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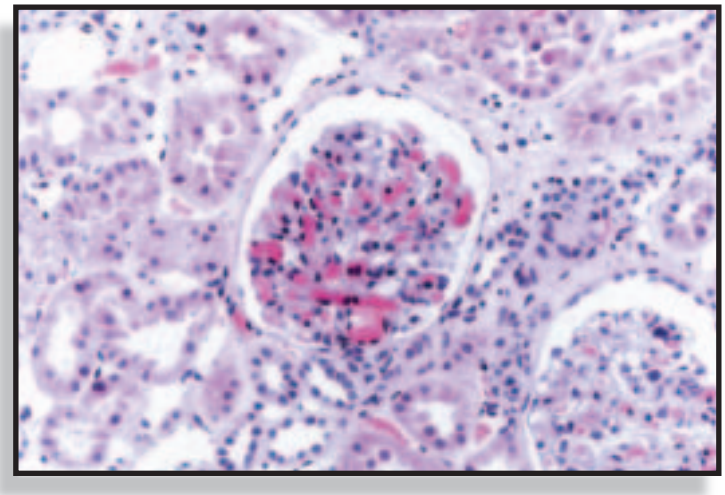

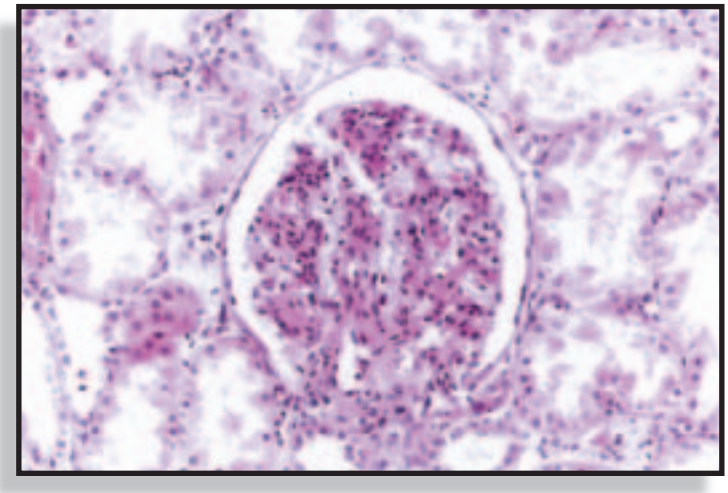

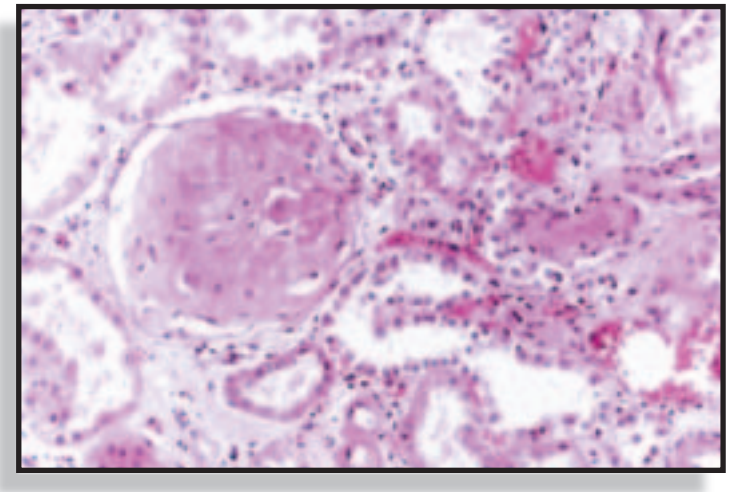

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NEW WEAPONS TO COMBAT AN ANCIENT DISEASE: TREATING DIABETES

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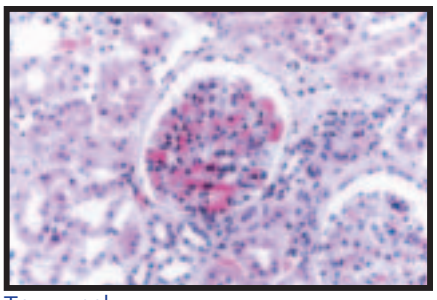

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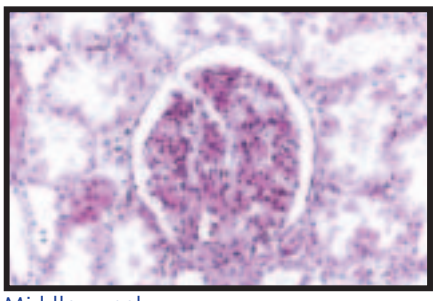

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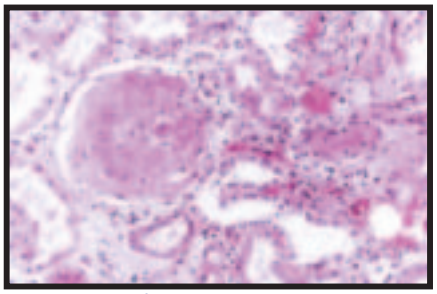

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COVER IMAGE: Microscopic images showing changes to the cellular structures of the kidney, known as glomeruli, as diabetes progresses. The non-diabetic glomerulus (top panel) has an abundance of small blood vessels which can be seen to contain many red blood cells. In diabetes, the small blood vessels in the glomeruli become reduced in size due to protein deposits within and around the blood vessels (middle panel). These deposits reduce the flow of blood, thereby impairing kidney function. Similar deposits occur in small blood vessels at many sites throughout the body and are the basis for the multi-organ nature of diabetes. As the disease progresses and deposits increase, the glomeruli in the diabetic kidney can become totally obliterated and non-functional (bottom panel). *Courtesy of Richard Lynch, MD, University of Iowa College of Medicine.*

DIABETES

New Weapons to Combat an Ancient Disease:

Treating Diabetes

By Margie Patlak

The Pima Indians of Arizona are known in history for the fierce battles they fought against neighboring Apache Indians. Now, however, remnants of the two tribes live in harmony amid the urban sprawl of Tucson. But today, many of these Pima Indians must fight a different yet deadly foe—type 2 diabetes—that hampers the body's ability to use the sugars in food for energy. The end result is telltale high levels of sugar in the blood and urine.

