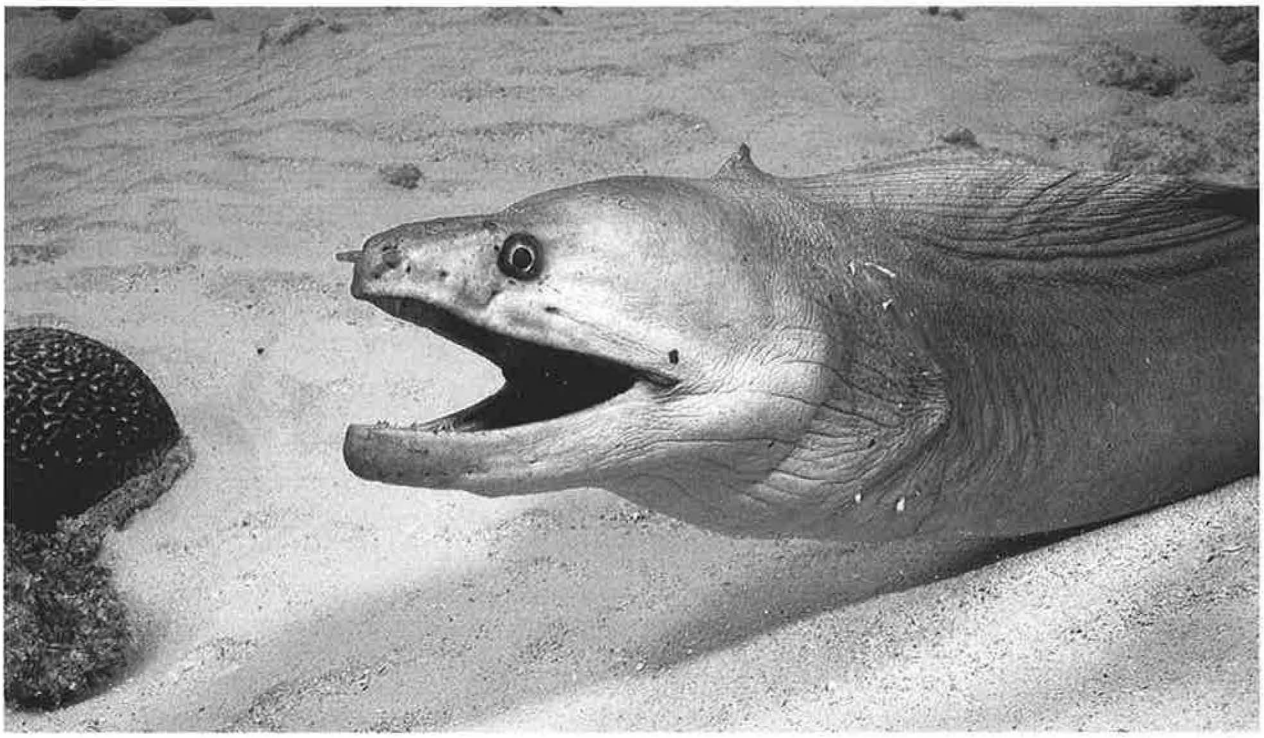

New Insights into Gastroesophageal Reflux Disease (GERD)
What It Does and Does Not Do

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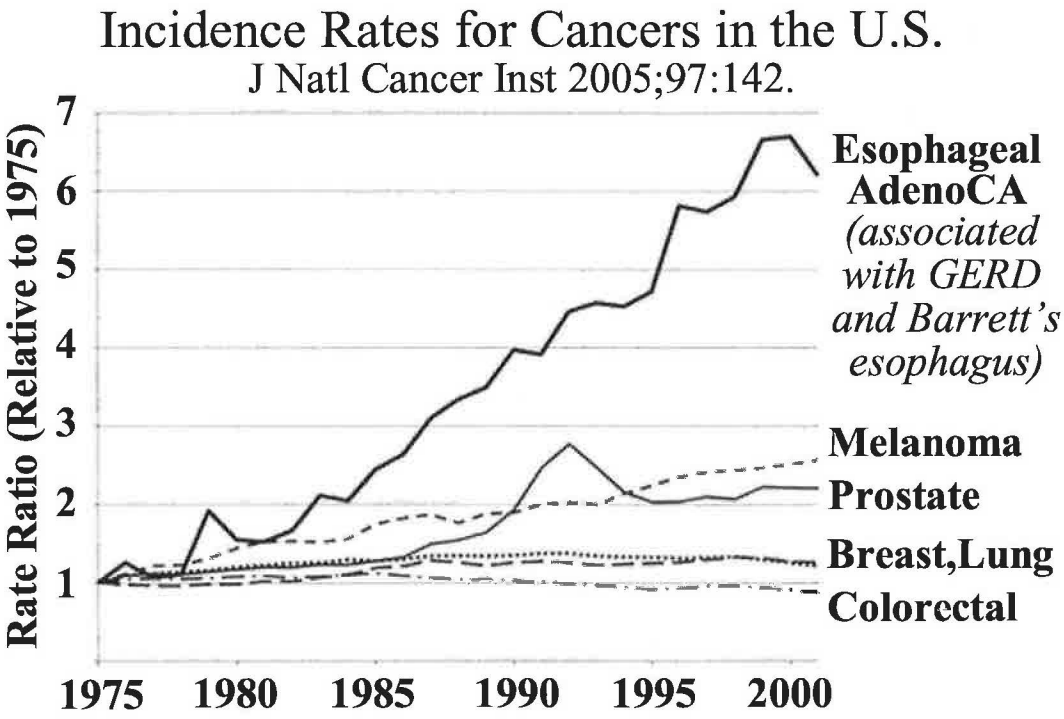
Biographical Sketch

