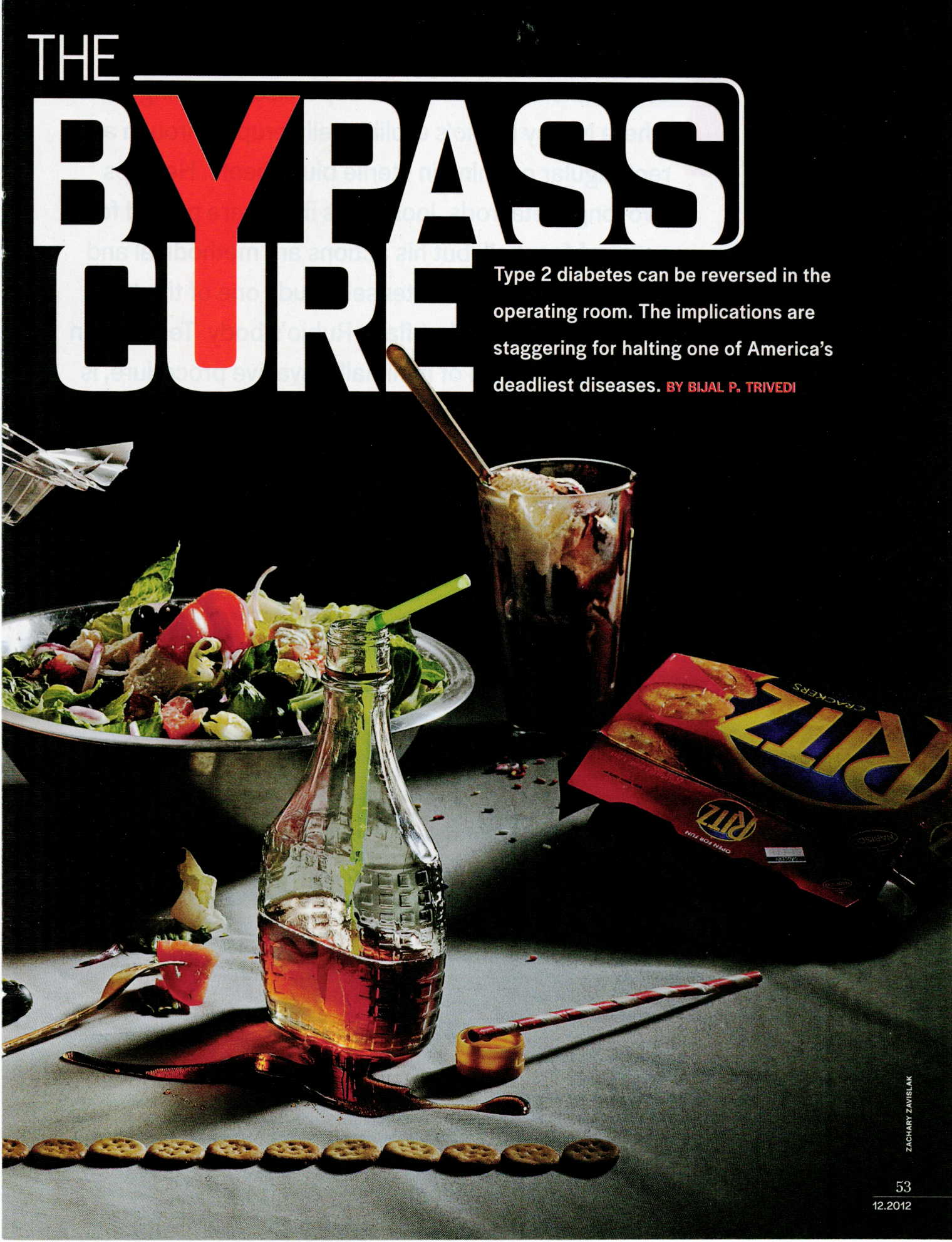
THE BYPASS CURE

Type 2 diabetes can be reversed in the operating room. The implications are staggering for halting one of America's deadliest diseases. BY BIJAL P. TRIVEDI



ZACHARY ZAVISLAK

Garbed in a blue surgical robe, mask, and cap, Dr. Julio Teixeira stands over a supersize operating table where Nancy Rubio's orblike belly erupts through a rectangular opening in sterile blue sheets. He grips two long metal rods, looking as if he were poised for a game of foosball, but his actions are methodical and gentle while his eyes intensely study one of the two large, flat screens that flank Rubio's body. Teixeira, an expert at this kind of minimally invasive procedure, is performing gastric bypass surgery, one of America's most common operations. But he also may be curing his patient of type 2 diabetes, literally overnight.