Diabetes causes numerous complications and could be fatal if left untreated. It strikes about half of all adult Pima Indians in this country, making them susceptible to premature death from heart disease and stroke and prone to blindness, kidney failure, nerve damage and limb amputations. But the Pima Indians aren't the only ones plagued with type 2 diabetes and its complications. This disease, which is common in virtually all ethnic groups, is rapidly reaching epidemic proportions in the United States. According to the Centers for Disease Control and Prevention, the incidence of diagnosed diabetes among adults increased 49 percent from 1990 to 2000; 17 million people have diabetes in this country; and more than 200,000 people die each year from related complications.

The costs of treating diabetes and its complications exceed $100 billion each year in the United States, and those costs are likely to soar in the near future. Some experts predict that 25 years from now as many as one in four people may develop diabetes; that is, unless we effectively battle the disease in its early stages, before it has a chance to wreak havoc in the body and cause irreversible damage. Fortunately, we have some weapons.

Over the last century, dozens of researchers have whittled away at the mystery of what causes diabetes, and we have gained an extraordinary amount of knowledge about the disease. That insight has blossomed into an armory of drugs that not only effectively treat type 2 diabetes, but also are also likely to prevent or forestall its development. Curious scientists exploring such basic questions as "What does the pancreas do?" and "What causes fat cells to mature?" have fine-tuned our understanding of what goes wrong in diabetes and how to right those wrongs.

Sweet Flow: The History of Diabetes

Diabetes is an ancient disease. Its symptoms, which include excessive drinking of water and frequent urination (to wash away the excess sugar in the blood), were noted on a scrap of Egyptian papyrus more than 3,500 years ago. The ancient Roman doctor Aretaeus of Cappadocia also gave a vivid description of diabetes, describing it as "a melting down of the flesh and limbs into urine."

Since then, many physicians have remarked on the sweet taste of diabetics' urine. Indeed, the technical term for this disease, diabetes mellitus, means "sweet flow" or "syphon." Because of this hallmark of diabetes, the disease was thought to be a disorder of the kidneys and bladder for more than two thousand years.

What caused sugar to show up in the urine of diabetics remained a mystery until 1889, when two European physicians conducted an experiment to settle a debate. Joseph von Mering wanted to know what role the comma-shaped organ nestled in between the stomach and small intestine played in digestion. One way to figure that out would be to remove the organ, called the pan-

creas, in experimental animals and see how such removal affected their functioning. But von Mering didn't think such a procedure was possible. His colleague, Oskar Minkowski, disagreed. To prove his point he took out the pancreas of a healthy dog.

A few days later, Minkowski noticed that the dog kept urinating on the laboratory floor, even though he was housebroken and taken out regularly. Recognizing that frequent urination is one of the symptoms of diabetes, Minkowski tested the dog's urine and found it was high in sugar. At this point, von Mering and Minkowski rightly suspected they had created diabetes by removing the dog's pancreas. Further study led them to conclude that the pancreas secretes a substance that affects the body's use (metabolism) of sugar.

That conclusion triggered a flurry of research aimed at isolating this substance, which was later given the name insulin. But such isolation proved difficult because insulin-containing pancreas extracts often also contained enzymes that ate up insulin or sparked severe reactions when tested in animals.

Fortunately, a 30-year old Canadian orthopedist with a slow practice and lots of time on his hands was intrigued by the quest to isolate insulin. This doctor, Frederick Banting, had never treated any diabetic patients and had little research expertise. But one night, when he was having trouble falling asleep, he got an idea of how to avoid the enzymatic digestion of insulin.

Figure 1. Canadian orthopedist Frederick Banting, medical student Charles Best, and an experimental diabetic dog. When Banting and Best showed, in 1921, that they could keep this dog alive with their insulin-containing pancreatic extracts, they opened the door to the exciting possibility of treating diabetic patients with insulin. *Image courtesy of the National Library of Medicine.*

Banting rightly suspected that when researchers made extracts of the entire pancreas, the digestive enzymes secreted by cells called acini destroyed the insulin made by other pancreas cells (beta cells). Other researchers had shown that when they blocked the pancreatic duct, which is an outlet for the digestive enzymes made by the pancreas, just the acini cells die.

Banting reasoned that if he tied off the pancreatic duct of dogs and waited several weeks until their acini cells died, he could prevent their destructive enzymes from contaminating the insulin-containing extracts he would later make from remaining pancreas beta cells. He convinced University of Toronto physiologist J.J.R. Macleod to let him try this game plan in Macleod's lab, along with a medical student, Charles Best. During the summer of 1921, while Macleod was vacationing in Scotland, Banting and Best isolated a pancreatic extract that instantly brought the blood sugar levels of severely diabetic dogs back to normal, relieved many of their symptoms, and kept them alive. The biochemist James Collip was then brought on board to help purify their extracts using methods developed to study enzymes. The efforts of these Canadians opened the door to the exciting possibility of treating diabetic patients with insulin.

At the time, there was no effective treatment for diabetes, which causes the body to gradually break down protein and fat stores

to supply its desperate need for energy. Children with diabetes wasted away, usually dying within a few years of being diagnosed with the disorder. So it was nothing short of miraculous, consequently, when a skeletal 14-year-old diabetic boy on the verge of death was restored to good health within a few months of being given regular injections of Banting and Best's insulin preparation in 1922.

With the introduction of insulin treatment, a diagnosis of diabetes was no longer a death knell. But insulin merely sustained life; it didn't cure diabetes. As diabetic patients lived longer, it became apparent that even with insulin therapy, the disease wreaked havoc on many of their organs and tissues. The complications of diabetes typically shorten the lifespan by about 15 years and increase the likelihood of a person becoming disabled.

