pump inhibitors. In our study, 100% of the patients had abnormal pH scores at baseline, as compared with 73% of those in the LOTUS trial, which may indicate that our patients had greater incompetence of the lower esophageal sphincter. This is supported by the fact that the majority of patients in our study (57%) reported either moderate or severe regurgitation at baseline, as compared with the LOTUS trial, in which the majority (68%) reported either no regurgitation or only mild regurgitation.

In our study, a significant reduction in esophageal acid exposure was achieved. At baseline, the median total percentage of time with acid exposure was 10.9%, which dropped to 3.3% at 1 year of follow-up ($P<0.001$). This significant reduction in esophageal acid exposure is indicative of an improved antireflux barrier, which translated into substantial symptom improvement, discontinuation of proton-pump inhibitors, and patient satisfaction for the majority of study patients at 3 years of follow-up. It is the totality of the clinical outcomes, not a single physiological factor such as pH measurement, that forms the basis for evaluating the effectiveness of a treatment. Acid in the distal esophagus does not indicate volume reflux, whereas regurgitation is a symptom of sphincter failure and volume reflux. Three years after implantation, only 1% of our patients had moderate or severe regurgitation, as compared with 57% at baseline.

The incidence of postprocedural dysphagia in our trial was similar to that in the LOTUS trial (and other fundoplication studies).[1-3] It is unclear how these two trials compare with regard to dilations, since the LOTUS trial allowed one dilation per patient and counted only patients who underwent more than one dilation, whereas we reported all dilations.

Murphy and Kearney inquire about postprocedural manometric abnormalities or motility disorders related to the magnetic sphincter device that are similar to those reported after Nissen fundoplications.[4] At 1 year, all our patients were evaluated with the use of manometry and barium esophagography, and we did not observe any clinically meaningful manometric changes from baseline or pseudoachalasia after magnetic sphincter augmentation. These results are reported in the Supplementary Appendix, available with the full text of our article at NEJM.org.

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Since publication of their article, Dr. Horgan reports having equity in Torax Medical. No further potential conflict of interest relevant to this letter was reported.

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Vitamin B_{12} Deficiency

TO THE EDITOR: In the review article describing vitamin B_{12} deficiency (Jan. 10 issue),[1] Stabler states that vitamin B_{12} is known as cyanocobalamin in the United States and hydroxocobalamin in Europe. As a result of a subgroup analysis of U.S. and European patients with renal impairment in the Vitamin Intervention for Stroke Prevention (VISP) trial,[2] it has been proposed[3] that these two forms of vitamin B_{12} are not clinically equivalent. The confounding effect that resulted when the European patients in the trial received methylcobalamin and the U.S. patients received cyanocobalamin may have influenced this trial result.[3] Stabler also states that high-dose oral vitamin B_{12} tablets are as effective as intramuscular monthly injections in correcting blood and neurologic abnormalities. However, patients with renal failure who are given cyanocobalamin accumulate cyanide, which can antagonize the beneficial homocysteine-lowering effects and asym-

metric dimethylarginine–lowering effects of vitamin B_{12}.[4] High doses of oral cyanocobalamin should be avoided in patients with renal impairment; instead, we suggest that methylcobalamin (available in the United States) or hydroxocobalamin rather than cyanocobalamin should be administered.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Stabler states that high-dose oral vitamin B_{12} therapy is as effective as intramuscular injections in correcting blood and neurologic abnormalities. This statement is based on results of a randomized study in which 38 patients with newly diagnosed cobalamin deficiency were randomly assigned to receive vitamin B_{12} either intramuscularly or orally. A total of 35 patients were evaluated. The efficacy of treatment in the two groups was similar. However, only 2 patients in each treatment group had neurologic dysfunction.[1] This small number makes oral therapy difficult to justify. There are no guidelines from the American Society of Hematology to officially address the efficacy of oral versus intramuscular vitamin B_{12} treatment. However, some experts in the field call for caution regarding oral vitamin B_{12} therapy in general and especially in patients with neurologic impairment.[2-4] Neurologic dysfunction caused by vitamin B_{12} deficiency can be irreversible and devastating if left untreated. Oral therapy may work just as well as parenteral therapy, but in patients who have vitamin B_{12} deficiency and neurologic dysfunction, treatment with parenteral vitamin B_{12} should be preferred until sufficient data are present to support oral therapy in this subpopulation.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHOR REPLIES: Killen and Brenninger point out that there are three forms of vitamin B_{12} (cyanocobalamin, hydroxocobalamin, and methylcobalamin) that are commercially available to clinicians, and they raise concern regarding cyanide toxicity from cyanocobalamin injections. A 1000-μg dose of cyanocobalamin contains 20 μg (0.78 μmol) of cyanide, which compares favorably to the level deemed allowable by the Environmental Protection Agency in drinking water (200 μg per liter), the amounts found in food and cigarette smoke, and the amounts used in animal models of toxicity.[1] The determination of whether the small amount of cyanide in cyanocobalamin would cause or prevent correction of neuropathy in smokers or patients undergoing hemodialysis would require blinded, randomized treatment trials in which both methylcobalamin and cyanocobalamin were strictly protected from light during manufacture, storage, dispensing, and administration, since they are light-labile, deteriorating to aquocobalamin.

