The prevalence of diabetes has increased worldwide mainly as a result of the obesity epidemic. In 2007, 23.6 million people in the United States were affected by diabetes, with type 2 diabetes comprising the majority of cases. Another 57 million people had prediabetes, characterized by impaired fasting glucose and glucose intolerance. Worldwide estimates of diabetes are as high as 171 million. The current treatment of type 2 diabetes is aimed at increasing insulin secretion, decreasing glucose absorption from the small intestine or improving insulin sensitivity. Tight glycemic control can reduce some of the complications of diabetes; however, this goal is often unattainable partly because of poor patient compliance, inadequate health care delivery, and the high cost of therapy. Several studies have shown that lifestyle intervention can slow the progression of prediabetes to diabetes, but whether this strategy can be implemented under everyday living conditions is uncertain. Given the burgeoning twin epidemics of obesity and diabetes, recent attention has been focused on gastrointestinal surgery as an alternative to behavioral and pharmacologic strategies for managing diabetes.

Bariatric surgery is undoubtedly the most effective treatment for severe obesity. In addition, studies have shown dramatic improvements in type 2 diabetes and dyslipidemia in severely obese patients after gastric banding, roux-en-Y gastric bypass and biliopancreatic diversion surgeries. Procedures involving bypass of the upper intestine produce greater normalization of glucose that precedes weight loss. It has been postulated that the entry of nutrients into the distal small intestine after roux-en-Y or other intestinal bypass procedures elicits a neuroendocrine response that reduces glucose and lipid levels, inhibits feeding, and reduces weight and fat. This so-called “ileal break” mechanism is thought to be mediated, at least partly, by hormones secreted by L-cells, such as glucagon-like peptide (GLP)-1 and peptide YY (PYY). In this issue of GASTROENTEROLOGY, Cummings et al have performed a comprehensive analysis of ileal interposition (IT) surgery in a rat model that closely mimics the “metabolic syndrome” in humans. The University of California at Davis Type 2 Diabetes Mellitus (UCD-T2DM) rat was created by crossing obese insulin-resistant Sprague-Dawley rats with Zucker diabetic fatty rats, which have a pancreatic β-cell defect. In longitudinal studies, UCD-T2DM rats developed obesity, insulin resistance, and hyperinsulinemia, followed by reduction of insulin levels and progressive hyperglycemia, indicative of β-cell failure. Untreated diabetic UCD-T2DM rats develop glycosuria, polyuria, hyperphagia, and weight loss. Cummings et al performed IT surgery as previously described. A midline incision was made under general anesthesia, and 10 cm of ileum segment located 5–10 cm proximal from the ileocecal valve was transected (Figure 1). The remaining ends of the distal ileum were anastomosed. Next, the upper small intestine was transected 5–10 cm distal to the ligament of Treitz, and the ileal segment was then interposed with its vasculature and innervation intact (Figure 1). Sham surgery was performed by transecting similar locations as IT surgery and reanastomosing the intestinal segments to their original sites. IT surgery delayed the onset of diabetes compared with sham surgery. After 1 year, 38% of IT rats developed diabetes compared with 78% of sham rats. Food intake was not different between IT and sham groups after 5 months, but the sham group became hyperphagic as diabetes progressed. Body weight was similar in IT and sham rats until 6 months, when the sham group lost weight as a result of diabetes. However, at the prediabetic stage (2 months), body fat, adipocyte size, and ectopic accumulation of triglycerides in liver and muscle were reduced in IT rats. Glucose tolerance was improved in IT rats, and this was associated with enhanced insulin secretion, and elevation of plasma GLP17–36. Plasma PYY and expression of PYY in the intestine were increased in response to an oral lipid load in IT rats. Plasma bile acids, pancreatic β-cell mass, and insulin content were increased after 2 months in IT rats. In contrast, gastric inhibitory peptide, ghrelin, and adiponectin levels were not altered substantially by IT surgery. Together, these results demonstrate that IT surgery improves glucose and lipid metabolism, and slows the development of type 2 diabetes. The studies would have benefitted from insulin clamp and tracer techniques to evaluate the effects of IT surgery on insulin sensitivity in liver, muscle, and fat. The mechanisms underlying how IT surgery affects lipid metabolism in adipose, muscle, and liver were not determined. Furthermore, the authors proposed that GLP-1, PYY, and bile acids may be involved in the metabolic effects of IT surgery, but did not carry out experiments to prove this hypothesis.
Despite these shortcomings, Cummings et al.\(^8\) deserve credit for showing for the first time that IT surgery can improve glucose and lipid metabolism, and delay the progression of prediabetes to diabetes. Apparently, the metabolic effects of IT surgery are not dependent on changes in food intake or weight. Similar to previous studies, IT surgery in UCD-T2DM rats increased plasma GLP-1 levels.\(^8,11,12\) GLP1 is encoded by the preproglucagon gene in intestinal L-cells, and is released in response to nutrients in the upper intestine.\(^13\) GLP-1 inhibits intestinal motility and potentiates insulin secretion.\(^13\) GLP-1 may preserve pancreatic β-cells by promoting differentiation and preventing death.\(^13\) GLP-1 may also enhance lipolysis.\(^13\) Cummings et al.\(^8\) did not determine if GLP-1 is a mediator of the antidiabetic effect of IT surgery. In another study, IT and duodenojenunal exclusion surgery increased plasma GLP-1 and decreased glucose levels in Goto-Kakizaki rats.\(^14\) This effect was reversed by GLP-1 receptor antagonism, indicating a causal role for GLP-1 in the antidiabetic effect of IT plus duodenojenunal surgery.\(^14\) PYY is expressed in L-cells and secreted in response to nutrients. PYY\(_{3-36}\) binds to Y2 receptors, increases fluid and electrolyte absorption from the ileum, inhibits secretions from the stomach and pancreas, and delays gallbladder and gastric emptying.\(^15\) PYY\(_{3-36}\) has been reported to decrease food intake when injected peripherally, but this finding is controversial.\(^15\) Nonetheless, the finding by Cummings et al that IT surgery increased PYY expression and plasma levels is consistent with other reports.\(^7,11\) IT surgery also increased plasma bile acid levels, likely through intestinal absorption.\(^8\) Elevated plasma bile acids have been associated with improvement of glucose and lipid metabolism.\(^16\)

