FEATURE ARTICLE

Anatomy of Reflux: A Growing Health Problem Affecting Structures of the Head and Neck

MICHAEL J. LIPAN, JOY S. REIDENBERG, AND JEFFREY T. LAITMAN*

Gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (LPR) are sibling diseases that are a modern-day plague. Millions of Americans suffer from their sequelae, ranging from subtle annoyances to life-threatening illnesses such as asthma, sleep apnea, and cancer. Indeed, the recognized prevalence of GERD alone has increased threefold throughout the 1990s. Knowledge of the precise etiologies for GERD and LPR is becoming essential for proper treatment. This review focuses on the anatomical, physiological, neurobiological, and cellular aspects of these diseases. By definition, gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus; when excessive and damaging to the esophageal mucosa, GERD results. Reflux that advances to the laryngopharynx and, subsequently, to other regions of the head and neck such as the larynx, oral cavity, nasopharynx, nasal cavity, paranasal sinuses, and even middle ear results in LPR. While GERD has long been identified as a source of esophageal disease, LPR has only recently been implicated in causing head and neck problems. Recent research has identified four anatomical/physiological "barriers" that serve as guardians to prevent the cranial incursion of reflux: the gastroesophageal junction, esophageal motor function and acid clearance, the upper esophageal sphincter, and pharyngeal and laryngeal mucosal resistance. Sequential failure of all four barriers is necessary to produce LPR. While it has become apparent that GER must precede both GERD and LPR, the head and neck distribution of the latter clearly separates these diseases as distinct entities warranting specialized focus and treatment. *Anat Rec (Part B: New Anat) 289B:261–270, 2006.* © 2006 Wiley-Liss, Inc.

KEY WORDS: laryngopharyngeal reflux; LPR; gastroesophageal reflux disease; GERD; lower esophageal sphincter; LES; upper esophageal sphincter; UES; esophageal motility; mucosal resistance

INTRODUCTION

Patients presenting with symptoms such as hoarseness, sensation of a lump in the throat (i.e., globus pharyngeus), and chronic cough have long been a thorn in the side of modern medicine, largely due to physicians' inability to identify the source of their ailments. The majority of patients feel better with little more than patience, but those with persistent problems have been a medical conundrum, often leading to frustration for both doctor and patient. Slowly, physicians began to identify acid reflux, which may travel to regions as far as the head and neck, as a causative agent of these various symptoms (Table 1). Over the last 15 years, carefully constructed human clinical trials have gradually added evidence that reflux of gastric contents causes a wide range of symptoms and clinical signs commonly called laryngopharyngeal reflux (LPR; Table 2). The symptoms themselves can cause a significant impact on quality of life, but the more important point is the implication of LPR as a risk factor for a number of life-threatening conditions such as head and neck cancers, asthma, sleep apnea, narrowing of the respiratory tract below the vocal folds (i.e., subglottic stenosis), and involuntary forceful adduction of the vocal folds (i.e., laryngospasm) (Koufman et al., 2002).

Dr. Lipan has recently graduated with an MD with distinction in research from Mount Sinai School of Medicine (MSSM), New York, and has begun an otolaryngology residency at Jackson Memorial Hospital in Miami, Florida. He has frequently presented aspects of his research findings on the anatomical underpinnings of gastroesophageal reflux disease and laryngopharyngeal reflux at meetings of the American Association of Anatomists (AAA) and the Association for Research in Otolaryngology.
Dr. Reidenberg is associate professor of anatomy and functional morphology and associate professor of medical education at MSSM. She is a recognized expert in the comparative biology of mammalian throats, with a particular interest in cetaceans. She was the 1999 recipient of the Basmajian-Williams and Wilkins Award of the AAA for excellence in teaching and research by a gross anatomist.
Dr. Laitman is a distinguished professor at MSSM, professor and director of the Center for Anatomy and Functional Morphology, professor of otolaryngology and of medical education. He is a member of the AAA Board of Directors. His research has focused on elucidating the distinctive developmental and evolutionary features of the human aerodigestive tract and how these may relate to human disease. In 1997, Drs. Laitman and Reidenberg advanced the theory that the particularly low position in the neck of the human larynx was the anatomical basis allowing for reflux of gastric material into portals of the head and neck.
*Correspondence to: Jeffrey T. Laitman, Mount Sinai School of Medicine, Center for Anatomy and Functional Morphology, Box 1007, New York, NY 10029. Fax: 212-860-1174; E-mail: jeffrey.laitman@mssm.edu

DOI 10.1002/ar.b.20120
Published online in Wiley InterScience (www.interscience.wiley.com).

© 2006 Wiley-Liss, Inc.

