



'He Who Knows Diabetes,

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Knows Medicine'

BY GARY GOLDENBERG

Such was the advice that the late Harold Rifkin, MD, the pioneering diabetologist and one-time president of the American Diabetes Association, gave to countless students at Albert Einstein College of Medicine. Indeed, diabetics may face serious complications such as heart disease, stroke, hypertension, amputations, kidney failure, blindness, or nerve disorders. To treat a patient with diabetes, the physician must be an endocrinologist, cardiologist, neurologist, nephrologist, ophthalmologist, gastroenterologist, and nutritionist all wrapped into one. Put another way, it takes a medical center to know diabetes.

It was this realization that sparked the formation of a national commission on diabetes in the mid-1970s, which persuaded Congress to create—under the aegis of the National Institutes of Health (NIH)—five centers of excellence in diabetes research and training.

One of the first NIH grants went to Albert Einstein College of Medicine, thanks to the efforts of Norman Fleischer, MD, a young staff endocrinologist. At its founding, in 1977, Einstein's Diabetes Research and Training Center (DRTC) was a modest affair, with just nine

research projects and less than a million dollars in funding. Eventually, under Dr. Fleischer's leadership, the DRTC came to play a significant role in what has been called the golden age of discovery in diabetes. Within a generation, DRTC helped to transform this severely debilitating and often fatal disease into a manageable chronic illness.

THE DARK AGES OF DIABETES

"When I went to medical school, in the 1960s, we didn't even think that getting blood sugar under control was that important," recalls Dr. Fleischer, who is Jacob and Jeanne E. Barkey Professor of Medicine, Division of Endocrinology director, and codirector of the DRTC at Einstein. "Even the doctors who thought that glucose monitoring was important had no way of doing it. There were no finger-stick blood tests. People were taking insulin, one shot a day, but you had no idea if it was working."

The situation was only slightly better a decade later, when Henry Shamoon, MD, now a professor of medicine at Einstein, was a resident at Bronx Municipal Hospital. "It was just about impossible to take care of people with diabetes," he says. "That was the dark ages in terms of our

understanding of the disease."

Soon, however, came the development of better ways to monitor blood glucose and administer insulin, followed by genetically engineered insulins, oral medications for controlling other aspects of metabolism, and the hemoglobinA1C test (which provides a months-long look at blood glucose levels). More recently, the Diabetes Control and Complications Trial, conducted at Einstein and elsewhere, demonstrated the critical importance of keeping blood glucose under tight control through monitoring, medication, diet, and exercise. The trial also highlighted the value of a team approach to diabetes care, involving physicians, nurse educators, dietitians, and behavioral therapists—a concept championed decades ago by Dr. Rifkin.

Thus, today, "the average person with diabetes can expect to live essentially a normal life, with some risk, and with a bunch of major inconveniences—but it is not a death sentence," says Dr. Shamoon.

NOT QUITE THE ENLIGHTENMENT

Even if the dark ages of diabetes are over, diabetes remains one of the country's most pressing medical problems. The sixth leading cause of

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death, diabetes costs the nation \$132 billion annually (in direct medical expenses plus costs related to disability, work loss, and premature mortality). An estimated 18.2 million people—6.3 percent of the population—have diabetes (mostly type 2). The circumstances are even worse in minority communities, such as the Bronx, where the incidence of diabetes is twice the national average. And the numbers everywhere are rising, as Americans grow steadily more obese and more sedentary, a disturbing trend that is filtering down to young children and adolescents. “This is an enormous looming problem, not only in this country, but worldwide,” says Dr. Shamoon.

Just as alarming, countless diabetics still do not receive proper treatment, a real tragedy since many of the complications of diabetes can be prevented or delayed. Says Dr. Shamoon, “We could spend the next 30 years productively engaged in getting everybody treated to current standards.”

This gloomy picture, however, belies the progress that diabetes researchers are making. Einstein’s DRTC, which now sponsors 44 major research projects, with a total funding of approximately \$33 million, is a shining example. Basic scientists at Einstein are beginning to understand, molecule by molecule, gene by gene, organ by organ, what causes the disease and its many complications, while their clinical counterparts are developing and testing new treatments and strategies for prevention. Moreover, the DRTC is active in a host of diabetes programs in hospitals and clinics throughout the Bronx, which constitute by far the largest community effort of its kind in the city.

