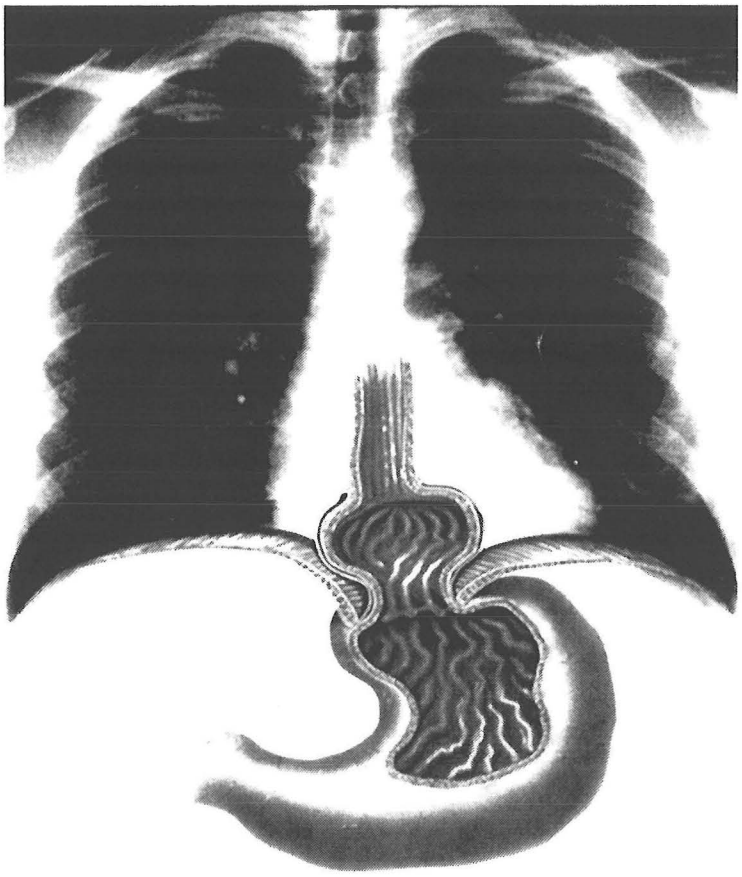
Gastroesophageal Reflux Disease

Medical Grand Rounds

September 14, 2000



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Gastroesophageal reflux disease (GERD) is the condition that results when the reflux of gastric material into the esophagus or oropharynx causes symptoms, tissue injury, or both. GERD is one of the most common chronic disorders of the gastrointestinal tract (1,2), and surveys suggest that approximately 20% of adult Americans experience GERD symptoms such as heartburn and acid regurgitation at least once each week (3,4). GERD can cause erosions and ulcerations in the squamous epithelium that normally lines the distal esophagus. Esophageal ulcerations can stimulate fibrous tissue deposition with esophageal stricture formation, and the ulcerated squamous epithelium can be replaced by a metaplastic, intestinal-type mucosa (a condition called Barrett's esophagus) that predisposes to malignancy. GERD recently has been shown to be a strong risk factor for esophageal adenocarcinoma (5), a tumor that has nearly quadrupled in frequency in the United States over the past two decades (6)

In addition to the classic manifestations of heartburn and regurgitation, GERD has a number of "atypical" manifestations (see table below). Acid reflux can cause chest pain that mimics ischemic heart disease (7). In some patients, refluxed gastric material reaches the oropharynx and causes globus, sore throat, burning tongue, dental erosions, and sinusitis (8). Aspiration of refluxed material into the airway can cause laryngitis and pulmonary problems such as chronic cough and asthma (9-11).

"Atypical" Manifestations of GERD

Chest pain
Globus
Sore throat
Burning tongue
Dental erosions
Sinusitis
Laryngitis
Chronic cough
Asthma

The development of GERD is a multifactorial process that involves dysfunction of mechanisms that normally prevent excessive gastroesophageal reflux, and of mechanisms that normally clear noxious material rapidly from the esophagus (12). These mechanisms are reviewed below.

The Antireflux Barrier

Ambient pressure in the abdomen ordinarily is higher than that in the chest and, consequently, gastroesophageal reflux would occur continuously in the absence of effective antireflux mechanisms (12). Two major elements comprise the normal antireflux barrier: 1) the lower esophageal sphincter (LES), and 2) the crural diaphragm (13).

Lower Esophageal Sphincter (LES). The LES is a segment of specialized, circular, smooth muscle in the wall of the distal esophagus that prevents reflux by maintaining a resting pressure some 10 to 30 mm Hg higher than that in the stomach (14). Although the muscle of the LES is morphologically indistinguishable from the muscle of the adjacent esophageal body, LES muscle exhibits a number of distinctive functional characteristics. Unlike muscle of the esophageal body, for example, strips of LES muscle develop spontaneous tension on stretching, and transmural electrical stimulation causes LES muscle strips to relax. With swallowing, the LES normally relaxes for 5 to 8 seconds to allow the swallowed bolus to enter the stomach.

In the 1940s and 1950s, Allison and others proposed that reflux esophagitis was due primarily to herniation of the stomach into the chest through the esophageal hiatus in the diaphragm (hiatal hernia) (15). The notion that GERD was caused by hiatal hernia prevailed until the 1960s when researchers observed that: 1) most patients with hiatal hernia had no signs or symptoms of GERD, 2) some patients with reflux esophagitis had no hiatal hernia, and 3) hiatal hernia repair often did not alleviate reflux esophagitis (16). In the early 1970's, investigators at Boston University reported that patients with GERD had feeble resting pressures in the LES, irrespective of the presence of hiatal hernia (Figure 1) (17).