To better prevent or treat diabetes and its complications, researchers needed to better understand what caused it. But progress on that front couldn't be made until scientists discovered that diabetes was not one disease, but at least two.

Discovery of Type 2 Diabetes

The remarkable success at using insulin to treat diabetes led to the notion that the disease was caused by a lack of insulin. But a series of observations in the 1930s by the British clinician Harry Himsworth led to a startling new view of diabetes. Curious about how diet affects sensitivity to insulin, Himsworth conducted a series of experiments in both animals and people that led him to the discovery that the body's use of sugar depends not only on how much insulin is present, but on how *sensitive* the body is to the effects of insulin.

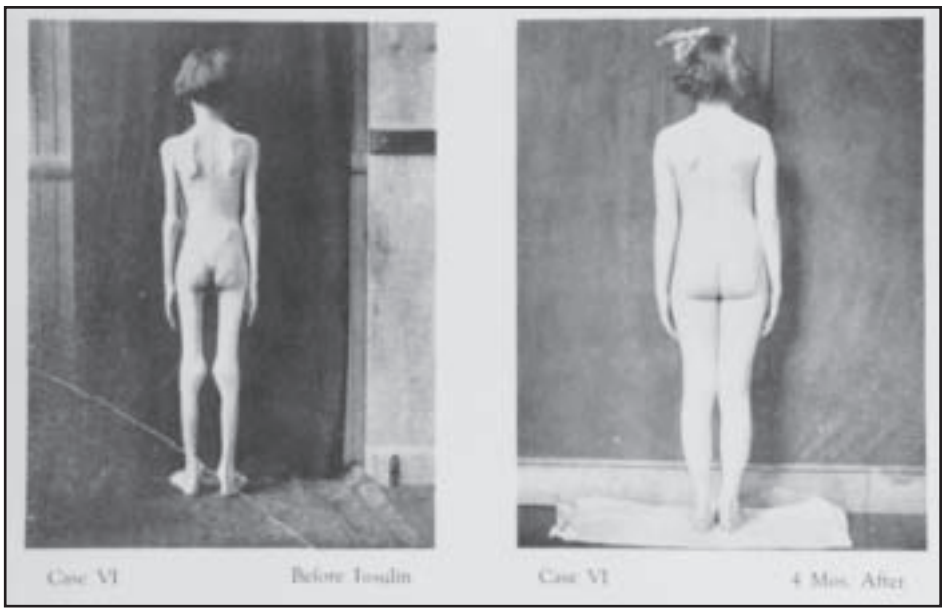

Figure 2. The photo on the left shows the gaunt condition of a diabetic child before beginning insulin therapy. This therapy dramatically improved the child's condition, as can be seen in the photo on the right. *Courtesy of Eli Lilly and Company Archives.*

So, he reasoned, diabetes could be caused not only by a lack of insulin but also by a lack of sensitivity to insulin. To test out this theory, Himsworth gave diabetic patients sugar and insulin simultaneously and then checked to see how well the insulin fostered their use of the sugar. If they were relatively insensitive to the effects of insulin, their blood sugar levels shot up. These experiments showed that there were two types of diabetes: type 1 and type 2. People with type 1 diabetes were sensitive to insulin and had a history of suddenly developing the disease at a young age; those with type 2 diabetes were relatively insensitive to insulin and tended to gradually develop a milder form of the disease at middle age or older.

Over several years, other researchers confirmed Himsworth's findings with more sophisticated techniques and revealed that most of those with diabetes (about nine out of ten) have type 2. Then in the 1950s, research by a nuclear physicist and an internal medicine doctor led to a surprise finding that changed the course of diabetes research and treatment and earned the scientists the Nobel Prize.

In the 1950s, Himsworth's notion that type 2 diabetes involved reduced sensitivity to insulin was not yet well accepted by the biomedical community. Another researcher, Arthur Mirsky, gave a different explanation for adult-onset diabetes—

that it was due to rapid enzymatic digestion of insulin. Rosalyn Yalow and Solomon Berson, researchers at New York's Veterans Administration Hospital, set out to test this hypothesis. They gave radioactively labeled insulin to people with and without diabetes. According to Mirsky's theory, the insulin given to those with diabetes should have disappeared more quickly than that given to normal individuals. But Yalow and Berson found it disappeared more slowly!

Puzzled, the researchers conducted additional tests that led them to conclude that the slower rate of disappearance was due to an immune response to the insulin used in the experiments. This response, which involved the production of antibodies, fouled up Yalow and Berson's attempts to test Mirsky's theory, but it led the researchers to discover something far more useful —a tool to measure circulating levels of insulin and other biologic compounds present in the blood at nearly invisible levels. The researchers combined the knack of antibodies to selectively seek out and latch on to highly specific substances with the ability of radioisotopes to be easily detected at miniscule levels. The end result was the radioimmunoassay—a technique that enabled researchers to measure exquisitely minute quantities of hormones (one thousand-billionth of a gram per milliliter of blood) and other compounds coursing through the bloodstream. This method is still in wide use today.

Figure 3. Nobel-prize-winning nuclear physicist Rosalyn Yalow. She used radioactive insulin and antibodies to show that type 2 diabetics often produce more than normal amounts of insulin. This was a major breakthrough in diabetes research that changed knowledge and treatment. *Photo courtesy of the National Library of Medicine.*

In 1960, Yalow and Berson used their new technique to measure and compare the insulin response to sugar in those with type 2 diabetes to those without the disease. They discovered that instead of producing less insulin after being given sugar, people with type 2 diabetes often generated *more* insulin than did those without diabetes. This perplexing finding was totally unexpected and jolted the diabetes research community. Other researchers then discovered that although people in the early stages of type 2 diabetes produce more than the normal amounts of insulin, over time their insulin levels fall until eventually they dip below that seen in normal individuals and their diabetes becomes severe.