THE MISSING LINK

One of the most far-reaching advances in diabetes research emerged just a few years ago from the laboratory of Michael Brownlee, MD, Anita and Jack Saltz Professor of Diabetes Research and professor of medicine and of pathology. A basic scientist, Dr. Brownlee concentrates on the biochemistry of diabetic complications.

“If there were no diabetic complications, dia-



Dr. Luciano Rossetti's research focuses on the neurobiology of appetite and metabolism.

betes would be like having a chronic thyroid condition, and not the major public health problem that it is,” Dr. Brownlee noted at a recent gathering of the American Diabetes Association (ADA). “The patient would take a pill or an insulin injection, and that would be all.”

Since the late 1960s, researchers have known that there are four distinct biochemical pathways by which hyperglycemia leads to complications. Although evidence back then suggested that the pathways are linked, no one could discern how. In a series of elegant experiments, Dr. Brownlee established that all four pathways arise from a single process involving overproduc-

tion of a toxic substance called superoxide, which is made by the mitochondria, the cells’ energy factories. “It turns out that insulin resistance [the initial phase of diabetes] causes fat cells to release large amounts of fatty acids,” Dr. Brownlee told the ADA audience. The fatty acids then enter cells that line the arteries and combine with oxygen, yielding excess amounts of superoxide. This, in turn, activates pathways that lead to atherosclerosis, clogging small and large arteries throughout the body.

The medical community has hailed the discovery as a new paradigm for research and drug discovery in diabetes. It has already led to the

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DIABETES EXPLAINED

Type 1 diabetes, formerly called juvenile diabetes or insulin-dependent diabetes, is usually first diagnosed in children, teenagers, or young adults. In this form of diabetes, the beta cells of the pancreas no longer make insulin because the body's immune system has attacked and destroyed them. Treatment includes taking insulin shots or using an insulin pump, making wise food choices, exercising regularly, and controlling blood pressure and cholesterol.

Type 2 diabetes, formerly called adult-onset diabetes or noninsulin-dependent diabetes, is the most common form of diabetes. People can develop type 2 diabetes at any age. This form of diabetes usually begins with insulin resistance, a condition in which fat, muscle, and liver cells do not use insulin properly. At first, the pancreas keeps up with the added demand by producing more insulin. In time, however, it loses the ability to secrete enough insulin in response to meals. Being overweight and inactive increases the chances of developing type 2 diabetes. Treatment includes using diabetes medicines, making wise food choices, exercising regularly, and controlling blood pressure and cholesterol.

Some women develop gestational diabetes during the late stages of pregnancy. Although this form of diabetes usually goes away after the baby is born, a woman who has had it is more likely to develop type 2 diabetes later in life. Gestational diabetes is caused by the hormones of pregnancy or a shortage of insulin.

Source: National Diabetes Educational Program, National Institutes of Health

identification of three new classes of medications for diabetic complications, two of which were found by Dr. Brownlee's team. One of the drugs is now in clinical trials in Europe.

For a lifetime of contributions to the field, Dr. Brownlee was awarded the coveted Banting Medal of the ADA in 2003, becoming only the third researcher to win diabetology's three highest scientific honors.

What makes this story especially poignant is that Dr. Brownlee himself was diagnosed at age eight as a type 1 diabetic. Back then, the odds were pretty low that he would survive past his 30s. Diabetes research, he says, has become his "personal and professional crusade."

BUILDING A BETTER BETA CELL

Another example of research with potential to stretch from the lab to the clinic is the work of Dr. Fleischer, who is developing cell transplants as a cure for patients with type 1 diabetes.

Lacking healthy pancreatic beta cells, type 1 diabetics don't make sufficient quantities of insulin. Right now, their only recourse is to take insulin shots or use an insulin pump. Transplants of healthy beta cells are a promising alternative. Unfortunately, this treatment is limited by an acute shortage of donor pancreases from which to harvest beta cells. To overcome this hurdle, Dr. Fleischer's team, which includes Sanjeev Gupta, MD, professor of medicine at Einstein, and scientists from Tel Aviv University and the University of California at Davis, has devised a way to coax human liver cells into becoming insulin factories. In a recent study, transplantation of these genetically manipulated cells into diabetic mice returned their blood sugar levels to normal.

