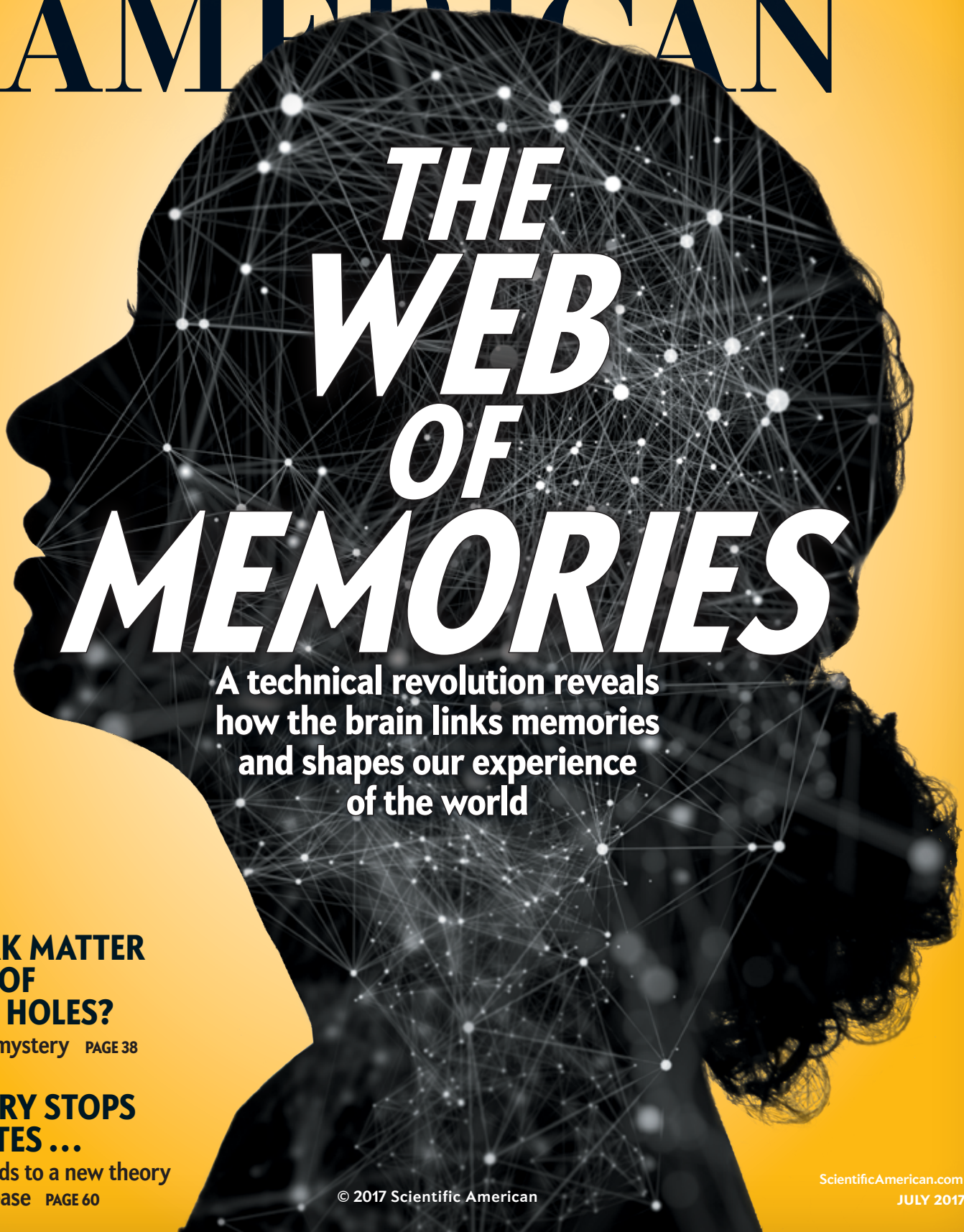


SCIENTIFIC AMERICAN



THE WEB OF MEMORIES

A technical revolution reveals how the brain links memories and shapes our experience of the world

PLUS

IS DARK MATTER MADE OF BLACK HOLES?

