

# Diabetes

## *The Evolution of a New Paradigm*

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We were not prepared for the observation that the gastric bypass could make diabetes go away. It's not the way discoveries are made. Usually laboratories get the good news first from test tubes, sometimes from animal experiments. Furthermore, entirely new findings on the big diseases, like diabetes or cancer, just don't come along very often.

The surprise came in 1982, in the early days of bariatric surgery, when our diabetic morbidly obese patients were relieved, yes, fully relieved, from their insulin requirements in a matter of days. We did not believe those initial glucose values, but our subsequent long-term studies confirmed the initial observation. By the time our series reached 608 patients with a 95% follow-up for 16 years, the Greenville version of the gastric bypass operation returned 83% of the patients with diabetes and 99% of those with impaired glucose tolerance to euglycemia.<sup>1</sup> Schauer and his group<sup>2</sup> recently corroborated our findings with an unusual congruence. In a study involving 1160 patients who underwent gastric bypass with laparoscopy, they also found that 83% of the 240 diabetic patients returned to euglycemia. They also confirmed our observation that the patients who did not respond fully were older and had the diabetes longer than the successful group, suggesting that early operation is indicated for the diabetic morbidly obese.

The operation produced more than just a return to normal glucose levels; it also improved the comorbidities and reduced the mortality from the disease. During the same time that we performed the gastric bypass on the 165 patients with diabetes, there were another 76 patients who were scheduled for surgery but who, at the last minute, cancelled their operations for personal reasons or because the insurance companies refused to pay for the procedures. The 2 cohorts did not vary significantly in gender, age, body mass index, or comorbidity. The mortality rates of the 2 groups, however, were sharply different. In contrast to the patients who underwent the gastric bypass and had a total mortality of 1% per year, the comparison group who did not have surgery died at the rate of 4.5% per year ( $P < 0.0001$ ).<sup>3</sup> In addition, the operation fully controlled the comorbidity of morbid obesity, including asthma, gastroesophageal reflux disease, Pickwickian Syndrome, pseudotumor cerebri, and stress incontinence, as well as reduce mortality from diabetes in the morbidly obese by >75%.

No other therapy has achieved such results. These studies reassure us that Type 2 diabetes mellitus is no longer a hopeless disease. These observations, however, are only the beginning. The real challenge is to exploit these advances to learn how we can combat type 2 diabetes mellitus, a disease that consumes 25 cents out of every health care dollar, more effectively.

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How does the gastric bypass achieve this remarkable remission? We have some clues. The decrease in food intake certainly plays a role. Dietary management with a reduction in calories, especially from carbohydrates, is a proven cornerstone of diabetic therapy. In addition, the vertical banded gastroplasty and gastric banding, 2 operations that depend only on the restriction of intake, can induce significant amelioration and, on some occasions, full remission of diabetes. However, excessive food intake cannot explain the etiology of diabetes nor can the reduction induced by the surgery explain the full remission. Not all obese patients are diabetic nor are all patients with diabetes obese.

What role does the gut play? And, of these roles, which is the more important—the decrease in food intake or the exclusion of food from part of the foregut? An ingenious answer to this puzzle is provided by the elegant experiments of Rubino and Marescaux<sup>4</sup> in this issue of the *Annals*. They performed a stomach-sparing version of the duodenal switch in 10- to 12-week Goto-Kakizaki rats, a spontaneous nonobese model of type 2 diabetes. Preoperative plasma glucose values of  $159 \pm 47$  mg/dL fell to  $96.3 \pm 10.1$  mg/dL ( $P < 0.01$ ). In addition, the operation strikingly improved glucose tolerance, inducing a greater than 40% reduction of the area under the blood glucose concentration curve ( $P < 0.001$ ). These effects were not seen in the sham-operated animals despite similar operative time, same postoperative food intake rates, and no significant difference in weight gain profile. In short, they induced full remission of diabetes by an intestinal bypass without a change in food intake or weight loss.

How might such a signaling system work? Imagine for a minute that there is an engineer managing the islets. What information would be needed to assure prompt delivery of insulin, cessation of secretion when the need is gone, and maintenance of inventory of the hormone? At the least, prompt notice that food is being ingested, the composition of the meal, quantity of the food, as well as the progress of the food through the gut. Plasma glucose levels alone would not suffice. These values have a lag time and they do not return to normal levels quickly after the organism stops eating.

It is far more likely that this phase of the control of the body's energy use depends on a complex series of sequential, integrated signals from a synchronized group of hormones that are secreted by the gut and capable of influencing insulin output and use. These include CKK, GIP, GLI-1, and ghrelin, among others. Additional fine tuning is probably

added from the fat stores, including leptin and adiponectin, from muscle, with additional modulation from the hypothalamus, a complex system of feedback for a complex task.

So how can we tie these observations into a new explanation of the pathophysiology of type 2 diabetes? Is the traditional teaching correct that insulin resistance and malfunction of the islets initiate the disease?

The new data, supported by the report in this issue of the *Annals*, supports the concept that diabetes is the result of overstimulation of the islets by one or several hormones produced in the foregut. Just as we have gastrinomas producing the Zollinger-Ellison syndrome, there may be another set of foregut endocrine cells that cause type 2 diabetes. The stimulation may be caused by a single abnormal hormone, a chord of hormones, or changed ratios between hormones. This impetus produces hyperinsulinemia which, in turn, is followed by insulin resistance. In this model, insulin resistance is not the cause but rather a defensive mechanism of the cell.

The trick now is to identify the errant signals.

Bariatric surgery is far more than just another surgical approach to obesity. It is a discipline that offers the first successful therapies for a broad variety of illnesses ranging from diabetes to pseudotumor cerebri. It opens entirely new areas for basic science inquiry. It will also force us to learn how to collect surgical data for large populations much more efficiently and accurately so that we can compare the various bariatric procedures, distinguish the indications for African-Americans and Caucasians because these 2 groups respond differently, and develop guidelines for approaches to pediatric obesity. Perhaps, most important, it will provoke us to pursue the cause of the obesity that has become a worldwide epidemic.

We have a lot of work to do.

## REFERENCES

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