The net result of all these findings was the hypothesis that to compensate for their lack of sensitivity to insulin (insulin resistance), people with type 2 diabetes initially produce excess insulin. That excess allows them to sufficiently convert the sugar in their diet to energy their tissues can use. But eventually the insulin-producing cells in the pancreas deteriorate and can't keep up with the need for insulin. At this point, these people's diabetes becomes severe, requiring insulin treatment.

If this is an apt scenario, then people should produce higher than normal amounts of insulin *before* they become diabetic. Research by many investigators in the 1980s and 1990s showed that this was indeed the case. This led to the notion that type 2 diabetes is a slowly progressing disease that starts many years before people develop any obvious signs of the disease. And it begged the obvious question, "What can be done to stop this debilitating progression?"

Detecting Pre-diabetes

Before that question could be addressed, researchers had to answer another question: "How can you detect diabetes-bound patients?" Detecting high insulin production or insulin resistance was not practical or reliable enough in a clinical setting. More evidence was needed to pin down the suspect pre-diabetic patient.

Fortunately, researchers had several tantalizing clues to go by, including an observation by Himsworth in the 1930s that many people with type 2 diabetes tended to be obese and have high blood pressure and atherosclerosis. These traits could be attributed to the older age at diagnosis of type 2 diabetes, rather than to the diabetes itself. But later research revealed that Himsworth was on to something, because type 2 diabetes is a multi-faceted metabolic disorder in which far more is disrupted than just blood sugar levels.

This research uncovered that people with insulin resistance and/or those that produce excessive amounts of insulin often have a cluster of abnormalities known as the "metabolic syndrome." These abnormalities not only can serve as a clinical red flag for preventive measures, they can also help explain the mystery of why people with diabetes frequently succumb to cardiovascular and kidney disease.

Telltale signs of the metabolic syndrome include high blood levels of triglycerides combined with low blood levels of high-density lipoprotein (HDL) cholesterol—traits that dramatically increase the risk of developing heart disease. Based on studies on animals and on liver cells grown in the laboratory, we now know that signs of the metabolic syndrome develop when people first start producing too much insulin and stem from insulin's effect on the liver. People with the metabolic syndrome also tend to have high blood pressure, which heightens their risk of stroke and heart and kidney disease. Obesity, especially excess abdominal fat, is another facet of the metabolic syndrome. Genetic research with mice led to the discovery of hormones released by fat cells that seem to foster or worsen insulin resistance.

The most reliable marker of impending diabetes is an elevated blood sugar level following a meal (impaired glucose tolerance) that isn't quite high enough to suffice for a diabetes diagnosis. This marker tends to occur several years after the body has been exposed to high amounts of insulin and shortly before diabetes is diagnosed.

A recent study found that up to one in four adult Americans has the metabolic syndrome. That's a disturbing finding considering that between 5 and 10 percent of patients with metabolic syndrome develop diabetes every year.

Fortunately, there are more than a dozen drugs on the market now that are likely to help prevent or delay people from progressing from pre-diabetes to diabetes or can treat the disorder once it ensues. Additionally, researchers in fields as diverse as toxicology, physiology, pharmacology, biochemistry and cell biology are helping to develop drugs that hold promise for being more effective than those currently on the market.

The Development of Oral Drugs for Type 2 Diabetes

One of the first oral drugs for type 2 diabetes that can delay the need for insulin shots was discovered by a French university pharmacologist during World War II. Marcel Janbon was trying to find an effective treatment for typhoid. When he tested a drug called sulfonylurea in animals, it caused them to behave bizarrely and sometimes to die. Curious about why this happened, Janbon investigated further and discovered the drug caused the animals' blood sugars to drop precipitously.

Quick to switch gears and see how this drug might benefit diabetics, Janbon convinced a medical colleague, August Loubatieres, to try it on his diabetic patients. The drug triggered a fall in these patients' blood sugars. Experiments by Loubatieres and others, with animals and with isolated pancreas, later revealed that the sulfonylurea stimulated pancreas cells to release insulin.

In 1958, the first of four sulfonylureas came on the market to treat type 2 diabetes. These drugs can often delay a patient's need for insulin by several years, but for each year of use, sulfonylureas become ineffective in about 10 percent of patients. These drugs also do not counter the central defects in diabetes—insulin resistance and excessive insulin production—nor do they prevent many of the complications of diabetes.

People with type 2 diabetes needed a better alternative—a drug that could both lower blood sugar levels and help prevent diabetes complications. One of the first drugs shown to do both is a chemical cousin of the active compound in a diabetes folk remedy, the plant goat's rue or French lilac. This plant had been used since medieval times to treat diabetes and is rich in a compound known as guanidine.

But as is true for many folk remedies, guanidines had side effects that were too dangerous to warrant their use to routinely treat diabetes. A number of researchers tried to synthesize less toxic versions of guanidine that still lowered blood sugar levels. One of those versions, called a biguanide because it was comprised of two molecules of guanidine linked together, was first synthesized in 1922 by two English chemists.

Dogged by toxic reactions, many researchers abandoned their efforts to develop biguanides into anti-diabetes drugs once insulin became available. The torch wasn't taken up again until the 1940s, when doctors tried using biguanides to treat people afflicted with malaria or influenza because there were no other treatments available for these often-fatal diseases. A side effect of the drug—the lowering of blood sugar—sparked the interest of the French doctor Jean Sterne, who decided to study one of the biguanides called metformin.

Sterne confirmed the blood sugar-lowering property of metformin in his animal and clinical studies and also showed that the drug had none of the serious side effects that haunted the other guanidines and biguanidines. In 1959, metformin, given the brand name Glucophage (sugar-eater), made its clinical debut in France and soon found widespread use in a number of European countries.