"The question now is how to refine this process so we can start thinking about trials in humans," says Dr. Fleischer. "These cells are transplants, so the biggest problem is rejection. You don't want to treat these patients with toxic immunosuppressants. It's different with heart, kidney, or liver transplants, which are usually lifesaving interventions. However, for patients with type 1 diabetes, we have a pretty good therapy—insulin—so the bar for transplantation is very high."

The solution may come from a collaborative project with Marshall Horwitz, MD, professor and chair of microbiology and immunology, who is attempting to make the pancreatic cell transplants immunologically stealth. His solution is to borrow traits from cold viruses, which have an

annoying ability to outsmart the body's immune response, for a time at least. "When you get a cold, why does it last for two weeks?" Dr. Fleischer explains. "The answer is that the virus makes proteins that downregulate your immune system, so you don't reject the virus quickly. If we can express the same proteins in our transplant cells, they are less likely to be rejected."

FAT: GETTING SOME RESPECT

In another DRTC laboratory, the focus is fat. For years, fat got no respect. It was considered a passive tissue that did little else but store energy in times of plenty (a good trait back on the savannah when food was often scarce, but a liability in our calorie-rich environment). Scientists knew that excess fat—or adipose—tissue contributes to insulin resistance, but exactly how was not clear. Then, about 10 years ago, came the discovery that fat cells produce a hormone called leptin. The more fat one accumulates, the more leptin is released into the bloodstream. Eventually, the brain gets the message that the body would do well to consume fewer calories.

Leptin was hailed as the next great hope for curing obesity and ameliorating diabetes. "In theory, it was an attractive therapeutic target, but not in practice," says Philip Scherer, PhD, an associate professor of cell biology. "Obese people actually have an awful lot of leptin, but they are resistant to it." Clearly, there are more pieces to the puzzle.

On the heels of the leptin discovery, Dr. Scherer unearthed another fat hormone, adiponectin. It took five years for his lab to develop tools to measure the hormone in circulation and to build mouse models for assessing its function. So far, what scientists know is that adiponectin plays a role in maintaining blood glucose levels by making the liver more sensitive to insulin. Adiponectin also is implicated in cardiovascular disease, possibly through some sort of inflammatory process.

That fat may contribute to inflammation has led researchers to look at diabetes in a new light. Says the researcher, "In the last few years, we have come to appreciate that diabetes is in effect a low-level inflammatory disease. The question arises, Where does this inflammation originate? Many would argue that it originates primarily from adipose tissue." It appears that fat cells don't directly cause inflammation; rather, they release substances that potentiate the effects of macrophages, a type of immune cell that infiltrates adipose tissue as fat stores expand.

Until researchers find a cure, the best hope for combatting type 2 diabetes is prevention.

There's also evidence connecting adipose tissue to infectious disease and to cancer.

So, fat is finally getting its due. "We need to take a look at adipose tissue from multiple perspectives," says Dr. Scherer. "It's obviously important in metabolism, but that's only part of the story. Fat cells are ubiquitous. You find them everywhere in the body, except the brain. By sheer mass, they make up half of your body weight. This is a significant 'organ' that we're talking about."

THE GUT-BRAIN AXIS

As Dr. Scherer's work would suggest, there is ample need for a research center devoted solely to the links between obesity and diabetes. In fact, Einstein established just such a center in 2004, with the help of a \$1.5 million gift from the Skirball Foundation. The Jack H. Skirball Institute for Nutrient Sensing in Diabetes and Obesity will focus on the mechanisms of the brain that stimulate and suppress appetite.

One of the principal investigators at the new institute is Gary Schwartz, PhD, professor of medicine and of neuroscience, who is examining the neurobiology of eating. Eating seems so simple: You get hungry, so you eat; when you get full, you stop. But behind the scenes is a dizzyingly complex array of receptors and signals along the so-called gut-brain axis. When foods are ingested, Dr. Schwartz explains, all sorts of signals are relayed to the brain—from sensory cells in the eyes, nose, and mouth that promote ingestion, from sensory cells that detect the mechanical distention of the stomach, from secretory cells that line the gastrointestinal tract, and from the nutrients themselves. All these signals provide feedback to the brain, through the bloodstream or the nervous system, affecting how much, how long, and how often we eat.

"We are interested in identifying the types of signals that are available in the GI tract that bring about the end of feeding, how they are transmitted, where they act in the central nervous system," says Dr. Schwartz. He also is studying how fat hormones modulate gut-brain communication, and how the various signaling mechanisms are altered in obesity.