Stuart Jon Spechler, M.D. is Chief of the Division of Gastroenterology at the Dallas VA Medical Center, Professor of Medicine, and Holder of the Berta M. and Cecil O. Patterson Chair in Gastroenterology at The University of Texas Southwestern Medical Center at Dallas. Dr. Spechler is a graduate of Boston University School of Medicine. Before moving to Dallas in 1997, he was the Director of the Center for Swallowing Disorders at the Beth Israel Hospital and Harvard Medical School. Dr. Spechler's research has focused primarily on disorders of the esophagus, especially gastroesophageal reflux disease (GERD) and its complications. He chaired the VA Cooperative Study on GERD, and he has published more than 200 scientific reports, editorials, review articles, and book chapters on esophageal disorders. He is perhaps best known for his work in the area of Barrett's esophagus. Dr. Spechler has served on the editorial boards of numerous journals including *Gastroenterology*, *Gut*, *Alimentary Pharmacology and Therapeutics*, and *Diseases of the Esophagus*, and he has chaired the Gastroenterology Teaching Project of the American Gastroenterological Association (AGA). He is presently Chair of the Esophagogastroduodenal Section of the AGA Council, and Co-Chair of the AGA Institute/AMA Physicians Consortium for Performance Improvement in GERD.

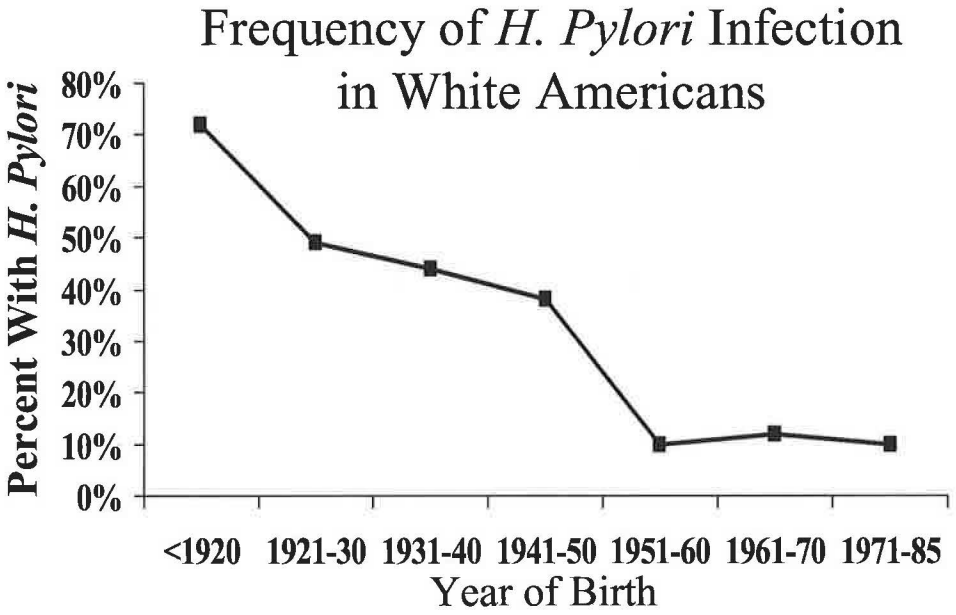
GERD, Barrett's Esophagus and Esophageal Adenocarcinoma

Surveys have shown that 10% to 20% of adults in the general population of Western countries experience heartburn, the cardinal symptom of gastroesophageal reflux disease (GERD), at least once a week (1). It has been estimated that Americans spend $9.3 billion each year for the evaluation and treatment of GERD (2). Chronic GERD can result in Barrett's esophagus, the condition in which an abnormal intestinal-type epithelium replaces reflux-damaged esophageal squamous epithelium, and GERD and Barrett's esophagus are the major risk factors for esophageal adenocarcinoma (3-5). The incidence of esophageal adenocarcinoma in the United States has increased by more than 600% since 1975, far outpacing the rising incidence of other tumors like melanoma and prostate cancer (6). Both Barrett's esophagus and esophageal adenocarcinoma have a strong predilection for white men, and patients with Barrett's esophagus develop esophageal adenocarcinoma at the rate of approximately 0.5% per year (7). Some proposed explanations for the rising incidence of esophageal adenocarcinoma are discussed below.



Obesity. Obesity has been established as a strong risk factor for esophageal adenocarcinoma (8). In the United States, the prevalence of obesity (defined as a body mass index (BMI) $\geq$ 30) has increased substantially over the past three decades, paralleling the increase in the frequency of esophageal adenocarcinoma (9). The mechanism underlying the association between cancer of the esophagus and obesity is not known, but may be related to the fact that obesity predisposes to the development of gastroesophageal reflux disease (GERD), and that obesity is associated with insulin resistance that results in high serum levels of insulin-like growth factor-1, which might increase proliferation in esophageal epithelial cells (8,10).

