TITLE: Gastroesophageal Reflux Disease and the Otolaryngologic Manifestations
SOURCE: Dept. of Otolaryngology, UTMB, Grand Rounds
DATE: February 3, 1999
RESIDENT PHYSICIAN: Jim C. Grant, M.D.
FACULTY: Francis B. Quinn, Jr., M.D.
SERIES EDITOR: Francis B. Quinn, Jr., M.D.

“This material was prepared by resident physicians in partial fulfillment of educational requirements established for the Postgraduate Training Program of the UTMB Department of Otolaryngology/Head and Neck Surgery and was not intended for clinical use in its present form. It was prepared for the purpose of stimulating group discussion in a conference setting. No warranties, either express or implied, are made with respect to its accuracy, completeness, or timeliness. The material does not necessarily reflect the current or past opinions of members of the UTMB faculty and should not be used for purposes of diagnosis or treatment without consulting appropriate literature sources and informed professional opinion.”

The backward flow of gastric contents into the esophagus produces a well recognized clinical disorder referred to as gastroesophageal reflux disease. In a well cited paper from Asher Winkeltein (1935), the notion of "peptic esophagitis" was introduced. The paper elegantly described the clinical symptoms of several patients in which the cause was proposed of esophageal inflammation secondary to a refluxate of hydrochloric acid and pepsin. A few years later, gastroesophageal reflux was equated with "hiatal hernia" sparking a fervor of surgical correction of the diaphragmatic defects. As progress was made, especially in regards to gastrointestinal manometry, the presence of a high pressure zone was noted in the distal esophagus which was later denoted as the lower esophageal sphincter. Physiologists have concentrated study on this area which has certainly promoted a better understanding of the pathophysiology of reflux disease. There are several other interplaying factors, however, that are considered as the cause of GERD.

The connection between gastroesophageal disease and a constellation of laryngopharyngeal / pulmonary manifestations has been a topic of great debate. Cause and effect can be difficult to establish; however, an increasing number of published animal studies, prospective controlled clinical trials, and case reports have bolstered the claim that there is an association. While several details of reflux as the etiology of several disorders remains to be elucidated, significant success has been documented in curing the supposed manifestations through reflux targeted management.

Natural Barriers to Gastroesophageal Reflux.

There are a number of naturally occurring barriers to prevent the high pressure gastric contents from readily refluxing into the lower pressure distal esophagus. The antireflux barrier may be roughly broken down to four lines of defense – (1) the lower esophageal sphincter, (2) esophageal acid clearance, (3) epithelial resistance, and (4) the upper esophageal sphincter.
**Lower Esophageal Sphincter.**

The lower esophageal sphincter is considered the greatest barrier to preventing gastric reflux. While anatomically ill defined, it is generally regarded as a thickening of the muscularis propria in the distal 1.5 to 3.0 cm. In the functioning state, it has the following abilities – (1) maintains an markedly elevated resting pressure relative to the proximal stomach and distal esophagus, (2) reduction of the resting pressure to equal the intragastric pressure in response to more proximal esophageal distension (i.e. food bolus), and (3) contract in response to various physiological stimuli. It has been found that the lower esophageal sphincter is controlled by a delicate balance among the intrinsic tone of the smooth muscle, the myenteric plexus within the segment, central neural influences felt to be mediated from the vagus nerve, and local hormonal mediators.

Using precise manometric studies in human subjects, it has been found that the LES is tonically contracted at rest with a mean pressure of 20 mm H2O. This sharply demarcates this region from the low pressure in the distal esophagus from the high intragastric pressures. The details regarding the exact innervation is not well understood but experimental data suggest that a neurally mediated cholinergic component is important in LES competence. For instance, bilateral vagal resections in a canine study showed that the resting pressure of the sphincter fell 30 – 40% of normal. Applying atropine to this region brought about the same pressure reduction in this animal study. It has also been postulated that an inhibitory pathway involving a non-adrenergic neurotransmitter may be responsible for the physiological relaxation at the initiation of swallowing a food bolus. Local hormonal mediators have also been shown to modulate the lower esophageal pressure. For instance, gastrin, angiotensin II, pitressin, and motilin markedly increase the basal tone, while vasoactive intestinal peptide, glucagon, and secretin reduce the contractile tone.

Local and regional anatomical factors on the lower esophageal sphincter are equally important. The overall length of esophagus that is intraabdominal plays an important antireflux barrier as there is less dependence on the action of the lower esophageal sphincter. The elevated intraabdominal pressures subjects the esophageal lumen to an extrinsic compressive force. Secondly, the "cardiac angle" refers to the normally acute angle at which the distal esophagus / esophageal sphincter inserts into the stomach. The angle of insertion conveys protection from reflux through a valve effect. The phrenoesophageal ligament inserts into this region which further defines the acute angle as well as assisting the diaphragm as a gross mechanical barrier between the thoracic and abdominal cavities. Finally, the crural diaphragm is felt to impart a "phasic" component to the tonic high pressure of the lower esophageal sphincter, based on EMG studies. Resection of a portion of the crural diaphragm directly reduced the LES to 25% of normal in a canine study.

