rent ulcer bleeding remained significantly higher in the *H pylori*–negative idiopathic ulcer cohort (25.2 vs 3.0%; $P < .0001$). In a multivariate analysis, *H pylori*–negative, idiopathic ulcer remained an independent risk factor associated with recurrent ulcer bleeding and with mortality (Figure 1*B*). Mortality in idiopathic ulcer patients was mainly attributable to malignancy, sepsis, and renal failure; mortality owing to uncontrolled gastrointestinal bleeding was low.

This prospective cohort study confirms increased rebleeding rates and mortality in patients with a history of *H pylori*–negative, idiopathic, bleeding ulcers compared with those with *H pylori*–positive bleeding ulcers. Although advanced comorbidity contributed to the higher mortality, *H pylori*–negative status per se also predicted mortality. These observations suggest that long-term prophylaxis with a gastroprotective or anti-secretory agent may be justified in these patients.

See page 525.

Effects of Bariatric Surgery on Liver Injury

Severe obesity is implicated in the development of nonalcoholic fatty liver disease (NAFLD). Accumulation of fat in the liver, and subsequent development of an inflammatory response in fatty liver, may ultimately lead to fibrosis and liver failure. Bariatric surgery has been shown to improve biochemical signs of liver injury in NAFLD, but it is unclear whether this is associated with a favorable impact on the occurrence and evolution of liver fibrosis.

In this issue of GASTROENTEROLOGY, Mathurin et al report on a prospective, single-center study in obese patients who were evaluated for bariatric surgery. A total of 381 patients were prospectively enrolled. Gastric banding, biliointestinal bypass, and gastric bypass procedures were performed in 56.2%, 22.8%, and 21% of the patients, respectively. Liver biopsies were performed during the operative procedure in 98.7% of patients at baseline and in 80% of patients after 1 and 5 years. The NAFLD score was obtained as the sum of steatosis, ballooning, and lobular inflammation scores. The presence and extent of fibrosis were also semiquantitatively assessed on the biopsies. Insulin resistance was quantified from baseline insulin and glucose levels.

In a multivariate analysis, insulin resistance and alanine aminotransferase (ALT) levels were independent predictors of baseline steatosis. The same factors, and age, were independent predictors of the presence of inflammation. Bariatric surgery induced a significant improvement in body mass index (BMI), systolic blood pressure, ALT, γ-glutamyl transferase, serum triglycerides, cholesterolemia, and insulin resistance. The presence and extent of steatosis decreased significantly 5 years after bariatric surgery (Figure 2). Severe steatosis was found in 32.8% at baseline and only 8.8% after 5 years. Ballooning improved significantly 1 year after bariatric surgery, with no further improvement after 5 years. In a multivariate analysis, baseline steatosis and refractory insulin resistance were independent predictors of persistence of steatosis at 5 years.

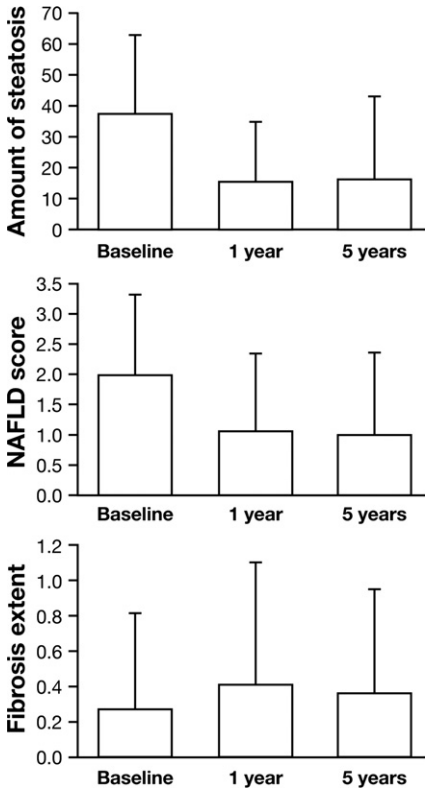

Figure 2. Influence of bariatric surgery on the amount of steatosis (*top*), on NAFLD score (*middle*), and on extent of fibrosis (*bottom*) after 1 and 5 years, compared with baseline.