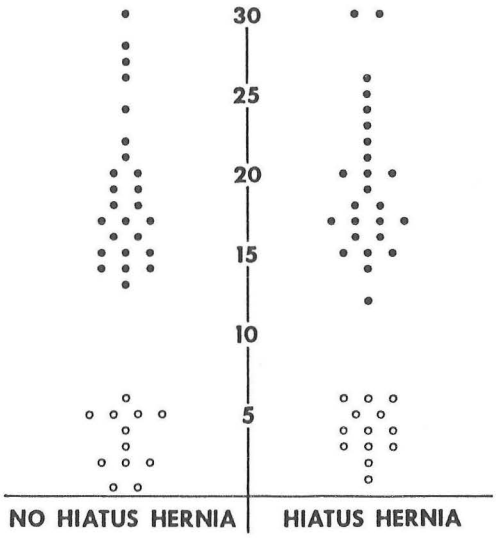

Figure 1
LES pressure (mm Hg) is shown on the y-axis. Open circles represent patients with symptoms of GERD. Closed circles represent patients without GERD symptoms. These data could not be reproduced in subsequent studies.
Reprinted from N Engl J Med 1971;284:1053 (reference 17).

These investigators downplayed the role of hiatal hernia in GERD, and popularized the concept that the disorder was caused by an LES that was intrinsically too weak to prevent reflux. Subsequently it was found that many patients with GERD had normal resting LES pressure values, an observation that cast doubt on the concept that the LES was the primary antireflux barrier (18). In the 1980s, Dodds and his colleagues showed that episodic collapse of LES pressure, a phenomenon called transient LES relaxation (TLESR), was the major mechanism for reflux both in normal individuals and in patients with GERD (19,20). When LES pressure falls to zero during a TLESR, the sphincter no longer functions as an antireflux barrier. Unlike the brief, appropriate LES relaxations that accompany primary (swallow-induced) peristalsis, TLESRs are not preceded by swallowing and last from 10 to 45 seconds (21). In addition, TLESRs are associated with relaxation of the crural diaphragm, a phenomenon that also favors gastroesophageal reflux (see below).

The TLESR is part of the normal belch reflex that is triggered by gaseous distention of the stomach (21). In this situation, the TLESR allows gas to escape from the gastric fundus. The nucleus tractus solitarius in the medulla is involved in the reflex, both in integrating sensory information from the stomach, and in controlling the neural circuits that trigger the TLESR (22). Medullary neurons with γ-aminobutyric acid B ($GABA_B$) receptors appear to inhibit TLESRs

(23). Cholinergic blockade with atropine also inhibits TLESRs through a central mechanism (24). The sphincter relaxation that characterizes a TLESR is mediated by the activation of cholecystokinin-A receptors in LES muscle (25). Brief episodes of gastroesophageal reflux occur every day in normal individuals, and the vast majority of these episodes are the result of TLESRs. In patients with severe GERD, approximately 70% of reflux episodes are the result of TLESRs; the remaining reflux episodes are associated with a variety of events including periods of feeble basal LES pressure, swallow-induced LES relaxation, and sudden elevations in abdominal pressure (14). TLESRs occur approximately 2-6 times per hour in normal subjects, and 3-8 times per hour in patients with GERD. Approximately 40% to 50% of TLESRs in normal subjects are accompanied by acid reflux, whereas acid reflux is observed in 60% to 70% of TLESRs in patients with GERD.

Crural Diaphragm. The esophagus passes from the chest into the abdomen through the diaphragmatic hiatus, a tunnel-like opening in the right crus of the diaphragm. By encircling the distal esophagus, the crural muscle can function as an external sphincter that buttresses the LES and prevents gastroesophageal reflux. During inspiration, when the abdomino-thoracic pressure gradient increases so as to favor reflux, the diaphragmatic crurae contract and pinch the distal esophagus. The pinching effect of the crurae helps to prevent reflux during inspiration, and during the sudden increases in abdominal pressure that accompany events such as coughing, sneezing, and straining. TLESRs often are accompanied by relaxation of the crurae, and studies in dogs have shown that gastroesophageal reflux does not occur during a TLESR unless the episode is attended by neural inhibition of the crural diaphragm (26).

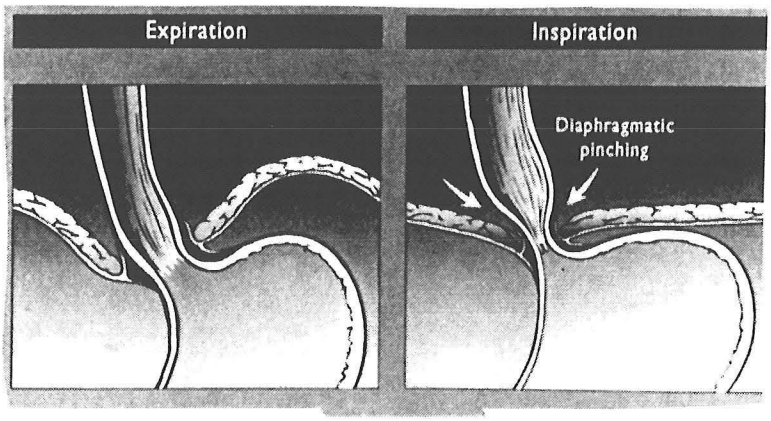

Figure 2
Antireflux effect of the crural diaphragm.
Reproduced from Spechler SJ. Esophageal disorders. Unit 9 of the
Clinical Teaching Project of the American Gastroenterological Association

Anatomic features of the gastroesophageal junction. In addition to the LES and crural diaphragm, certain anatomic features of the gastroesophageal junction appear to contribute to the antireflux barrier. For example, the acute angle formed by the junction of esophagus and stomach (the angle of His) may function as a one-way flap valve that prevents reflux. Also, a segment of the distal esophagus ordinarily is located within the abdomen where it is subject to high ambient pressure that tends to force the walls together, thereby preventing reflux (27).

Disruption of the antireflux barrier by hiatal hernia. Hiatal hernia frequently accompanies severe GERD. It has been known for decades that large hiatal hernias are associated with low LES pressure (28), but only recently has the mechanism underlying this

association been elucidated (29). During a standard esophageal motility study, esophageal pressures are measured by transducers that are placed in the lumen of the esophagus. The "LES pressure" measured during such a study reflects pressure on the transducer that is generated by both the LES muscle (intrinsic sphincter) and the crural diaphragm (extrinsic sphincter). A better term for this value would be "gastroesophageal junction pressure," but the term "LES pressure" is conventional (see Figures 3 and 4).

