seemed to be well tolerated and proved superior to TPN and bowel rest with regard to cost and complications (JPEN J Parenter Enteral Nutr 1997;21:14–20). A follow-up study from Greece reported very similar findings in patients with severe necrotizing pancreatitis (Br J Surg 1997;84:1665–1669). Over the past 10 years, there have been several clinical trials that reported the same conclusion, and the results were included in a recent meta-analysis by Marik and Zaluga (BMJ 2004;328:1407–1412).

The present article by Eatoch et al is of considerable interest as, on first reading, it appears to show that food-induced stimulation of the pancreas does not exacerbate acute pancreatitis. The natural extrapolation would then be to feed patients in the simplest way possible. Although this surprising conclusion may prove to be valid, there is insufficient evidence in the present study to draw this conclusion. Controlled studies in humans have shown that the stimulatory effects of feeding into the stomach are no different to feeding in the proximal jejunum, and that feeding needs to be delivered at least 40 cm past the ligament of Trietz to avoid pancreatic stimulation (Eur J Clin Invest 1999;29:1053–1059). Furthermore, there is some doubt whether "jejunal" feeding really was jejunal because the first half of the patients randomized to jejunal feeding were fed with *nasogastric* feeding tubes pulled through the pylorus by endoscopy and "clipped into the jejunal mucosa to hold position." We are not told what kind of endoscope was used, but if it was a standard instrument, the tube was most likely clipped to duodenal mucosa. The authors' suggestion that the injured pancreas cannot respond to food stimulation is refuted by recent studies that have shown the following: (1) trypsin continues to be synthesized, even in necrotizing pancreatitis (Am J Physiol Gastrointest Liver Physiol 2005;289:181–187); (2) the diminished luminal secretion can be stimulated by duodenal feeding (Gastroenterology 2003;124:A84); and (3) exacerbation has been demonstrated during proximal enteral feeding (JPEN J Parenter Enteral Nutr 1997;21:14–20, Clin Gastroenterol Hepatol 2003;1: 315–321). The importance of these concerns is that both forms of feeding may have been equally proinflammatory, raising the question of whether the patients would have been better off with no feeding. This point was acknowledged by the authors and was highlighted by Dr Koretz's Selected Summary (Gastroenterology 2005;128:798–799) on Marick and Zaluga's meta-analysis of the published clinical trials on this subject.

The other concern we have about nasogastric feeding is technical. There is no argument that nasogastric feeding will work in patients with mild disease (although such patients can eat and should not be tube-fed), but our experience with patients with severe disease complicated by pancreatic necrosis, fluid collections, and multiple organ failure is that nasogastric feeding is ineffective and potentially dangerous. Generally, such patients have poor gastric emptying secondary to duodenal compression. Consequently, nasogastric feeding will increase gastric residual volumes, increase aspiration risk, and result in ineffective feeding because gastric decompression will be mandatory. Unfortunately, no comment was made in the present study whether nasogastric decompression was needed in any patient, including the one with duodenal obstruction. We are left, therefore, with the similar situation of TPN feeding in the 70s where the nutritional intervention caused more complications than nutritional benefit. We suspect, therefore, that the outcome of the controlled trial of interventional feeding versus no feeding suggested by Koretz in his Selected Summary (Gastroenterology 2005;128:798–799) would undoubtedly show that no feeding is better under these conditions.

In summary, the Glasgow group needs to be congratulated for sharing with us their extensive experience with stimulatory feeding in acute pancreatitis. However, before "pancreatic rest" is taken out of the management portfolio, stimulatory enteral feeding has to be compared to nonstimulatory feeding in the subgroup of patients who most need nutritional support and who have all the mortalities, namely those with complicated severe disease. Although TPN is the best way of ensuring "pancreatic rest," its complications unfortunately outweigh its benefits. Alternatively, proximal feeding could be compared to distal feeding where the feeding tube is advanced as far down the jejunum as possible. As the number of eligible patients is relatively small, this question can only be answered in a rigorous multicenter study.

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ENDOSCOPIC BUBBLE: CAN IT BUST THE OBESITY BUBBLE?

Mathus-Vliegen EM, Tytgat GN (Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands). Intragastric balloon for treatment-resistant obesity: safety, tolerance, and efficacy of 1-year balloon treatment followed by a 1-year balloon-free follow-up. Gastrointest Endosc 2005;61:19–27.

Intragastric balloons for management of obesity arrived with much fanfare in the 1980s. Marred by prohibitive complications, the balloon concept was crucified before it could take off (Gastroenterology 1988;95:213–215) only to be resurrected again using a novel intragastric balloon manufactured by Bioenterics (BioEnterics Corp, Carpinteria, CA)—a smooth, seamless balloon made of inert, nontoxic silicone elastomer that is resistant to gastric acid, with a radiopaque self-sealing valve that allows adjustment of the volume in a range of 400–800 mL.