Dr. Schwartz's ultimate goal is to identify therapies that can tap into the body's natural feedback systems for controlling appetite, providing a pharmacologic alternative to gastric bypasses, and other surgical strategies for obesity. "All of these surgical strategies can be viewed as ways to increase feedback from the gastrointestinal tract. You can't eat as much, and you feel full faster. It's effective for many. However, if there were drug-related therapies that can mimic this effect at mealtime, they would go a long way toward mitigating against obesity."

Luciano Rossetti, MD, another principal

investigator in the Skirball Institute and the director of the DRTC, is also interested in the neurobiology of appetite and metabolism, with a particular focus on the hypothalamus, a portion of the brain. Researchers have long known that eating behavior is regulated by indirect signaling, whereby nutrients in food stimulate the secretion of hormones into the bloodstream, which carries these signals to the brain. Dr. Rossetti has hypothesized that there is a more direct signaling mechanism at work.

"In animal models at least, we are finding strong evidence that there is nutrient sensing in the brain," says Dr. Rossetti, who is also Judy R. and Alfred A. Rosenberg Professor of Diabetes Research. Apparently, a small group of neurons in the hypothalamus is capable of detecting the presence of nutrients, particularly fats, in the blood, which then trigger the brain to make alterations in food intake and glucose metabolism.

Thus far, the theory has held true in tests on



Dr. Elizabeth Walker and her team are designing interventions that they hope will motivate patients to seek proper care. Back row from left: Emelinda Blanco, Severa M. Sanchez-Bravo, Kathleen McCabe, Maria S. Mera, Hector J. Cariello, Jennifer R. Case. Front row from left: Dr. Arlene Caban and Dr. Walker.

rats. In one experiment, scientists injected a drug that blocks a critical enzyme into the animals' hypothalamuses, essentially signaling that they were getting a sufficient amount of fat in their diet. The animals were left to eat as much as they pleased, but they consumed only about half the normal amount of calories and they had lower serum glucose levels.

"Nutrient sensing is one of the first things that fails in animals that are susceptible to metabolic disorders," says the researcher. "Within days after they are put on a voluntary overfeeding regimen, the brain fails to respond to hormones and nutrients, and this quickly leads to severe insulin resistance and obesity."

10 TO 15 POUNDS OF PREVENTION

Until researchers find a cure, or at least better treatments, for type 2 diabetes, the best hope for combating this growing public health problem is prevention. Fortunately, type 2 diabetes can be prevented or delayed in persons at high risk for the disease using relatively simple interventions, as demonstrated by the ongoing NIH-sponsored Diabetes Prevention Program (DPP), involving Einstein and more than two dozen other centers across the nation. In a recent DPP study, participants reduced the incidence of diabetes by 58 percent with lifestyle interventions, and by 31 percent with the oral medication metformin, as compared with placebo.

"The good news is that the interventions were really modest," says Jill Crandall, MD, an assistant professor of medicine and the current leader of Einstein's portion of the DPP. "On average, people lost about 10 to 15 pounds and exercised by walking about 30 minutes a day. Small steps, big rewards—which happens to be the motto of the National Diabetes Education Program," an NIH effort.

DPP researchers are now studying the interventions' long-term effects as well as the natural history of the diabetes. "On average, people have already had diabetes for five or ten years by the time they are diagnosed, so we don't have a full understanding of when the micro- and macrovascular complications begin to occur," says Dr. Crandall.

Dr. Crandall is also leading the Heart Disease Risk in Older Adults with Diabetes Study. Also known as HeartROADS, the study addresses the relationship between the characteristic mild hyperglycemia that occurs in the elderly and heart disease risk. Whether cardiovascular disease, the major consequence of type 2

diabetes, can be prevented by intensive glucose control is a question left unanswered by the landmark Diabetes Control and Complications Trial of a decade ago. "There has been a lot of debate about whether the heart disease of diabetes is due to elevated levels of blood sugar or abnormalities in blood lipids. I'm partial to the theory that even mild levels of hyperglycemia can impair the heart. But there hasn't been the definitive study to answer this question," she explains.