At just under five feet, Rubio is an obese 208 pounds, nearly double the 120- to 130-pound healthy weight for a person her height. The 52-year-old native of Ecuador developed type 2 diabetes after her children were born more than two decades ago. Her condition worsened as a fast-food diet packed on the pounds: Pizza and Chinese food were her favorites. Obesity increases type 2 diabetes risk, and often the two go hand in hand.

Over many years, Rubio's body broke down her calorie-packed diet into glucose, a sugar, which was absorbed into her blood. Her pancreas produced insulin that unlocked her cells so the glucose could enter and produce the energy she needed to function. If the body cannot produce insulin (as is the case in people with type 1 diabetes), or if the cells ignore or resist insulin (as is common in type 2 individuals), blood glucose levels rise, sparking the crippling complications of diabetes. In Rubio's case those complications included arthritic knee pain as her joints struggled with her heft, high blood pressure, elevated cholesterol, and high blood sugar.

With more than 25 million cases nationally, type 2 diabetes is America's leading cause of blindness in adults under age 75, kidney failure, and amputation. It also raises the risk of nerve damage, heart disease, and stroke. In 2007 diabetes treatment and indirect medical costs ran to $174 billion in the United States. As obesity spreads across this country and across the world, those costs are rapidly on the rise.

The best way to combat type 2 diabetes, doctors traditionally say, is through diet and exercise-induced weight loss, which sometimes remedies insulin resistance. But many patients never manage to sustain the changes for long, and improvements can take months or years, if they come at all. When lifestyle changes fail, patients must control their blood glucose with regular insulin injections or oral medications. The medical costs for an individual with diabetes are typically 2.3 times higher than for someone without the disease. The day before her operation, Rubio told me she had tried dieting but could not shed weight, even though she understood the consequences. "I was afraid diabetes would affect my feet and cause gangrene," she explained through a translator, her eyes welling with tears.

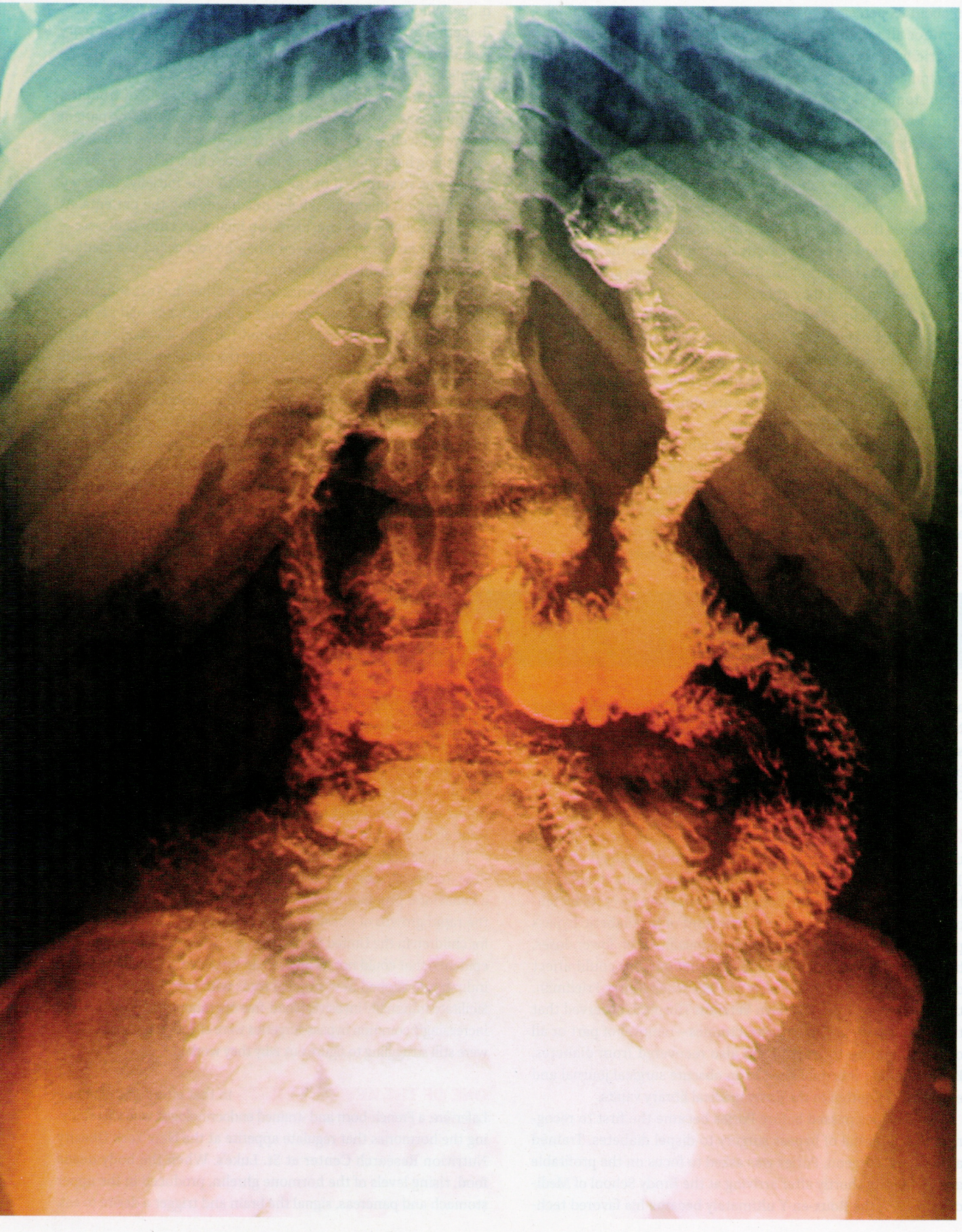
Desperate, Rubio opted for bypass surgery: a shortcut to lose her excess weight and, perhaps, to save her life. The Roux-en-Y gastric bypass—named for the 19th-century Swiss surgeon César Roux, who first performed surgery to reroute the small intestine—is known to be physically effective. The modern version of the Roux-en-Y (pronounced roo-en-why) involves reducing the stomach to a little pouch, to curb eating and appetite, and then connecting that pouch to a lower section of the intestine. By using less of the intestine, fewer nutrients are absorbed, and the patient loses weight.

