Is Type 2 Diabetes an Operable Intestinal Disease?

A provocative yet reasonable hypothesis

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Type 2 diabetes, which accounts for 90–95% of all cases of diabetes, is a growing epidemic that places a severe burden on health care systems, especially in developing countries. Because of both the scale of the problem and the current epidemic growth of diabetes, it is a priority to find new approaches to better understand and treat this disease. Gastrointestinal surgery may provide new opportunities in the fight against diabetes. Conventional gastrointestinal operations for morbid obesity have been shown to dramatically improve type 2 diabetes, resulting in normal blood glucose and glycosylated hemoglobin levels, with discontinuation of all diabetes-related medications. Return to euglycemia and normal insulin levels are observed within days after surgery, suggesting that weight loss alone cannot entirely explain why surgery improves diabetes. Recent experimental studies point toward the rearrangement of gastrointestinal anatomy as a primary mediator of the surgical control of diabetes, suggesting a role of the small bowel in the pathophysiology of the disease. This article presents available evidence in support of the hypothesis that type 2 diabetes may be an operable disease characterized by a component of intestinal dysfunction.

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With an estimated over 300 million affected individuals by 2025, the lifetime risk of developing type 2 diabetes will approximate 20% (1). Because of the scale of the problem and the current epidemic growth, it is a priority to find new approaches to better understand and treat type 2 diabetes.

Unfortunately, the etiology of this condition is still elusive and conventional therapeutic modalities cannot achieve a cure. Furthermore, if medical therapy is suspended, invariably, plasma glucose rises and the disease progresses. In fact, type 2 diabetes is usually considered a relentless and progressive disease. This knowledge is now being challenged by a growing body of evidence that remission of diabetes, that is, long-term restoration of normal glycemia and glycated hemoglobin levels without medications, can often be achieved after bariatric surgery (2–5). Return to euglycemia and normal insulin levels are observed within days after surgery (5), suggesting that weight loss alone cannot entirely explain why surgery improves diabetes. Recent experimental studies point toward the rearrangement of gastrointestinal anatomy as a primary mediator of surgical control of diabetes (6). Although the exact molecular explanation remains to be elucidated, these findings suggest the possibility that gastrointestinal bypass operations may tackle dysfunctional intestinal mechanisms responsible for abnormalities of glucose homeostasis. This hypothesis represents a new paradigm, which characterizes type 2 diabetes as an intestinal disease, potentially amenable to surgical treatment. This article analyzes the available evidence in support of such a hypothesis.

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Abbreviations: BPD, bilio-pancreatic diversion; DJB, duodeno-jejunal bypass; GIP, gastric inhibitory peptide; GLP, glucagon-like peptide; RYGB, Roux-en-Y gastric bypass.

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TYPE 2 DIABETES: IS IT AN INTESTINAL DISEASE? — The rapid resolution of diabetes after Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) and experimental studies in rodents suggest that the control of diabetes after gastrointestinal bypass operations is a direct consequence of the rearrangement of gastrointestinal anatomy and not only the result of decreased caloric intake and weight loss. This result further supports the knowledge that the gastrointestinal tract plays an important role in energy homeostasis, consistent with the evidence that many gut hormones are involved in the regulation of glucose homeostasis.

Therefore, it is reasonable to assume that significant anatomical rearrangements of the gastrointestinal tract may cause changes in energy and glucose homeostasis, which eventually influences diabetes. However, it would be important to understand whether this occurs as the effect of changes that improve glucose homeostasis per se or as the result of reversing abnormalities of glucose metabolism. The latter hypothesis implies that the gastrointestinal tract may harbor critical mechanisms for diabetes pathophysiology.

It is possible that different anatomical changes in gastrointestinal anatomy may result in distinct effects on glucose homeostasis. Ileal interposition, an operation that consists of the interposition of an isolated segment of ileum into the jejunum, increases glucagon-like peptide (GLP)-1 and peptide YY (PYY) levels in rodents (20), possibly because of the early stimulation of the distal small bowel with relatively undigested nutrients (21). The rise of GLP-1 and peptide YY may improve insulin secretion and possibly action. De Paula and coworkers recently reported early outcomes of ileal interposition in humans (22), suggesting that the operation could improve diabetes. Long-term data, however, are not yet available at the time of this writing.

