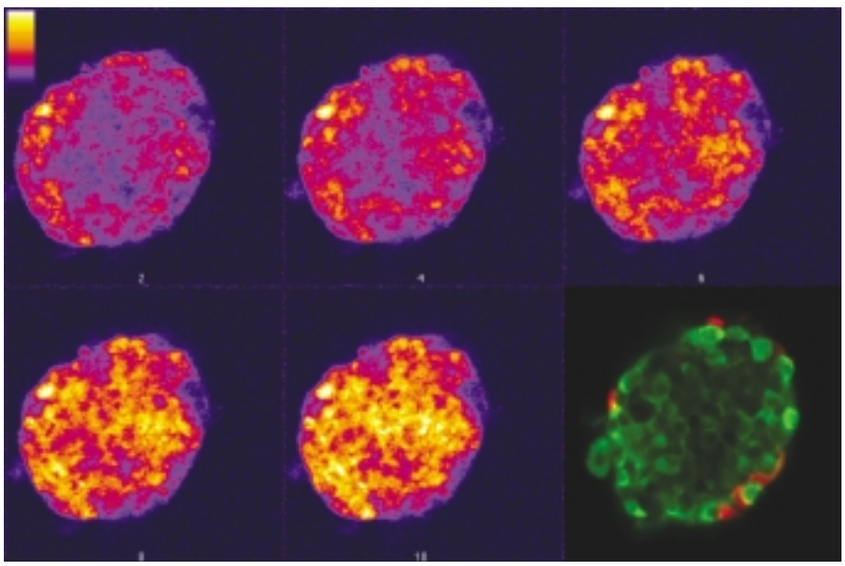
The techniques, which include two-photon excitation microscopy, also enable Piston to watch mouse islets grow a new blood supply when they are transplanted into another part of the body. This information could lead to improvements in islet transplantation as a treatment for type 1 diabetes.

"Islets are really a cellular transplant as opposed to an organ transplant. They have to develop new blood vessels," explains Dr. Alvin C. Powers, associate professor of Medicine and Molecular Physiology & Biophysics at Vanderbilt, who is studying how new blood vessels form in transplanted islets. "How do cells that are transplanted survive, and how can you improve that process?"

Whole animal studies

Many studies of how glucose is produced or used have been conducted in dogs because their blood vessels are large enough to allow detailed studies of glucose, insulin and all of the other factors that play a role in the disease.

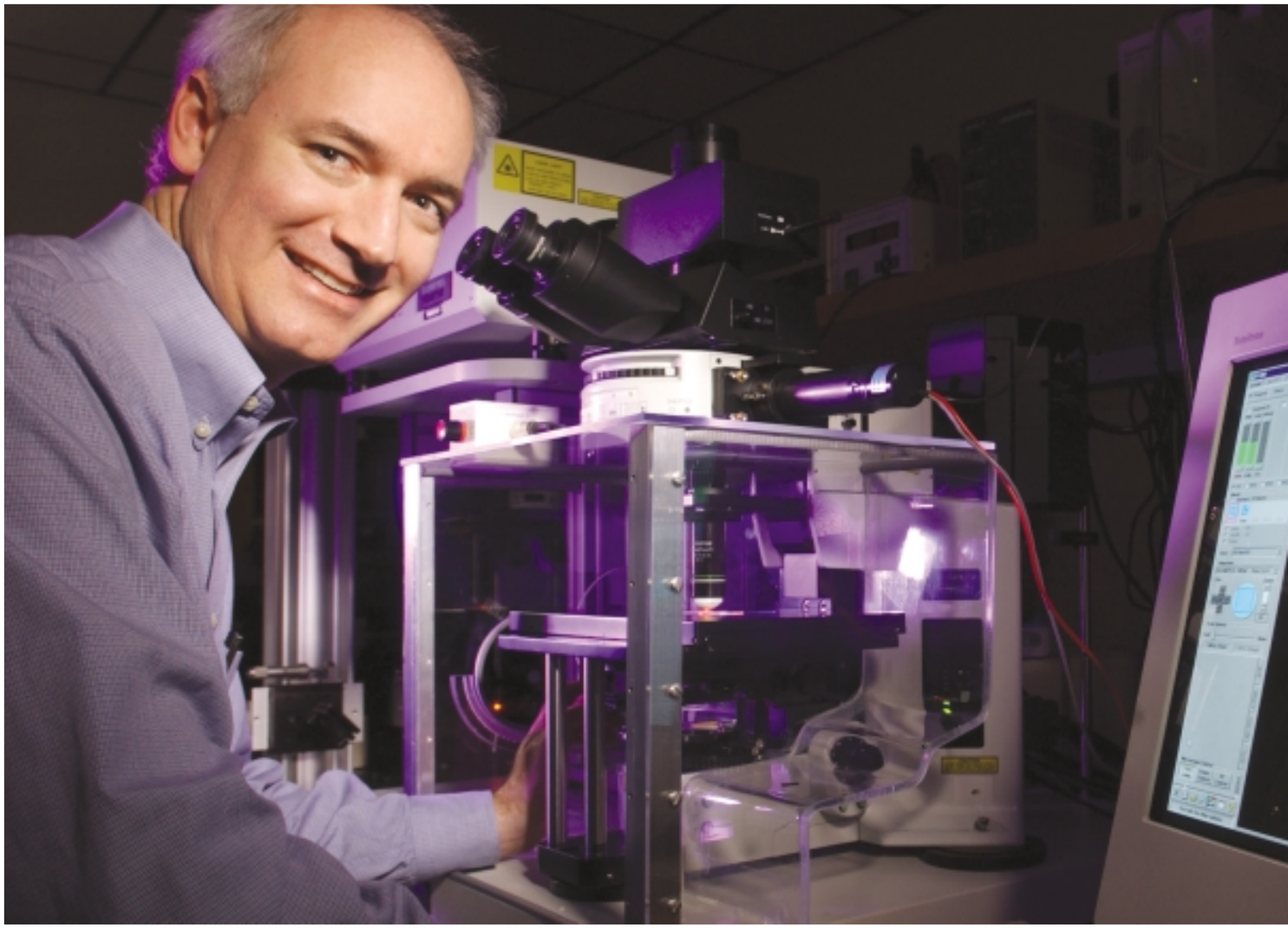
At Vanderbilt, Masakazu Shiota, Ph.D., assistant professor of Molecular Physiology & Biophysics, has miniaturized a method for measuring insulin sensitivity in muscle so it can be applied to rats and mice. The technique enables researchers to