A cosmic mystery PAGE 38

SURGERY STOPS DIABETES ...

... and leads to a new theory of the disease PAGE 60



MEDICINE

OPERATION: DIABETES

Surgery that shortens intestines gets rid of the illness, and new evidence shows the gut—not simply insulin—may be responsible

By Francesco Rubino

Clinician and scientist **Francesco Rubino** is chair of the department of metabolic and bariatric surgery at King's College London and a surgeon at King's College Hospital. He is compensated as a member of scientific advisory boards for GI Dynamics and for Fractyl, companies developing intestinal diabetes treatments, and is a consultant to medical device makers Ethicon and Medtronic.



WHEN I BEGAN TRAINING AS A SURGEON ABOUT TWO DECADES AGO, I was eager to treat tumors, gallbladder stones, hernias and all other conditions within reach of a scalpel. Surgery seemed like a direct solution to some serious problems.

Type 2 diabetes was not one of them. Operations focus on single body parts, but doctors knew diabetes damaged multiple organs at the same time and involved a widespread failure to make efficient use of a blood glucose-regulating hormone, insulin. Clearly, this was not something that could be easily cut into or cut out.

But then one afternoon in the summer of 1999, my view of diabetes, and my career, took a radical turn.

I had just moved from Italy to New York City to start a fellowship in minimally invasive surgery at what is now called the Icahn School of Medicine at Mount Sinai. I was in the library trying to read about some technical aspects of an operation called biliopancreatic diversion when I stumbled across something odd. The operation is used on severely obese people. It makes them lose weight by shortening the route food takes through their intestines, bypassing nutrient-absorbing sections. Many of these patients had type 2 diabetes, which accompanies obesity. What struck me, however, was that as soon as one month after the surgery, these people had completely normal blood sugar levels. They had not yet lost much weight, they were eating without calorie or sugar restrictions, and they were not taking any diabetes medication. Still, most of them remained diabetes-free for years after surgery.

I was truly puzzled. How could an operation fix blood sugar problems in a disease that, all the textbooks said, is chronic, progressive and ultimately irreversible? Diabetes could be managed, but it was not supposed to go away.

Racking my brain for an explanation, I recalled that the small intestine produces hormones that stimulate the pancreas to

make extra insulin. Could the surgical change to the anatomy affect these hormones in some way that restored normal glucose metabolism? Or could the gut harbor other mechanisms of disease that surgery was able to correct? If so, surgery could be used to treat diabetes, and understanding how surgery produced this effect could also provide a clue to diabetes' elusive cause.

At that time, in the late 1990s, we were just realizing the world was in the midst of an epidemic of the disease that continues today. The most recent estimates by the International Diabetes Federation and World Health Organization suggest at least 415 million people around the globe have the disorder, and the number is predicted to climb to about 650 million by 2040. (Ninety percent of these people have type 2 disease; the rest have another form of the illness, type 1, when the pancreas simply does not make enough insulin.) Finding the cause and a cure could save millions of lives.

After a sleepless night, excited by the possibilities, I went in the morning to my supervising surgeon, Michel Gagner, with the idea. He thought I was on to something. Together we approached our medical school officials to ask them to run a clinical trial in humans and see if surgery could improve diabetes more than conventional therapies, even in people who are not severely obese. Our proposal was turned down, not just then but repeatedly in the ensuing months.

The rejection was disappointing, though perhaps not surprising. Diabetes has been treated for centuries by diet, tablets and shots. Because the cause was presumed to be some dysfunction in the insulin-making cells of the pancreas, as well as the way the body handles that hormone, slicing into people and

IN BRIEF

Forty-five medical organizations now recommend operations originally intended for weight loss as standard treatment options for type 2 diabetes.