Although many suggested that RYGB may control diabetes in a similar way as ileal interposition, that is, by increasing GLP-1 levels, the more complex anatomy

of the RYGB suggest different or at least additional mechanisms. Likening RYGB to ileal interposition is probably inaccurate; in fact, unlike RYGB, ileal interposition preserves gastro-duodenal continuity, en-route with the transit of food. On the other hand, the length of bypassed bowel in a standard proximal RYGB is such that nutrients empty into the mid- or distal jejunum, not in the ileum, as in ileal interposition.

Our research sought to specifically investigate the mechanisms of action of the gastrointestinal bypass procedures, using duodeno-jejunal bypass (DJB) as a model of RYGB. Two hypotheses have been proposed to explain which part of the typical anatomical rearrangement of RYGB (Fig. 1) is essential for the effect on diabetes. The "hypothesis of the distal bowel" holds that diabetes control results from the expedited delivery of nutrient chyme to the distal intestine, enhancing a physiologic signal that improves glucose metabolism (23,24). Potential candidate mediators of this effect are GLP-1 and/or other distal gut peptides. An alternative hypothesis is that the exclusion of the duodenum and proximal jejunum from the transit of nutrients may prevent secretion of a putative signal that promotes insulin resistance and type 2 diabetes ("hypothesis of the proximal intestine") (25,26). Although no obvious candidate molecules have been identified to date, this hypothesis implies a direct involvement of the proximal small intestine in the etiology of insulin resistance.

We recently performed a study that supports the "proximal" hypothesis as a dominant mechanism in improving glucose homeostasis after RYGB (27). We found that whereas DJB (gastro-jejunostomy + duodenal exclusion as in RYGB) greatly improves diabetes in GK rats, performing an equivalent shortcut for ingested nutrients to the hindgut, without excluding nutrient flow through the proximal intestine (via a simple gastro-jejunostomy), does not improve diabetes in the same animal model (Fig. 2). In addition, diabetic abnormalities of glucose tolerance return in DJB-treated animals when nutrient flow through the proximal intestine is surgically reestablished via the normal gastro-duodenal route, despite preserving the gastro-jejunostomy. Similarly, in animals that originally underwent a simple gastro-jejunostomy without benefits, diabetes is greatly improved by a re-operation in which the proximal intestine is excluded from nutrient flow, but the gastro-jejunostomy is left intact. These findings demonstrate that isolating a segment of proximal intestine from nutrient flow is important in mediating the improvement of glucose tolerance after gastrointestinal bypass procedures and support the hypothesis that a putative factor originating in the proximal small bowel may impair insulin sensitivity in diabetic patients.