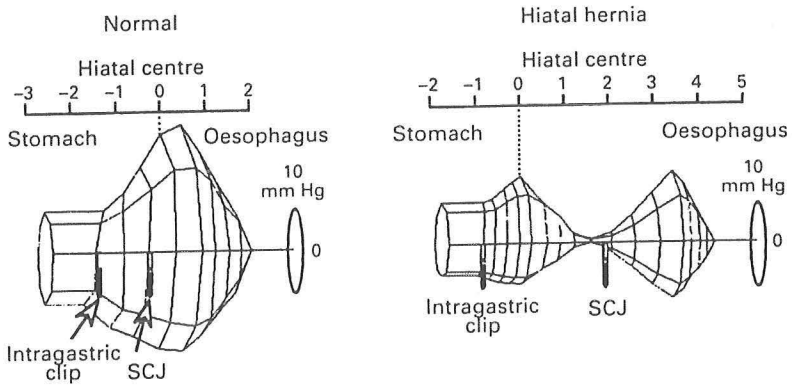

Figure 3
3-D pressure topography of the gastroesophageal junction.
Position zero is the midpoint of the diaphragmatic hiatus; the positive and negative values on the scale represent distance in cm from the midpoint. SCJ represents the position of the squamocolumnar junction at the end of the esophagus. The circumference of the oval represents a pressure value of 10 mm Hg. In normal subjects (left panel), there is a single hump of maximal pressure at the diaphragmatic hiatus caused by the combined effects of the crural diaphragm and LES. In patients with hiatal hernia (right panel), there are two pressure humps: one at the diaphragmatic hiatus that reflects pressure generated by the crural diaphragm, and one several cm above the hiatus that represents pressure generated by the LES muscle.
Reprinted from Gut 1999;44:476 (reference 29).

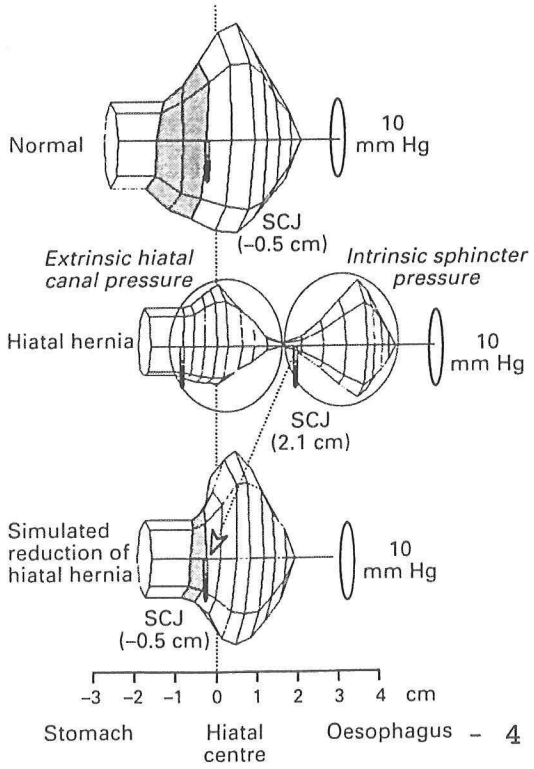

Figure 4. Computer-simulated reduction of hiatal hernia. When the two pressure humps seen in patients with hiatal hernia are superimposed (i.e. the LES is repositioned at the esophageal hiatus), the resultant pressure topography is similar to that of the normal subjects. Reprinted from Gut 1999;44:476 (reference 29).

With a large hiatal hernia, the LES muscle is displaced up into the chest, dissociated from the crural diaphragm. The intrinsic pressure generated by the sphincter muscle of the esophagus may be normal but, when separated from the crural diaphragm that ordinarily contributes to the pressure at the gastroesophageal junction, the measured "LES pressure" value appears to be low. With such a large hiatal hernia that dissociates the internal and external sphincters of the distal esophagus, reflux may occur during the elevations in abdominal pressure caused by events such as inspiration, coughing, and staining. In this situation, the crurae can no longer buttress the LES by pinching the distal esophagus. Rather, contraction of the crurae creates an intrathoracic pouch of stomach whose contents are readily available for reflux. Compared to normal individuals, furthermore, patients with large hiatal hernias exhibit an increased frequency of TLESRs induced by gastric distention (30). All of these mechanisms appear to contribute to GERD in patients who have large hiatal hernias.

Gastric Contents and Gastric Emptying

To damage the esophageal mucosa, the refluxed gastric contents must be caustic. Caustic agents that might be present in the gastric juice include acid and pepsin produced by the stomach, and pancreatocobiliary products such as bile salts, lysolecithin, and pancreatic digestive enzymes that can enter the stomach in a retrograde fashion (from the duodenum through the pylorus). In the era before potent antisecretory medications such as proton pump inhibitors, physicians debated the relative contributions of the different gastric contents to the pathogenesis of reflux esophagitis. The modern clinical observation that aggressive acid inhibition with proton pump inhibitors almost always results in the healing of reflux esophagitis suggests that refluxed material other than acid and pepsin contributes little to esophageal damage in GERD (31). Some authorities have proposed that the reflux of bile may play a carcinogenetic role in Barrett's esophagus, and that non-acid reflux may contribute importantly to some of the extraesophageal manifestations of GERD (32). Few data directly support these allegations, however.

Using sensitive radionuclide tests, delayed gastric emptying has been found in more than 50% of patients with GERD (33). With delayed gastric emptying, gastric material available for reflux lingers in and distends the stomach. Gastric distention has at least two undesirable effects for patients with GERD: 1) Gastric distention stimulates gastric acid secretion, and 2) Gastric distention is a potent trigger for TLESRs that allow the acid to reflux into the esophagus.

Esophageal Clearance Mechanisms

To injure the esophagus, caustic refluxed material must have a sufficient duration of contact with the mucosa. The duration of contact is a function of esophageal clearance mechanisms, which include: 1) gravity, 2) peristalsis, 3) salivation, and 4) bicarbonate secretion by the submucosal glands of the esophagus. When a bolus of acid enters the esophagus, most of the material is cleared by the combined effects of gravity and peristalsis (32). The small quantity of residual acidic material that escapes clearance by gravity and peristalsis might cause mucosal damage if it were not neutralized by swallowed saliva (which is highly alkaline) and, to a lesser extent, by bicarbonate secreted into the lumen by the submucosal glands of the esophagus (34,35).