**Esophageal Acid Clearance.**

In asymptomatic, healthy subjects who underwent 24 hour pH probe testing, it has been estimated that gastroesophageal reflux occurs up to a full one hour a day. While reflux is considered a normal, physiological event, reflux esophagitis is not. There are several factors that are implicated in the development of reflux esophagitis, including (1) length of time the gastric contents are in contact with the esophageal mucosa, (2) the potency of the gastric contents, and
(3) the capacity of the esophagus to neutralize and clear the caustic contents from the mucosal surface. The cornerstone to successful acid clearance is effective, purposeful esophageal motility and salivary flow. Peristaltic activity of the esophagus has been characterized as primary, which is initiated from proximal stimulation (i.e. swallowing food bolus) and secondary, which is initiated from irritant stimulation of the distal esophagus (i.e. reflux). Secondary peristaltic activity is felt to be extremely effective at removing the overall volume of refluxate. For instance, perfusion of the distal esophagus with 15 cc of acid promptly initiated a secondary peristaltic wave which reduced the volume to 1 cc in less roughly 15 seconds. While the secondary peristaltic wave can reduce the overall volume, the pH remains roughly the same in this esophageal segment. It requires the neutralizing effect of saliva to reduce the acid load on the mucosa. A reflex pathway is initiated following the introduction of an acidic refluxate that promotes a significant increase in salivary flow, increased bicarbonate concentration within the saliva, and causes spontaneous swallowing activity every 30 to 60 seconds until adequate buffering has occurred. In a functioning system, the pH can be buffered to greater than 4.0 within 5 minutes.

**Esophageal Epithelial Resistance.**

From a histiological perspective, there is multilayered barrier that imparts an inherent tissue resistance to damage. Mucus has viscoelastic and gel properties that is known to serve as an excellent barrier to the penetration of the larger molecules, such as pepsin, but has little protection against the much smaller hydrogen ion. Protection against the hydrogen ion is seen as the second layer, termed the "unstirred water layer", that has significant alkaline properties. Below this, the intercellular bridges between the epithelial cells and the actual cell membrane protect against pepsin, trypsin, hydrogen ions, etc. The final line is the subepithelial blood flow that easily removes toxic products from the area, brings bicarbonate to act as a buffering sink, and can increase blood flow in response to inflammatory mediators.

**Upper Esophageal Sphincter.**

As discussed by Koufman, the upper esophageal sphincter and the cricopharyngeus muscle are terms that are used interchangeably. Anatomists have disagreed whether this muscle is distinct from the inferior constrictor. Its innervation comes from the pharyngeal plexus, the vagus (parasympathetic input), and the glossopharyngeal nerve (sensory). Like the lower esophageal sphincter, the cricopharyngeus is in a state of tonic contraction, with relaxation mediated from vagal stimulation. Experimental data shows that the UES pressure increases in response to acidity in the distal esophagus as well as with transient increases with inspiration. This has suggested at least two distinct roles of the UES – (1) the prevention of aerophagia during inspiration and (2) to act as an upper esophageal barrier to gastroesophageal reflux.

**Pathophysiology of Gastroesophageal Reflux Disease.**

As an understanding of the complex interplays of normal esophageal physiology has increased, the theories of the etiology of gastroesophageal reflux has also changed. In the 1940’s, the hiatal hernia was the leading explanation of reflux disease. Chronic hypotension of the lower esophageal sphincter, and more recently, transient lower esophageal sphincter relaxation has
been the major focus in uncovering the predisposing pathophysiological conditions causing reflux. While pathology at the level of the LES remains pivotal cause of GERD, it is important to appreciate that the disease is largely multifactorial. Several aspects of the normally occurring barriers to GERD and their dysfunction will be addressed.

Lower Esophageal Sphincter Hypotension / Transient Lower Esophageal Sphincter Relaxation.

Interference with the lower esophageal sphincter to maintain adequate tone is one of the best characterized defects in patients with gastroesophageal reflux disease. Data that associate this deficiency with reflux has come from three sources. First, mechanical disruption of the LES results in a very significant rate of esophagitis, typically severe. This has been seen in patients after segmental resection of the distal esophagus for malignancy as well as in patients who underwent a Heller myotomy for achalasia treatment. Second, static manometric measurements taken from patients with symptoms of GERD have shown that there is generally a lower basal tone at the level of the LES when compared to controls. Several studies have also directly correlated the severity of esophagitis with the degree of LES hypotension. Finally, the third source of information is the identification that pharmacological or surgical manipulations that increase the LES tone has lead to a decrease in reflux episodes and to an increase of esophageal mucosal healing. Recently, the concept of transient lower esophageal sphincter relaxation has been introduced to explain the cause of gastroesophageal reflux disease in patients with normal LES basal tone on static manometry. It has been postulated that the LES pressure is normal on a sustained basis, but that pathological, transient hypotensive episodes allows reflux activity. This theory has been the focus of several early studies, but largely remains an unknown at this time.

There are pharmacological, physiological, and pathological conditions that well described in causing lower esophageal sphincter hypotension. Examples of pharmacological or exogenous agents known to cause LES pressure decreases includes diazepam, barbiturates, calcium channel blockers, NSAIDS, theophylline, and nicotine. Dietary elements such as fat, chocolate, ethanol, carminatives (peppermint, spearmint), and caffeine have all been shown to also potently decrease the sphincter pressure. Spicy foods have not been correlated with causing reflux but can exacerbate symptoms from their irritative effect on the already inflammed esophagus. Certain normal physiological conditions are also known to cause lower esophageal sphincter incompetence leading to a higher incidence of GERD. Pregnancy is notorious for inducing GERD in otherwise normal woman and is caused by two factors – (1) increased intraabdominal pressure from the growing fetus and (2) progesterone induced LES relaxation. Additionally, infants may be predisposed to more functional reflux and "regurgitation" as the sphincter tone does not attain normal, mature levels until approximately 6 months of age. The pathological causes for lower esophageal sphincter incompetence are numerous; however, those systemic disorders with myogenic or neurological components are usually fraught with reflux as a co-morbidity. Well known disorders include scleroderma, amyloidosis, diabetes mellitus, and hypothyroidism which cause dysfunction at the level of the LES as well as in esophageal motility.
**Peristaltic Dysfunction.**