Still concerned about Glucophage's potential toxicity, however, the Food and Drug Administration didn't approve its use in the United States until 1995. By that time, laboratory studies with animals had shown that metformin mainly works by lessening the liver's production and release of sugar into the bloodstream. The drug also was shown to boost the use of sugar by muscle tissue. Studies show metformin lowers blood sugar levels by nearly one-third—as effectively as sulfonylureas do. But unlike these drugs, metformin also lowers blood triglyceride levels by 10 to 15 percent and slashes the risk for a heart attack or stroke nearly in half. Metformin also enhances weight loss, which by itself can help in the treatment or prevention of type 2 diabetes.

Also encouraging was the revolutionary study that showed, in 2002, that metformin reduced by one-third the number of those with pre-diabetes—people with impaired glucose tolerance—that progressed to diabetes during a three-year period. For the first time, a drug was shown not only to treat diabetes but also to prevent it from occurring, at least in the short term. (The same study also found that by losing just 7 percent of their body weight and walking a half-hour a day five times a week, volunteers with impaired glucose tolerance were able to halve their risk of developing diabetes within three years.)

But to many, the most significant breakthrough in type 2 diabetes treatment since insulin is the development of drugs that counter insulin resistance. These drugs didn't come on the market until the 1990s, and they were not discovered by researchers diligently searching for a diabetes cure. Instead, scientists exploring the functions of a curious cell organelle, and others interested in the actions of blood fat-lowering drugs, as well as researchers testing what causes fat cells to develop, all contributed pieces of knowledge that came together to provide new insights into diabetes.

Peroxisomes: A New Cellular Structure

One of those researchers was the Belgian, Christian de Duve. Captivated by a research project he pursued during medical school, de Duve gave up a career in medicine in the 1940s to study chemistry. He then began a series of studies at Rockefeller University aimed at figuring out how exactly insulin works. But

he had trouble isolating an enzyme (a biological catalyst) he thought might play a key role in modulating insulin's effects in the liver.

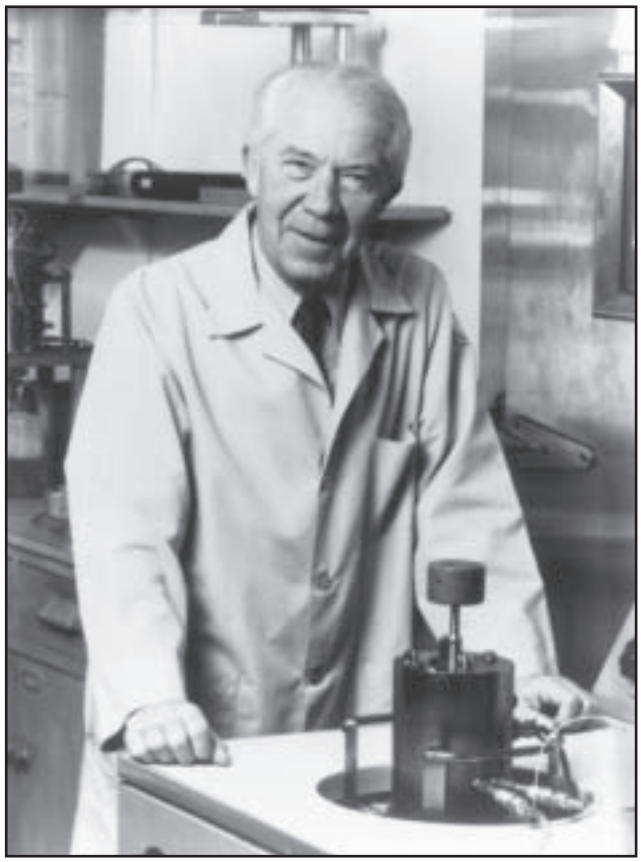

Figure 4. Curiosity about a perplexing biochemical finding led Nobel-prize winning researcher Christian de Duve to open the door to a new avenue of research on cellular vesicles called peroxisomes. This research resulted in the development of innovative drugs for type 2 diabetes. *Courtesy of the Rockefeller University Archives.*

This difficulty triggered him to separate a slurry of mashed-up rat liver cells into a number of enzyme-laden portions. He found the enzyme he was looking for in one of these portions. But perennially curious, de Duve didn't stop there. He set out to analyze the enzyme contents of the other fractions he had isolated.

Then he got stumped by the finding that some of his enzyme-rich fractions weren't very active —they weren't readily breaking down the chemical foods they were supposed to digest. This led him to suspect that these enzymes were being held captive within sack-like structures that prevented the enzymes from interacting with other compounds. As he noted in his book *Lysosomes in Biology and Pathology,* this finding was "essentially irrelevant to the object of our research [on insulin action], but it was most intriguing. I had a strong hunch that we had stumbled upon something important which fully justified what I thought would be only a temporary deviation from our chosen direction."

De Duve never returned to studying the mechanism of insulin action. Instead he made use of a relatively new tool, the electron microscope, to discover what was lurking in his enzyme-laden fractions. The invention of the electron microscope in the 1930s allowed scientists to peer into cells under high magnification and see structures that were invisible under the standard light microscope. This opened up a whole new world and revealed that the jelly-like substance between the cell nucleus and outer membrane harbored a number of mysterious components.

"We were very anxious to take a look at our purest fractions [under the electron microscope]", de Duve noted in his Nobel lecture. In the 1960s, when he and his colleagues did so, they were thrilled to discover the sack-like structures they had previously only imagined from their biochemical studies. De Duve gave the small circular sacks the name peroxisomes because of their knack for generating hydrogen peroxide. He later won the Nobel Prize for this and other discoveries.

Little did de Duve know at the time, that by forsaking his research on insulin action for studies of peroxisomes and other cell organelles, he launched a path of research that has helped immensely in elucidating how insulin works!

Peroxisomes gave scientists an intriguing new puzzle—what role did these organelles play in the body? One of the first clues to solving that mystery was discovered while investigating the effects of a blood fat-lowering drug. Researchers discovered the drug caused the livers of rats to enlarge. Trying to figure out why, investigators looked at liver cells from these treated rats under the electron microscope and saw that they were chock full of peroxisomes. The drug apparently triggered the proliferation of peroxisomes.