This sequence of images, showing beta cells in an isolated mouse islet becoming more metabolically active in response to glucose, was created using two-photon excitation microscopy. The technique monitors the rise in the autofluorescence of NADH, one of the molecular byproducts of metabolic reactions. The final image in the sequence shows an islet stained with antibodies that attach to the beta cells (green) and the alpha cells (red).

Courtesy of David Piston, Ph.D.

ANNE RAYNER POLLO



measure how much radiolabeled glucose is absorbed by muscle in response to a continuous infusion of insulin.

These studies are helping researchers determine how glucose gets into the muscle cell, and what may be going on when tissues become resistant to insulin, says David H. Wasserman, Ph.D., director of the federally funded Mouse Metabolic Phenotyping Center at Vanderbilt. The center, one of four in the country, helps develop new mouse models of diabetes to further research in the disease.

Animal studies also are shedding light on the complications of the metabolic syndrome. Two years ago, for example, Drs. MacRae Linton and Sergio Fazio at Vanderbilt and their colleague, Dr. Gokan Hotamisligil at Harvard, found that they could protect mice from atherosclerosis by eliminating a protein linked to insulin resistance.

The adipocyte fatty-acid-binding protein (aP2) is produced by adipocytes (fat cells), which contribute to insulin resistance, and also by macrophages, inflammatory cells that play a crucial role in atherosclerosis.

The researchers studied apoE-deficient mice, a widely used mouse model of high cholesterol and atherosclerosis. Mice that lacked aP2 were dramatically protected from atherosclerosis, even though they remained insulin resistant, suggesting that the expression of aP2 by macrophages promotes atherosclerosis.

This finding was confirmed in the following way: apoE-deficient mice lacking expression of aP2 only in macrophages were similarly protected from developing atherosclerosis. Earlier studies found that obese mice lacking aP2 expression in adipose tissue showed increased insulin sensitivity. Thus, aP2, which links two major features of the metabolic syndrome, is a potential drug target for preventing both atherosclerosis and insulin resistance.