Esophageal clearance and salivary neutralization of refluxate has been discussed in regards to its effectiveness as an antireflux barrier. Kahir and colleagues concentrated on esophageal clearance times in patients with symptomatic GERD. They found that 48% of the studied patients had reduced esophageal peristaltic activity, both primary and secondary, that resulted in a significantly increased time for acid clearance as compared to the control group.\(^{19}\) While the cause of disordered peristaltic activity was not specifically addressed, this study illustrates that in addition to a functioning lower esophageal sphincter, the esophagus must have the capability to remove the refluxate. As discussed earlier, scleroderma, amyloidosis, diabetes mellitus, hypothyroidism, as well as alcohol abuse, familial visceral myopathy, and others, interfere with successful esophageal motility. The volume and quality of saliva can not be ignored as its role in buffering the lower esophagus. Xerostomia is the result of many factors including pharmacologic, autoimmune (Sicca syndrome), and post radiation therapy that has shown to increase the risk for reflux esophagitis in patients with otherwise normal esophageal motility and LES basal pressure.

**Gastric Factors.**

A correlation has been established between the frequency and severity of reflux to an increase in gastric volume and content in the gastric juice. Both volume and content of the refluxate are dependent on the following factors – (1) gastric acid secretion rate, (2) gastric emptying rate, (3) and duodenal gastric reflux. Patients with Zollinger-Ellison syndrome (gastrinoma) profoundly oversecrete hydrochloric acid and pepsin that grossly overwhelms the normal barriers. There has been a reported 60% or greater incidence of severe reflux esophagitis.\(^ {20}\) Delayed gastric emptying results in gastric distension which physiologically imparts a protective mechanism by increasing the lower and upper esophageal sphincter resting pressures. This hardly explains the significant incidence of reflux disease in patient with known gastric motility disorders, i.e. diabetic neuropathic gastroparesis. Providing a possible explanation, it has been experimentally illustrated that while the basal tone increases, there is a 4-fold increase in the episodes of transient lower esophageal sphincter relaxations.\(^ {21}\)

**Otolaryngology Manifestations of Reflux Disease**

Gastroesophageal reflux disease has long been implicated as a causative factor in various upper aerodigestive diseases. While the co-existence of gastroesophageal reflux with laryngopharyngeal /pulmonary diseases has been well documented, precisely delineating reflux as the cause has been far more difficult. From a historical perspective, Cherry and Marguiles (1968) recognized that gastric refluxate in the larynx might be the causative factor in posterior laryngeal inflammation, laryngeal contact ulcers, and laryngeal granuloma formation, as their noted significant clinical improvement with antireflux treatment.\(^ {21}\) These case reports were followed experimentally in an animal model. It was found that similar laryngeal lesions (contact ulcer, granulomas, and inflammation) could be reproduced with the application of gastric juices on the laryngeal mucosa. Although gastric acid induced characteristic mucosal changes in the larynx, was gastroesophageal reflux the etiology of numerous inflammatory as well as neoplastic conditions in the upper aerodigestive tract?
Koufman and others investigators have introduced convincing data correlating GERD with laryngopharyngeal / pulmonary disease. In an elegant thesis article, Koufman presented his findings of otolaryngologic manifestations of gastroesophageal reflux disease based on symptom survey, results of 24 hour pH probe monitoring, outcomes of antireflux treatment, and an animal model illustrating the role of acid and pepsin in the development of laryngeal injury. He estimated that 10% of the patients with laryngeal complaints have gastroesophageal reflux disease as the primary disorder. Based on the symptom survey, Koufman noted that those patients presenting with a reflux induced laryngeal disorders were "atypical" in comparison to the more "heartburn-esophagitis" patient usually seen by the gastroenterologist. By "atypical", this subgroup of patients are defined by their conspicuous, and surprising, absence of overt reflux esophagitis and the corresponding symptoms such as heartburn or regurgitation. The reason for this disparity is unknown. In the literature, the otolaryngology patient with a suspected GER-related disorder had heartburn as a symptom in a minority of the patients. This has been seen in a number of independent studies – Ossakow et al (1987) 6% (N=63), Toothill et al. (1991) 20% (N=207) and Koufman (1991) 43% (N=197).

The incidence of esophagitis in the otolaryngology patient was also correspondingly low. For instance, Wiener et al (1989) showed that in 33 otolaryngology patients presenting with chronic hoarseness, 79% had an abnormal pH-metry results while 73% had no evidence of esophageal inflammation on endoscopic exam.

The clinical conditions or symptoms described by Koufman as the most common gastroesophageal reflux-associated otolaryngologic disorders are –

- (1) reflux laryngitis (with or without granuloma formation,
- (2) cervical dysphagia,
- (3) globus pharyngeus,
- (4) chronic cough,
- (5) laryngeal / tracheal stenosis, and
- (6) laryngeal carcinoma.

The most common symptoms, in decreasing order, seen by Koufman of reflux-associated laryngopharyngeal disease are –

- (1) hoarseness,
- (2) chronic cough,
- (3) globus pharyngeus,
- (4) heartburn / regurgitation,
- (5) chronic throat clearing, and
- (6) cervical dysphagia.