***H. pylori* infection.** Although *H. pylori* is a type I (definite) carcinogen for adenocarcinoma of the distal stomach, this infection has not been identified as a risk factor for esophageal adenocarcinoma (11). Indeed, it appears that infection with *H. pylori*, particularly with cagA+ strains, actually protects against these tumors. The mechanism of this alleged protective effect is not clear, but it has been suggested that *H. pylori* infections which cause a severe pangastritis can decrease gastric acid secretion, thereby protecting against the development of GERD (12). The frequency of H. pylori infection in the United States has been declining for decades (13). Thus, some have proposed that the declining frequency of *H. pylori* infection may be contributing to the rising frequency of esophageal adenocarcinoma (14).

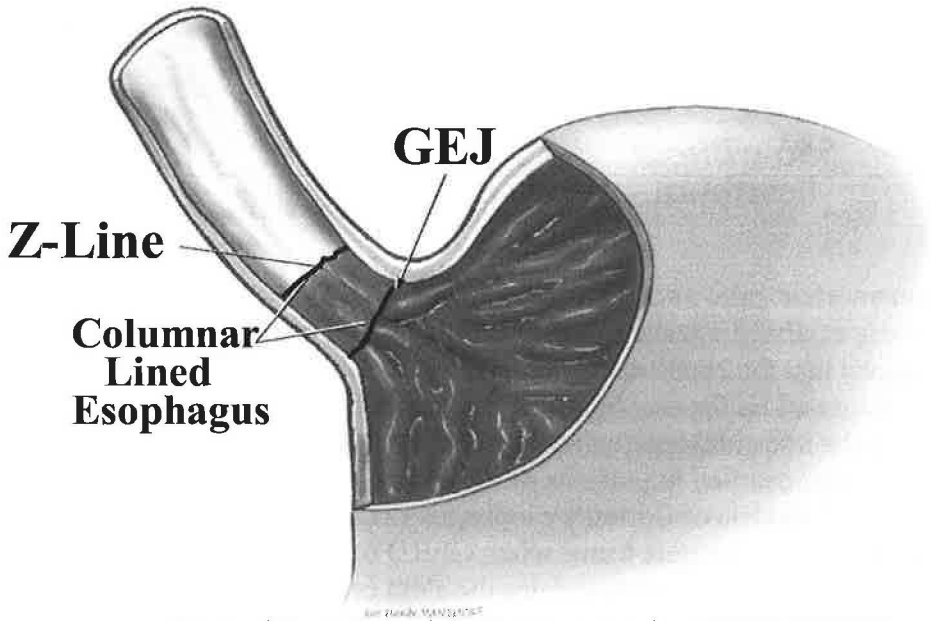


Data from Parsonnet. Aliment Pharmacol Ther 1995;9 (suppl 2):45.

Dietary nitrate as a risk factor for esophageal adenocarcinoma. Recent studies suggest that the gastroesophageal junction (GEJ) region is an especially hostile place. One recent study has shown that, after meals, there is a pocket of acid at the GEJ that escapes the buffering effects of ingested food (15). This postprandial acid pocket has a mean length of 2 cm, beginning in the most proximal stomach and extending more than 1 cm above the squamo-columnar junction (Z-line) into the distal esophagus. Another recent study has shown that the very distal esophagus (5 mm above the Z-line) of healthy volunteers is exposed to acid for more than 10% of the day (16). Potential consequences of such persistent acid exposure at the GEJ include not only acid-peptic injury, but also exposure to high concentrations of nitric oxide (NO) generated from dietary nitrate (NO_3^-) in green, leafy vegetables. Most ingested nitrate is absorbed by the small intestine and excreted unchanged in the urine, but approximately 25% is concentrated by the salivary glands and secreted into the mouth where bacteria on the tongue reduce the recycled nitrate to nitrite (NO_2^-). When swallowed nitrite encounters acidic gastric juice, the nitrite is converted rapidly to nitric oxide (NO). After nitrate ingestion, high levels of NO have been demonstrated at the GEJ (17). NO can be genotoxic and, potentially, carcinogenic. Thus, the GEJ is exposed repeatedly to acid, pepsin, NO, and other noxious agents

in gastric juice. Tissues exposed chronically to agents that induce injury and inflammation may change into other types of tissue that are less susceptible to damage by those agents. This process is called metaplasia, and metaplasia at the GEJ is a very common condition (18). When intestinal metaplasia extends above the GEJ into the distal esophagus, the condition is called Barrett's esophagus (4).