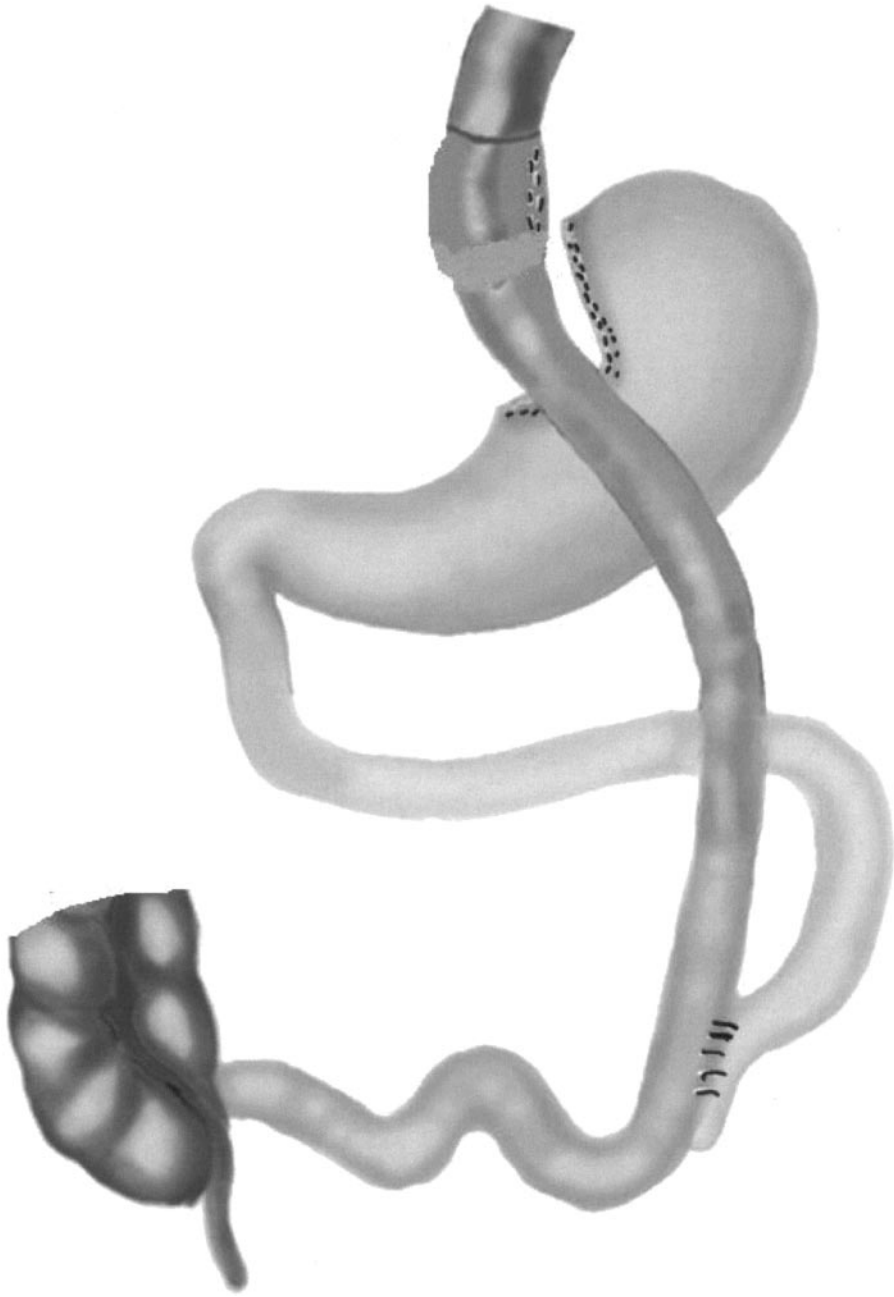

Figure 1—*Roux-en-Y gastric bypass.*

Other observations give further support to this hypothesis. In fact, if gastrointestinal bypass procedures worked only by enhancing a mechanism and/or signal with positive influence on insulin sensitivity and/or secretion (i.e., GLP-1, reduced glucose absorption, weight loss, etc.), one should expect that gastrointestinal bypass surgery should always improve glucose homeostasis, whether the operation is performed in diabetic or in otherwise healthy individuals. In contrast with this expectation, we observed that when DJB is performed in nondiabetic animals (Wistar rats) glucose tolerance is worse than that of matched sham-operated controls, in striking contrast with the marked improvement seen in di-

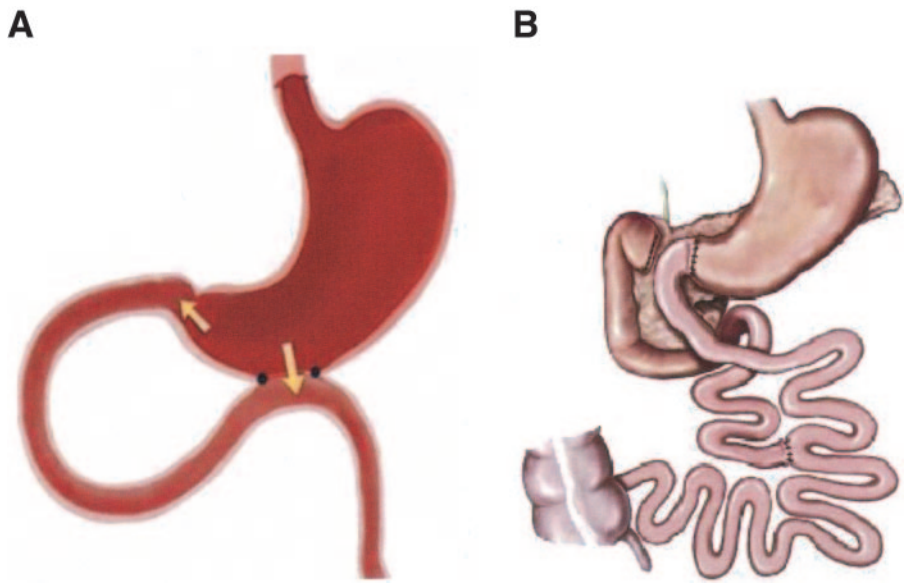

Figure 2—*Enhancing delivery of nutrients to the hindgut without excluding nutrient flow through the proximal intestine (via a simple gastro-jejunostomy [*A*]) does not improve diabetes diabetic GK animals. The DJB* (B)*, which creates similar shortcuts of nutrients as in gastro-jejunostomy, but also includes the exclusion of the proximal intestine from the flow of nutrients, improves glucose tolerance and fasting glycemia in diabetic GK rats. This experiments shows that the exclusion of the duodenum is critical for the effect on diabetes.*

abetic GK rats after DJB (27). These data are consistent with the results of clinical investigations showing impairment of glucose tolerance in nondiabetic humans who have undergone surgical exclusion of the duodenum (i.e., for the treatment of peptic ulcer or gastric cancer) (28).