The procedure will almost surely cause Rubio to shed weight rapidly. But now it is clear that the effects of gastric bypass can reach much deeper. That one, fairly routine surgery will probably also banish Rubio's diabetes.

In March of last year, the International Diabetes Federation endorsed bariatric surgery as a type 2 diabetes treatment for obese patients, citing studies indicating that it triggers remission

An X-ray depicts the upper gastrointestinal tract of an obese patient six months after gastric bypass surgery. The reduced size of the stomach makes this patient feel fuller sooner, resulting in consumption of less food.

ZEPHYR/SCIENCE PHOTO LIBRARY



in about 85 percent of patients. Bariatric surgery is the umbrella term for all weight-loss surgeries reserved for obese patients. Gastric bypass is a subset of these surgeries that first divides the stomach into a small and large pouch and then connects the small stomach pouch to the lower small intestine; Roux-en-Y is the most popular gastric bypass surgery in the group.

The federation's endorsement was an extraordinary validation of decades of research and medical experience showing that surgery to reduce food intake can alter the biochemistry of the entire body. It also marked the beginning of a major new assault on diabetes.

The more than 200,000 gastric bypasses performed in the United States each year can offer only limited help for the 25 million diabetics in this country alone. The challenge is even greater in the global context: The International Diabetes Federation estimates that by 2030, some 439 million people worldwide will have type 2 diabetes. Lack of insurance and patients' reluctance to undergo an operation also make bypass surgery an unlikely cure-all. But now that researchers are beginning to understand what Teixeira calls the "magic" of gastric bypass, they are aiming to find a chemical treatment that does the same thing.

"We can probably figure out exactly why bariatric surgery triggers remission and develop the medicine to stop diabetes," says Walter Pories, chief of surgery at East Carolina University's Brody School of Medicine, who first showed that the illness vanished after such operations. "Then we don't need surgery."

Some researchers have already pinpointed certain hormones and amino acids that are key players in type 2 diabetes. Today Nancy Rubio had to go into the operating room at St. Luke's–Roosevelt Hospital in New York City. Tomorrow people like her may be able to take a pill that sets them free from the double traumas of diabesity and insulin injections.

By 2030, 439 million will have type 2 diabetes. We can't operate on all of them.

PERHAPS THE BIGGEST SURPRISE about the bypass cure is that it is still so poorly understood by medical science. Teixeira can see firsthand that simply by replumbing the GI tract, he can also reprogram the body's hormones and reset its metabolism. Three days after surgery, one-third of his diabetic bypass patients leave the hospital needing no insulin, or on lower doses, before ever losing a pound. The fact that surgery could affect diabetes was first noted as early as 1955, when Murry Friedman, then a surgeon at the Brooklyn Veterans Hospital, observed that three of his patients given gastrectomies—removal of part or all of the stomach—to treat ulcers also recovered from diabetes. But his finding was published in an obscure surgical journal and essentially forgotten in the dusty medical library vaults.