While the incidence of heartburn and regurgitation was higher than in other published studies, the gastrointestinal symptoms were generally mild. Further questioning of those with GI complaints found that 40% had fewer than three occurrences per week, 40% had an average of one episode per day, while only 20% had frequent daily episodes of heartburn or regurgitation. Various pulmonary disorders have also been examined critically to determine their association with GERD. Most notably has been asthma, but recurrent pneumonia, bronchitis, bronchiectasis, and pulmonary fibrosis has also been investigated.
The gastroesophageal reflux-associated presenting symptoms and manifestations in the pediatric population has some notable differences than the adult patient. Most, if not all, infants have functional gastroesophageal reflux that gradually improves with time. Pathologic reflux is far less common, estimated at less than 2-3% of normal infants. Neurologically handicapped children are at the greatest risk for significant complications from GERD. In the pediatric gastroenterology literature, it is felt that reflux generally abates in 55% of infants by 10 months of age and in 81% of infants by 18 months of age. Anatomically, there are several factors explaining reflux disease. As previously discussed, lower esophageal sphincter pressure is low at birth and progressively matures to normal adult levels at 6 months of age; furthermore, the cardiac angle is obtuse at birth, gradually becoming acute with growth. Pyloric stenosis, gut malrotation, and congenital gastrointestinal webs and strictures are unique anatomical anomalies in this population that can be related to severe reflux. As in the adult population, several pharmacological agents predispose to reflux disease, i.e. theophylline. Food allergy has also been implicated, and should be entertained, as a cause of gastroesophageal reflux disease. As an example, Iacona et al tested 204 children with documented GERD for cows milk allergy, finding that 42% had a positive allergy test.

In infants and small children, the symptoms of gastroesophageal reflux disease may present in very subtle ways. Nonverbal, unspecific clues such as irritability, crying, sleep disturbances, and decreased appetite may be the early signs. A review of 600 cases of GER in children under the age of two revealed 25 cases of feeding resistance as the only outward sign of this disease. Apneic events with bradycardia in infants has been postulated to be a manifestation of GERD, although the causality remains uncertain at this time. Likewise, asthma in children has been evaluated a sign of significant reflux. An interesting atypical presentation of gastroesophageal reflux requires mention – Sandifers syndrome. Abnormal head and neck posturing associated with reflux disease is the defining characteristic, felt to be a response to the pain of reflux in the distal, sensitive esophagus. Antireflux treatment leads to resolution of the posturing.

Several of the common otolaryngologic manifestations of gastroesophageal reflux will be discussed in detail. Supporting evidence for gastroesophageal reflux as the cause for these manifestations is presented in a combination of several forms, namely – (1) animal models, (2) evaluating the frequency of co-existence of the otolaryngologic disorder with reflux, and (3) indirectly through outcome studies using antireflux treatment.

**Reflex Laryngitis.**

Hoarseness is a common symptom with many patients having "non-specific laryngitis". For the chronic patient with laryngeal granulation tissue or "posterior laryngitis", Koufman insists that evaluation for reflux disease be given priority. Several studies have supported reflux as a possible cause for chronic laryngitis, providing diagnostic data illustrating a high incidence of GERD and successful outcome with reflux directed management. For instance, using a combination of pH-metry, manometry, and acid perfusion testing in a group of patients with laryngeal contact ulcers, Ohman et al found that 74% had gross evidence of esophageal dysfunction, suggesting reflux as a major factor. In a more recent study by Hanson et al, the outcome of aggressive, prolonged antireflux treatment in patients with chronic laryngitis was presented. They claim an impressive 96% overall success rate in the treatment of 203 patients,
with outcome measures based on resolution of symptoms as well as telescopic evidence of reversal of laryngeal mucosal injury. Similarily, Deveney et al presented thirteen patients with chronic hoarseness and laryngeal findings of inflammation, contact ulcers, and granulation tissue. He notes all patients had abnormal pH-probe monitoring and gives an overall 82% successful outcome (hoarseness resolved / laryngeal lesions healed) with antireflux treatment, albeit surgical in these study group.

**Globus Pharyngeus.**

A foreign body sensation in the throat (globus pharyngeus) may be from a variety of causes including mechanical, inflammatory, or neoplastic. While the role of GERD as an etiologic factor in the development of globus pharyngeus is controversial, most would agree that reflux may be one of the causes. Three mechanisms for the development of GER-related globus pharyngeus are –

- (1) actual inflammation and swelling of laryngopharyngeal structures as a result of direct exposure to the gastric refluxate,
- (2) referred discomfort from esophagitis in the absence of direct reflux on the laryngopharyngeal mucosa, and
- (3) reflex hypertonicity of the UES from esophageal reflux.

**Cervical Dysphagia.**

Oropharyngeal dysphagia has been defined as difficult passage of solids or liquids from the mouth to the upper esophagus. Five causes of cervical dysphagia have been described in the literature --

- (1) cerebral,
- (2) peripheral neuropathic,
- (3) muscular,
- (4) cricopharyngeal dysfunction, and
- (5) local factors (i.e. inflammation from reflux).

The role of reflux in cervical dysphagia was investigated by Henderson who found that as many as 50% of patients with documented GERD had cervical dysphagia as a prominent symptom. In attempting to explain the etiology of cervical dysphagia, Ellis reported a significantly higher upper esophageal pressure in reflux patients, suggesting that cricopharyngeal hypercontractility may produce this symptom. While the exact cause of GERD-associated cervical dysphagia is unclear, it is evident that this a common complaint in reflux patients.

**Pulmonary Disorders.**

The association between gastroesophageal reflux disease and a constellation of pulmonary disorders such as asthma, recurrent pneumonia, bronchitis, and pulmonary fibrosis have received attention in the recent literature. It is estimated, from several studies, that the co-existence of GERD and pulmonary disease ranges from 45 - 65% of children and 33 - 90% of adults. It has
been found that there is a high incidence of abnormal results from pH probe testing in this patient population, reported at 50% for chronic cough and 44% in asthmatics from a recent study. Other studies have supported a higher rate of abnormal diagnostic tests specific for reflux disease in patients with pulmonary complaints.