In summary, preventing duodenal passage of nutrients by gastrointestinal bypass operations improves glucose tolerance only in diabetic patients, whereas it is detrimental for glucose homeostasis when performed in normal subjects. These findings are consistent with the possibility that the surgical bypass of the proximal small intestine reverses a putative intestinal mechanism characteristic of diabetic patients, but not of normal individuals. Accordingly, type 2 diabetes might be characterized by a component of duodenal-jejunal dysfunction.

The "anti-incretin" theory

To explain how duodenal exclusion improves diabetes and the possible contribution of the proximal small bowel to the pathophysiology of this disease, we developed the "anti-incretin" theory (5,26,27). The current view of the so-called "enteroinsular axis" is entirely based on the concept of incretins. Known incretins include gastric inhibitory peptide (GIP) and GLP-1, whose actions on β-cells largely overlap. Incretin actions include enhancement of glucose-stimulated insulin secretion, β-cell growth (anti-apoptotic action of incretins), and improved insulin action (29–31). Thus, the incretin system promotes actions that may eventually lead to hypoglycemia, a condition that could be lethal if not timely treated.

Therefore, it is reasonable to postulate the existence of a counterregulatory mechanism stimulated by the same passage of nutrients. Such an "anti-incretin system" would have opposite actions to those of incretins, that is, decreased insulin secretion, reduced insulin action (or resistance to insulin), and reduced β-cell growth. In concert, these actions would prevent incretin-induced hypoglycemia. While a balanced coordinated production of incretins and anti-incretin(s) is necessary to maintain normal glucose excursions, a shift toward excessive production of "anti-incretin" would cause insulin resistance, diminished insulin secretion, and β-cell depletion—in other words, type 2 diabetes (Fig. 3). Likewise, an insufficient production of "anti-incretin(s)" (i.e., after surgeries that prevent passage of nutrients in proximal segments of the small bowel) may cause instability in the system and not efficiently balance the effects of incretins, leading to hyperinsulinemia, hypoglycemia, and β-cell proliferation. Thus, while an excess production of anti-incretin may be involved in the pathophysiology of type 2 diabetes, defective anti-incretin production after gastrointestinal bypass operations may also explain some rare complications of RYGB such as nesidioblastosis (16), or the postprandial hypoglycemia and dumping syndrome that can follow gastrectomy with duodenal exclusion.

With current knowledge, there are no obvious candidates for the "anti-incretin" role. The anti-incretin may indeed be an unknown hormone or a known factor for which functions are not yet completely understood. It is of interest, however, that the action of GIP and the expression of its receptor are defective in diabetic patients (31,32). Furthermore, the early phase of insulin secretion after glucose stimulation, which is regulated by GIP (33), is characteristically blunted in type 2 diabetes (34). These abnormalities are consistent with the existence of a proximal anti-incretin factor interfering with the GIP system (proximal incretin). The reversal of the alteration of the early phase of insulin secretion after RYGB (35) suggests a possible recovery of normal GIP functions after the operation. Further research in this direction is necessary. Focusing attention on the duodenum and proximal small bowel represents a fascinating research opportunity that could hopefully open new avenues for the search of the cause of diabetes.

TYPE 2 DIABETES: IS IT AN OPERABLE DISEASE?

Background data

A meta-analysis involving 136 studies for a total of 22,094 patients showed that type 2 diabetes was completely resolved in 76.8% and resolved or improved in 86.0% of patients who had undergone bariatric surgery (7). The same study showed that complete remission of diabetes occurs in 48% of patients after laparoscopic gastric banding, 84% after RYGB, and >95% after BPD (7). The remission of diabetes after RYGB and BPD is also durable, and recurrence of diabetes >10 years after surgery is rare (8). Intriguingly, whereas remission of diabetes after laparoscopic gastric banding typically occurs over several weeks to months (9), consistent with the consequences of weight loss, RYGB and BPD can cause complete remission of diabetes within days to weeks after surgery, long before substantial weight loss has occurred (4,5).