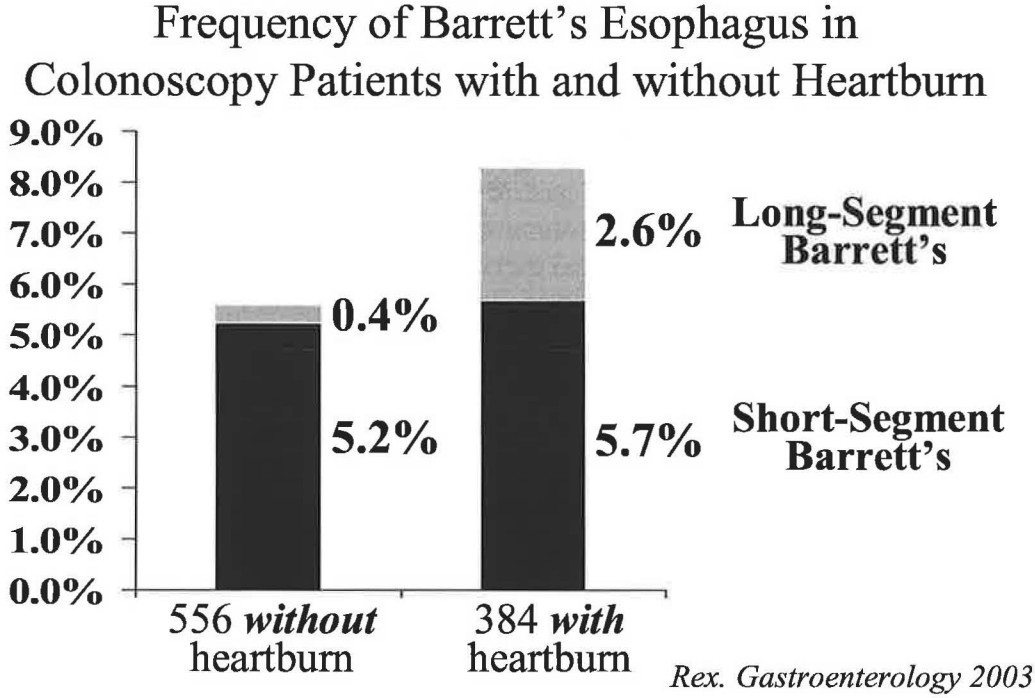
Recognizing Barrett's esophagus. The juxtaposition of pale squamous epithelium and reddish columnar epithelium forms a visible line (the Z-line) at the squamo-columnar junction (see figure below). The GEJ, the level at which the esophagus ends and the stomach begins, is defined by the most proximal extent of the gastric folds. When the Z-line is located proximal to the GEJ, as in the figure below, there is a columnar-lined segment of esophagus. If biopsy specimens from that segment show intestinal metaplasia, then the patient has Barrett's esophagus, which can be categorized further according to the extent of the metaplastic lining. Patients who have ≥3 cm of intestinal metaplasia have long-segment Barrett's esophagus, whereas those with <3 cm of metaplasia have short-segment Barrett's esophagus.



Adapted from Spechler. Gastroenterology 1999;117:218.

Recent studies suggest that Barrett's esophagus is a common condition among individuals in the general population, irrespective of whether they have GERD symptoms. Among 961 American patients scheduled for elective colonoscopy who agreed to have an upper gastrointestinal endoscopy performed for research purposes, Barrett's esophagus (predominantly short-segment variety) was found in 6.8%. Interestingly, short-segment Barrett's esophagus was found in 5.7% of the 384 patients who complained of heartburn and in 5.2% of the 556 patients who had no heartburn (see figure below) (19). In an endoscopic study of 1,000 individuals in the general population of Sweden, 16 (1.6%) were found to have Barrett's esophagus (mostly short-segment) and only 9 of those 16 had symptoms of GERD (20). These data suggest that screening programs which target patients with heartburn will miss many individuals with short-segment Barrett's esophagus who are at risk for esophageal adenocarcinoma. Therefore, such screening

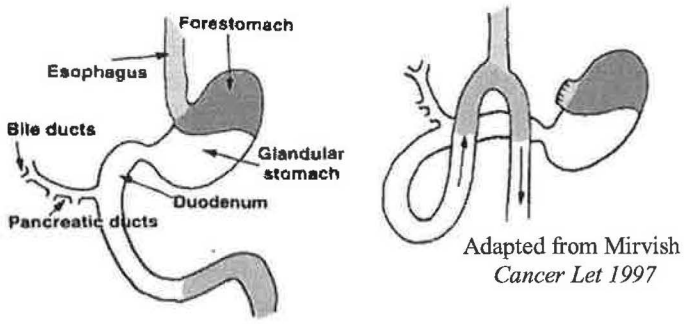
programs can have only limited impact on esophageal cancer mortality rates. Indeed, there is little evidence that existent programs have prevented deaths from esophageal adenocarcinoma (21).



Bone marrow stem cells and Barrett's esophagus. The mechanisms underlying the pathogenesis of the specialized intestinal metaplasia of Barrett's esophagus are not known. Early investigators proposed that the condition developed when columnar epithelium from the proximal stomach migrated up the esophagus. This hypothesis is no longer favored because it does not account for the intestinal-type cells characteristic of Barrett's metaplasia and because metaplasia has been demonstrated in portions of the esophagus that are not contiguous with the stomach in some animal models of Barrett's esophagus (21,22). Today, the most popular hypothesis is that Barrett's esophagus forms when GERD damages the superficial layers of the esophageal squamous epithelium, and stimulates the stem cells in the basal layers to undergo abnormal differentiation (23-26). Others have proposed that the specialized intestinal metaplasia of Barrett's esophagus develops from progenitor cells located in the ducts of the esophageal mucosal glands (27). In either case, the progenitor cells for Barrett's esophagus have been assumed to reside within the esophagus itself.