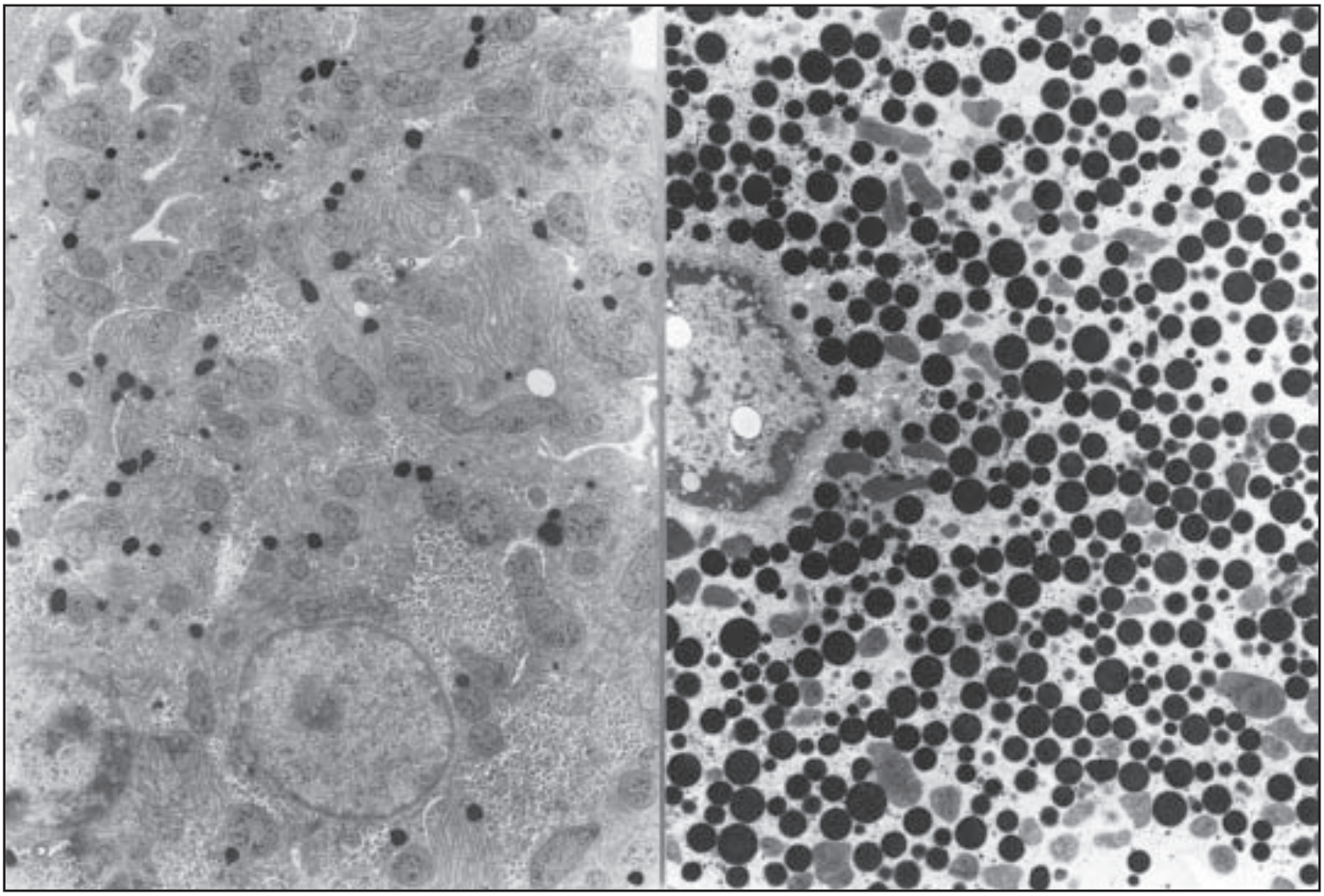

Figure 5. The round and darkly stained organelles known as peroxisomes are few in number in the rat liver cell seen on the left. But when these cells are exposed to drugs that "turn on" receptors called PPAR's, peroxisomes dramatically increase in number, as can be seen in the rat liver cell on the right. Discovery of the PPAR's has fostered a new breed of type 2 diabetes drugs that holds promise for countering the insulin resistance that is a hallmark of the disorder. *Courtesy of Janardan K. Reddy, MD, Northwestern University Medical School.*

This discovery raised the possibility that peroxisomes might foster the breakdown of fats. Studies by cell biologists and biochemists supported by the National Institutes of Health in the 1970s and 1980s showed this to be true. Peroxisomes contain more than 40 enzymes that also foster the breakdown of carbohydrates.

During this time, researchers also discovered that a number of compounds caused peroxisomes to rapidly multiply in cells—by as much as a hundredfold. How these compounds triggered such a dramatic proliferation of peroxisomes remained a mystery until a pair of toxicologists from the United Kingdom explored this enigma.

Isabelle Issemann and Stephen Green surmised that compounds that triggered peroxisomes to multiply so rapidly must work using a mechanism akin to that used by steroid hormones such as cortisol or estrogen. Like a hand slipping into a glove, these hormones bind to proteins (nuclear hormone receptors) in the nuclei of cells. When hormones or compounds of the same size and shape as the hormones bind to these nuclear hormone receptors, they act like switches that quickly turn on a number of genes controlling a series of biochemical reactions.