GERD often is associated with impaired esophageal acid clearance. Manometric studies have shown that 25% to 48% of patients with reflux esophagitis exhibit abnormalities in peristalsis (e.g. failed peristalsis, hypotensive peristalsis) that can interfere with esophageal emptying (36,37). Reflux that occurs during sleep can be particularly damaging to the

esophagus for several reasons related to esophageal clearance. In recumbency, gravity retards the clearance of refluxed material. Swallowing and salivation virtually cease during sleep and, therefore, there is no primary peristalsis and little saliva available to clear acid from the esophagus.

Cigarette smoking has been shown to increase esophageal acid exposure by increasing the frequency of acid reflux events and by decreasing salivary flow (38,39). Large hiatal hernias also can impair esophageal clearance, because esophageal material that is emptied into the hernia sac often returns to the esophagus (retrograde flow), either during the LES relaxations that normally accompany swallowing, or during contractions of stomach muscle that push the gastric contents in both antegrade and retrograde directions (40).

Esophageal Mucosal Resistance

Compared to the stomach and duodenum, the esophagus is highly susceptible to acid-peptic injury (41). Gastric and duodenal epithelial cells are shielded from luminal acid by a prominent coat of mucus, and by a layer of unstirred water that is rich in bicarbonate (Figure 5).

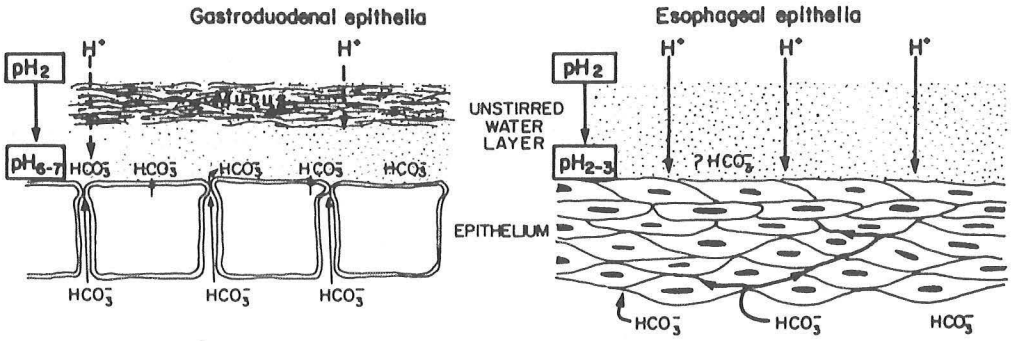

Figure 5. Pre-epithelial defenses of the gastroduodenal and esophageal epithelia. Reproduced from Am J Gastroenterol 1996; 91:1692 (reference 41).

In contrast, the stratified squamous epithelium of the esophagus has only a rudimentary cover of mucus and acid-buffering fluid that provides little protection from attack by H^+ ions. In the stomach and duodenum, minor peptic lesions are repaired quickly through a process called rapid restitution in which epithelial defects left by cells that have succumbed to peptic injury are sealed promptly by the migration of adjacent, healthy cells. Also, acid-induced gastroduodenal damage results in the formation of a protective cap of mucus, cellular debris, and bicarbonate ions that clings to the injured epithelium like a bandage to facilitate the healing process. The squamous epithelium of the esophagus lacks the capacity for both rapid restitution and mucus cap formation. Consequently, exposure of the acid-damaged esophagus even to small amounts of refluxed acid can perpetuate and extend the initial peptic injury.

Despite its relative vulnerability, the esophagus has some capacity to resist acid-peptic attack (42). To penetrate the esophageal epithelium, H^+ ions either must pass through the cell membrane or through intercellular spaces where ion movement is restricted by tight junctions and by intercellular material such as lipid and mucin. Both the squamous cell membranes and their intercellular junctional complexes pose substantial barriers to the passage of H^+ ions. Nevertheless, exposure to relatively high concentrations of acid can overwhelm these barriers. H^+ ions that enter the epithelial cells are buffered by intracellular proteins, phosphate, and bicarbonate. Also, squamous cell membranes have ion transport systems that can extrude H^+

ions out of the cell. These transport systems include a Na^+/H^+ exchanger and a Cl^-/HCO_3^- exchange mechanism. Finally, the esophageal blood supply provides post-epithelial protection by removing noxious substances that are extruded from the epithelial cells (e.g. CO_2 and H^+ ions), and by supplying bicarbonate that is used for buffering acid in the intercellular space.

Ambulatory esophageal pH monitoring studies have shown that normal individuals experience brief episodes of acid reflux each day (41). Apparently, the normal epithelial defenses are sufficient to prevent these brief episodes from causing esophageal injury. Most patients with reflux esophagitis have an abnormally prolonged duration of esophageal acid exposure that overwhelms the normal epithelial defenses. However, some patients have reflux esophagitis even though 24-hour pH monitoring studies demonstrate a normal daily duration of acid reflux (43). These patients may have yet uncharacterized defects in their epithelial protective factors.

NSAIDS and GERD

Epidemiologic studies suggest that the ingestion of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) can contribute to GERD (44). Patients with esophageal strictures appear to be especially susceptible to NSAID-induced esophageal injury (45). Many NSAID preparations are caustic to the mucosa, and severe local injury can result when a stricture or motility abnormality impedes passage of the NSAID tablet into the stomach. In a recent study, furthermore, the NSAID ibuprofen was shown to significantly increase gastroesophageal acid reflux in patients who had symptomatic GERD (46).

Helicobacter Pylori and GERD

A number of recent reports have suggested that gastric infection with *H. pylori* may help to protect the esophagus from the development of GERD and its complications (47). For example, one large, prospective study of consecutive patients in a general endoscopy unit found that *H. pylori* infection was significantly less common in patients with reflux esophagitis than in control patients without reflux disease (48). Labenz et al. found that patients with duodenal ulcers whose *H. pylori* infections were eradicated with antibiotics developed reflux esophagitis twice as often as those whose infections persisted (Figure 6) (49).