Recently, our research group at the Dallas VA Medical Center became intrigued by studies suggesting that injuries in a number of organs may heal through the proliferation and differentiation of multipotential progenitor cells derived from the bone marrow rather than from the injured organ itself (28,29). For example, epithelial cells containing Y chromosomes have been found throughout the gastrointestinal tract of female animals and women who received bone marrow transplants from male donors (30,31). We hypothesized that, under certain circumstances, the specialized intestinal metaplasia of Barrett's esophagus also might arise from bone marrow-derived progenitor cells, and we tested our hypothesis in an established rat model of esophageal injury (32).

Esophagojejunostomy in Rats



Normal Anatomy Esophagojejunostomy

Results in severe, ulcerative esophagitis and intestinal metaplasia

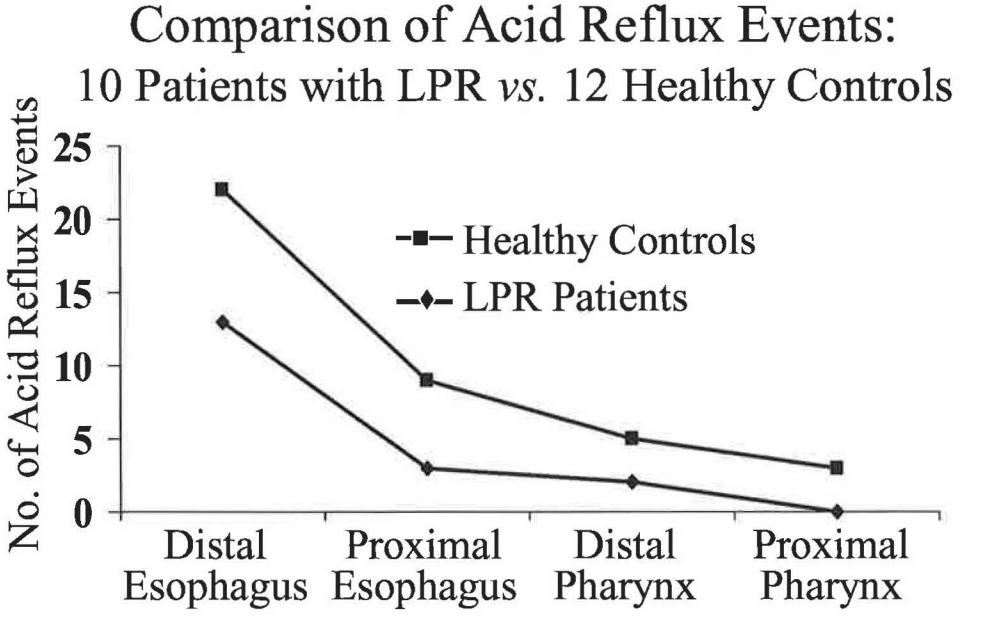
We administered a lethal dose of irradiation to female rats, after which we reconstituted their bone marrows by intravenous injection of bone marrow cells from male rats. Ten days later, the irradiated rats were randomly assigned to undergo either esophagojejunostomy, a procedure that causes severe reflux esophagitis with intestinal metaplasia, or sham operation. The rats were sacrificed at 8 weeks, and serial sections of the snap-frozen esophagi were cut and mounted on slides. The first and last sections were used for histological evaluation; intervening sections were immunostained for cytokeratin to identify epithelial cells and analyzed for Y chromosome by fluorescence *in situ* hybridization (FISH). Histological evaluation of the esophagi from rats that had esophagojejunostomy revealed ulcerative esophagitis and multiple areas of intestinal metaplasia. FISH analyses showed that some of the squamous epithelial cells and some of the columnar epithelial cells lining the glands of the intestinal metaplasia were positive for Y chromosome. These observations suggest that multipotential progenitor cells of bone marrow origin contribute to esophageal regeneration and metaplasia in this rat model of Barrett's esophagus. We speculate that a stem cell origin might underlie the malignant predisposition of Barrett's metaplasia.

GERD and Laryngopharyngeal Reflux

Otolaryngologists believe that GERD frequently causes chronic laryngeal inflammation with symptoms that include hoarseness, excessive throat clearing, cough, sore throat and globus (33). It has been estimated that approximately 10% of all patients who visit otolaryngologists emerge with a diagnosis of GERD-induced laryngeal injury (34). The injury presumably results when gastric juice refluxes into the esophagus, traverses the upper esophageal sphincter, and contacts the larynx whose structures have been shown to be exquisitely sensitive to acid-peptic damage (35). Acid refluxing into the esophagus also can trigger vagally-mediated reflexes that cause throat clearing and coughing which, in turn, cause laryngitis, and it has been shown that acid in the esophagus increases the sensitivity of the cough reflex (36). Laryngoscopies in