This randomized, 2-year, double-blind trial consisted of three phases: (1) balloon or sham treatment of adults with treatment-resistant obesity (3 months); (2) balloon treatment for additional 9 months in whom a preset weight-loss goal was achieved in the sham and balloon treatment groups; and (3) follow-up for an additional year after removal of the balloon at 1 year. Forty-three treatment-resistant patients (mean body mass index [BMI]: 43.3 kg/m^2) were enrolled. Five patients did not meet the preset weight-loss goal (nonresponse, 11.6%). Three patients did not tolerate the balloon (7.0%), with endoscopy demonstrating severe esophagitis. Three other patients developed esophagitis that was related to use of nonsteroidal anti-inflammatory drugs albeit prohibited (2 patients) or substantial weight loss with balloon treatment (1 patient). In intention-to-treat analysis, sham- and balloon-treated groups had a similar mean weight loss of 11.2 kg (9.0%) and 12.9 kg (10.4%), respectively, during the first 3 months. During months 3 to 6, patients who had sham therapy in months 0–3 lost 8.8 kg (7.9%) during the first 3 months of balloon treatment. In contrast, patients in the balloon-treatment group lost 3.9 kg (3.5%) during months 3–6 (their second balloon treatment period). The overall weight loss was

20 kg (16.1%) and 16.7 kg (13.4%) after 6 months in the sham/balloon- and in the balloon/balloon-treated groups (not significant), respectively. After 1 year of balloon treatment, a mean weight loss of 21.3 kg (17.1%) was achieved in all patients, of which 12.6 kg (9.9%) was maintained at the end of the second balloon-free year; 47% of patients sustained a greater than 10% weight loss, with considerably reduced co-morbidity. In 33 patients who completed the study per protocol, weight loss was 25.6 kg (20.5%) after 1 year and 14.6 kg (11.4%) after 2 years; 55% maintained a weight loss of greater than 10%.

Interventional complications occurred in 1.6% (2/128) and balloon deflations in 2.3% (3/128). The authors concluded that the intragastric balloon seemed to be safe for patients with treatment-resistant obesity but was not a treatment option in a fifth of patients. Although an independent benefit of balloon treatment beyond diet, exercise, and behavioral therapy could not be demonstrated in the first 3 months, balloon treatment for 1 year resulted in substantial weight loss, the greater part of which was maintained during the balloon-free second year.

Comment. Obesity is currently defined as a BMI of 30 kg/m^2 or greater, and a BMI between 25 and 29.9 kg/m^2 is termed overweight. Two thirds of U.S. adults are overweight or obese and about 5% are extremely obese (BMI of 40 kg/m^2 or greater), and the numbers swelled by 5% from 2000 to 2001. Each year, an estimated 300,000 U.S. adults die of obesity-related causes. About 9.4% of U.S. health care expenditure is for management of obesity and complications such as diabetes, cardiovascular disease, stroke, liver disease, and sleep apnea, which are directly linked to the obesity epidemic (JAMA 1999;282:1530–1538, 2001;286:1195–1200, 2002;288:1723–1727, 2003;289:76–79, Med Sci Sports Exerc 1999;31:663–667).

Based on the extensive meta-analysis of medical and surgical treatments of obesity (Ann Intern Med 2005;142:532–546, 2005; 142:547–559], the U.S. Preventive Services Task Force has recently provided the following guidelines to clinicians on the management of obesity (BMI $\geq$30 kg/m^2): (1) Counsel all obese patients on lifestyle and behavioral modifications such as appropriate diet and exercise and set goals for weight loss specific for each patient; (2) Consider drug therapy for obese patients who fail to achieve their weight loss goals through diet and exercise alone, along with counseling of the drugs' side effects, the lack of long-term safety data, and the temporary nature of the weight loss achieved with medications; options include sibutramine, orlistat, phentermine, diethylpropion, fluoxetine, and bupropion and the choice of agent will depend on the side effects profile of each drug and the patient's tolerance of those side effects; (3) Surgery for patients with a BMI of 40 kg/m^2 or greater who instituted but failed an adequate exercise and diet program (with or without adjunctive drug therapy) and who present with obesity-related co-morbid conditions, such as hypertension, impaired glucose tolerance, diabetes mellitus, hyperlipidemia, and obstructive sleep apnea, after counseling about the long-term side effects, such as possible need for reoperation, gallbladder disease, and malabsorption; (4) Refer to high-volume centers with surgeons experienced in bariatric surgery (Ann Intern Med 2005;142:525–531).