Recent studies have evaluated the combination of IT surgery and sleeve gastrectomy in diabetic patients.\(^17,18\) Ten patients with poorly controlled diabetes underwent laparoscopic sleeve gastrectomy and IT surgery.\(^17\) During a follow-up period of 2–16 months, 7 patients had diabetes remission, and the remaining 3 showed significantly decreased requirement of oral hypoglycemic agents. All the patients experienced weight loss and remission of hypertension, microalbuminuria, and insulin resistance.\(^17\) In a prospective study, 38 nonobese diabetic patients were randomized to 2 versions of laparoscopic IT and sleeve gastrectomy surgery.\(^18\) After 2 years, both groups attained lower hemoglobin A1c, cholesterol and triglyceride levels, and the body mass index was also reduced. These studies demonstrate the feasibility, safety, and efficacy of sleeve gastrectomy and IT surgery on diabetes and other metabolic outcomes. Unlike IT surgery alone, it is likely that weight loss contributes significantly to the metabolic outcome of IT and sleeve gastrectomy surgery.\(^17,18\)

There is strong evidence that IT surgery and other intestinal bypass procedures are effective in the treatment of diabetes.\(^7\) The paper by Cummings et al.\(^8\) also raises the intriguing possibility that IT surgery may be a preventative strategy for delaying the progression of prediabetes to diabetes in patients with metabolic syndrome. However, questions remain about how IT surgery could be applied to the millions of people worldwide with metabolic syn-
drome. Although delaying the onset of diabetes with IT surgery may decrease the risk of end-organ complications, what specific criteria will be used for selecting at-risk prediabetic patients? Furthermore, it is noteworthy that IT surgery delayed but did not fully prevent the development of diabetes in rats. Likewise, there is no guarantee that the procedure will be effective in the long term in prediabetic patients. Thus, the risk-benefit of IT surgery has to be considered. Another provocative finding is the increase in GLP-1 after IT surgery. If GLP-1 is shown in later studies to play a major role in the metabolic actions of IT surgery, can pharmacologic treatment, such as GLP-1 agonists, mimic the delayed onset of diabetes conferred by IT surgery? In that case, why not use GLP-1 agonists rather than IT surgery for diabetes prevention? The gastrointestinal tract produces several bioactive peptides besides those measured in this study. The discovery of peptides and novel molecules affected by IT surgery and other intestinal bypass procedures may reveal potential targets for prevention and treatment of diabetes.

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Conflicts of interest
The authors declare no conflicts of interest.