What makes bariatric surgery so effective in controlling diabetes? A simple,

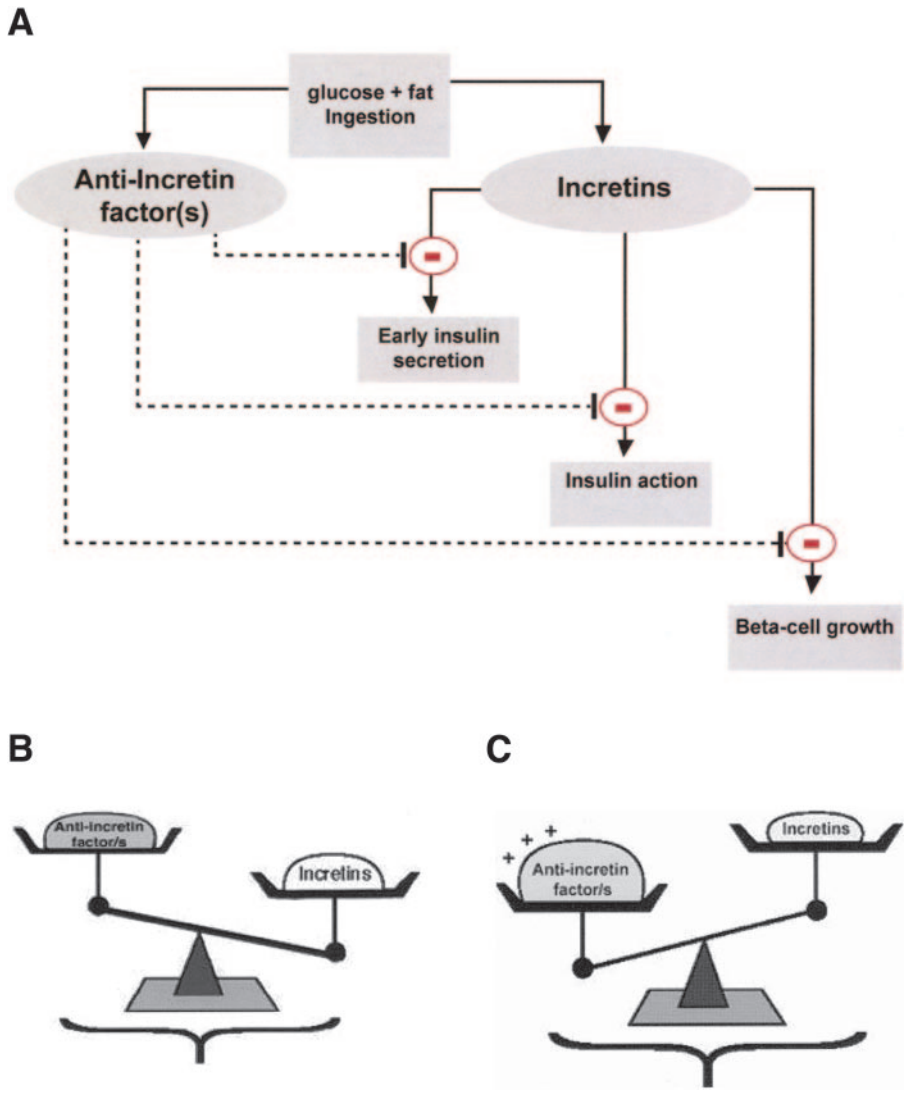

Figure 3—*The anti-incretin hypothesis to explain the alterations of glucose metabolism in type 2 diabetes.* A*: The passage of nutrients through the proximal small intestine may trigger, in addition to the known incretin response, a concomitant counterregulatory signal ("anti-incretin factor") aimed to prevent hypoglycemia. This signal would exert opposite actions compared with incretins (decreased insulin secretion, decreased β-cell proliferation, and inhibition of insulin action). While a balanced and coordinated production of incretins and anti-incretin(s) is necessary to maintain normal glucose excursions, an insufficient production of "anti-incretin(s)"* (B) *may not efficiently balance the effects of incretins, leading to hyperinsulinemia, hypoglycemia, and β-cell proliferation (nesidioblastosis). In contrast* (C)*, a shift toward excessive production of anti-incretin would cause insulin resistance, diminished insulin secretion, and β-cell depletion, all features of type 2 diabetes. The anti-incretin hypothesis is a possible unifying mechanism to explain the origin of type 2 diabetes as well as some of the typical effects of gastrointestinal bypass procedures on glucose homeostasis, including diabetes resolution or its complications, such as hyperinsulinemic postprandial hypoglycemia and nesidioblastosis.*

