Validation of gastric emptying by $^{13}$C-spirulina breath test. We apologize for not citing all studies that have validated the $^{13}$C-Spirulina gastric emptying breath test. Before this study, the test has been validated against scintigraphy in a cumulative total of 154 healthy people and 144 patients with upper gastrointestinal symptoms and is responsive to perturbation of gastric emptying with pramlintide, erythromycin, and atropine.\(^3\) The intra-individual and inter-individual variabilities are comparable with those for scintigraphy.\(^8\) In addition, the $^{13}$C-Spirulina gastric emptying breath test has also been used in more than 2000 patients in phase I and phase II pharmaceutical investigations of prokinetic drugs under sponsors’ investigational new drug exemptions (personal communication, AB Diagnostics), some of which have been published.\(^9\)\(^10\)

The inverse relationship between fasting blood glucose level and gastric emptying half-time was observed not only at the first but also at the second visit (Figure 1 in the article), showing that the relationship was replicated and therefore not likely to be a random observation.

Dr Pasricha suggests that “other confounding variables that may affect gastric emptying, such as body mass index or fat content in the diet, were not taken into account.” Consistent with the known phenotype of type 2 diabetes mellitus, the average body mass index in these patients was 33.8 kg/m\(^2\). The study in rats cited by Dr Pasricha suggests that a high-fat diet delayed gastric emptying in rats with diet-induced obesity by activating hormonal mechanisms.\(^11\) The effects of a short-term high-fat diet on gastric emptying in humans are inconsistent.\(^12\)\(^13\) Indeed in a prior study from our group, dietary supplementation with 500 kcal fat in excess of required calories for 2 weeks did not significantly alter gastric motor functions such as gastric emptying and accommodation.

In the current study, delayed gastric emptying was associated with vagal dysfunction, which is linked to diabetes and not to dietary intake or obesity. Hormonally mediated reflexes that retard gastric emptying cannot explain the observed rapid gastric emptying, which was documented in 20% of our patients.

We agree that future studies are essential to shed light on these and other important questions.

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Histologic Healing in Inflammatory Bowel Disease Clinical Practice: A Reliable Target?

Dear Editor:

In their recent article, Peyrin–Biroulet et al\(^1\) explored the yield of histologic healing in ulcerative colitis (UC). However, some issues still limit the use of histologic healing as a therapeutic target in clinical practice.

First, a validated standard system for grading histologic activity does not exist. Validation is a prerequisite to standardize reporting and grading. The Geboes score is one of the most complete and frequently used scores,\(^2\) but it needs to be validated in larger studies.

Second, the exact definition of histologic remission and histologic healing, as well as their impact on clinical outcome of the disease, have yet to be clarified.

Third, the optimal staining method for grading the severity of inflammation is still unclear. H&E is the most frequently used staining, but other expensive methods, such as immunohistochemistry, may provide more information.

Fourth, the timing and site of the biopsy to show normalized histology have to be clarified. This is because histology may vary according to the site of the biopsy. For example, Rosenberg et al\(^3\) recently showed that histologic features of inflammation in the proximal colon were found in 34% of patients with left-sided colitis.

Fifth, is histologic healing a reliable target in clinical practice?

We know that mucosal healing is associated with significant outcomes in managing inflammatory bowel disease. Bouguen et al\(^4\) found that endoscopic assessment of disease severity associated with adjustments of medical therapy increases the likelihood of mucosal healing in Crohn’s disease (CD) patients. Hence, the so-
called “Treat-to-Target”\textsuperscript{5} strategy currently is proposed for managing CD patients.

We also know that histologic healing is associated with significant outcomes, ranging from a reduced risk of relapse\textsuperscript{5,6} to a reduced risk of colorectal cancer in UC patients.\textsuperscript{7} However, current data found that histologic healing is not an easy goal to reach, and that inflammation may persist despite clinical-endoscopic remission.\textsuperscript{3} Rosenberg et al\textsuperscript{3} found that histologic features of inflammation may be detected in 54\% of UC patients receiving maintenance therapy, and 37\% of them had at least moderate inflammation based on Geboes scores.

This occurs not only when patients are treated with mesalamine or steroids, in which the percentage of histologic remission varies greatly, but also when patients are treated with anti–tumor necrosis factor (TNF)-\(\alpha\). We found recently that histologic healing (defined as a Geboes score of 0) may be reached in only 13\% of CD patients after 2 years of treatment with infliximab (IFX) or adalimumab, despite the vast majority of them obtaining and maintaining clinical remission.\textsuperscript{8}

We found also that histologic inflammation persists despite deep remission with treatment with anti–TNF-\(\alpha\). We also found that 40.4\% of UC patients had at least 1 biopsy specimen with evidence of any histologic inflammation when in deep remission with treatment with IFX, and 19.1\% had biopsy specimens that met the Geboes criteria for abnormal histologic inflammation.\textsuperscript{9} The same occurred in CD patients in deep remission. We recently found that 83.8\% of CD patients had at least 1 biopsy specimen with abnormal histologic inflammation (Geboes score, \(\geq1\)) when in deep remission with treatment with anti–TNF-\(\alpha\). Subdividing patients according to the severity of histologic inflammation, we found that mild inflammation was found in 29.7\% of patients, moderate inflammation was found in 45.9\% of patients, and severe inflammation was found in 8.1\% of patients. Of note, any significant difference in histologic damage was found among CD patients in deep remission for the past 6, 12, or more than 12 months.\textsuperscript{10}

Although limited by the retrospective design, our data confirm a subanalysis of controlled studies. For example, the Active Ulcerative Colitis Trial 1 (ACT 1) study found that only one third of IFX-treated UC patients who reached mucosal healing showed a complete absence of histologic signs of inflammation.\textsuperscript{11}

Hence, before considering histologic healing as a reliable target for the treatment of inflammatory bowel disease, especially in clinical practice, large prospective studies have to address the key issues mentioned earlier. In that, we share the caution expressed by Peyrin-Biroulet et al.\textsuperscript{1}

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Conflicts of interest
The author discloses no conflicts.

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