Using a probe to find genes similar to those that produce nuclear hormone receptors, Issemann and Green discovered a novel gene in mice. The researchers then deciphered the protein coded by this gene and produced large quantities of it. They called this protein PPAR, an acronym for peroxisome proliferator activated receptor. Using var-

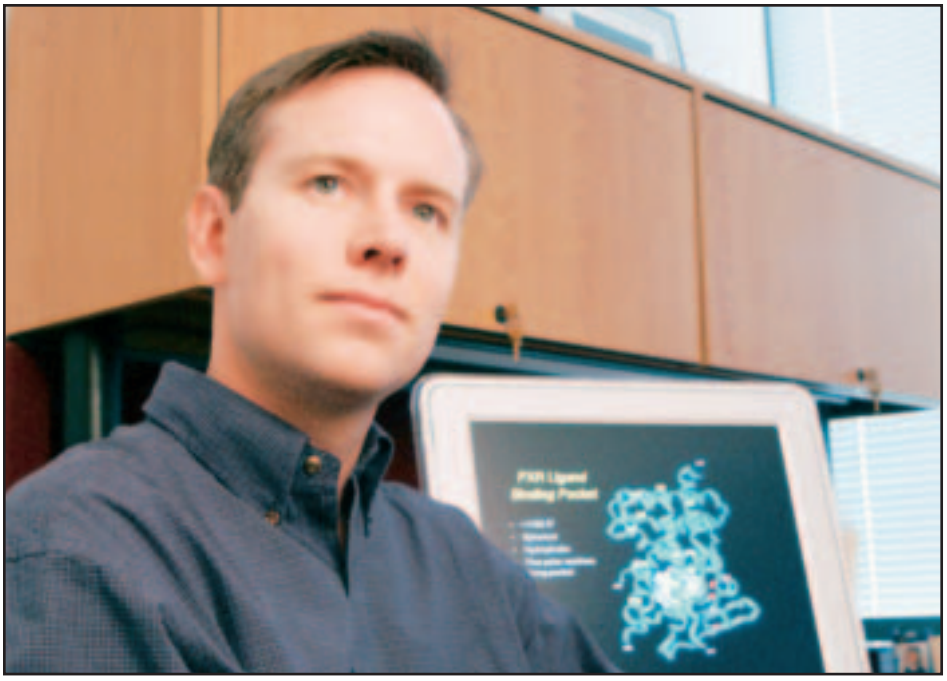

Figure 6. Molecular biologist Steven Kliewer's discovery that glitazones activate PPAR receptors led to the development of new anti-diabetes drugs. *Photo courtesy of University of Texas, Southwestern Medical Center.*

ious biochemical tools, the researchers showed that PPAR was activated by the same compounds that trigger the multiplication of peroxisomes in cells. In other words, the researchers had nabbed the elusive switch for peroxisome proliferators and reported their results in 1990. Since then, a family consisting of several different PPARs has been discovered in cells from humans and other species. All of these PPARs appear to play key roles in insulin resistance and the breakdown of fats.

Linking PPARs to Insulin Resistance

Steps on the path linking one of these receptors, called PPAR gamma, to type 2 diabetes were first taken in the 1970s by a Japanese pharmaceutical company called Takeda. Because intensive breeding efforts had successfully led to the development of type 2 diabetic mice, researchers at Takeda had a way to easily screen for anti-diabetic compounds. Takashi Soda and his colleagues tested a number of potential drugs on these diabetic animals to see if they lowered their blood sugar.

One drug, called ciglitazone, not only lowered blood sugar, but also caused a remarkable drop in insulin production and triglyceride levels in type 2 diabetic animals and increased their sensitivity to insulin. Unlike any other diabetic medication on the market at that time, ciglitazone seemed to counter the insulin resistance and excessive insulin production that underlies type 2 diabetes! The drug also tackled some aspects of the metabolic syndrome, such as high triglyceride levels and impaired glucose tolerance, in obese non-diabetic animals. These findings suggested the drug could not only be used to treat diabetes, but pre-diabetes as well, perhaps preventing or delaying the onset of diabetes and its complications.

The Japanese researchers published their findings in 1983. This prompted excitement in the pharmaceutical research community. Scientists at several drug companies directed their efforts toward tweaking various chemical portions of ciglitazone to create more potent anti-diabetes drugs, known as glitazones. But no one knew how these drugs worked.

That riddle was solved by molecular biologists at the Glaxo Research Institute in North Carolina, who were trying to figure out what causes fat cells to mature. Other scientists had shown that PPAR gamma was produced in large amounts by mature fat cells. In addition, researchers had reported that glitazones induced precursor fat cells (pre-adipocytes) to mature into fat cells. Putting two and two together, Steven Kliewer and his colleagues used some clever laboratory manipulations to show, in 1995, that glitazones activated PPAR gamma.

This discovery gave researchers a major new target for anti-diabetes drugs—compounds that could activate PPAR gamma. Two such drugs, rosiglitazone (Avandia) and pioglitazone (Actos), came on the market in