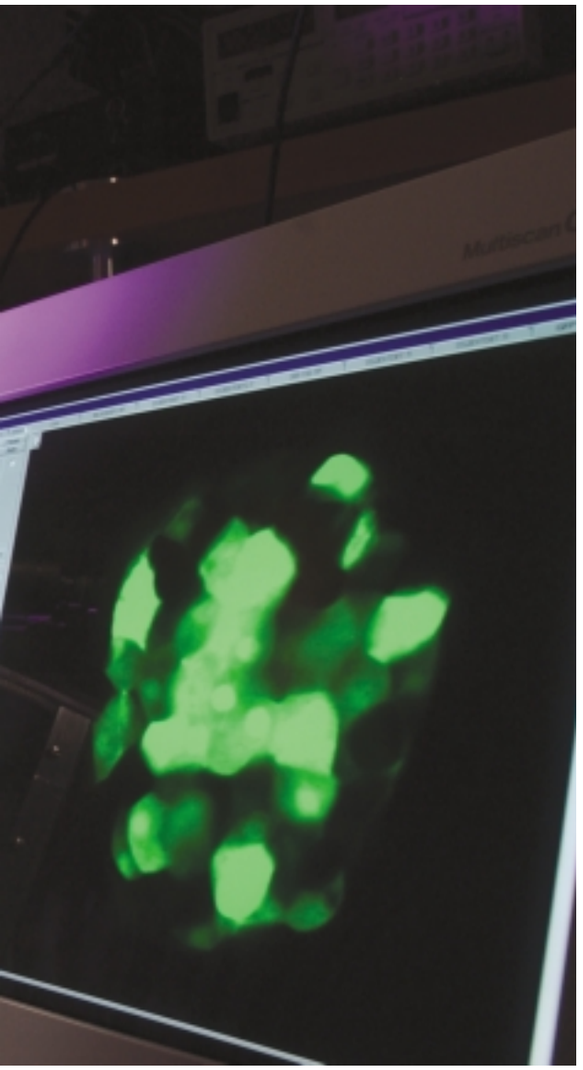
Viral vectors as Trojan Horses

One of the new tools in the researchers' armamentarium is the recombinant adenovirus, a common respiratory virus that has been genetically engineered so that it is relatively harmless.

Earlier this year, researchers at Baylor College of Medicine in Houston and Shiga University in Otsu, Japan, reported they had used this tool to completely reverse diabetes in mice that had high blood glucose because of non-functioning beta cells.

The researchers inserted genes for beta cell growth and transcription factors into the genetic material of the adenovirus. After injection into the bloodstream, the viral "vector" traveled to the liver. There, the imported genes, also called "transgenes," expressed factors that seemed to stimulate formation of new, insulin-secreting beta cells and reversed the hyperglycemia.

While more study of these "transgenic" mice is needed before the technique can be attempted in humans, this finding, reported in the journal *Nature Medicine*, raises hopes for a gene therapy that could reverse type 1 diabetes in humans.



David Piston, Ph.D., demonstrates two-photon excitation microscopy, a technique he has pioneered to study the sequence of intracellular events leading to insulin secretion, and what may go wrong in diabetes. "We know so little," he says. "It's going to take a long time and a lot of very insightful experiments to really dissect this out."

Adenovirus vectors also have proven useful in exploring the relationship between obesity and insulin resistance.

For example, Newgard and his colleagues recently tested an adenovirus vector that contained the gene for malonyl-CoA decarboxylase, an enzyme that essentially can "melt fat" out of tissue. The vector was used to carry extra copies of the gene into the livers of rats that had become insulin resistant after being fed a high-fat diet.

The researchers found that when the enzyme was over-expressed and specifically melted fat out of the liver, insulin sensitivity in the muscles improved.

"Somehow melting the fat out of the liver is a signal to restore insulin action in the muscle," Newgard says. "So there's tissue networking going on (messages sent between organs and tissues) that we are only at the threshold of understanding."

Knock-out mice

Another important research tool pioneered by Magnuson and his colleagues at Vanderbilt involves the use of "tissue-specific knock-out" mice – animals in which a gene has been inactivated in a specific tissue like the liver or pancreas by an enzyme called Cre recombinase.

In 1999, for example, Magnuson, Dr. C. Ronald Kahn, president and director of the Joslin Diabetes Center in Boston, and their colleagues discovered that beta cells have their own functional insulin receptors. When these receptors are "knocked out," the beta cells don't secrete insulin normally in response to a rise in blood glucose.

This finding suggests that insulin can regulate its own secretion and that impaired regulation may contribute to inadequate insulin secretion that is a hallmark of type 2 diabetes.

"There is nothing that is so precise, so accurate and so useful as that (Cre) enzyme," Magnuson says. "It is like a cruise missile for manipulating the mouse genome."

"We are in a truly golden era of biomedical research," adds Kahn. "The technologies and the insights we have into basic biology and genetics and biochemistry are so great and so powerful that we can do almost any experiment that we think about.

"What is limiting in many cases are both the monetary and the human resources to do that … The number of people training in pediatric diabetes and endocrinology is very small considering the number of young people now who are developing not only type 1 diabetes but also type 2 diabetes and obesity."

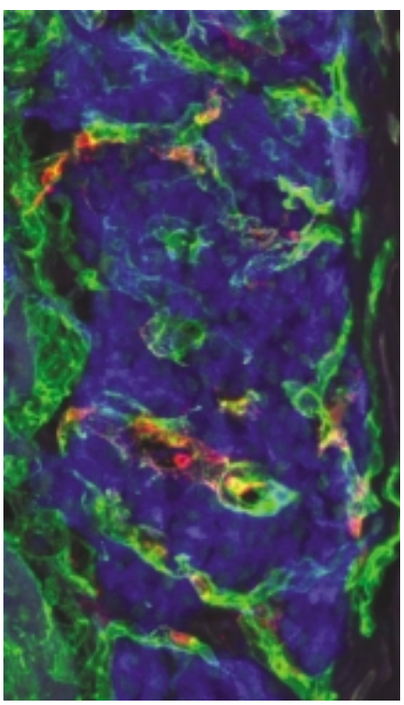
Another pressing need is public education and other measures to stem the rising tide of obesity and diabetes.