Two decades passed before Pories became the first to recognize the potential of bypass surgery to dispel diabetes. Trained as a general surgeon, Pories was asked to focus on the profitable area of obesity shortly after arriving at the Brody School of Medicine in 1977; the Roux-en-Y ultimately became his favored technique. When a colleague asked him to try the surgery on an obese diabetic patient, he agreed reluctantly, noting that the surgery would be riskier because diabetic patients are usually more prone to infections and require greater insulin regulation.

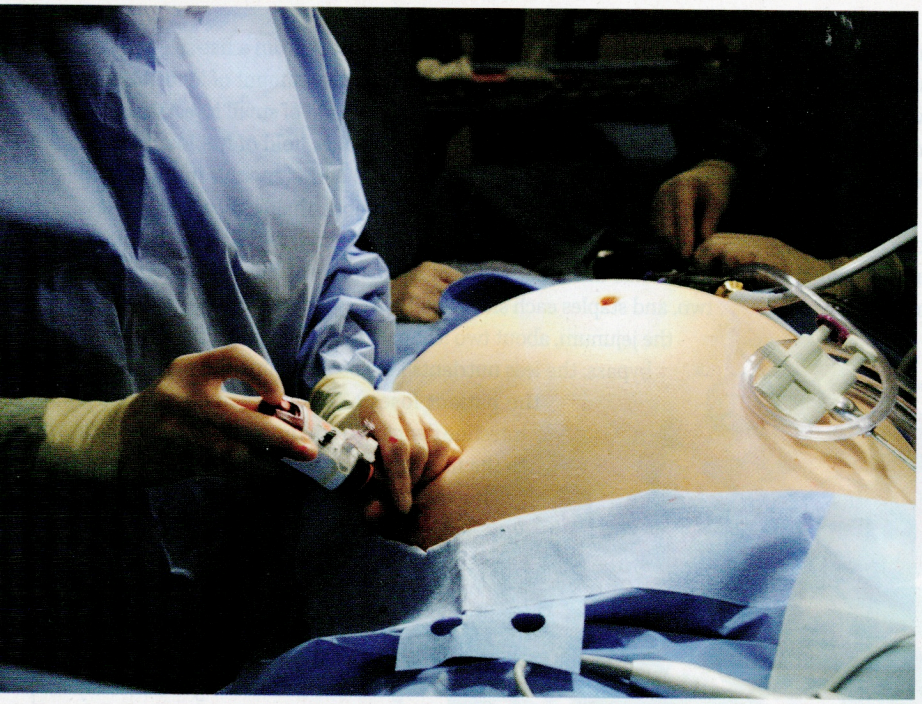
"After the surgery we were prepared for all sorts of troubles, but there was no evidence of diabetes," Pories recalls. The patient recovered well, and his diabetes seemed to have vanished. The same thing happened with the next three obese diabetic patients. Pories was so surprised by the change that he initially suspected his colleagues might have been misdiagnosing the patients. At the time diabetes was considered an incurable, chronic disease—it couldn't just disappear. Even when he rechecked the medical tests, Pories remained unconvinced.

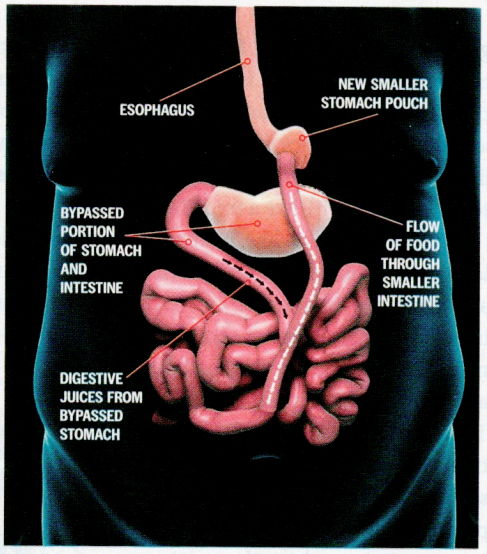
For their fifth patient, Pories and the other doctors sought out the most severe diabetic case they could find. She had sky-high blood sugar of 495 (normal is around 100) and was taking a high dose of 90 units of insulin daily. After the operation, the woman's blood sugar levels plummeted. "The day after surgery, she needed eight units of insulin, and on the sixth day only four. That was the last day she ever required any insulin at all," Pories says. "First we were astonished and then just delighted that, good heavens, this means that diabetes can be reversed." He recalls that it was "such a wild idea" that his group conducted several more surgeries over the next few years before publishing their results in 1982.