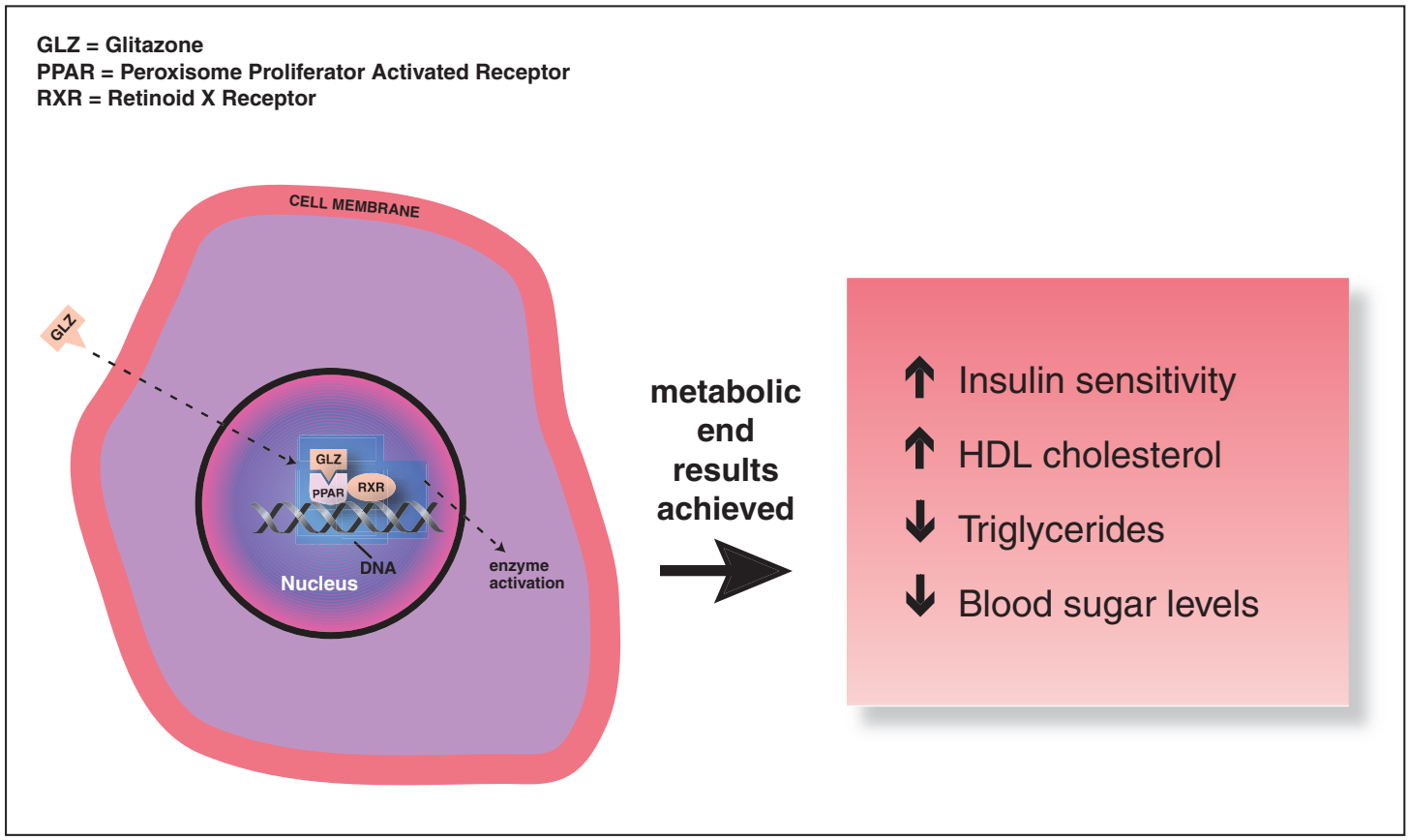

Figure 7. Glitazones, a new type of drug for type 2 diabetes, work by binding to receptors known as PPAR's, that are found in the cell nucleus. After binding to the glitazone, the PPAR hooks up with another receptor protein called RXR. The glitazone-PPAR-RXR complex then latches on to the DNA within the nucleus to quickly turn on a number of genes controlling a series of biochemical reactions. This results in the enhancement of a number of metabolic processes. The end result is greater insulin sensitivity and HDL cholesterol production, and lower triglyceride and blood sugar levels. *Designed by Corporate Press.*

1999. During this same year, researchers reported that people born with a genetic mutation that disables PPAR gamma all show the hallmarks of the metabolic syndrome—insulin resistance, diabetes, high blood pressure, low HDL cholesterol and high triglyceride levels. This finding further supported the notion that drugs that activate PPAR might be effective at preventing or treating diabetes. Indeed, one glitazone drug given to type 2 diabetes-prone rodents prevented them from developing the disorder. It also prevented the loss of insulin-producing cells in the pancreas that is normally seen in the late stages of type 2 diabetes in these animals (and in humans).

Researchers are currently testing Avandia and Actos to see if they can prevent type 2 diabetes or its complications in people. In the meantime, millions of people in this country take these drugs because they have already proven so effective as treatments for this condition. These drugs reduce type 2 diabetics' blood sugar levels by about a quarter. Actos prompts a nearly 20-percent drop in type 2 diabetics' triglyceride blood levels, while boosting HDL-cholesterol levels by 13 percent. Avandia causes a drop in insulin levels that may be beneficial over the long term.

New PPAR activators, including those that also activate PPAR alpha and/or delta, are expected to be even more effective than the glitazones currently available. Researchers are currently testing these drugs in animals and humans. Basic research has also uncovered other drug targets for type 2 diabetes, including molecules that carry glucose into cells and gut proteins that trigger insulin release. Drugs that boost the actions of these molecules are showing promise in initial tests as well.

Indeed, the benefits of basic research for type 2 diabetes have recently exploded. Within the last decade alone, 10 new drugs to treat or prevent the disorder have come on the market and many more are expected soon. This blossoming of effective anti-diabetes drugs offers a ray of hope to counter the gloomy forecast of a rapidly expanding diabetes epidemic.

The battle against diabetes isn't over yet. But the more we learn about how this disease operates, the more we increase our odds of waging a winning battle. Thanks to the curiosity, ingenuity, and determination of scientists from a number of fields, from nuclear physics and chemistry, to toxicology and cell biology, we now have powerful new weapons to combat an old debilitating disease.

Biographies

Margie Patlak writes about biomedical research and health from the Philadelphia region. She has written for *Discover, Glamour, Physician's Weekly, Consumer Reports on Health, The Washington Post,* the *Los Angeles Times,* the *Dallas Morning News* and numerous other publications. She also writes frequently for the National Institutes of Health and the National Academy of Sciences. This is her third article for the Breakthroughs in Bioscience series.

Barbara C. Hansen, Ph.D., is a professor of physiology and the director of the Obesity and Diabetes Research Center at the University of Maryland. Obesity, diabetes and aging are closely linked, with the combination, including dyslipidemia and hypertension sometimes referred to as the Metabolic Syndrome. Dr. Hansen's lab is concerned with the mechanisms that link these, and ultimately with discovery of the underlying causes and with the development of successful treatments to delay their onset and/or mitigate their consequences.

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