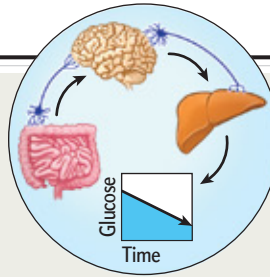
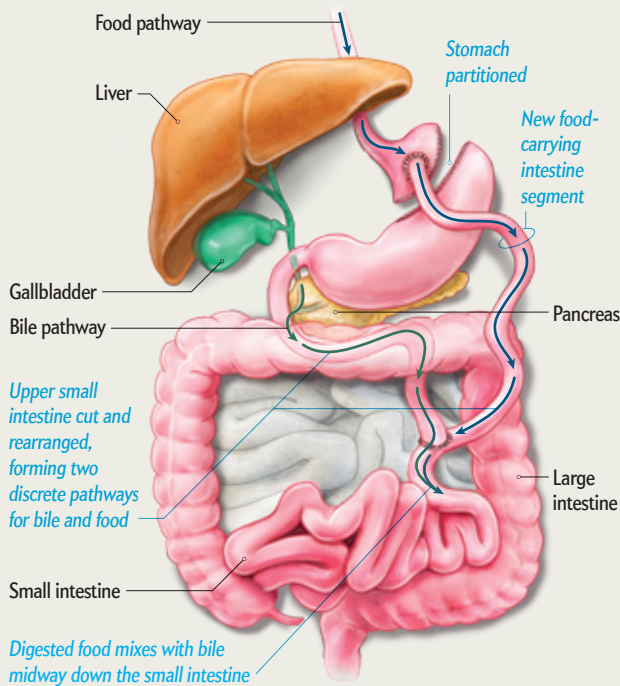
Numerous clinical trials show that surgery controls diabetes better, faster and longer than diet changes and drugs do.

Surgical success links diabetes to the intestines. Operating may work because it changes gut hormones, bile acids or gut bacteria or removes a disease cause.

Cutting Out Diabetes

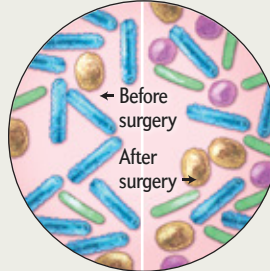
Weight-loss surgery, which changes the anatomy of the gastrointestinal tract, has turned out to be a powerful treatment for type 2 diabetes and is now recommended by more than 40 different medical societies. Researchers have begun to identify the mechanisms through which an operation can improve blood glucose control.

One common operation, called a Roux-en-Y gastric bypass, shortens the length of the upper intestine in which food mixes with digestive juices. Not only does this reduce absorbed calories, it limits the stimulation of intestinal cells by passing nutrients.



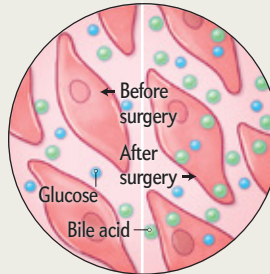
Neural Circuits

The intestines have branches of nerves, such as the vagus nerve, that send signals to and from the brain. These neural circuits alert the brain when the intestines detect passing nutrients. The brain then signals the liver to suppress glucose production. This feedback is enhanced after GI bypass operations.



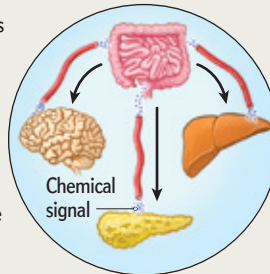
Gut Microbes

The gut microbial community influences a person's energy-harvesting efficiency. By altering the characteristics of intestinal contents, operations cause changes in the population of microbes. Such modifications can result in a higher metabolic rate and better glucose control.



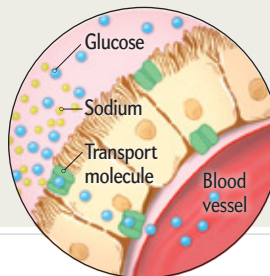
Bile Acids

Bile acids from the liver and gallbladder flow into the top of the small intestine. They also circulate in the blood like hormones, regulating cell metabolism. Surgery increases circulating bile acids and makes organs more sensitive to insulin.