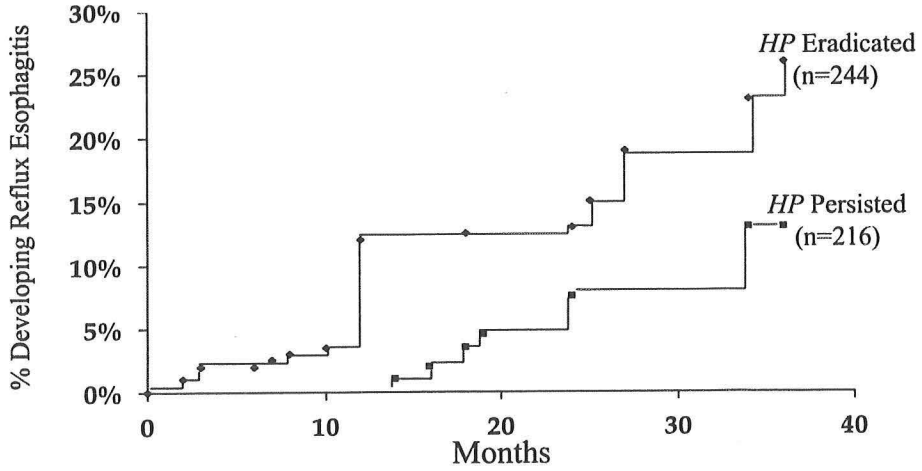

Figure 6. Development of reflux esophagitis in duodenal ulcer patients who had *H. pylori* infection eradicated, and in those with persistent *H. pylori* infection.
Data from Gastroenterology 1997; 112:1442 (reference 49).

Furthermore, the eradication of *H. pylori* infection has been found to render proton pump inhibitors less effective in elevating the gastric pH in some patients (50), and one study has shown that patients who have reflux esophagitis and *H. pylori* infection respond significantly better to PPI therapy than their uninfected counterparts (51). Graham and others have proposed that *H. pylori* infections which cause pangastritis also cause a decrease in gastric acid production that protects against GERD (52). Presently, the role of *H. pylori* infection in GERD is disputed.

Endoscopy for Patients with GERD

For patients with GERD, an endoscopic examination of the esophagus can answer the four clinical questions listed below:

Clinical Question	Implications of a "Yes" Answer
Is there reflux esophagitis?	Establishes a diagnosis of GERD
Is the esophagitis severe?	Potent antisecretory therapy (e.g. a PPI) will be needed
Is there an esophageal stricture?	Esophageal dilation may be needed
Is there Barrett's esophagus?	Regular endoscopic surveillance should be advised

The clinician should appreciate that endoscopy does not always answer the question, "Does the patient have GERD?" The endoscopic finding of reflux esophagitis establishes a diagnosis of GERD, but *a normal endoscopic examination does not eliminate GERD as a cause of symptoms.* Gastroesophageal reflux can cause disabling symptoms without causing visible esophageal damage (53). Endoscopic examination reveals esophagitis in only approximately 50% of patients who complain of frequent heartburn, and a number of studies suggest that heartburn severity is not a reliable index of esophagitis (54-56). Furthermore, the esophagus typically appears normal endoscopically in patients who have only extraesophageal symptoms of GERD (9). Patients with classic heartburn who respond readily to conventional antireflux therapy can be assumed to have GERD, and endoscopy is not necessary simply to confirm that diagnosis. Without endoscopic examination, however, it is not possible to answer all of the four clinical questions listed above.

The Practice Parameters Committee of the American College of Gastroenterology has recommended the following guideline on when to perform endoscopic evaluation for patients with GERD (57): "If the patient's history is typical for uncomplicated GERD, an initial trial of empirical therapy (including lifestyle modification) is appropriate. Patients in whom empiric therapy is unsuccessful or who have symptoms suggesting complicated disease should have further diagnostic testing. Selected individuals who have longstanding symptoms or who require continuous therapy may need endoscopic screening for Barrett's esophagus." In another publication dealing specifically with Barrett's esophagus (58), this same committee recommended that, "Patients with long standing GERD symptoms, particularly those $\geq$50 years of age, should have upper endoscopy to detect Barrett's esophagus." Symptoms that might suggest complicated disease requiring early endoscopic evaluation (without an empiric trial of therapy) include fever, anorexia, weight loss, dysphagia, odynophagia, and bleeding. Although these proposed approaches to patient management seem reasonable, it is important to recognize that they are merely committee recommendations whose efficacy has not been established by formal clinical investigation. Also, there is no clear consensus regarding which is the most appropriate medication to use for initial empiric therapy of GERD, i.e. a histamine H2-receptor blocker or a proton pump inhibitor.

Management of Patients with GERD

When planning a management strategy for patients with GERD, it is important to appreciate that the efficacy of any antireflux therapy is inversely related to the severity of the underlying reflux esophagitis, i.e. the worse the esophagitis the poorer the healing rate (1,59). A treatment that is highly effective for mild esophagitis may be virtually useless for patients with severe disease (60). This section outlines a step-wise approach to the therapy of GERD. However, for patients who are found to have severe, ulcerative, reflux esophagitis, it is appropriate to begin therapy immediately with potent acid-suppression (i.e. by administering a proton pump inhibitor) rather than proceeding step-wise through trials of agents unlikely to effect healing. Conversely, it may not be appropriate to begin the treatment of very mild GERD with a proton pump inhibitor.

Life-Style Modifications. It is traditional to recommend that the management of GERD begin with the following life-style modifications aimed at decreasing esophageal acid exposure:

1) Elevate the head of the bed on 4" to 6" blocks. This exploits the effect of gravity on esophageal clearance.
2) Advise weight loss for obese patients. In theory, obesity might increase abdominal pressure and thereby promote reflux.
3) Avoid recumbency for 3 hours after meals. TLESRs associated with gastroesophageal reflux occur most commonly after meals, and recumbency delays esophageal clearance of the refluxed material.
4) Avoid bedtime snacks. These may trigger TLESRs and stimulate nocturnal acid secretion, thereby promoting nocturnal reflux that can be especially damaging to the esophagus.
5) Avoid fatty foods, chocolate, peppermint, onions, and garlic. These foods may decrease LES pressure and delay gastric emptying, thereby promoting acid reflux.
6) Avoid cigarettes and alcohol. These agents may decrease LES pressure. Cigarette smoking also may decrease salivation that is important for esophageal acid clearance.
7) Avoid drugs that decrease LES pressure and delay gastric emptying. These include drugs that have anticholinergic effects, and calcium channel blocking agents.
8) Avoid NSAIDs.