Inflammation was not significantly altered during follow-up. NAFLD scores improved significantly after 1 year and persisted at 5 years (Figure 2). The percentage of patients with probable or definite nonalcoholic steatohepatitis decreased significantly from 27.4% to 14.2%.

An increase in fibrosis was seen 1 year after surgery, with no significant further increase at 5 years (Figure 2). However, the vast majority of patients (95.7%) maintained a low fibrosis score (no more than focal pericellular fibrosis in zone 3). No significant differences were seen between the types of bariatric procedures used, and fibrosis evolution was not related to changes in the BMI of patients. In multivariate analysis, only fibrosis at baseline was an independent predictor of fibrosis worsening at 5 years.

This study confirms that bariatric surgery is associated with improvement in steatosis and ballooning, mainly in the first year, and persisting at 5 years. This improvement is closely linked with improvement in insulin resistance. On the other hand, some worsening of fibrosis is seen at 5 years. However, the low incidence of severe fibrosis suggests that weight loss associated with bariatric surgery does lead to worsening of fibrosis in general, but increasing fibrosis may be a feature of a subgroup with a more severe natural history.

See page 532.

Different Microbiome Patterns in Normal, Inflamed, and Barrett's Esophagus

The spectrum of disease in the distal esophagus caused by reflux ranges from inflammation to stricture

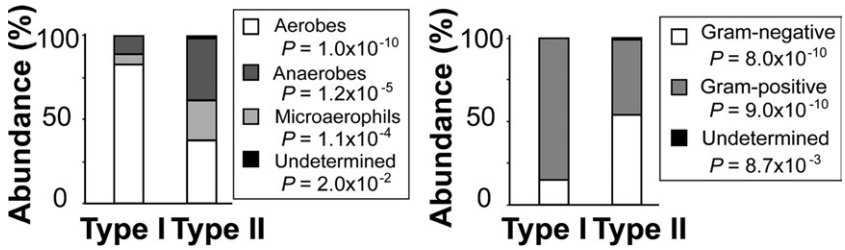

Figure 3. Characterization of the microbiome in the distal esophagus. A type I microbiome is associated strongly with normal esophagus, whereas a type II microbiome is associated with esophagitis/Barrett's metaplasia. (*Left*) Comparisons of microbiome types according to culture conditions. (*Right*) Comparisons of microbiome types according to staining properties.

formation to Barrett's metaplasia to adenocarcinoma. Although the etiology of pathologic reflux is related to transient lower esophageal sphincter relaxation, the reason for these transient relaxations is not known. One novel hypothesis is that the microbiome may contribute to the local environment of the esophagus and play a pathogenic role, although this aspect has never been previously investigated.

In the study by Yang et al, distal esophageal biopsies from 12 normal, 12 esophagitis, and 10 Barrett's metaplasia subjects were analyzed by 16S ribosomal RNA survey to determine microbial speciation and patterning. Using hierarchical cluster analysis that was validated by normal reference range calculations from phenotypically guided analyses, samples could be segregated into a type I cluster that was strongly associated with normal esophagus biopsies (11/12 samples), and a type II cluster that was strongly correlated with inflamed/Barrett's metaplasia biopsies (7/12 esophagitis and 6/10 Barrett's samples), and that the 2 clusters were statistically different. The type I microbiome was dominated by the Gram-positive *Streptococcus* genus, present in 82.2% of samples compared with 13.5% in the type II microbiome, whereas the type II microbiome was dominated by anaerobic/microaerophilic bacteria (61.1% vs 16.3% in type I) that showed an abundance of Gram-negative bacteria (53.4% vs 14.9% in type I), including *Veillonella, Prevotella, Haemophilus, Neisseria, Rothia, Granulicatella, Campylobacter, Porphyromonas, Fusobacterium,* and *Actinomyces* (Figure 3).