Gut Hormones

The small intestine contains cells that release hormones into the bloodstream when nutrients stimulate them. These hormones can trigger activity in the liver, pancreas, and other organs that affects blood sugar levels. Gastric bypass operations shorten some intestinal segments, thus changing the amount of released hormones.



Glucose Transport

During digestion, glucose is taken from food particles in the intestine, moved through its lining and into the bloodstream. The process relies on special transport molecules that need sodium to work properly. In surgery a primary sodium source—bile—is rerouted away. That hinders transport molecules, lowering diabetic glucose spikes after a meal.

cutting out parts of intestines as a remedy must have seemed like heresy and a foolish risk.

Two decades later the heresy is starting to become conventional wisdom.

There are now dozens of animal studies and at least 12 randomized, controlled clinical trials involving hundreds of people that have explored surgery first developed for weight loss as a treatment for type 2 diabetes. They all show that reducing the surface of the gastrointestinal (GI) tract exerts more powerful effects on diabetes than any other existing therapy. And it is not simply the result of losing weight. In many patients, blood sugar levels go back to normal within

weeks, long before fat levels or pounds start to melt away. In general, about 50 percent of patients are diabetes-free after surgery, and some have stayed so for years. The remaining people demonstrate major improvement of blood sugar control and can drastically reduce their dependence on insulin or other medication.

The evidence is so strong that last year 45 medical societies endorsed GI surgery as a standard diabetes treatment option even for patients who are mildly obese. Furthermore, knowledge about the mechanisms by which surgery on the gut affects glucose metabolism is inspiring the development of nonsurgical approaches that target the small intestine.

GATHERING EVIDENCE

IN THE WEEKS AFTER my startling library discovery, as our proposals for testing surgery in humans with diabetes were being denied, I dug further into the medical literature for evidence that could bolster my case. I learned that physicians have been observing diabetes improvement after surgery on the GI tract for almost a century. In 1925 an article in the *Lancet* described the almost overnight disappearance of excess sugar in the urine, a symptom of diabetes, after one gastrointestinal operation to treat a peptic ulcer. After GI surgery became a treatment for severe obesity in the mid-1950s, similar observations became more common. During the 1980s and 1990s, many reports noted the antidiabetic effects of this kind of surgery, including a landmark study by surgeon Walter Pories of East Carolina University and his colleagues that involved more than 120 patients and was unequivocally entitled “Who Would Have Thought It? An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus.”

Despite such compelling observations, surgery was not considered as a serious therapy for diabetes itself. One major stumbling block was that to many physicians, it seemed more likely that postoperative weight loss—rather than the operation itself—caused the positive effects.

An impressive 89 percent of surgery patients with diabetes were not taking insulin five years after their operation.

Resolving that debate one way or another became important after Gagner and I were unable to start clinical studies. I turned to rats to investigate whether surgically altering the GI tract could influence glucose metabolism directly, independent of weight change. I had moved to the European Institute of Telesurgery in Strasbourg, France. There my co-workers and I took lean rats with type 2 diabetes and gave them a duodenal-jejunal bypass (DJB), an experimental operation designed to shorten the intestinal tract while maintaining the size of the stomach. (The idea is to avoid mechanical impediments to the intake of food.) Postsurgery, our rats showed improved glucose metabolism whether or not their food intake or body weight had changed.