Regarding the association of pulmonary disorders with reflux, two mechanisms have been proposed --

- (1) activation of a reflux initiated vagal reflex pathway from the esophagus to the lung, resulting in bronchoconstriction, and
- (2) microaspiration of gastric contents into the lung, resulting in bronchospasm and an exudative mucosal reaction.

Supporting these mechanisms have been studies which have shown the following in patients with underlying pulmonary disease --

- (1) presence of lipid laden macrophages from broncho-alveolar lavage in asthmatic children,
- (2) scintigraphic studies showing radioisotope material in the lungs after intragastric instillation of the radioactive material, and
- (3) distal esophageal perfusion in adult asthmatic subjects showing a sharp increase in airway resistance shortly after.

Aside from studies designed to elucidate the cause-effect relationship, the literature has witnessed many reports of successful pulmonary treatment outcomes when reflux was targeted. Meta-analysis of twelve studies involving a total of 302 adults and 75 children found that 81% had improvement or elimination of pulmonary symptoms after medical / surgical management of reflux. In a cited, controlled study in Chile of asthmatic patients (N=81) with documented reflux, they were randomly divided into a placebo / medical management (cimetidine) / or surgical management group. At six months, there was a statistically significant improvement in the mean symptom and medicine score of the medical and surgical groups as compared to the placebo. In a longer follow-up of five years, however, it was found that only the surgical group had long term effects on controlling their asthma.

**Laryngeal Carcinoma.**

Gastroesophageal reflux disease as a factor in the development of laryngeal carcinoma has been examined. Case reports of young adults with laryngeal cancer and no identifiable factor (tobacco or alcohol use) except for the co-existence of reflux disease has raised the question of its possible role in the development of cancer. Most patients with laryngeal cancer, however, have a significant history of tobacco use, and many with excessive alcohol use. Interestingly, data collected in laryngeal cancer patients shows a greater incidence of reflux disease than the normal population. For instance, Morrison et al estimated that 48% of laryngeal cancer patients had symptoms of reflux based on a retrospective chart review spanning twenty years. In explaining this finding, tobacco and alcohol use are known to adversely modify almost all the physiological defenses to GERD -- namely...
- (1) decreases LES basal pressure,
- (2) promotes esophageal dysmotility,
- (3) reduces mucosal resistance,
- (4) delays gastric emptying, and
- (5) stimulates gastric acid secretion.

Diagnostic testing in laryngopharyngeal cancer patients with 24 hour double pH probe monitoring found abnormal results in 71% of the patients in this group (58% had reflux detected on the pharyngeal probe), leading Koufman to suggest that GERD may be a significant, unidentified cofactor in the carcinogenic process.

**Subglottic Stenosis.**

The possibility that GERD may be a cause in acquired subglottic stenosis was first suggested by Bain et al who identified adult patients with SGS and severe, uncontrolled GERD. Koufman has presented data showing the significant co-existence of reflux disease with laryngeal stenosis. Abnormal pH testing was found in 72% of the patients (11 pediatric and 21 adults). An animal study was also undertaken showing the deleterious effects of gastric refluxate on the laryngeal mucosa, showing the eventual progression to stenosis with intermittent exposure. Indirect evidence for the role of GERD in SGS comes from a higher surgical failure rate in laryngotracheoplasty in children having reflux disease. With extensive experience in this area, Coton has strongly advocated a pre-operative "reflux workup" before undertaking surgical repair of subglottic stenosis. Indeed, the incidence of reflux disease is high in this group. Walner et al. presented a finding that 50% of patients with subglottic stenosis had a marginal to high risk of reflux based on the severity of pH-metry. Echoing the current literature in its inability to definitively establish causality, these authors caution that while the incidence of GERD is three times that of the normal pediatric population in the SGS child, it does not provide direct evidence of causing or contributing to subglottic stenosis.

**Diagnostic Tests For Gastroesophageal Reflux Disease.**

The diagnostic methods used in evaluating gastroesophageal reflux disease either examine for complications of reflux, i.e. esophagitis, or demonstrate and qualitatively measure reflux.

**Barium Esophagography.**

Barium esophagography has its greatest utility in detecting the complications of GERD rather than demonstrating or measuring reflux – namely, showing erosive esophagitis, esophageal rings, and strictures with fair sensitivity and specificity. It is also helpful in identifying other anatomical problems such as pyloric stenosis or intestinal obstructions. In evaluating for reflux, however, it has some major limitations. For instance, Ott et. al. showed that the barium swallow combined with fluoroscopy found radiographic reflux in only 25% of the patients studied having endoscopic proven esophagitis.
Acid Perfusion Test.

Also referred to as the Bernstein test, the distal esophagus is perfused first with normal saline and then with a continuous rate with 0.1 N hydrochloric acid via a nasogastric tube until symptoms of reflux are elicited or 45 minutes have passed. A positive Bernstein test is considered if the patient experiences heartburn or chest pain. The literature has found the sensitivity and specificity much lower than that proposed by Bernstein, et al who described both at 95%. The acid perfusion test may have its utility more in explaining reflux as the cause of atypical chest pain.

Esophagoscopy and Biopsy.

Endoscopic examination of the distal esophagus and gastroesophageal junction in patient with "typical" reflux usually reveals hyperemia, erythema, and an obliteration of the otherwise well demarcated squamocolumnar junction. More significant damage is characterized by erosions and ulcerations. Histologically, reflux esophagitis is characterized by basal cell hyperplasia resulting in increased length of the stroma pili, an eosinophilic infiltrate, and a non-specific polymorphonuclear / lymphocyte infiltration. Esophagoscopy is the "gold standard" for the gastroenterologist in diagnosing GERD. For the otolaryngology patient, however, there may not be identifiable esophageal inflammation despite the fact that reflux is actually demonstrated by other diagnostic tools (i.e. pH probe).