"The Human Genome Project will not solve the obesity and diabetes epidemic," asserts Dr. Frank Vinicor, director of diabetes translation for the U.S. Centers for Disease Control and Prevention. "We're not going to find a magic pill … We have to start addressing primary prevention or we're going to be overwhelmed."

"Ultimately to prevent obesity, diabetes and high blood pressure, we're going to have to get to the children," adds David G. Schlundt, Ph.D., associate professor of Psychology at Vanderbilt who is involved in diabetes prevention efforts. "Once you're 45 years old and weigh 300 pounds and have high blood pressure and diabetes, there's only so much that can be done." **LENS**

Beta cells are blue in this image of mouse pancreatic islets that have been transplanted beneath the capsule, or outer layer of the kidney. Endothelial cells that line blood vessels are shown in green. Some of them grow into the islets from the underlying kidney. Other endothelial cells, found within the islets and transplanted with them, continue to grow and are shown in red.

Courtesy of Marcela Brissova and Alvin C. Powers, Vanderbilt Division of Endocrinology.



An interview with NIDDK director Allen Spiegel

Forging new partnerships

JUDY G. ROLFE

Dr. Allen M. Spiegel directs the National Institute of Diabetes and Digestive and Kidney Diseases, which supports and directs much of the nation's research on diabetes.

Spiegel is an internationally recognized endocrinologist whose research has helped define the genetic basis of several endocrine diseases.

Recently he shared his thoughts about the importance of investing in basic research and the need for greater collaboration – among universities, the government, private industry and the general public – to address the challenges of diabetes.

by Bill Snyder

Lens: What are some of the major priorities of the Institute?

Spiegel: Because of its enormous public health significance, diabetes is clearly one of our major priorities. For example, we're investing substantial resources in the Beta Cell Biology Consortium (BCBC), because insulin-secreting beta cells are at the heart of both types 1 and 2 diabetes. The BCBC is a recently formed group that typifies a newer approach to biology and medical research. We still rely on the creativity of individual investigators, but to tackle some of the large issues, it's really vital to bring together a number of investigators. That's exactly what we're trying to do. The goal of the consortium, coupled with other efforts, is nothing less than to understand everything there is to know about

the beta cell, every gene that is expressed. It is possible to do this now, at every stage of development; to identify stem cells in the pancreas; to work with embryonic stem cells, according to the President's guidelines; to determine what is necessary to create a sufficient quantity of beta cells and islets needed to replace beta cell function in animal models of diabetes and eventually in patients.

Within the funding levels provided, the NIDDK will continue to support a scientifically robust research portfolio that addresses all the diseases within its mission. This portfolio includes fundamental laboratory research; "discovery" research that brings new insights from the laboratory into clinical testing; clinical research of promising treatment and prevention strategies; and the translation of important results from clinical trials, not only in the scientific literature, but also through public outreach, information and education efforts.

Lens: What will be needed to achieve success? What are the barriers?

Spiegel: There is cultural change needed at the level of the university and academic medical center in order to foster multi-disciplinary investigations. It is increasingly important to bring in the mathematical and physical sciences, computational biology. The sheer volume of data we are inundated with from advances in genomics and proteomics, for example, mandates that biology take on more of a 'math' kind of tone.

Equally important is the need to break down some barriers between universities, and allow investigators to come together so they can apply their talents. The current system of promotion tends to discourage this. If you are part of a collaborative effort, it's hard to identify the individual contributions upon which, historically, decisions of tenure have been made.

Lens: How important is NIH funding in diabetes research?

Spiegel: Extremely important; relative stability in funding is particularly important. In the early 1990s, the funding of the NIH hit a real low. Under those circumstances, sadly, the success rate of applicants for research grants began to plummet. It had a ripple effect, discouraging individuals from going into science.

In the past three years, NIH-wide funding of diabetes research has increased substantially, from $688 million in the 2000-2001 fiscal year, to an estimated $946 million in the coming fiscal year (2003-2004).

One of the powerful messages that needs to be disseminated is: You can't go from feast to famine. Investment in medical research is something that pays off, not only in terms of improving quality of life and preventing mortality, but economically. The entire biotechnology industry was built on the fundamental investment of NIH resources.

Lens: How important is it for universities and the government to collaborate with industry? What are the barriers to successful collaboration?

Spiegel: This is a vital partnership. A prime example is recombinant DNA technology, which largely came out of curiosity-driven research about restriction enzymes. Through the private sector, it was converted into an enormously successful enterprise that is delivering new, innovative treatments.

But this partnership with industry has to be assiduously framed and monitored, not only to guarantee appropriateness and safety in clinical trials, but also to ensure the sharing of resources, data and research findings. In recent years, universities have promulgated some very clear guidelines regarding the need to publish and how to address real or perceived conflicts of interest, both as individuals and institutions.