Even then there was not much reaction in the medical community. Thirty years ago bypass surgery was risky, involving a large, bloody incision and mechanical metal arms to pry apart the heavy, fatty abdominal walls and hold them in place while surgeons operated elbow-deep in the gut. Patients had long recovery times, and complications could be severe. Pories hunkered down, continuing to collect data and build his case. In 1995 he published a 14-year follow-up showing that bypass surgery proved to be a long-term solution for four out of five diabetic patients.

This time Pories's extraordinary findings began to attract notice. Researchers had come to recognize obesity as a disease rather than a behavioral problem. And by the first decade of the 21st century, the rapid growth of obesity—rates doubled for adults and tripled for children in the United States between 1980 and 2008—made it an epidemic that could not be ignored. In response, the medical device industry developed new surgical tools with extra-long handles to facilitate minimally invasive, blood-free operations on the obese. The increasingly common bypass surgeries were effective, but researchers were still struggling to figure out why they worked.

ONE OF THE KEY SCIENTISTS in that effort was Blandine Laferrère, a French-born and -trained endocrinologist who was studying the hormones that regulate appetite at the New York Obesity Nutrition Research Center at St. Luke's. When the body needs food, rising levels of the hormone ghrelin, produced in the upper stomach and pancreas, signal the brain and trigger a desire to eat.





Left: A laparoscopic surgeon places an instrument into the abdomen during a Roux-en-Y gastric bypass. Above: An illustration of the male abdomen and gastrointestinal tract after a Roux-en-Y operation.

At the end of a meal, specialized endocrine cells in the wall of the small intestine release other hormones (like cholecystokinin, glucagon-like peptide-1, and oxyntomodulin) that signal satiation. In obese individuals these signaling networks malfunctioned, Laferrère knew, leaving them perpetually hungry. When she saw how bypass surgery patients at St. Luke's lost weight—and their diabetes—after a single operation, she became intrigued.

"Endocrinologists didn't announce, 'Let's find out the role of the gut in type 2 diabetes,'" Laferrère says. "It just happened that the surgeons did this type of surgery for weight loss, and that turned out to have a spectacular effect on the remission of type 2 diabetes."

In studying the mechanism behind diabetes remission, Laferrère focused on incretins, a group of hormones that spur about half of the insulin produced during meals. "I read these fantastic papers from Europe from the mid-1970s and early 1980s," she says. Werner Creutzfeldt, a German doctor who studied gut hormones that regulated insulin, described an "incretin effect" in which partially digested food exits the stomach of healthy people and enters the small intestine, triggering incretin production. Incretin, in turn, causes the pancreas to crank out insulin, keeping blood sugar down to its proper level. But in diabetics the incretin effect is blunted, and insulin production is thus reduced.

Inspired by Creutzfeldt's research, Laferrère decided to measure incretin levels and insulin secretion after meals, and also before and after gastric bypass surgery. After studying just three diabetic bypass patients, she could see that the surgery was triggering dramatic shifts in hormone levels. Shrinking the stomach and rerouting the small intestine rebooted the incretin effect, boosting the body's insulin production within a month. At the same time, the symptoms of diabetes waned. "I was stunned," Laferrère says. "I had never seen such a magnitude of effect." Her finding made the cover of *Diabetes Care* in 2007.

Then, to determine if this change was caused just by weight loss, Laferrère paired a control group of patients with gastric bypass patients, matching for age, duration of diabetes, and ethnicity. The control group was placed on a diet aimed at having them lose as much weight as the bypass patients, enabling her to compare body chemistry meaningfully between the groups. After two months, all patients had dropped at least 22 pounds, and Laferrère began measuring the amount of incretin and insulin in their blood. To her surprise, neither incretin levels nor their influence rose in the dieters. The comparison showed that the bypass operation itself seemed to start the hormone networks: The surgery patients were receiving a metabolic bonus that diet-induced weight loss alone could not provide.

THE BONUS POWER OF BYPASS SURGERY was something Julio Teixeira had long suspected. Some 15 years ago, during a fellowship at New York Medical College, he observed morbidly obese patients undergo open bariatric surgery—an old-school Roux-en-Y, done with giant incisions and often yielding horrendous complications. When he finished his training in 1998, he developed a simplified, minimally invasive version of the Roux-en-Y. In 2001 he moved to Albert Einstein College of Medicine in New York and began teaching his methods to other surgeons, using the longer-handled tools that had been developed for performing surgeries on obese patients. For four years Teixeira fine-tuned his techniques and ran six-week boot camps where surgeons could learn his procedures.