Data that support the efficacy of these life-style modifications in controlling GERD are limited, and it is unclear how many patients who are prescribed such modifications actually implement the measures.

Antacids and Alginic Acid. Antacids and alginic acid can temporarily relieve episodic heartburn (58,60,61). However, few data are available on the utility of these agents for healing reflux esophagitis, or for the long-term management of GERD symptoms.

Histamine H2-Receptor Blocking Agents. For patients with mild GERD who respond well to life-style modifications, medications may not be necessary, and antacids can be used to relieve occasional episodes of heartburn. For patients with persistent symptoms, histamine H2-receptor blocking agents can be prescribed. Four agents are available in the United States (cimetidine, ranitidine, famotidine, and nizatidine), and all are similar in efficacy and side effect profiles. When administered in conventional doses, the histamine H2-blockers are safe medications that can be expected to relieve GERD symptoms and heal esophagitis within 12

weeks in approximately one-half to two-thirds of all patients (59-64). These agents are most useful for patients with GERD of mild to moderate severity in whom high rates of healing can be anticipated. Healing rates with H2-blockers are poor for patients with severe reflux esophagitis, however (60). High doses of histamine H2-receptor blockers (up to 8 times the conventional dose) have been used effectively to treat esophagitis in resistant cases (65,66), but this approach generally is not recommended. Few data document the long-term efficacy of H2-blockers used in any dosage, and tolerance to these agents is known to develop (67). For patients with severe GERD, it seems preferable to use a more potent inhibitor of gastric acid secretion (i.e. a proton pump inhibitor) than to use high-dose H2-blocker therapy.

Prokinetic Agents. In theory, prokinetic agents might decrease gastroesophageal reflux by increasing LES pressure and by enhancing gastric emptying (68). Only two prokinetics have been used widely in the United States - metoclopramide and cisapride. Metoclopramide, a dopamine antagonist, has some therapeutic efficacy in patients with mild GERD. The use of metoclopramide is limited by its frequent side effects such as agitation, restlessness, somnolence, and extrapyramidal symptoms that occur in up to 30% of patients. Cisapride, a serotonin-4 ($5\text{-}HT_4$) receptor agonist, appears to work as a prokinetic by increasing the availability of acetylcholine released from enteric neurons. A number of studies have shown therapeutic efficacy for cisapride in patients with mild GERD. However, as of July 14, 2000, Janssen Pharmaceutica discontinued the marketing of cisapride because the drug was found to cause lethal cardiac arrhythmias in patients with a number of predisposing conditions. Consequently, cisapride is no longer available for the treatment of GERD.

Sucralfate. Sucralfate is an exceptionally safe medication that has some demonstrated efficacy in the treatment of mild reflux esophagitis (69,70). Relatively few published data are available on the use of sucralfate in GERD, however, and the drug has never achieved popularity as an antireflux therapy.

Proton Pump Inhibitors. The proton pump inhibitors (PPIs) omeprazole, lansoprazole, rabeprazole, and pantoprazole have been shown to be extremely effective agents for the treatment of GERD. Like the four H2-receptor blockers discussed above, the four available PPIs are similar in efficacy and side effect profiles. A fifth agent, esomeprazole, will be available soon. Preliminary studies suggest that, when used in conventional dosage, esomeprazole may effect marginally higher rates of healing of reflux esophagitis than other PPIs (71). In patients with mild to moderately severe reflux esophagitis treated with PPIs in conventional dosages, healing rates of 80% to 100% can be expected within 8 to 12 weeks (59,62,64). Very severe (grade 4) reflux esophagitis may persist despite conventional-dose PPI therapy in up to 40% of cases, however (71). In most such resistant cases, the esophagitis usually can be healed by increasing the dose of the PPI (72-75). Recent studies also have shown that aggressive acid suppression with PPIs improves dysphagia and decreases the need for esophageal dilation in patients who have peptic esophageal strictures (76,77).

For patients with severe GERD who respond to proton pump inhibitors, GERD returns shortly after stopping the drug in the majority of cases, and maintenance therapy is required (78). For most patients, the dose of PPI necessary to maintain remission is at least the dose required to heal the acute esophagitis. This phenomenon is illustrated in Figure 7 which shows the results of a study on maintenance therapies for GERD (78). One hundred fifty-nine patients with reflux esophagitis that healed within eight weeks of treatment with omeprazole 20 mg QD were

randomly assigned to receive long-term maintenance therapy with daily omeprazole (20 mg QD), weekend omeprazole (20 mg on 3 consecutive days of the week), or daily ranitidine (150 mg BID). At 12 months, actuarial analysis revealed an 89% rate of sustained remission for patients treated with daily omeprazole compared to rates of only 32% and 25% for those treated with weekend omeprazole and daily ranitidine, respectively (P<0.001).

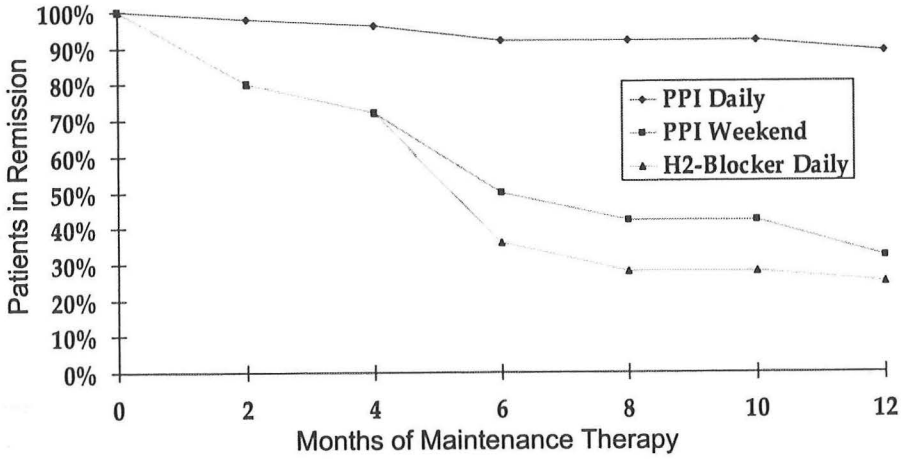

Figure 7
Maintenance therapy for patients with reflux esophagitis.
Data from Gut 1994;35:590 (reference 78).