Lens: What are some other challenges to translating research findings into benefits for patients?

Spiegel: One translational block is in the dissemination of information. It's well established, for example, that certain drugs called ACE inhibitors are unequivocally effective in halting the progression of diabetic kidney disease. Why aren't we applying this knowledge far and wide? We just launched the National Kidney Disease Education Program, which in its pilot phase is targeting four cities – Atlanta, Ga., Baltimore, Md., Cleveland, Ohio, and Jackson, Miss. – which have a disproportionately high level of end-stage kidney disease, mostly among African Americans. If we can get the information out about the importance of measuring protein in the urine and using ACE inhibitors where indicated, for example, we can really make an impact.

The use of information technology also can be very important. One really needs to look at chronic diseases through a different management model, one that focuses on flagging reminders, making sure people are monitored. This increases cost in the short run, but it can make a huge difference in the long run in terms of reduced hospitalization.

Lens: What about prevention?

Spiegel: Preventing disease is a high priority, and much of our research is aimed at understanding how better to prevent chronic and costly diseases such as diabetes. If we don't do this, we're really in for trouble simply because the health care system is not going to be able to sustain itself, faced with a diabetes epidemic and its attendant complications – amputations, blindness, kidney failure and cardiovascular mortality.

Our Diabetes Prevention Program (DPP) showed clearly that type 2 diabetes can be prevented or at least delayed in the majority population as well as all ethnic and minority groups, including African Americans, Hispanic Americans, American Indians and Asian American/Pacific Islanders who are at highly disproportionate risk. We are now building on the DPP results to develop cost-effective ways to prevent type 2 diabetes in adults and in adolescents, who increasingly are developing the disease.

With regard to obesity, we need research that will address ways to interfere with inappropriate cues and signals that lead to overeating. Behavioral efforts have been successful. That is the powerful message of the DPP. We're not talking about running a marathon here. We're saying that, for a group of individuals we can identify who are at particularly high risk, a targeted effort aimed at early lifestyle changes would be effective.

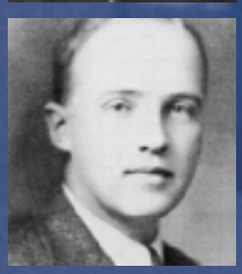
It becomes a matter of public policy, informed by serious research, that tells us whether having soft drinks in vending machines and the absence of physical education in schools predisposes children to obesity. We are launching a type 2 diabetes school-based prevention effort with appropriate rigorous controls that will inform the public policy debate.

But the public needs to participate. The public must ask its leaders to act on informed data. That's the only way we can advance. **LENS**

Grabbing the golden ring

Insulin, glucose meters and the control of an ancient disease

by Mary Beth Gardiner



Pictured above: Dr. Frederick Banting (top) and Charles H. Best, co-discoverers of insulin.

A century ago a diagnosis of diabetes was a death knell. There was little a physician could offer in the way of help, other than home remedies and desperation diets that only slowed the inexorable wasting of flesh to skin and bone. Opium dulled the anguish.

The discovery of insulin in 1921 was as close to a medical miracle as humanity has seen. The Lazarus-like recovery following injection of the pancreatic extract into a child lying literally on its deathbed seemed surreal. Within weeks, hollow cheeks turned plump and pink, frail limbs supple and sturdy.

Initial exuberance was tempered, however, as it became clear that though insulin might pull a person from the brink of death, it was not a cure. And the treatment wasn't perfect – the injections caused bruising and painful abscesses. Maintenance of the syringes was elaborate and time-consuming. Monitoring of urine glucose levels was crude and cumbersome. And because nutritional thinking of the day said that carbohydrates could not be tolerated, physicians exhorted patients to drink quarts of cream and eat thrice-boiled vegetables, saccharin-flavored agar, and up to 60 grams of meat a day to restore vitality.

Managing the disease left little time for enjoying life.

Today, there is still no cure, but living with diabetes isn't nearly the struggle it once was. Thanks to the efforts of countless basic and clinical researchers over the past hundred years, what we know about the disease – what goes awry in the body and how to prevent or control it – has expanded remarkably.

THE LONG LINE OF INCREMENTAL DISCOVERIES that brought us to our current understanding of diabetes extends back more than 3,000 years. The Ebers' Papyrus, which dates from 1552 B.C. Egypt and is our oldest preserved medical document, noted the most prominent symptom of the disease, frequent and voluminous urination accompanied by excessive thirst and emaciation. In the first century A.D., Aretaeus coined the name diabetes from the Greek word for "pipe-like," and described the affliction as a "melting down of flesh and limbs into urine."

The association between sugar and diabetes was initially recognized in the sixth century by an Indian physician, Susruta, who wrote of diabetes as the honey urine disease. Gradually, the Latin word for sweet – "mellitus" – was added to distinguish the disease from

Diabetes insipidus, a pituitary disorder in which large volumes of sugar-free urine are passed.