Recent meta-analysis of 147 studies on surgical treatment of obesity provides an excellent insight on the role of surgery in the management of obesity (Ann Intern Med 2005;142:547–559). Surgery results in 20–30 kg weight loss, far greater than what can be achieved with medical treatment, in patients with an average BMI of 40 kg/m^2 or greater, along with improvement in some co-morbid conditions. Weight loss is maintained for up to 10 years. Surgery is superior to medical management of patients with BMIs of 35–39 kg/m^2. Gastric bypass procedures result in more weight loss than gastroplasty. Morbidity is high (20% adverse events) and mortality is $<$1% with the bariatric procedures in current use (gastric bypass, laparoscopic adjustable gastric band, vertical banded gastroplasty, and biliopancreatic diversion and switch). The laparoscopic approach results in fewer wound complications than an open approach (Ann Intern Med 2005;142:547–559).

Surgical strategies include global malabsorption (Jejuno-ileal bypass), pure restriction (vertical band gastroplasty and laparoscopic adjustable silicone gastric banding), combined restriction and minimal malabsorption (Roux-en-Y gastric bypass), and selective maldigestion and malabsorption (biliopancreatic diversion) (Gastrointest Endosc 2003;57:86–94). From a plumber's (endoscopist) point of view, these operative strategies boil down to a few basic operational concepts—either reduction of gastric reservoir and/or re-routing of gastrointestinal flow with development of malabsorption. Could this be accomplished by endoscopists? Yes, it is certainly feasible! This is largely due to sustained efforts of innovators in therapeutic endoscopy such as Mathus-Vliegen and Tytgat and others around the globe thinking outside the confines of the conventional endoscopy, who were instrumental in the development of endoluminal suturing (Gastrointest Endosc 1996;44:133–143), creation of gastroenteric anastomosis (Gastrointest Endosc 2001;53:780–784), and transluminal surgery (Gastrointest Endosc 2003;58:585–591, 2004;60:114–117) to create a platform for endoscopic endoluminal bariatric procedures. In fact, vertical band gastroplasty was created successfully in postmortem stomachs (Gastrointest Endosc 2002;55:254–256), and results of endoscopic gastroplasty on weight reduction in 10 obese patients was recently presented (Gastrointest Endosc 2005;GI:AB106).

To put the elegant clinical experimental work of Mathus-Vliegen and Tytgat in perspective, it is critical to review prior use of the gastric balloon. Although insertion of a gastric balloon as a gastric volume reduction procedure and induction of early satiety is an attractive concept, the gastric balloon did not take off well and had a rough ride from the start! In a randomized controlled trial, 59 obese patients showed no benefit of the Garren-Edwards gastric balloon (Gastrointest Endosc 1989;35:381–385). An earlier study by Mathus-Vliegen et al using a 500-mL bubble (Ballobes; DOT ApS, Rodovre, Denmark) and randomization (sham-sham, sham-balloon, balloon-sham, and balloon-balloon groups) for over a 35-week period also failed to show any benefit (Gastroenterology 1990;99:362–369). Lack of effectiveness, unacceptable adverse effects, and spontaneous deflations of the intragastric balloon led the experts in this field to put a moratorium on routine clinical use of these balloons (Gastrointest Endosc 1987;33:323–327). Recently, a Brazilian study evaluated an intragastric balloon in 323 obese patients for 6 months, with 85 of these subjects followed for 1 year after the removal of balloon. At 6 months, there was a significant reduction in weight (-15.2 ± 10.5 kg). The percent excess weight loss (%EWL) was $48.3\% \pm 23.3\%$. Eighty-five patients followed up for 1 year had %EWL of $50.9\% \pm 28.8\%$. Eleven patients (3.4%) required removal of the balloon because of patient intolerance. One patient required surgery for small bowel obstruction because of deflation of the balloon (Obes Surg 2004;14:991–998).

Mathus-Vliegen and Tytgat should be congratulated for completing their voyage successfully and should be applauded for their persistence in getting their data out to the public while the two U.S. centers failed to take off! Despite the small numbers of patients

studied, several take-home messages are obvious from this rigorous, well-controlled study lasting for 2 years: The intragastric balloon is not for everybody—certainly not for patients with peptic ulcer, large hiatal hernia, severe erosive esophagitis, esophageal or gastric varices, patients on anticoagulants, and patients with previous bariatric surgery. Although independent benefit of balloon treatment beyond diet, exercise, and behavioral therapy could not be demonstrated in the first 3 months, balloon treatment for 1 year resulted in 21.3 kg weight loss (17.1%), of which 12.6 kg (9.9%) was maintained during the balloon-free second year.

It is intriguing to note that "after many requests, permission was obtained to publish our single-center results." I am glad that the authors persisted. Otherwise, another balloon story would have blown away in vain! Where does the intragastric balloon fit in the paradigm of management of obesity: as a first line for mild to moderate obesity or as a bridge to bariatric surgery in morbid obesity? Will it have a sustained effect on obesity-related co-morbid conditions?