Gastroesophageal Scintigraphy.

In this study, a 99m technetium labeled sulfur colloid bolus is delivered into the stomach and reflux episodes are captured by the gamma camera. Despite early enthusiasm for this test as a method to quantitate reflux disease, several investigators have questioned its reliability. In fact, the reported sensitivity of radioisotope scanning in otolaryngology patients with otherwise proven GERD has been reported to be 11%.

Lipid Laden Macrophage.

It has been postulated the presence of lipoid intracellular inclusions in macrophages is due to acid reflux into the tracheobronchial tree. Corwin and Irwin showed that there is a significant increase in lipid-laded macrophages in children with pulmonary complications felt to be related to GERD. In addition to acid aspiration, other conditions may cause an increase in lipid laden macrophages such as those causing functional obstruction, i.e. pulmonary fibrosis, bronchiectasis. The specificity of the test is unknown and requires tracheobronchial sampling.

Prolonged pH Monitoring.

While other diagnostic methods have relied on (1) demonstration of esophagitis (barium esophogram, endoscopy), (2) reproduction of symptoms by provocative testing (acid perfusion test), (3) demonstration of abnormal esophageal function (manometry), and (4) non-quantitative demonstration of reflux (radionuclide scanning), ambulatory 24 hour pH probe monitoring has the ability to accurately quantitate reflux episodes. This has been considered the "gold standard"
in the otolaryngology literature for evaluating for reflux. It has been established as a standard to consider a pH drop to 4.0 or less as a reflux event, as it has been demonstrated by Tuttle et al that the symptom of heartburn occurs at a pH of less than 4. Many laboratories have established normal standards for the distal esophagus in regards to pH times in both positions (supine, upright, and total) as well as total time. From a large number of studies in normal subjects, the average person refluxed 5.68% of the time in an upright position, refluxed 1.91% of the time in a supine position, and as a total, refluxed 4.19% of the time. An abnormal result of the pH probe has been taken at two standard deviations from control data.

Using a specially designed pH catheter, it is possible to perform simultaneous esophageal and pharyngeal 24 hour monitoring in an ambulatory setting. This has gained wide acceptance especially for detecting pharyngeal reflux event. The pharyngeal probe is positioned approximately 2 cm above the upper esophageal sphincter, while the lower probe is placed 5 cm above the lower esophageal sphincter. The patients signal, by means of a portable microprocessing unit, the time of eating a meal, changes in posture or activity, and onset / type of symptoms. Various methods of data analysis are possible. The most common measures include total reflux time, the number of reflux episodes, and the number of episodes lasting longer than five minutes. The length of time necessary to monitor esophageal pH changes has been the subject of speculation. While 24 hours has been the general standard, some centers have reported reducing the length of testing (i.e. 12 hours) has given similar patterns of reflux in symptomatic patients and control subjects. A shorter testing period certainly meets with increased acceptance and tolerance by patients. For now, however, the 24 hour ambulatory pH monitor is the standard for reflux quantification.

**Esophageal Manometry.**

Esophageal manometry, introduced in the 1950’s, has provided a wealth of information in regards to the motor activity of the esophagus. Through manometry, lower and upper esophageal pressures can be measured and the refluxate clearance potential of the esophagus may be determined through measurement of contraction amplitude, duration, and timing of the peristaltic movements. Its use has allowed the correlation of lower esophageal resting pressure with severe esophageal reflux. Esophageal manometry has the potential for a predictive value in those patients that will likely fail conservative management – namely, those with sphincter incompetence and esophageal motor discoordination. While abnormal esophageal manometry is not diagnostic of reflux disease, it has utility in evaluating esophageal factors that may predispose to reflux.

**Treatment of Gastroesophageal Reflux.**

With a better understanding of the prevalence, pathophysiology, and clinical manifestations of gastroesophageal reflux disease, a successful approach to treatment has been formulated. The conservative aspect of treatment begins with modifying factors that are associated with GERD as well as medical management. For the recalcitrant cases, surgical management may be warranted.
Modifiable Factors Associated with GERD.

A. **Body Position.** For a substantial fraction of reflux patients, the frequency and duration of reflux episodes are directly influenced by posture. In normal patients, physiologic reflux occurs more commonly while upright than supine; whereas, in chronic reflux patients, reflux is generally seen more commonly while supine. Studies using distal pH monitoring in GERD patients has demonstrated that elevation of the head of the bed six inches or more reduces the number of reflux episodes and improves the time of acid clearance from the esophagus. For infants, the American Academy of Pediatrics endorses the supine sleeping position in those without reflux, but concede to side positioning as an acceptable alternative for those infants with GERD. The left lateral decubitus position has been found to produce the best results in reducing the number of reflux episodes.

B. **Dietary.** The role of dietary factors in GERD focuses on either their effects on LES pressure or their direct irritative effects on the esophageal mucosa. Those foods markedly reducing lower esophageal sphincter pressures include chocolate (methylxanthines), carminatives, and foods that are high in fat content. Ingestion of a high fat meal has been found to decrease the lower esophageal sphincter pressure for up to three hours after eating. High fat content meals has also reduced the gastric emptying rate, implicating it as a major dietary factor predisposing to reflux. A number of poorly tolerated foods provoke symptoms in reflux patients by mechanisms other than inhibition of LES pressure. For instance, some cause increase acid secretion (cola, beer, and milk) while others have been found to directly irritate the esophageal mucosa (orange juice, coffee, tomato juice). Alcoholic beverages reduce LES pressure and adversely affects esophageal peristaltic activity. Clearly, diet modification is essential in the treatment program.