quite logical explanation would be that by inducing massive weight loss in patients who are morbidly obese, bariatric surgery just eliminates the condition (obesity) that puts the patient at risk for diabetes. According to this explanation, diabetes should remit only when this type of surgery is performed in obese individuals and as a consequence of substantial weight loss.

To investigate whether or not diabetes control is the result of treating obesity and inducing weight loss, we performed an experimental study in Goto-Kakizaki (GK) rats, a spontaneous nonobese model of type 2 diabetes (6). This study showed that a stomach-preserving DJB (Fig. 4) dramatically improves fasting glycemia and glucose tolerance, independent of weight loss and/or decreased caloric intake. This study was the first experimental demonstration that the anti-diabetic effect of gastrointestinal bypass surgery is not unique to obese individuals and that weight loss/decreased caloric intake cannot entirely explain why surgery improves type 2 diabetes.

Preliminary clinical studies seem to confirm these findings also in humans. Cohen et al. (10) performed DJB to treat diabetes in two patients who were non–morbidly obese. In spite of the fact that the operation did not cause significant changes in BMI and body weight, these patients had normal plasma glucose and A1C levels. Remission of diabetes in non–morbidly obese patients has also been reported after RYGB and BPD (11–13). Earlier reports also documented diabetes improvement and/or remission after gastrectomy and partial gastric resections (14), which, like DJB and RYGB, are characterized by a variable degree of bypass of the proximal small bowel.

All together, these studies show that gastrointestinal bypass operations can achieve control of diabetes by mechanisms that are independent of the treatment of obesity and surgically induced weight loss. Hence, type 2 diabetes is, per se, potentially amenable to surgical treatment.

FROM BARIATRIC TO "DIABETES SURGERY"

— Using surgery explicitly to treat diabetes is a revolutionary concept and represents a disruption to current therapeutic paradigms. For this reason, many physicians might be reluctant to accept the idea of a surgical treatment of type 2 diabetes. Scientific data, however, suggest that a surgical approach to diabetes is more than a heretical suggestion.

The meta-analysis of Buchwald et al. (7) showed that RYGB results in an average 50–60% long-term excess weight loss. Hence, RYGB, and likewise other bariatric operations, rarely return patients to an entirely normal condition. Losing 50–60% of the excess weight indeed means that, in many patients, the remaining 40–50% of the excess weight is not eliminated by the operation. Technically, many patients remain overweight or frankly obese and fail to achieve "complete remission" of obesity. This is in striking contrast with the evidence that >80% of patients who undergo RYGB and >90% of those who undergo BPD experience a complete sustained remission of type 2 diabetes. Therefore, if con-