In the seventeenth century, English physician Thomas Willis added a urine taste test to the criteria for diagnosing diabetes. It wasn't unusual for physicians to first suspect diabetes in men by noting the presence of crystals on their shoes. With the beginnings of modern chemistry in 1775, the source of the sweetness was identified as sugar, and by 1815 it was known to be glucose.

During these years, the only therapeutic advice was dietary. The nineteenth-century French physician Apollinaire Bouchardat, who required daily urine analysis of his patients, recognized that fasting reduced glucose levels and prescribed a spare diet. Observing that exercise increased carbohydrate tolerance, he admonished his patients, "You shall earn your bread by the sweat of your brow."

Yet the real breakthrough in treatment was to come not from dietary prudence but from basic physiological studies of glucose metabolism that began in the latter half of the nineteenth century.

In 1869 a German pathologist, Paul Langerhans, discovered the existence of two systems of cells in the pancreas: the acinar cells, secreting the pancreatic juice into the digestive system, and islets floating between the acini, with some as yet unknown function. In 1889 Oscar Minkowski and Joseph Von Mering removed the pancreas from a dog and witnessed symptoms indistinguishable from diabetes.

The two German physiologists went on to eliminate acinar cell secretion as the culprit when, after tying off the ducts that feed digestive juices from the pancreas to the gut, diabetes did not develop. By the early twentieth century, a direct link had been made between diabetes and damage to the islet cells.

Failure piled upon failure as scientists from around the world went in search of the "internal secretion" responsible for diabetes. The gold ring was finally grabbed by a Canadian surgeon and a medical student in the summer of 1921. Dr. Frederick Banting and Charles H. Best, in collaboration with J.J.R. Macleod and J.B. Collip, successfully reversed diabetes in a depancreatised dog by injecting a concoction of pancreatic extracts, which the researchers later named "insulin."

The discovery was front-page news around the world. Appeals from families of diabetic patients poured in, and after Banting and Best tested the extract on themselves and found it safe, the first insulin injection in a diabetic patient was given to 14-year-old Leonard Thompson in January 1922. Thompson, who had been surviving on the "starvation" diet, weighed less than 65 pounds and was near death. Insulin saved his life.

SINCE 1922, MUCH HAS BEEN DONE to better insulin therapy, both in terms of improved insulin preparations and ease of use. Purification of insulin reduced adverse reaction at the injection site, and modification of the insulin molecule has led to greater control over the duration of its effects, which translates to fewer injections.

Initially, all insulin was isolated from either beef or pork pancreas tissue. Before long, demand for insulin was outgrowing the supply of slaughterhouse pancreases. It was a great relief when, in 1979, recombinant DNA techniques made high-volume production of human insulin possible. The U.S. Food and Drug Administration approved the use of the new insulin – called Humulin – in 1982.

Meanwhile, the years between 1950 and 1970 saw leaps in our understanding of glucose metabolism and insulin's role in it. Vanderbilt was one of the foremost places in the world for metabolism research, due in large part to the efforts of Charles "Rollo" Park, a physician scientist who helped define how insulin "carries" glucose into cells. Assuming the helm of a physiology department of only two scientists, he set out to build a program centered on metabolism of sugars.

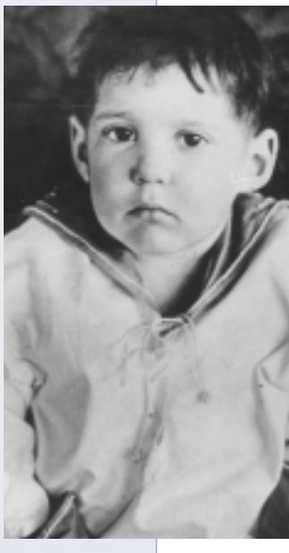
Park's work and reputation attracted an impressive array of talent to Vanderbilt, including Nobel laureate Earl Sutherland, Jr. and diabetes clinician Oscar B. Crofford.

In the 1970s and 1980s, research discoveries and therapeutic innovations came fast and furious. For diabetic patients, the horizon glimmered with hints of an improved ability to monitor and control glucose levels. The means for measuring hemoglobin A1c, a way of monitoring longer term glucose control, was developed in 1977, and the first insulin pump was introduced in 1979. In that same year, trials for the use of laser photocoagulation in the treatment of diabetic retinopathy began. In the early '80s, other methods of insulin delivery were being explored – including microencapsulated islet cells and nasal insulin – and new, more powerful blood glucose-lowering drugs entered the market.

By this time, a series of publications from a number of laboratories had suggested that tight control of blood glucose levels could prevent or retard the onset of diabetic complications. As a result of these reports, in 1983 the government launched the Diabetes Control and Complications Trial. Widely considered the best-run clinical trial ever carried out, the DCCT showed unequivocally that rigorous control of blood glucose reduces the risk and severity of long-term complications.