"By 2005 we realized we were doing more than just obesity surgery; we were really manipulating the metabolism of these patients," Teixeira says. He noticed dramatic improvements in blood chemistry and in clinical conditions like diabetes, high cholesterol, and hypertension. "These patients, in a month, were off all their meds." Puzzled because the changes were much too rapid to result from weight loss, he decided to join Laferrère at St. Luke's seven years ago.

"There are over 200 hormones in the GI tract," Teixeira explains as we chat in his office at St. Luke's. All of those hormones are vying to control your eating behavior. Ghrelin drives the urge to eat. Stretch receptors in the stomach signal when to stop. This hardwired system worked well for our hunter-gatherer ancestors constantly strug-

FROM LEFT: DR. BARRY SLAVEN/GETTY IMAGES; GETTY IMAGES

gling to find enough food for survival. In the modern world—where cheap, high-calorie food is available all around—taste, smell, emotion, learning, memory, and food addiction tend to override our biological cues and entice us to eat even when there is no need. "We are living in a time of overabundance, and we are engineered to hold on to these calories. It's like a trap," Teixeira says.

Surgeon-scientists like Teixeira are seeking biological manipulations that will help set us free. His work focuses on changing the architecture of the stomach and rerouting the small intestine, which is an exceedingly complex organ—hardly a homogeneous, 23-foot pipe carrying food from the stomach to the large intestine, as was once believed. There are three sections of the small intestine, each lined with unique cells that secrete their own hormones and play distinct roles. If you chop out or bypass certain sections, then, particular hormones can be reduced or eliminated.

The first and shortest section of the small intestine, just under one foot long, is the duodenum, which connects directly to the stomach. The duodenum blends partially digested food with bile, a bitter yellow-green liquid made in the liver that helps digest fats. From there the food passes through the eight-foot midsection of the small intestine, the jejunum, where fingerlike projections absorb vital sugars, amino acids, vitamins, and small proteins. The final stretch of small intestine, the ileum, secretes incretins and absorbs more nutrients before emptying into the large intestine for elimination. By cutting and pasting these intestinal links into new configurations, Teixeira can profoundly reconfigure the body's chemistry.

Now in that operating room, guided by a video camera and a high-powered light, he stands over Nancy Rubio and performs the surgery through five "keyholes"—half-inch cuts that serve as neat, blood-free portals. Teixeira snips, staples, and stitches, maneuvering a pair of two-foot rods designed for obese patients whose girth keeps the surgeon more than an arm's length away. The intestine does not resemble the neat line drawings found in textbooks. It looks like a sloppy pile of pale pink sausage covered by yellow pudding. In a healthy individual, this fatty blanket is less than an eighth of an inch thick, lacy and almost transparent. Rubio's intestine is covered with an inch-thick deposit of fat that further complicates the operation.