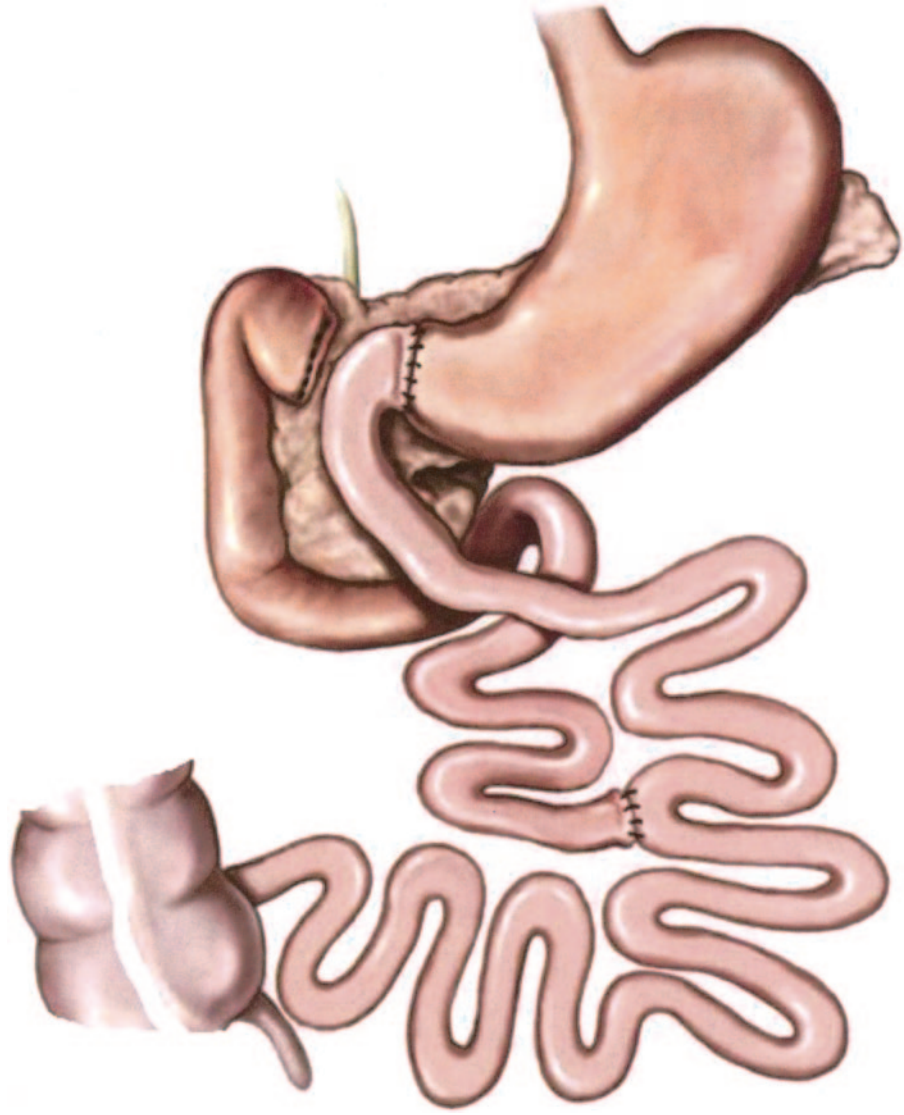

Figure 4—*Duodeno-jejunal bypass.*

sidered only in terms of ability to induce disease remission, RYGB (and BPD) seem to be even more effective in diabetes than in obesity itself. This paradox suggests that the definition of "bariatric operations" might be inadequate to define surgical procedures that result in more than just weight loss. It would perhaps be more appropriate to consider the definition of "diabetes surgery" for these operations when they are performed in patients with type 2 diabetes, regardless of their degree of obesity. In fact, inducing diabetes remission is certainly a more important benefit than weight loss per se, even in a morbidly obese patient. Increasing evidence also shows that RYGB and BPD are capable of inducing significant changes in gut hormones and regulatory factors of energy homeostasis (15), supporting the notion that these operations are indeed truly metabolic procedures.

TIME FOR CLINICAL TRIALS OF DIABETES SURGERY

— Because surgery is a therapeutic modality with potential mortality and morbidity, the choice of a surgical option to treat type 2 diabetes should be based on a careful evaluation of the risk-to-benefit ratio. There are indeed several potential risks in performing diabetes surgery. Micronutrient deficiency and potential long-term complications of gastrointestinal bypass procedures (i.e., postprandial hypoglycemia, nesidioblastosis, etc.) (16) may occur and must be considered when balancing benefits with risks.

While considerable data are available about the long-term efficacy and morbidity of surgery in morbidly obese patients, admittedly, the experience in patients with less severe obesity is still modest. Clinical trials are therefore necessary to evaluate whether or not surgery may be preferable to other treatment options in this patient population.

However, if an indiscriminate use of surgery to treat diabetes is potentially harmful and should be carefully prevented, on the other hand, ignoring the opportunity offered by surgery is not an option either, at a time when a medical cure is not available and diabetes grows at epidemic rates. To provide a timely answer to both these concerns, the Diabetes Surgery Summit was organized in Rome, Italy, on 29–31 March 2007 under the auspices of more than 20 major international scientific societies. This event was the first multidisciplinary consensus conference on gastrointestinal surgery to treat type 2 diabetes and included a voting panel of over 50 international authorities in the field of diabetes and bariatric surgery.

A consensus statement with all the recommendations from the Diabetes Surgery Summit will be published later this year, with guidelines for both clinical practice and research. After discussing available evidence from animal studies and early clinical series, experts at Rome's Diabetes Surgery Summit recognized that clinical trials are not only justified at this time, but they actually represent a priority for medical research.