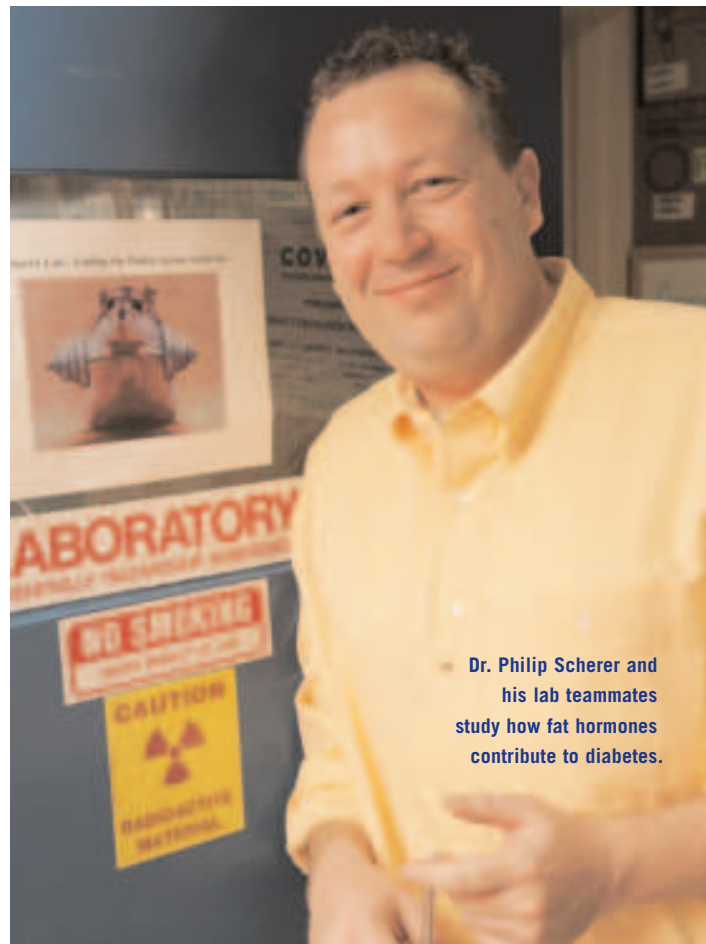
PUTTING THEORIES INTO PRACTICE

Elizabeth Walker, DNSc, professor of medicine, also works on diabetes prevention strategies, but with a focus on motivation and behavior. Her experiences as a public health nurse earlier in her career taught her that "management of diabetes, or any chronic disease, is really up to the patient. If patients aren't motivated or activated to use them, then it doesn't matter that treatments have been developed."

The challenge for diabetes sufferers, she says, is that "life intervenes. You'd think it would be enough to tell patients that they need to get regular dilated eye exams or else they might go blind. But if it means they have to sit in a clinic for six hours and miss a day of work, it's not such a simple choice. They're just trying to take care of the day-to-day stuff. So part of our interventions are just reality checks, changing their perceptions of the risks."

Evidently, a little motivation can go a long way. Preliminary data from her NIH-funded "Vision is Precious" study show that a simple telephone intervention provided by health educators can significantly increase the rate of retinopathy screening among a diverse low-income population of diabetics, as compared to a standard print intervention.

In another NIH study, Dr. Walker is testing whether a telephone intervention can increase medication adherence, a particular problem with diabetics, many of whom have to take a number of pills for controlling blood sugar as well as several drugs for lowering blood pressure and cholesterol.



Dr. Philip Scherer and his lab teammates study how fat hormones contribute to diabetes.

In sum, says Dr. Walker, "We are trying to design interventions that provide self-management support for patients, to do what the primary-care doctor probably does not have the time or resources or knowledge to do—which is to take care of all the interpersonal, psychosocial details that activate patients to get proper care."

A MAJOR PUBLIC HEALTH ISSUE

If physicians don't yet "know" diabetes, they are getting quite familiar with the disease. In the meantime, most experts in the field would probably agree that to stop diabetes, we need a society-wide effort.

"I see this as a major public health issue, like seat-belt use and smoking cessation," says Dr. Crandall. "There has to be a major commitment to structural changes in our society. We have to change the types of food that are available, the way people eat, the way we educate people about nutrition, the way insurance companies reimburse for nutrition counseling."

"We have the means for preventing most cases of diabetes," adds Dr. Shamoon. "These approaches have been replicated in studies around the world. The question arises, Do we have the social and economic will in this country to develop programs to stop this disease?" ■