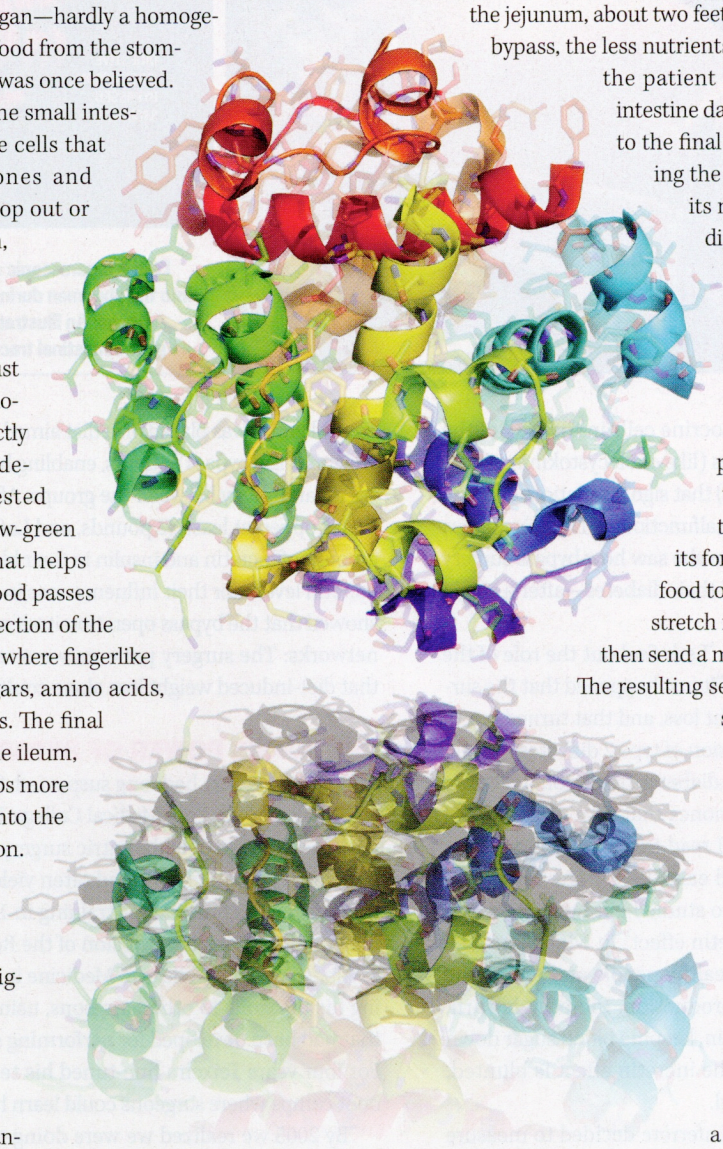


Illustration shows the 3-D structure of insulin, a hormone that must stay exquisitely regulated to keep obesity and disease at bay.

Teixeira plans to reduce Rubio's stomach from a fist-size bag to a thumb-size pouch, drastically limiting the amount of food she eats. He also intends to reconnect it to a section of small intestine much farther down the digestive tract. He takes hold of Rubio's stomach and studies an area about two inches wide, "enough space to hold four ounces of food"—the volume of about half a juice box, and less than one-tenth its normal capacity. He snips through the stomach, which has the consistency of a banana peel, dividing the organ in two, and staples each side shut. He sews the mini-stomach pouch to the jejunum, about two feet past the duodenum. (The longer the bypass, the less nutrients are absorbed, and the more weight the patient loses.) Teixeira then connects the intestine dangling from the large stomach pouch to the final stretch of the small intestine, creating the Y junction that lends the procedure its name. This allows the stomach's vital digestive juices to drain into the gut.

As Teixeira stitches up Rubio's new mini-stomach, he glances my way. "This is the fun part for me. I get to build something that actually gets to work tomorrow."

The surgery delivers a one-two punch against diabetes, the first structural and the second hormonal. Structurally, Rubio's stomach is one-tenth its former size. It takes only a few ounces of food to expand her pouch and stimulate the stretch receptors in the stomach wall, which then send a message to the brain signaling fullness. The resulting severe reduction in caloric intake will speed her weight loss.

How the second, hormonal punch achieves its effect is not so obvious. When food exits the pouch, it shoots straight into her midgut, continuing largely undigested until it reaches the Y junction and combines with the acidic brew of stomach juices. "The whole point is that undigested food goes directly into the small intestine," Teixeira explains, "where we think it is unleashing a whole bunch of new hormonal systems." This flood of hormones is thought to send diabetes into remission by bumping up insulin production, which then triggers the absorption of glucose from the bloodstream.

BYPASS SURGERY MAY BE SO GOOD at curing diabetes because malfunctions in the duodenum, the first part of the small intestine, cause the disease. That still-controversial hypothesis comes from another pioneer of diabetes surgery, Francesco Rubino, chief of gastrointestinal metabolic surgery at Weill Cornell Medical College in New York. When exposed to nutrients en route from the stomach,

LAGUNA DESIGN/GETTY IMAGES

chemical secretions from the duodenum block insulin production or cause insulin resistance, he believes. Either way, bypass surgery that circumvents the duodenum may prevent this malfunction.

Rubino bases his hypothesis on a series of experiments he did in 2004 on diabetic rats. He sewed an impermeable silicone sleeve to the lower edge of the rats' stomachs, blocking contact between food and the duodenum. Fencing off the duodenum in this way enabled the rats to consume sugary liquids without raising their blood sugar, eventually improving their symptoms of diabetes. When Rubino repeated the experiment with a perforated sleeve, the rats' diabetes recurred. Since then, a team at Massachusetts General Hospital Weight Center and Gastrointestinal Unit in Boston duplicated these results, showing that a gastric sleeve mimics the effects of gastric bypass, prompting weight loss and glucose control. Rubino's experiments inspired a human gastric sleeve that is now being tested in clinical trials in Chile and the Netherlands, with the Dutch team reporting successful weight loss and improved diabetes.