OPEN QUESTIONS FOR FUTURE CLINICAL RESEARCH

— In recent years, it has been frequently proposed that the standard BMI cutoff of 35 kg/m^2 (17,18) for considering bariatric surgery should be lowered to 30 kg/m^2 in patients with diabetes. Although this strategy may be a reasonable approach, it reflects a tendency to consider surgical treatment of type 2 diabetes just as a mere extension of bariatric surgery. This approach is misleading, if not inaccurate. Although initially it will be necessary to use limited BMI ranges when including patients in future clinical trials of diabetes surgery, the aim of such studies should be to find better criteria for patient selection and for changing the focus from BMI to diabetes-specific parameters.

In fact, BMI alone is not ideal to accurately evaluate the risk-to-benefit ratio in diabetic patients. There is presently no scientific evidence that any clear BMI cut-

off can distinguish between patients in whom surgery can resolve diabetes and patients in whom surgery would be ineffective for this purpose. Studies in rodents have shown that DJB improves diabetes both in obese (Zucker *fa/fa* rats) (19) and lean (GK rats) (6) type 2 diabetic animals, consistent with several clinical observations of diabetes remission when RYGB or BPD are performed in moderately obese (11,12) or even lean patients (13). On the other hand, other parameters may better define both the risk from diabetes and the diabetes-related outcomes of surgery. For instance, conventional bariatric operations do not seem to induce similar control of glycemia in patients with type 1 diabetes; therefore, it may be more useful to use parameters that can clearly distinguish type 2 from type 1 diabetes (i.e., antibodies, C-peptide levels, etc.) rather than BMI levels.

Furthermore, large clinical series have consistently and independently shown that the relatively few patients whose diabetes does not completely resolve after RYGB have typically suffered from the disease for a long time (usually >8–10 years) and required more insulin to maintain glycemic control before surgery (4,5). These findings suggest that end-stage β-cell failure, characteristic of longstanding type 2 diabetes, may render these patients' condition irreversible. Accordingly, a surgical approach should be offered early rather than late in the natural course of the disease. Hence, evaluating pancreatic insulin reserve could be more appropriate than any BMI cutoff to predict effective control of diabetes after surgery.

Physicians could be convinced to consider surgical treatment of diabetes as possible only in patients with BMI in the range of severe obesity (>35 kg/m^2), based on the common concern that performing "bariatric" operations in less severely obese patients may result in excessive body weight loss. However, evidence exists from both animal studies and clinical series that gastrointestinal bypass procedures do not cause significant body weight loss when performed in subjects with normal body weight and BMI. For instance, while DJB reduces weight gain in obese Zucker rats (19), it does not affect weight gain profiles in both normal (Wistar) (19) and diabetic (GK) lean animals (6). Consistent with these animal studies, recent experience in humans show that DJB can achieve adequate diabetes control in overweight patients (BMI 29–30 kg/m^2) without causing significant weight loss (10). BPD also has been reported to resolve type 2 diabetes in lean humans without causing weight loss (13).

Another question for future clinical trials is which of the various conventional bariatric operations is best suited to treat diabetes. It would require randomized clinical studies to properly answer this question; however, it seems clear that some procedures have greater potential efficacy (RYGB, BPD) than others. Future research may also help devise new surgical operations that could retain the benefit on diabetes without the potential drawbacks of current bariatric procedures. For instance, techniques such as DJB, which preserves an intact stomach and involves no excluded gastric remnant, may be a good option, especially in countries with a high incidence of gastric cancer, where leaving behind an excluded stomach (such as after standard RYGB) may be a source of concern. New approaches and devices (i.e., transgastric and endoluminal techniques) also hold potential interest for the treatment of diabetes and could further minimize the invasiveness of interventional diabetes therapy.

CONCLUSIONS — Conventional gastrointestinal operations for morbid obesity have been shown to dramatically improve type 2 diabetes, resulting in normal blood glucose and glycosylated hemoglobin levels, with discontinuation of all diabetes-related medications. Often, return to euglycemia and normal insulin levels are observed within days after surgery, suggesting that weight loss alone cannot entirely explain why surgery improves diabetes. Recent experimental studies point toward the rearrangement of gastrointestinal anatomy as a primary mediator of the surgical control of diabetes. These findings raise the possibility that putative mechanisms from the proximal small bowel may be implicated in the pathophysiology of type 2 diabetes. All together, these data suggest a novel revolutionary concept about an old disease: type 2 diabetes may be an operable intestinal illness.

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