As you ponder, let me leave you with an important historical fact about the relation between the Dutch and the U.S and a wise quote by Woodrow Wilson. Exactly 225 years after John Adams' trip to Amsterdam (1780) on a diplomatic mission to gain political and financial support from the Dutch Republic for the fledgling United States of America, we continue to seek and learn from the Dutch!

We should not only use the brains we have, but all that we can borrow.
—Woodrow Wilson

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DIABETES AND HEPATOCELLULAR CARCINOMA: ASSOCIATIONS, BIOLOGIC PLAUSIBILITY, AND CLINICAL IMPLICATIONS

Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB (Houston Veterans Affairs Medical Center, Houston, Texas). Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. Gut 2005;54:533–539.

Hepatocellular carcinoma (HCC) is a grave complication of cirrhosis. In the United States, the age-adjusted incidence of HCC has recently more than doubled, increasing from 1.4 per 100,000 during the period from 1975 to 1977, to 3.0 per 100,000 during 1996–1998 (Ann Intern Med 2003;139:817–823). While infection with hepatitis C virus (HCV) accounts for approximately half of this increase, infection with hepatitis B virus (HBV) and alcoholic liver disease (ALD) do not explain the remainder of this rise (Arch Intern Med 2000;160:3227–3230, J Clin Gastroenterol 2002;35:266–269, Gastroenterology 2004;127:1372–1380). Though non-alcoholic fatty liver disease (NAFLD) has been implicated as a cause of HCC (Gastroenterology 2002;123:134–140), the primary risk factor in a significant number of cases of HCC has yet to be determined.

Previous studies in the literature have suggested an association between HCC and diabetes mellitus (DM). In this study by Davila et al, the authors conduct a population-based, case-control study with two major purposes: first, to assess whether an association between DM and HCC exists; and second, to examine the impact of other known risk factors for HCC on that association.

The sample population was drawn from the Surveillance, Epidemiology, and End-Results (SEER)-Medicare database, which links information in the cancer registry with Medicare claims data. Cases were defined as patients aged 65 years or older enrolled in Medicare between 1994 and 1999 who were confirmed to have HCC by histology, cytology, tumor marker, direct visualization, or radiology. Controls were Medicare beneficiaries aged 65 years or older who did not have cancer. Risk factors were subsequently identified for all subjects from Medicare claims data using the International Classification of Diseases (ICD-9) codes for DM, HBV, HCV, ALD, hemochromatosis, obesity, dyslipidemia, HIV, and nonspecific cirrhosis. Diabetes, obesity, and dyslipidemia were included only if they were present during the 3 years prior to the index diagnosis of HCC to reduce the likelihood of these conditions being caused by end-stage liver disease. The other risk factors were included if they were identified either during the 3 years prior or 2 years after the initial HCC diagnosis. Statistical methods included χ^2 analysis, calculation of odds ratios (OR) with 95% confidence intervals (CI), and multivariate logistic regression.

The database yielded 2061 HCC cases and 6183 non-cancer controls. Patients with HCC were more likely to be male (65.6% of the HCC cases vs 36.4% of the non-cancer controls), non-white (33.7% vs 17.9%), and dually enrolled in Medicare and Medicaid, a proxy for low socioeconomic status (27.1% vs 14.5%). As expected, patients with HCV, HBV, ALD, and hemochromatosis were more likely to have HCC (adjusted ORs, 24.42, 23.94, 69.62, and 8.88, respectively).

The key finding in this study is that 43.3% of patients with HCC had diabetes compared with 19.4% of the non-cancer controls (unadjusted OR, 3.18; 95% CI, 2.85–3.54). Among these HCC patients with diabetes, the authors note that 56.5% did not have other identifiable risk factors for HCC, while HCV, HBV, ALD, and hemochromatosis were found in 22.3%, 8.2%, 24.2%, and 4.7%, respectively (some patients had multiple risk factors). When the risk of HCC in patients with DM was adjusted for age, sex, race, SEER registry location, and Medicare/Medicaid dual enrollment in the multivariate analysis, the adjusted odds ratio was essentially unchanged at 3.08 (2.74–3.46). When this was further adjusted to exclude the set of known risk factors, the adjusted OR was 2.87 (2.49–3.30). Additionally, there was a synergistic interaction between diabetes and HCV (OR of 36.88 compared with 24.42 for HCV alone), which was not found with the other risk factors.

The group of cases was further subdivided into those with HCC without known risk factors (termed idiopathic HCC) and those with HCC due to known risk factors (HBV, HCV, ALD, and hemachromatosis). There was no difference between these groups for rates of obesity (7.2% vs 7.0%) and dyslipidemia (32.5% vs 34.5%). Diabetes was less frequent in the idiopathic group compared with the known risk factor group (41.0% vs 46.6%; unadjusted OR, 0.80; 95% CI, 0.67–0.95). Finally, a univariate analysis showed diseases related to the metabolic