The study indicates that a shift from a Gram-positive microbiome in normal esophagus to that of a Gram-negative anaerobic microbiome in inflamed/Barrett's esophagus. It is not known if the type II microbiome plays a causative role in reflux, but lipopolysaccharide from Gram-negative bacteria, assuming its presence before pathologic reflux, might induce lower esophageal sphincter relaxation via activation of inducible nitric oxide. Alternatively, the type II microbiome may develop as a result of reflux. However, the study demonstrates a complex microbiome that rivals that of the skin and mouth, and opens up a new avenue for investigation of the distal esophagus and reflux.

See page 588.

New Compounds to Prevent HCV Cell Entry and Infection

Current therapy for hepatitis C (HCV) infection is based on peginterferon-α and ribavirin, is only effective in ~50% of patients treated, and has significant side effects. Preventing or controlling HCV infection is not yet clinically optimal, and there is no vaccine developed to date despite evidence that HCV may gain cell entry through a potentially conserved mechanism involving receptor-mediated endocytosis. Recently, phosphorothioate oligonucleotides structured as amphipathic DNA polymers showed evidence of blocking HIV-1 entry into cells, but this has not been examined for HCV infection.

In the study by Matsumura et al, phosphorothioate oligonucleotides (PS-ON), and phosphodiester 2′-*O*-methyl ribose oligonucleotides (PO-ON) that lack the phosphorothioate modification and stabilize the oligonucleotide from nuclease degradation, were synthesized and used in cell culture and cell binding assays of HCV infection, and in a mouse model stably transplanted with human hepatocytes. PS-ON, but not PO-ON, prevented HCV infection in cell models,

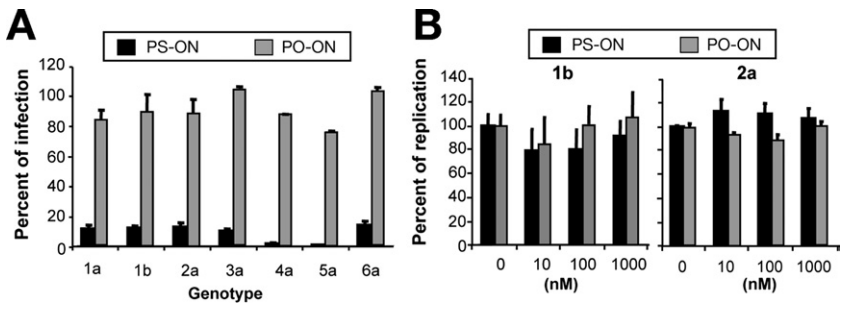

Figure 4. Effect of phosphorothioate oligonucleotides (PS-ON) on infection of various HCV genotypes and HCV replication. (*A*) HCVpp harboring E1E2 glycoproteins from genotypes 1a, 1b, 2a, 3a, 4a, 5a, and 6a were inoculated into Hep3B cells and simultaneously treated with 100 nmol/L of degenerate PS-ON and phosphodiester 2′-*O*-methyl ribose oligonucleotides (PO-ON) that stabilizes the oligonucleotide from nuclease degradation (40-mer). Luciferase activities were determined 2 days later. (*B*) Subgenomic RNA or genotype 1b Con1 or 2a JFH1 were transfected into Huh7.5 cells. Four hours after transfection, a set of transfected cells was harvested as a control for transfection efficiency, and the remaining cells were treated with 100 nmol/L of PS-ON and PO-ON. Cells were then harvested at 72 hours post-transfection and luciferase activities determined. The replication level was presented as the ratio of the luciferase activity of the sample at 72 hours over that of 4 hours. Percentages of replication were determined by dividing the replication level of treated over that of untreated samples.