Other investigators corroborated this finding using DJB and other procedures in different animal models. Then, in the early part of this century, they demonstrated it in people. During the past decade at least a dozen randomized clinical trials have been conducted, and all have shown similar results. In one of these studies, Geltrude Mingrone of the Catholic University of Rome, along with myself and other colleagues, showed that five years after surgery in 38 patients, more than 80 percent either were in complete remission from the disease or were able to maintain good control of blood sugar levels with small amounts of medication or with diet and exercise alone. Data from another

trial of 96 surgical patients conducted by Philip Schauer and his colleagues at the Cleveland Clinic showed that although about 45 percent needed insulin before their operation, an impressive 89 percent were not taking the drug five years after their operation. Surgery may also reduce such complications of the disease as heart attack, stroke and diabetes-related mortality more than standard treatments, according to the large Swedish Obese Subjects study.

The safety of these procedures compares well with that of other commonly performed operations, including gallbladder surgery or hysterectomy, which are generally considered low-risk interventions. Several economic analyses suggest that the cost of surgery (roughly \$20,000 to \$25,000 for a procedure in the U.S.) may be balanced within two to three years by reduced spending on diabetes medications and care.

THE GUT AS A SWEET SPOT

WHY DOES SURGERY WORK SO WELL? No one is sure yet, but the GI tract has emerged as a key player both in the normal glucose metabolism and in the dysfunctions associated with diabetes. There are at least five ways the gut exerts such influence: through hormones, bile acids, molecules that move glucose out of the intestines, microbes that live within the intestines, and neural circuits.

The lining of the GI tract holds specialized cells that respond to food nutrients and other stimuli by releasing hormones. These substances then stimulate insulin secretion from the pancreas or affect feelings of hunger and fullness. Changes in the anatomy of the GI tract through surgery curtail the time that food takes to travel over these cells, reducing contact and stimulation in some tract segments. That also means more food is available when it reaches subsequent segments. The overall result is increased levels of some hormones and decreased secretion of others.

Elegant studies in human patients by David Cummings of the University of Washington showed that gastric bypass operations suppress circulating levels of ghrelin, a hunger-inducing hormone that also appears to regulate how certain cells take up glucose. Carel W. le Roux, now at University College Dublin, and other researchers have demonstrated that an intestine-shortening operation called a Roux-en-Y gastric bypass and some similar procedures boost levels of other hormones known as incretins that increase insulin production.

Bile acids, another type of molecule that regulates how the body uses energy, are also affected by GI operations for weight loss. Familiar to many for their role in digesting food, bile acids also enter the bloodstream and signal cell receptors in various organs and tissues. The signals cause cells to ramp up their use of lipids and glucose. Gastric surgery can heighten circulating bile acid levels, which helps cells to get glucose from the blood. Studies also show that bile acids can prevent immune system cells called macrophages from accumulating in fat tissue. Fewer macrophages reduce inflammation and insulin resistance, which are hallmarks of obesity and type 2 diabetes.

Surgery can also affect another mechanism that contributes to diabetes: glucose transport molecules. During digestion, food particles are broken down within the intestines and glu-

cose is extracted. The glucose moves through the intestinal lining and into the bloodstream with the help of these transport molecules. The molecules need high concentrations of sodium to work properly. But in some types of gastric surgery, food-carrying segments of intestine are rerouted to bypass their primary sodium sources—bile and pancreatic digestive juices. Without sodium, the activity of glucose transport molecules is slowed down significantly, which, in turn, improves blood glucose control by reducing glucose spikes after a meal.

Microbes in the gut may also play a role. The GI tract hosts trillions of microorganisms. Certain species help the body extract energy from food and produce chemicals that reduce inflammation and insulin resistance. Because GI surgery alters the acidity of the gut as well as the amount and chemical composition of nutrients within the intestines, it can change the local microbe population. Lee Kaplan of Harvard Medical School and his colleagues showed this can affect metabolism. They started by giving a group of mice gastric bypass operations. Several weeks later the researchers transplanted gut bacteria populations from these mice into nonoperated mice whose native bacteria had been eradicated. This second group of mice was put on a high-fat diet. They gained little weight and improved their metabolism greatly when compared with rodents that received bacteria transplants from mice that did not get surgery.