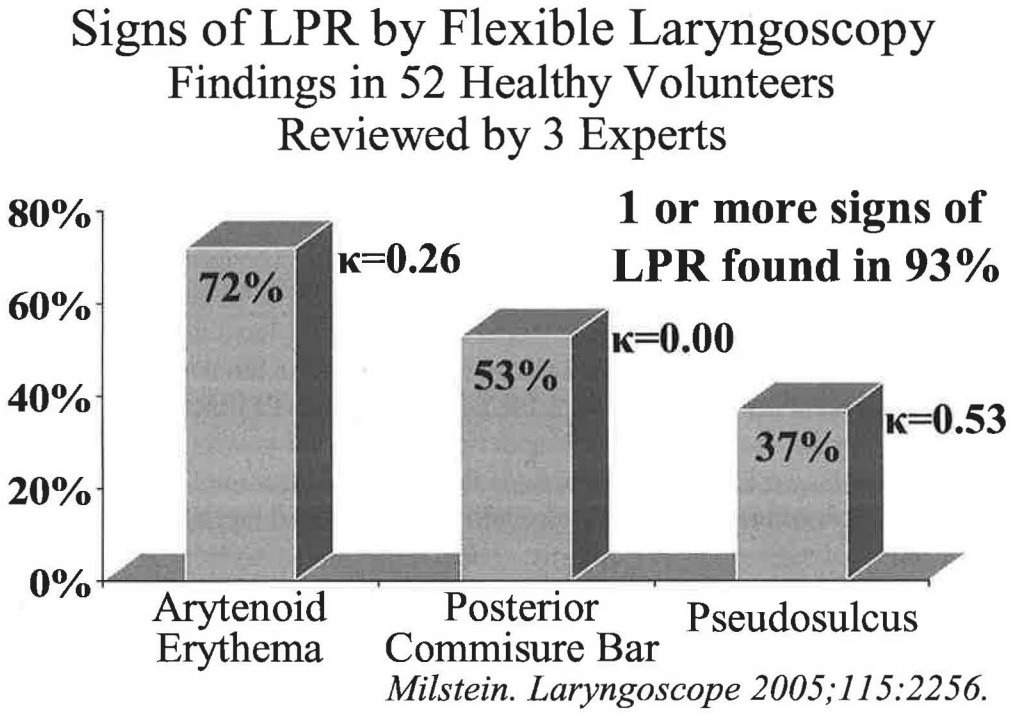
patients with symptoms of laryngopharyngeal reflux (LPR) typically reveal mucosal thickening, erythema, and edema in the posterior larynx, precisely where gastric juice that refluxes into that region might be expected to pool. Nevertheless, gastroenterologists have become increasingly skeptical and reluctant to accept this common otolaryngological diagnosis (33,37).

One reason is that most patients who are diagnosed with LPR have no typical GERD symptoms (e.g. heartburn, regurgitation) and no endoscopic signs of reflux esophagitis (37,38). For those patients, the refluxed gastric juice presumably homes into its laryngeal target like a cruise missile, damaging nothing else in its path. This should not be surprising, say the believers, because animal studies have shown that laryngeal structures are exceptionally sensitive to acid-peptic injury (38). Unlike the esophagus, furthermore, the larynx has little ability to clear refluxed acid. For example, the larynx is not exposed continually to alkaline saliva that can neutralize and wash away acidic material (39). Similar reasoning is evoked to explain the observation that approximately 50% of patients thought to have reflux laryngitis have normal esophageal acid exposure by conventional pH monitoring studies in which the pH electrode is positioned 5 cm above the lower esophageal sphincter (40). Even studies performed with pH electrodes positioned in the proximal esophagus and pharynx fail to show consistent and reproducible differences in proximal esophageal and pharyngeal acid exposure between control subjects and patients with alleged LPR (41,42). The believers are unfazed by those data, arguing that virtually any amount of acid that reaches the larynx, even a drop, is enough to cause damage. It does not matter that the total amount of acid reflux is in the normal range. Any amount of refluxed acid that reaches the larynx may be sufficient to cause damage. Although these explanations for the lack of esophageal disease and the inability to document abnormal laryngeal acid exposure consistently in patients who allegedly have LPR are plausible, they do seem somewhat contrived and based more on faith than on data.

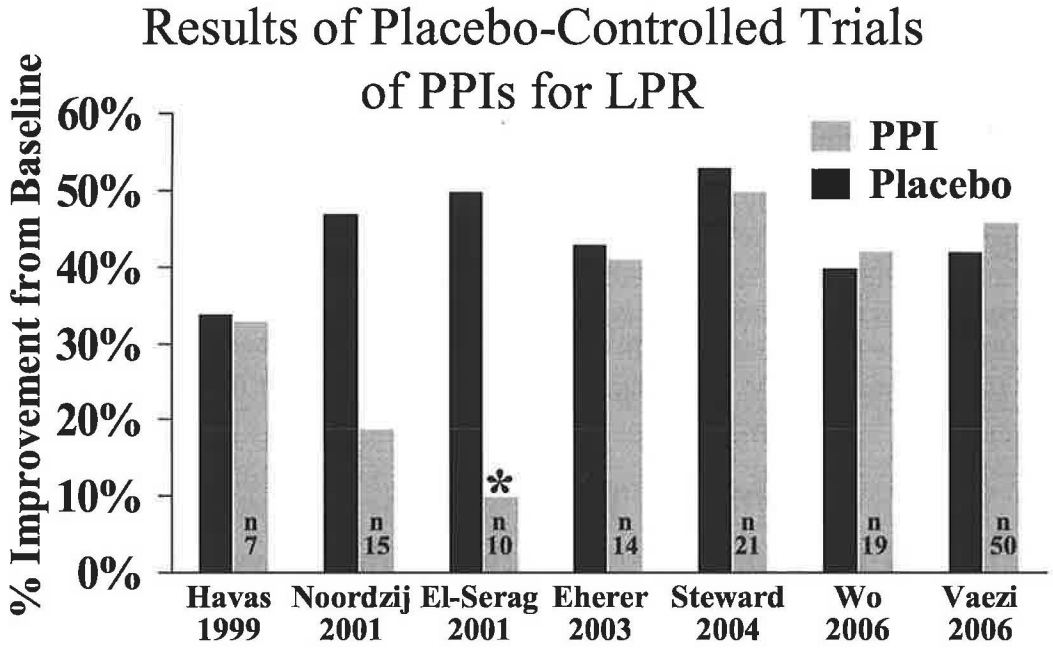


Shaker. Laryngoscope 2003;113:1182.