For patients with severe GERD, furthermore, the PPI maintenance dose requirement often increases with time. One long-term study of patients who had severe GERD treated with a maintenance dose of omeprazole (20 mg per day) found that relapses occurred frequently (at the rate of 1 per 9.4 treatment-years), and that patients often required increasing doses of omeprazole (up to 120 mg per day) to maintain GERD in remission (74).

The profound acid suppression that can be achieved with the use of PPIs has raised theoretical concerns regarding their long-term safety. Protracted acid suppression can elevate the serum level of gastrin, a hormone that has trophic effects on the stomach and colon, and might result in colonization of the stomach with bacteria that can convert dietary nitrates to carcinogenic nitrosamines. These effects conceivably might contribute to the development of gastric and colonic neoplasms. Furthermore, some data suggest that sustained acid suppression with PPIs might hasten the development of gastric atrophy in patients who are infected with *Helicobacter pylori* (79), and that chronic PPI therapy might interfere with vitamin B12 absorption (80). Despite these theoretical concerns, there are no reports of tumors or nutritional deficiencies clearly attributable to the use of PPIs after more than a decade of extensive clinical experience with these agents (57).

Antireflux Surgery. There are a number of different antireflux operations (e.g. Nissen, Belsey, Toupet fundoplication), but all share some fundamental features (81-83). In all these procedures, the surgeon creates an intra-abdominal segment of esophagus, reduces the hiatal hernia, approximates the diaphragmatic crurae, and wraps a portion of the gastric fundus around the distal esophagus (fundoplication). These maneuvers create a barrier to gastroesophageal reflux through a number of potential mechanisms (84,85). The surgery narrows the angle of His

which may create an antireflux flap-valve effect. Restoration of the distal esophagus to the positive pressure environment of the abdomen also may prevent reflux. Reduction of the hiatal hernia and approximation of the diaphragmatic crurae may enable the crural diaphragm to buttress the LES and to pinch the distal esophagus during inspiration, thereby restoring a normal antireflux mechanism. The fundoplication itself may act as a one-way valve, and also may prevent the distention of the gastric fundus that can trigger TLESRs.

A number of reports have described excellent results for fundoplication, with more than 85% of patients experiencing relief of their signs and symptoms of GERD (81-83). However, few studies on this issue have been prospective and randomized. A large Department of Veterans Affairs cooperative study conducted in the late 1980's prospectively compared the efficacy of available medical and surgical therapies for GERD (86). The 247 study subjects all had GERD complicated by Barrett's esophagus, esophageal ulceration, esophageal stricture, or severe erosive esophagitis. Antireflux life-style modifications were prescribed for all patients regardless of treatment group. Patients were randomly assigned to receive one of three types of treatment: continuous medical therapy, symptomatic medical therapy, or surgical therapy. Continuous medical therapy included antacid tablets and ranitidine taken on a daily basis regardless of symptoms; metoclopramide and sucralfate were added in a stepwise fashion for patients who remained symptomatic. For patients in the symptomatic medical therapy group, drug therapy was used only for control of symptoms. Therapy in these patients began with antacid tablets; ranitidine, metoclopramide, and sucralfate were added in a stepwise fashion for symptoms that could not be controlled with antacids alone. Patients in the surgical therapy group had Nissen fundoplications. All three therapies resulted in significant improvements in the symptoms and endoscopic signs of GERD for up to two years (Figure 8). However, surgical therapy was significantly better than both medical therapies administered for the two-year duration of the study. Overall satisfaction with therapy also was better for patients in the surgical group. This prospective, randomized study clearly demonstrated that surgical therapy was superior to medical therapy (without PPIs) for the short-term treatment of GERD.