C. **Cigarette Smoking.** Cessation of smoking in reflux patients has shown to significantly reduce the frequency of reflux episodes while improving the quality of the mucosal barrier in the distal esophagus. In addition, smoking has deleterious affects on salivary production (volume secreted and alkaline pH) that has been shown to reverse on elimination of smoking.

D. **Medications.** A number of commonly used medications decrease LES pressure and promote esophageal motor disturbances. Identifying the offending medication and choosing an alternate will greatly improve the therapeutic outcome. Theophylline has been extensively examined and is well known to cause lower and upper esophageal sphincter hypotension while inducing gastric acid secretion. In a study of asthmatics on theophylline, 80% had significantly reduced LES pressure compared to a control group. Other medications that are known to affect the lower esophageal sphincter are nitrates, anticholinergic agents, meperidine, diazepam, morphine, oral contraceptives and calcium channel blockers.

E. **Obesity.** While weight loss is generally advocated by physicians for obese patients with gastroesophageal reflux, the supporting data remains unclear. For instance, several studies have failed to show an association between excessive weight and decreased lower esophageal sphincter pressures. It has been postulated, however, that the increased gastroesophageal pressure gradient may facilitate reflux when transient LES relaxations occur.
A lack of well controlled trials has prevented definitive evaluation of the efficacy of simply environmental modifications in patients with GERD. The few published studies, however, support the efficacy of these modifications as well as acknowledging their limitation. The simplicity and cost of these interventions, nonetheless, justify their consideration for all patients suffering with this disorder and certainly are essential for successful treatment outcome.

Medical Management

A. **Histamine Blockers.** H-2 antagonists are now considered the cornerstone of medical management for gastroesophageal reflux disease. Four are currently available for clinical use – cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), and nizatidine (Axid). These agents bind the H2 receptors on the gastric parietal cell, resulting in inhibition of basal and stimulated acid secretion. The conventional doses of these medications can reduce the 24 hour of acid secretion by 60 – 70%. Comparative, non-biased trials among the available H-2 antagonists in treating reflux patients have shown equal treatment success -- in short, one is no better than the other. Regarding safety profile, H-2 antagonists have very few side-effects in both children and adults. An important concern, however, is with drug – drug interactions. For example, cimetidine can inhibit hepatic metabolism of certain drugs which may result in elevated plasma levels of certain co-administered medications such as phenytoin, warfarin, and theophylline.

In a large meta–analysis of treatment outcomes reported in the gastroenterology literature, it has been shown that reflux symptoms were relieved in approximately 50% of the patients in which H-2 blockers were used at conventional doses over 6 – 12 weeks. In addition, endoscopic improvement of the esophageal mucosa ranged from 31 – 88%, with complete healing of the esophageal mucosa in 27 – 45%. It has been noted that in the severe cases, standard ulcer healing doses may not be adequate and higher dosing regiments have been advocated. Limited data suggests that there is an enhanced therapeutic advantage by doubling or tripling the total dose of the H-2 blocker -- namely, cimetidine at 800 mg bid, ranitidine at 150 to 300 mg qid, famotidine at 40 mg bid, and nizatidine at 300 mg bid.

B. **Proton Pump Inhibitors.** Omeprazole (Prilosec) and lansoprazole (Prevacid) are two recently new agents introduced for the medical management of reflux. By irreversibly binding to the H/K ATPase proton pump, a single dose profoundly suppresses basal and stimulated acid secretion. This has been estimated at roughly 90% of normal. Omeprazole was evaluated in the US for patients with various grades of endoscopically evaluated esophagitis from mild (grade I) to severe (grade III) for 12 weeks and were found to have 100% healing rate for grade I and a 91% healing rate for the grade III lesions. The proton pump inhibitors show greater effectiveness in patients that are resistant to histamine-2 blockers and should be regarded as a second line medication or as an initial, short term choice for severe cases. A meta-analysis of the studies comparing these two classes of drugs clearly shows superior therapeutic outcomes over 12 weeks of treatment. Specifically, there was a mean healing rate of 78% when using omeprazole and 42% when using H-2 blockers. In addition, it has been estimated that less than ten percent of the patients are ultimately resistant to omeprazole treatment.
Regarding the safety profile, there have been no clinically significant adverse events or changes in laboratory values with the use of omeprazole over twelve weeks in patients with erosive esophagitis. Nonetheless, the FDA currently approves the use of omeprazole only for short term use (4 – 8 weeks), with an additional 4 weeks for the rare instance of the poorly responsive patient. Some of the concerns in long term use include the potential consequences of bacterial overgrowth and hypergastrinemia. The marked hypochlorhydria may result in intragastric bacterial colonization and production of nitrosamine compounds which has been found to increase the risk of infection and gastric carcinoma. Additionally, long term studies with omeprazole in the rat demonstrated gastric enterochromaffin-like cell hyperplasia and carcinoid formation; however, this had not been seen in patients outside of the US who had been on omeprazole for greater than four years.

C. Prokinetic Agents. These drugs focus on modifying gastroesophageal motility and esophageal sphincter pressures. Bethanechol acts on cholinergic receptors to increase LES pressure and increase the amplitude of esophageal peristaltic contractions; however, it has been found clinically to relieve only the mildest of reflux symptoms and while failing to show benefit in healing esophageal lesions. At the dose recommended for reflux disease, there are considerable undesirable central nervous system side effects such as fatigue, somnolence, insomnia, blurred vision, and tardive dyskinesia. Metoclopramide (Reglan) stimulates gastrointestinal smooth muscle through its inhibition at dopamine receptors while enhancing the release of acetylcholine. It has been shown to produce dose dependent increases in LES pressure, accelerate gastric emptying, and coordinate gastrointestinal activity. Like bethanechol, there are very few case reporting significant improvement of reflux symptoms and mucosal healing. This drug also has significant central nervous system side effects such as lethargy, tardive dyskinesia, as well as inducing galactorrhea by causing hyperprolactinemia. Cisapride (Propulsid) is a recently introduced prokinetic drug that acts locally on the gastrointestinal tract without the untoward CNS problems. It appears to increase intestinal smooth muscle contractility by augmenting the release of local neurotransmitters (probably acetylcholine) at the level of the myenteric plexus. The LES pressure and esophageal contraction amplitude are therefore increased. It has been shown that in patients with mild esophagitis (grade I), cisapride had the same therapeutic effectiveness as ranitidine. For more severe cases of reflux, however, the response was limited.