Another reason to question the diagnosis of LPR is that the characteristic laryngoscopic findings of mucosal thickening, erythema and edema in the posterior larynx are both subjective and nonspecific. In the esophagus, similar subjective endoscopic findings for reflux esophagitis have been shown to correlate poorly with histological signs of inflammation and with pH monitoring results, and interobserver agreement in identifying those subtle mucosal changes has been abysmal (43,44). The non-specificity of the laryngoscopic findings of LPR has been highlighted in a recent study of 52 healthy volunteers, 93% of whom were found to have one or more laryngoscopic changes of LPR (45). Several other studies have found no significant correlations among laryngoscopic findings of LPR, laryngeal symptoms, and pharyngeal pH monitoring results (37). Thus, there is no clear-cut "gold standard" for the diagnosis of LPR and this confounds the interpretation of all available studies on the disorder. How accurate can a study's conclusions be if the very diagnosis of the condition under investigation is in doubt?

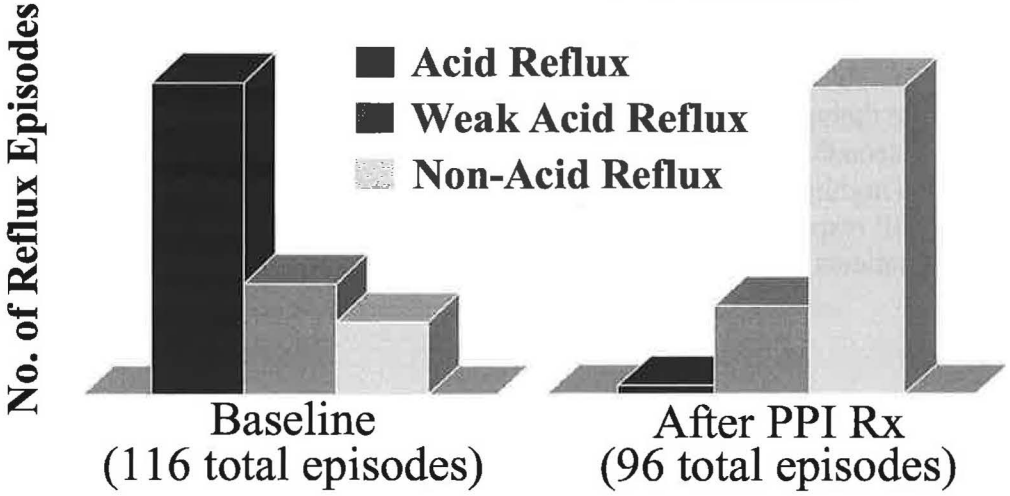


Perhaps the most compelling reason to question the validity of LPR as a diagnosis is the delayed and inconsistent response to antireflux therapy. Unlike typical GERD symptoms which often disappear within days of starting proton pump inhibitors (PPIs) in conventional dosages, uncontrolled studies suggest that improvement of LPR symptoms typically requires months of high-dose PPI therapy (35). Among seven placebo-controlled studies of PPI treatment for the condition (46-52), furthermore, only one showed a statistical advantage of PPI over placebo for healing both the symptoms and laryngoscopic signs of LPR (48).



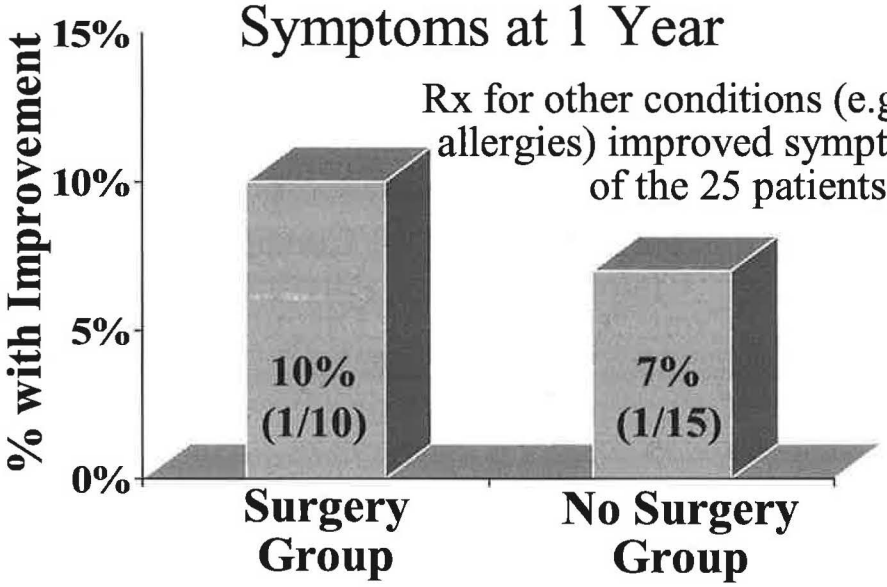
One of the potential explanations for the persistence of reflux laryngitis despite effective antisecretory therapy is that non-acidic gastric juice continues to reflux and irritate the larynx. Studies using multichannel intraluminal impedance monitoring have demonstrated that reflux of non-acidic material persists during PPI therapy (53). Surgeons have argued that fundoplication may be the treatment of choice for LPR because, unlike PPI therapy which is directed at gastric acid secretion, fundoplication blocks the reflux of all gastric material (54). A recent report from the Cleveland Clinic strongly refutes that surgical argument, however (55). The Cleveland Clinic group enrolled 72 patients who had symptoms and laryngoscopic signs of LPR in a prospective study of high-dose PPI therapy. After 4 months of treatment, 47 patients improved substantially and 25 did not, even though esophageal pH monitoring studies showed that PPI therapy had normalized their esophageal acid exposure. The 25 non-responders were offered treatment with fundoplication, and 10 agreed to have the surgery. Although the fundoplications normalized esophageal acid exposure in all 10 patients, only 1 (10%) reported substantial improvement in LPR symptoms one year later, whereas 1 of the 15 patients (7%) who refused surgery and continued PPI therapy also reported improvement (P=1.0). Subsequent treatment for conditions that can cause laryngeal symptoms other than GERD (e.g. allergies, asthma) resulted in symptomatic improvement in an additional 2 of the 10 surgical patients and in 6 of the 15 who refused surgery. The authors concluded that fundoplication does not improve LPR symptoms reliably in patients who do not respond to PPI therapy, and they recommend early evaluation for causes of laryngitis other than GERD in such patients.