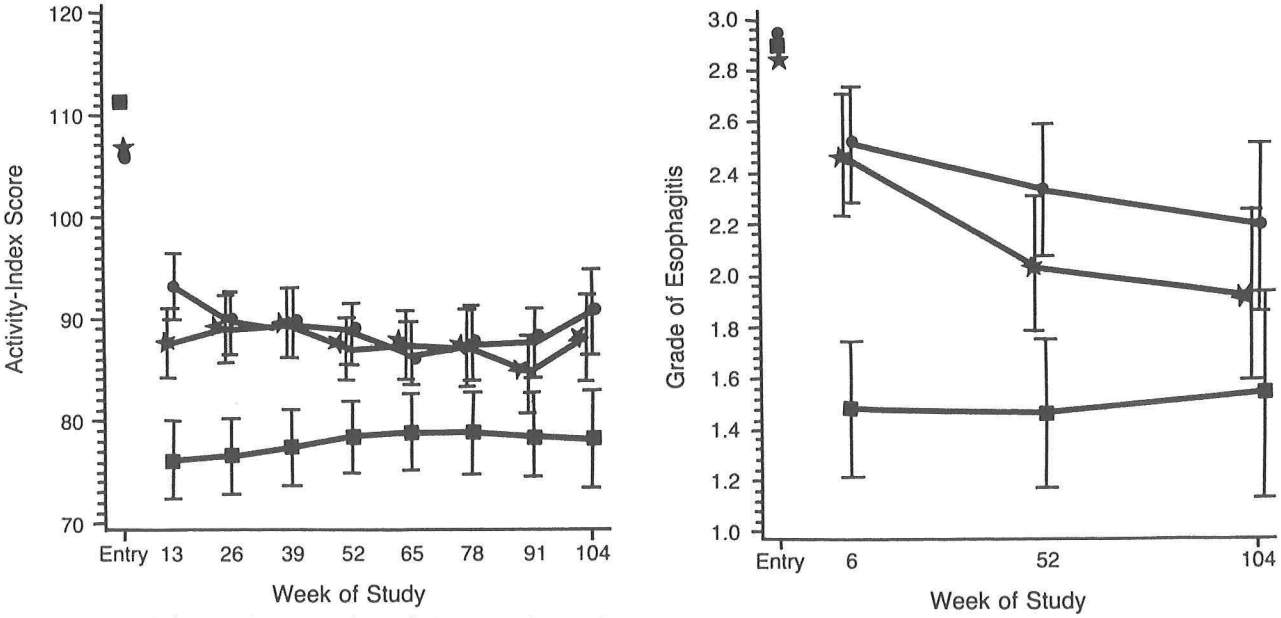

Figure 8. Results of GERD therapies on symptoms (activity index score) and grade of esophagitis. Values are for continuous medical therapy (stars), symptomatic medical therapy (circles), and surgical therapy (squares). Reprinted from N Engl J Med 1992; 326:786 (ref 86).

Antireflux surgery now can be performed laparoscopically, and a number of reports have described the short-term results of laparoscopic fundoplication (82,83,87-89). The technique of laparoscopic Nissen fundoplication is virtually identical to that of the open procedure, and the mortality rate is between 0.2% and 0.4% (87,90). The laparoscopic approach has become popular, not because it is safer or because it produces a better functional result than the open procedure, but because of proposed advantages in the degree of postoperative discomfort, duration of hospital stay, and cosmetic outcome (91). Two recent randomized trials of laparoscopic and open Nissen fundoplication found no significant differences in the functional results of the two procedures (i.e. relief of GERD symptoms, reduction in esophageal acid exposure) (92,93). However, one of those studies was terminated prematurely because an interim analysis showed an excess of adverse outcomes in the group treated laparoscopically (93). Furthermore, at least one study has shown that the primary factor involved in overall patient satisfaction with antireflux surgery is the relief of GERD symptoms, not the operative approach (94). These observations suggest that the availability of laparoscopic surgery should not be a major factor in the physician's decision regarding the advisability of fundoplication. The primary decision for the clinician is whether or not the patient should have an antireflux operation, not how the operation should be performed.

One of the most crucial and controversial issues concerning the role of antireflux surgery in the treatment of GERD relates to the long-term outcome of the procedure. Relatively few reports deal with the late results of fundoplication, and those that do describe contradictory findings. Some investigators have reported success rates that exceed 90% at 10 to 20 years after open fundoplication (95,96), whereas others have described breakdown of the operation and the return of reflux esophagitis in more than 50% of cases within 6 years (97). Furthermore, the conclusions of long-term studies on fundoplication often have based on subjective results alone, and few reports have included objective evidence for control of GERD (e.g. results of endoscopic examinations and 24-hour esophageal pH monitoring studies) (98). Fundoplication has been performed laparoscopically only since 1991, and so long-term results are not yet available for laparoscopic antireflux surgery.

We recently reported the preliminary results of a follow-up study on the patients who participated in the VA cooperative study on reflux disease described above (86,99,100). The follow-up study is unique in providing data on the long-term outcome of a well-defined cohort of patients who had participated in a prospective, randomized trial of medical and surgical treatments for GERD. Using a professional search agency, we determined the whereabouts of 239 (97%) of the original 247 study patients. 129 of the 160 known survivors agreed to participate in the follow-up study that included a GERD history, GERD symptom scoring, endoscopic examination, and completion of the SF-36 general health and well-being form. There were 79 deaths involving 33 (40%) of the 82 surgical patients and 46 (28%) of the 165 medical patients. Survival over a period of 140 months was significantly shorter in the surgical group (P=0.047, RR 1.57, 95% CI 1.01 to 2.46). During the follow-up period of 10 to 13 years, we found that surgical patients were significantly less likely to take antireflux medications regularly and, when antireflux medications were discontinued, their GERD symptoms were significantly less severe than those of the medical patients. However, 62% of the surgical patients took antireflux medications on a regular basis, and there were no significant differences between the groups in the rates of neoplastic and peptic complications of GERD, overall physical and mental well-being scores, and overall satisfaction with antireflux therapy. For reasons that are not clear, antireflux surgery was associated with a significant decrease in long-term survival.

Endoscopic Antireflux Procedures. Two new endoscopic therapies for GERD have recently been approved by the Food and Drug Administration – the Bard® endoscopic suturing system and the Stretta™ radiofrequency energy system. The Bard® endoscopic suturing system uses an endoscopic sewing machine device to plicate the gastroesophageal junction from the mucosal side. The Stretta™ system delivers radiofrequency (microwave) energy that creates thermal lesions in the LES muscle. Although these devices are FDA approved and they are being sold to physicians for clinical application, there are no controlled trials demonstrating the efficacy of the procedures. The small clinical studies (the largest has only 64 patients) that are available on these procedures presently are reported only in abstract form (101-104). Consequently, the efficacy of these endoscopic techniques is not known. Furthermore, it is not clear how the procedures create an antireflux barrier (if in fact they do), and the safety of the techniques is questionable even though no serious complications were observed in the small clinical studies.

Before recommending these procedures, the clinician should consider that GERD is a very uncommon cause of mortality (105). Despite the rising incidence of esophageal adenocarcinoma, GERD is a benign condition in the vast majority of affected patients. The VA cooperative study discussed above found that esophageal cancer was an uncommon cause of death even for patients with severe GERD, and there was no significant difference in the rate of esophageal cancer development between groups of medically and surgically treated patients (99,100). Indeed, the long-term survival for the surgical patients was shorter than that for the medical group. Rather than preventing deaths from cancer, the use of the invasive therapy unexpectedly was associated with a higher long-term mortality rate. In light of these findings, the new endoscopic antireflux procedures should not be recommended with the promise that they will prevent esophageal adenocarcinoma. The wise clinician will await the results of controlled, clinical trials before recommending invasive and potentially hazardous therapies for the treatment of a benign condition that is easily controlled with safe medications.

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