Improvements in insulin delivery and glucose monitoring were essential to conducting the DCCT, and by the time the lessons from the study became public in the early 1990s, diabetic patients had gained the ability to measure blood glucose levels at home, rather than having to go to a doctor. This newfound self-sufficiency allowed the tighter control that the DCCT touted, but patients soon found that freedom came at a price: a greater risk of hypoglycemic episodes. Innovations such as non-invasive glucose meters and implantable insulin pumps are helping to overcome the risk, however, making insulin-dependence an easier condition to bear.

And so the efforts continue. Yet with all that's been discovered about diabetes, much remains to be learned. To achieve a world without diabetes, whether through prevention or by cure, is the ultimate goal of these many efforts. At this rate, perhaps a second miracle is not too much to hope for. **LENS**



Pictured here: A 3-year-old boy before, and several weeks after becoming one of the first patients to receive insulin in 1922.

Photos courtesy of Eli Lilly and Company Archives

ANNE RAYNER POLLO

Beth Barker is a senior at Franklin High School in Franklin, Tenn.

Junk food in schools

Vending machine sales – at the expense of student health?

BY BETH BARKER

Schools nationwide are packed with vending machines that provide schools with extra funding. These machines are often stocked full of sugary sweets at the expense of students' health.

Michael Jacobson, executive director of the Center for Science in the Public Interest, a consumer advocacy group in Washington, D.C., recently told ABC News "Our society should be doing everything possible to encourage kids to eat healthy diets, and what are we doing? We are bombarding them with junk food advertising. We are putting junk food wherever they go."

Two years ago, researchers at Children's Hospital Boston and the Harvard School of Public Health reported that children who drink a lot of sugar-sweetened beverages are at higher risk of becoming obese. Obesity, in turn, can lead to heart disease, high blood pressure and diabetes.

Soft drinks are not the only problem. Gary Tanksley, a health science education teacher at Franklin High School in Franklin, Tenn., believes that vending machines – and the junk food they contain – should be taken out of schools. "They are detrimental to students' health and are contrary to the health lessons kids should be learning," he says.

School officials respond that they depend on vending machine revenue to supplement the budget they get from the county. "These vending machines bring a fixed sum of about $50,000 to (Franklin High) yearly," says assistant principal Todd Campbell. "Without the vending machines, the school would lack needed funds."

Other schools are reevaluating their views on vending machines.

Last year in nearby Nashville, the public school board voted to limit availability of foods of "minimal nutritional value" in vending machines. Los Angeles public schools are phasing out the sale of carbonated drinks loaded with sugar, and public schools along the upper Mississippi in Iowa and Illinois recently installed dairy-only vending machines stocked with milk, yogurt and cheese to encourage healthier snacking habits.

Financial pressures can make it difficult for schools – and states– to break the vending machine habit, however. California recently passed a law that mandates healthier snack foods in school vending machines, but it won't take effect unless additional funds for free and reduced-price meals are appropriated by the end of this year.

At Franklin High, there are more than 45 vending machines serving about 1,650 students. The only low-sugary options they offer are water and PowerAde.

The machines are supposed to be turned off during the lunch hours, but that policy is often ignored. As a result, many students are diverted from healthier food choices in the cafeteria. "Our cafeteria has a good variety of healthy items for students," cafeteria manager Linda Jones says. "Vending machines hurt our business desperately."

Franklin High's athletic director Kathy Caudill, has a different view. "Athletes need to eat to maintain energy at the end of the day," she says. "With a bit of searching, (they) can find an appropriate snack food in the vending machines."

Athletes are often active enough to burn off the calories from snack foods, but many non-athletic students also indulge themselves with the plethora of snack choices. Candy is being purchased from the machines every period of the day, Tanksley says.

If vending machines are a necessary evil to supplement funds not provided through "free public education," they should at least be stocked with healthier options like power bars, bananas, orange juice and milk. **LENS**

Am I at risk for type 2 diabetes?

To assess your risk for type 2 diabetes, check each items that apply to you. The more items checked, the higher your risk.

- ❑ I am over 45 years of age.
- ❑ I am overweight (see below).
- ❑ I have a parent, brother, or sister with diabetes.
- ❑ My family background is African American, American Indian, Asian American, Pacific Islander, Hispanic American/Latino.
- ❑ I have had gestational diabetes, or I gave birth to at least one baby weighing more than 9 pounds.
- ❑ My blood pressure is 140/90 or higher, or I have been told that I have high blood pressure.
- ❑ My cholesterol levels are not normal. My HDL cholesterol ("good" cholesterol) is 35 or lower, or my triglyceride level is 250 or higher.
- ❑ I am fairly inactive. I exercise fewer than three times a week.

Of these risk factors, being overweight tops the list.

To find out if you are overweight, calculate your body mass index (BMI).

A healthy BMI for adults – regardless of age or sex – is between 18.5 and 24.9. Adults with a BMI of 25.0 to 29.9 are considered overweight; those with a BMI of 30.0 or more are considered obese.