Reflux Episodes in 6 Healthy Volunteers Before and After PPI Treatment



Tamhankar. J Gastrointest Surg 2004;8:888.

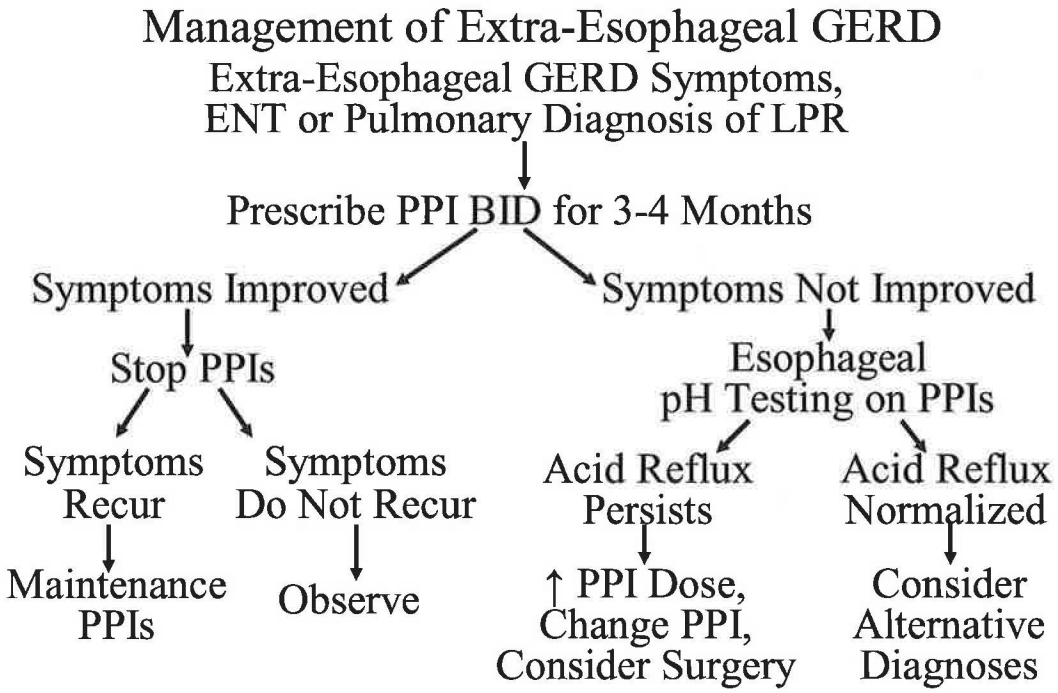
Improvement of Laryngeal Symptoms at 1 Year



Rx for other conditions (e.g. asthma, allergies) improved symptoms in 8 of the 25 patients

Swoger. Clin Gastroenterol Hepatol 2006;4:433.

This surgical experience with LPR raises some highly contentious issues in the field of GERD. The report highlights the fact that the diagnosis of LPR is often unsubstantiated and dubious. Progress in this area likely has been hindered by cavalier use of the term "LPR" by physicians, especially by otolaryngologists. Perhaps that diagnosis should be applied only to those patients whose laryngeal symptoms respond to antireflux therapy. Even this restriction may not be sufficient to eliminate diagnostic errors because the response to antireflux therapy can be so delayed. The fact that symptoms resolve after 6 months of PPI therapy can hardly be construed as proof that the therapy effected the cure. Nevertheless, in the absence of a diagnostic gold standard, it seems reasonable to require a response to therapy for the diagnosis of LPR to be accepted. This study also highlights a Catch-22 situation that continues to bedevil antireflux surgeons: Patients who will respond best to fundoplication are those who have responded best to PPI therapy (56); but, if patients respond so well to PPI therapy, then why do they need an operation?



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