Surgical Treatment

In the absence of overt complications, failure of medical therapy to satisfactorily control symptoms after a medial trail of at least 6 to 12 months may be a justifiable reason for undertaking operative management. The principles guiding antireflux surgery are well established. The objectives are (1) to sufficiently mobilize the distal segment so that a segment of approximately 3 – 4 cm is translocated to an intro-abdominal position, (2) to firmly attach this segment to adjacent intro-abdominal structures (most commonly the stomach), and (3) to calibrate the orifice so that its lumen is abruptly diminished as it enters the cardia position of the stomach. The last step is usually accomplished by a fundoplication that sharply defines and restricts the entry of the terminal esophagus into the stomach. Variations of repairs employing this principles have been developed by several surgeons, notably Nissen, Belsey, Skinner, Thal,
and Hill. Patients with evidence of delayed gastric emptying who are undergoing a fundoplication procedure, should be considered for pyloroplasty or pyloromyotomy.

**Outcome of Reflux Therapy Related to Otolaryngology Manifestations**

Gastroenterology literature has a wealth of outcome studies related to the resolution of gastrointestinal symptoms and complications of reflux disease. Less has been reported on therapeutic efficacy of reflux in regards to the laryngopharyngeal and pulmonary manifestations. Koufman described his outcomes in treating 182 patients with laryngopharyngeal symptoms and clinical evidence of reflux disease. The groups were subdivided into the following diagnostic subgroups based on symptoms or a history of or presence of laryngeal pathology:

- (1) chronic cough,
- (2) cervical dysphagia,
- (3) globus pharyngeus,
- (4) chronic laryngitis,
- (5) laryngeal / tracheal stenosis, and
- (6) laryngeal carcinoma.

The treatment regimen consisted of dietary and lifestyle modifications as well as ranitidine 150 mg bid. If the symptoms persisted after 8 weeks of treatment, the dose was then increased to 300 mg bid or tid. All patients were treated for a minimum of 6 months. Nissen fundoplication was offered to those with suspected medical treatment failure supported by an abnormal double probe pH study while on antireflux medications. Medical treatment failure as documented by pH metry was seen in 35% of the patients, 15% within the first six months and 20% subsequently. Of the diagnostic subgroups, those with the presence or past medial history of laryngeal stenosis were the most recalcitrant to medical management. In this group, the failure rate was 55%. Subsequently, this group represented the highest rate of fundoplication. The ultimate outcome after surgical management for the failure groups were not presented.

A more recent study by Hanson et al examined outcomes of antireflux treatment in chronic laryngitis. The outcome measures were based on the resolution of symptoms and changes in the findings of telescopic laryngoscopy. Symptoms elicited from this patient study group included, (1) persistent or recurrent sore throat in the absence of infection, (2) sensation of "postnasal drip" with throat clearing, (3) hoarseness, and (4) cough in the absence of pulmonary or tracheobronchial tree. Telescopic laryngoscopy findings were then recorded as mild to severe. The treatment plan was as follows – (1) antireflux precautions for 6 weeks, (2) famotidine 20 mg at bedtime for 6 weeks for those with persistent symptoms or clinically identifies laryngitis plus reflux precautions, (3) change to omeprazole at 20 mg at bedtime for six weeks in the failure group, and (4) increase to omeprazole dose to 40 – 80 mg qd for those failures at an additional 4 weeks. It was found that 51% (93/182) responded to precautions alone, while 77% (48/89) responded to the addition of famotidine 20 mg at night. Of the failures requiring omeprazole at the standard or higher dose, there was a reported 96% overall resolution of laryngeal symptoms as well as mucosal healing.
Regarding surgical outcomes, Deveney et al presented a study of a unique subgroup of patients with persistent laryngeal inflammatory lesions that were resistant to conservative management of reflux precautions and pharmacological management for 6 months or greater. Diagnostic tests for reflux had been positive in all patients. The ultimate treatment was Nissen fundoplication in this group of patients. Based on pre-operative laryngoscopy, all patients were noted to have diffuse erythema and edema of the vocal cords and larynx; while leukoplakia was clinically described in 46% (6/13) of the patients. Interestingly, 5 patients of 13 (38%) had a prior history of laryngeal carcinoma that had been previously treated. Following the fundoplication procedure, the patients were followed for 11 months reporting a 73% (8/13) success rate of reversing laryngeal pathology. While there may be confounding variables accounting for the laryngeal mucosal injury, this represents the extreme spectrum of treatment.

FOOTNOTES

2) Ibid.
5) Ibid, pg. 2350.
6) Ibid.
10) Ibid.
11) Ibid.
12) Ibid, pg. 2352.
13) Ibid.


15) Ibid.

16) Ibid, pg. 446.

17) Ibid.


23) Ibid.


26) Ibid, pg. 2358.

27) Ibid.


29) Ibid.


37) Ibid.


39) Ibid.

40) Ibid, pg. 560.


44) Ibid.

45) Ibid, pg. 2361.


55) Ibid, pg. 518.


58) Ibid, pg. 519.


61) Ibid.

62) Ibid.

63) Ibid, pg 519.


62) Ibid.