Abboud Leon and colleagues question whether high-dose oral vitamin B_{12} treatment is intensive enough for initial treatment in patients with neurologic disease. In two randomized trials of oral versus parenteral treatment, four patients[2] and seven patients[3] in the oral-treatment groups

had improvement, which was not different from the rates in the respective parenteral-treatment groups. The route of vitamin B_{12} delivery may be less important than the expected quantity delivered to tissues. Oral vitamin B_{12} at a daily dose of 2000 μg (20 μg absorbed on average) is equivalent to weekly injections of cyanocobalamin at a dose of 1000 μg (150 μg retained). Oral treatment has been successfully used in Sweden for almost 50 years.[4] However, patients with life-threatening megaloblastic anemia or severe myelopathy may benefit from rapid replacement with daily injections, although in the past cure has been accomplished with much lower and less-frequent doses.

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Since publication of her article, the author reports no further potential conflict of interest.

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Transient Sunitinib Resistance in Gastrointestinal Stromal Tumors

TO THE EDITOR: Sunitinib — an oral tyrosine kinase inhibitor targeting *KIT,* platelet-derived growth factor receptors α and β, vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3, and other receptors — is an effective second-line therapy for metastatic gastrointestinal stromal-cell tumors after the use of first-line imatinib.[1,2] If disease progresses during treatment with sunitinib, current therapeutic options are limited. We describe two patients who were successfully rechallenged with sunitinib after disease progression and had an objective response and a persistent clinical benefit.

Both patients, a 62-year-old man and a 58-year-old woman, underwent a gastric resection for a high-risk gastrointestinal stromal-cell tumor harboring *KIT* exon 11 mutations. When progression occurred to the peritoneum and liver, each patient began to receive imatinib at a dose of 400 mg per day and continued treatment for almost 3 years, with a prolonged partial response.

When disease progression was detected on computed tomography (CT), the dose of imatinib was increased to 800 mg per day. A few months later, for progressing disease, both patients began to receive sunitinib at a dose of 37.5 mg per day. They had a partial response that lasted more than 2 years. After further disease progression, both patients received nilotinib without a response and reexposure to imatinib without any benefit.

Each patient had a rapid decline in performance status, and sunitinib treatment was tried again. Within a few days, both patients' symptoms started to improve. CT scans showed a partial response.

The male patient had stable disease after 12 months of retreatment with sunitinib, whereas the female patient had progression after 9 months and began to receive regorafenib.

Mechanisms of resistance to sunitinib and other tyrosine kinase inhibitors that target VEGFRs are largely unknown, but studies involving patients with renal-cell carcinoma suggest that resistance may be transient.[3] The clinical histories of these two patients have similar features: the gastrointestinal site of the tumor, a prolonged response to imatinib and sunitinib, and a months-long interval before reexposure. In contrast to imatinib, in which secondary resistance is mostly due to emergence of new *KIT* mutations, mechanisms of sunitinib resistance are unclear.[4] Is resistance routinely reversible after a sunitinib-free interval, similar to the responses to platinum-based chemotherapy in patients with ovarian cancer after a platinum-free interval? The positive trial with regorafenib as third-line therapy versus supportive care is en-