Surgery's other well-known effect is on neural circuits that influence metabolism. One such circuit, for example, runs between the gut and the brain along a nerve called the vagus. It allows the small intestine to sense minute amounts of ingested nutrients and to inform the brain, which, in turn, suppresses glucose production in the liver and thereby lowers overall blood glucose levels. Experiments in rodents by Tony Lam of the University of Toronto and his colleagues have shown that GI bypass surgery increases activity in such nutrient-sensing mechanisms.

Finally, it is possible that surgery might remove some active insulin-blocking mechanism within the gut that could cause diabetes. The theory for this starts with the insulin-stimulating hormones, incretins. They need a counterweight. Left unchecked, incretins would flood the body with insulin after every meal. All people would suffer from low levels of blood sugar (hypoglycemia) after eating as the tide of insulin cleared glucose from the bloodstream. Because people do not routinely go into low-glucose comas after eating, something must block what incretins do. But if that countermechanism got extremely exaggerated, it would actually suppress the body's response to insulin—in other words, it could drive type 2 diabetes. Such substances, which I call “anti-incretins,” have not yet been identified conclusively, but suspects are starting to emerge.

Gut hormones such as somatostatin-28 and galanin all reduce insulin secretion in rodents. And there are more. In 2013 Mingrone and her co-workers harvested a swath of unidentified proteins from a segment of the GI tract in diabetic mice. When the proteins were injected into nondiabetic mice, they triggered severe insulin resistance. (The proteins did the same thing when injected into normal human muscle cells that were grown in the laboratory.) My belief is that gastric bypass surgery can reduce the amount or availability of these insulin-blocking anti-incretins and thus restore a normal metabolic balance to the body.

Whatever the exact mechanism, these and other observa-

tions point to a gastrointestinal origin of diabetes. Dysfunctional intestinal mechanisms, triggered by food, could also explain how global increases in fatty and carbohydrate-rich food in recent years, plus increases in overall food availability in many countries, could cause a disease epidemic.

ANTIDIABETIC DEVICES

BUT ALTHOUGH SURGERY may be a powerful remedy, it is never going to be a mass solution to a widespread problem. It requires hospitals, highly trained staff and a degree of risk that comes with using a scalpel on any patient. We need less invasive remedies. At least one may already be at hand: a small sleeve that can be inserted into the intestines through the throat and stomach.

The idea is to cover up the duodenum, the part of the GI tract just below the stomach. This is where bile and pancreatic juices first mix with partially digested food, altering the chemical characteristics of everything that continues down the intestines. Therefore, this one key spot can influence the GI tract downstream and most of the mechanisms of glucose control I have described.

In a set of experiments, my co-workers and I “walled off” the duodenum in diabetic rats by inserting a flexible silicone tube that let nutrients flow past this section. The food particles never touched duodenal lining cells or mixed with bile. Blood glucose control markedly improved. But then we poked holes in the tube, letting nutrients leak out. This modification sabotaged the antidiabetic effects.

Flexible plastic sleeves that shield the duodenum in humans already exist. They were developed to mimic the effects of a gastric bypass without surgery, and they have been approved for clinical use in Europe and South America. Patients who undergo the procedure have seen marked improvement in diabetic symptoms. There is also a newer approach, now in human trials, in which doctors slip a balloon-tipped device down the throat and into the duodenum. The balloon is then filled with hot water to burn away some of the cells that ordinarily react to nutrients. Early tests have shown promising results on type 2 diabetes, and further investigations are under way to confirm long-term durability of the effect.

This is not the first time in medicine that surgery has paved the way for other kinds of treatments. It is not even the first time with diabetes. In 1889 Oskar Minkowski created diabetes in dogs by removing the pancreas, and this work provided the fundamental clue that led Frederick Banting and Charles Best to discover insulin in 1921. Nearly a century later the success of operations highlights the GI tract as a target for other novel approaches to diabetes therapy, approaches that—I hope—will help patients as much or even more than injections of insulin. **SA**

MORE TO EXPLORE

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