Another prominent hypothesis explaining why gastric bypass might cure diabetes focuses on the other end of the intestine: the ileum, a region rich with incretin cells that stimulate insulin production. The Roux-en-Y operation shortens the intestine, bringing food into the ileum much earlier in the digestive process. This change, Teixeira says, might be the reason bypass patients' incretin and insulin levels rise after surgery, stabilizing their blood glucose.

Understanding the underlying mechanism of bypass surgery is an urgent goal because the expense and complexity of the operation place it out of reach for the majority of obese diabetics. Identifying the chemicals and networks that catalyze remission in type 2 diabetes would be a far more transformative advance, since it would help lead pharmaceutical companies toward new anti-diabetes drugs. Research teams worldwide have already joined the hunt.

In this vein, Laferrère has tried treating her patients with standard medications that were designed to mimic the effect of incretins. But although diabetes drugs that increase incretin levels are looking helpful, "they are just not as powerful as surgery," she says. Complex gastric surgery involves many areas of the intestine that can have many possible hormonal consequences, she notes, so "it would be foolish to think that altering incretins is the only response after gastric bypass."

In 2010 Laferrère embarked on another avenue of inquiry after she met Christopher Newgard, a biochemist and director of the Sarah W. Stedman Nutrition and Metabolism Center at Duke University Medical Center. Newgard's research showed that blood levels of three essential branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine, found in foods like fish, eggs, and legumes—decreased dramatically after gastric bypass surgery. As early as 1969, Philip Felig, then chief of endocrinology at Yale School of Medicine, observed that obese people, diabetics, and those with insulin resistance all have higher-than-normal blood levels of BCAAs. Putting those two pieces of information together, Laferrère wondered whether these amino acids might work in tandem with the incretins to facilitate diabetes remission after bypass surgery.

So Laferrère sent Newgard blood samples from both dieters and gastric bypass patients. In line with the hypothesis, Newgard found that BCAA levels plummeted by 40 percent in bypass surgery patients but remained unchanged in dieters. Were declining amino acid levels causing diabetes remission, or was remission causing BCAA levels to decline? Newgard cannot yet be sure. To explore the issue, he plans to feed obese, insulin-resistant rats a diet lacking BCAAs to see whether decreasing dietary sources of these amino acids improves blood sugar levels. If it does, he will then study BCAA chemical networks in living cells to determine promising targets for new drugs.

In complementary work done in 2011, cardiologist Robert Gerszten of Massachusetts General Hospital showed that high levels of BCAAs, along with two other amino acids (tyrosine and phenylalanine), can predict a patient's chance of developing diabetes. "These BCAA levels drift up 12 years before you develop diabetes," Gerszten says, "even though insulin and glucose levels remain the same." But he, too, is unable to answer the question of which comes first, the chemical changes or the diabetes remission. "We don't know whether you're eating too many amino acids, you're metabolizing amino acids poorly, and that's giving you diabetes, or whether diabetes messes up amino metabolism in ways we just don't know yet." Even if high levels of these amino acids are not causing diabetes, evidence suggests they are useful biomarkers for predicting who is at risk, enabling such people to adjust their lifestyle before they get sick. One plausible lifestyle change might be switching to a diet low in protein—eating less meat, nuts, beans, and lentils, for example—the main sources of BCAAs.

Targeted diabetes drugs could exploit the best aspects of the bypass effect.

TWO DAYS AFTER HER SURGERY, Nancy Rubio is in her room at St. Luke's waiting to be discharged. Is she through with diabetes? "She's done," Teixeira answers confidently. Laferrère will not call bypass a cure; it can be a lifetime remission, or just a temporary improvement. "But it's still a phenomenal thing," she says. "We can't do that in medical treatment unless the patients lose 100 pounds on their own." She dreams of what will someday be possible with targeted drugs that exploit the best aspects of the gastric bypass effect.

Less than a month later, Rubio sits with me in a St. Luke's waiting area, 23 pounds lighter and grateful for what surgery can already achieve. "With the diabetes I was scared of everything. They talk about heart attacks and amputations, say that the organs get damaged, the liver, the kidneys. Now I'm more calm," she says. "And I don't get anxious because I want to eat. Inside I feel like a weight has been lifted." She still monitors her sugar three times daily, each time rejoicing at her normal glucose levels: "Now that I'm better, I've forgotten that I ever used insulin."

Bijal P. Trivedi is an award-winning freelance writer who covers medicine, genomics, health, and nutrition. She lives in Washington, D.C., with her family.