You can calculate your BMI using the following formula:

BMI = [(weight in pounds) ÷ (height in inches) ÷ (height in inches)] x 703.

Or you can use a Web-based calculator or table to find your BMI (see www.cdc.gov/nccdphp/dnpa/bmi/bmi-adult.htm).

Waist size also provides a quick weight index – a waist circumference of more than 40 inches for men and more than 35 inches for women is considered overweight.

Do I have diabetes?

The symptoms of both type 1 and type 2 diabetes include increased thirst and urination, increased hunger, weight loss, extreme fatigue and blurred vision. A sudden onset of these symptoms is usual in type 1 diabetes. In type 2 diabetes, the symptoms may develop gradually, or not at all. People with type 2 diabetes may notice that they suffer from frequent infections, or that wounds heal slowly.

Should I be tested for diabetes?

Even if you do not have any of the symptoms listed above, if you are age 45 or older and have other risk factors, you should be tested. You should consider being tested even if you have no risk factors other than age.

If you are younger than 45, are significantly overweight, and have another risk factor, you also should consider being tested.

Sources for more information:

National Institute of Diabetes & Digestive & Kidney Diseases
www.niddk.nih.gov/health/diabetes/diabetes.htm

National Diabetes Information Clearinghouse
1 Information Way
Bethesda, MD 20892-3560
Phone: 1-800-860-8747
Email: ndic@info.niddk.nih.gov

American Diabetes Association
www.diabetes.org
1701 North Beauregard Street
Alexandria, VA 22311
Phone: 1-800-342-2383

Juvenile Diabetes Research Foundation International
www.jdrf.org
120 Wall Street, 19th Floor
New York, NY 10005
Phone: 1-800-533-2873

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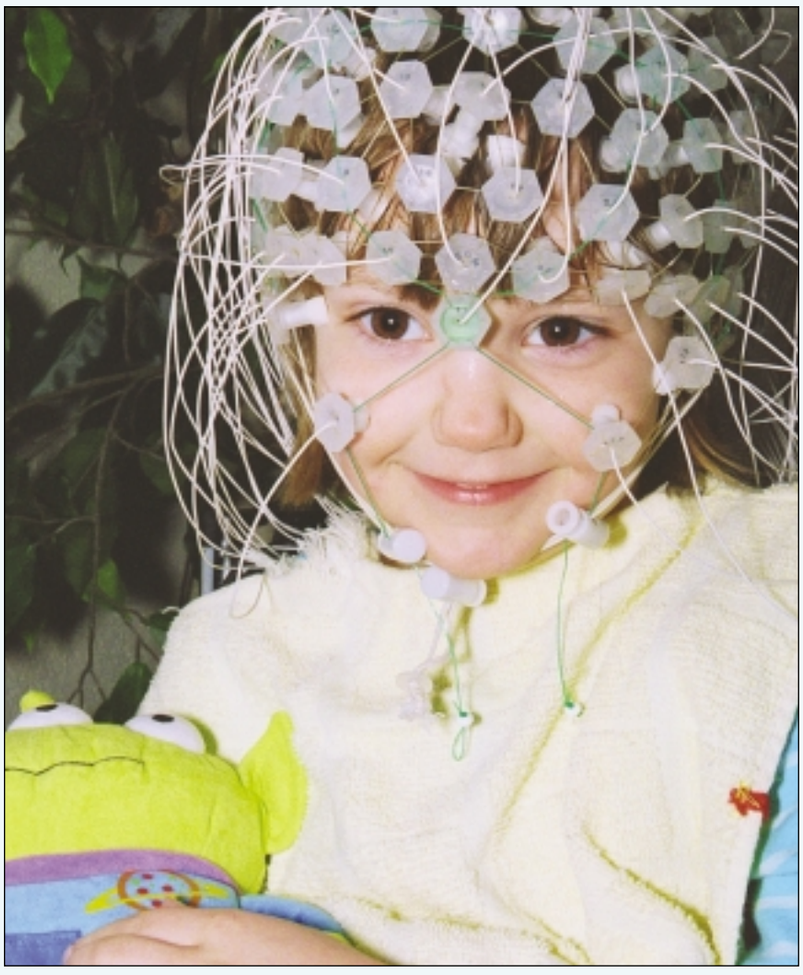
An array of electroencephalography (EEG) electrodes monitors brain activity in a study of communication and language development in young children at Vanderbilt's Peabody College.



LARRY WILLSON

IN THE NEXT ISSUE:

New views of the brain
Exciting new methods of imaging the brain are shedding light on schizophrenia and other disorders of brain function.

The search for a genetic link
What's causing the apparent rise in the incidence of autism? Researchers are seeking genetic and environmental clues.

Animal models
"Transgenic" and "knock-out" mice are yielding important insights into attention deficit/hyperactivity disorder (ADHD).

Lens

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