TABLE 1. Symptoms and conditions associated with laryngopharyngeal reflux grouped by anatomic site

Anatomic Sites	Symptoms	Conditions
Larynx	Hoarseness (Wiener et al., 1989; Smit et al., 2000) Voice fatigue Voice breaks Muscle tension dysphonia	Chronic laryngitis (Hanson et al., 1995) Subglottic stenosis (Little et al., 1985; Jindal et al., 1994) Laryngeal carcinoma (Ward and Hanson, 1988; Qadeer et al., 2005; El-Serag et al., 2001) Paroxysmal laryngospasm (Loughlin and Koufman, 1996; Maceri and Zim, 2001) Contact ulcer (Cherry and Margulies, 1968) Granuloma (Havas et al., 1999) Recurrent leukoplakia (Koufman, 1991) Vocal fold nodule (Kuhn et al., 1998) Laryngomalacia (Belmont and Grundfast, 1984) Arytenoids fixation Renke's edema Pachydermia
Oropharynx and laryngopharynx	Globus (lump in throat sensation) (Smit et al., 2000) Dysphagia Chronic sore throat (pain and irritation) Excessive Throat clearing Excessive phlegm/saliva	Pharyngeal carcinoma (Qadeer et al., 2005) Obstructive sleep apnea (Kerr et al., 1992; Demeter and Pap, 2004)
Lung and tracheobronchial tree	Wheezing Chronic cough (Irwin et al., 1993; Harding and Richter, 1997)	Asthma exacerbation (Harding and Richter, 1997)
Middle ear		Otitis media with effusion (Tasker et al., 2002)
Oral cavity	Halitosis	Dental erosions (Schroeder et al., 1995)
Sinuses		Chronic rhinosinusitis (Ulualp et al., 1999; Parsons, 1996)
Multiple Sites		Sudden Infant Death Syndrome (Thatch, 2000; Nielson et al., 1990)

TABLE 2. Synonyms for laryngopharyngeal reflux

Reflux laryngitis	Supraesophageal reflux
Laryngeal reflux	Extraesophageal reflux
Pharyngoesophageal reflux	Atypical reflux

Reflux is defined as a backward flow of fluid (Table 3). The passage of gastric contents into the esophagus is referred to as gastroesophageal reflux (GER; Fig. 1). GER by itself is considered physiological and occurs routinely in healthy individuals with no symptoms or signs of disease. In fact, after-dinner indulgences that contain ingredients such as chocolate, caffeine, nicotine, or alcohol may promote GER and thus relieve discomfort due to stomach distention following a large meal. However, excessive GER can damage the esophageal mucosa and cause inflammation, a condition commonly referred to as gastroesophageal reflux disease (GERD). This breakdown of the squamous esophageal epithelium is caused by pepsin in an acidic milieu and can lead to heartburn, mucosal ulceration, narrowing of the esophagus, a change to gastric epithelium (i.e., Barrett's metaplasia), and, eventually, esophageal cancer. GER can alternatively reflux through the length of the esophagus to reach the laryngopharynx and cause LPR, making GER a common first step for both diseases (Fig. 2). However, due to the differences in the subsequent progression of these diseases, GERD and LPR are clearly distinct from one another.

The impact of reflux is widespread. Abnormal reflux affects millions of Americans a year. One study demonstrated that 7% of those surveyed experienced heartburn daily, 14% noted heartburn weekly, with a total of 36% having heartburn at least monthly (Nebel et al., 1976). LPR may affect a smaller proportion of the population than GERD, but it is difficult to diagnose accurately and thus epidemiological studies are scarce. LPR has been reported in up to 10% of patients referred to otolaryngologists for treatment (Koufman, 1991) and 50% of patients with laryngeal and voice disorders (Koufman et al., 2000). Notably, President Clinton suffered from LPR, which led to chronic hoarseness during his first presidential campaign in 1992 and intermittently plagued him throughout his terms in office. Most importantly, the diagnosis of GERD has been increasing at an alarming rate, more than tripling between 1990 and 2001 (Altman et al., 2005). This rise has become a substantial burden on our population, which is likely to continue to worsen.

Over the last 35 years, evidence for the association of reflux and ailments of the pharynx and larynx has been mounting, and this cause-and-effect relationship is gradually being accepted by physicians. The susceptibility of the human aerodigestive tract to

TABLE 3. Definition of terms related to gastric reflux, including typical patient presentation to physicians for each disorder

Reflux	A backwards flow used clinically to describe retrograde flow of body fluid	
Gastroesophageal reflux (GER)	Physiologic reflux of gastric contents into the esophagus not associated with retching or emesis (Stein et al., 1998)	Patients asymptomatic
Gastroesophageal reflux disease (GERD)	Excessive GER exceeding epithelium defenses and eliciting symptoms (i.e., heartburn) or histopathologic injury (i.e., esophagitis) (Kahrilas and Lee, 2005)	Patients usually present to gastroenterologists
Laryngopharyngeal reflux (LPR)	Reflux of gastric contents into the laryngopharynx. Although most patients have LPR without GERD, some may have both. (Koufman et al., 2002)	Patients usually present to otolaryngologists (4%–10% of otolaryngology patients and 50% of patients with voice disorders have LPR associated complaints) (Ormseth et al., 1999)

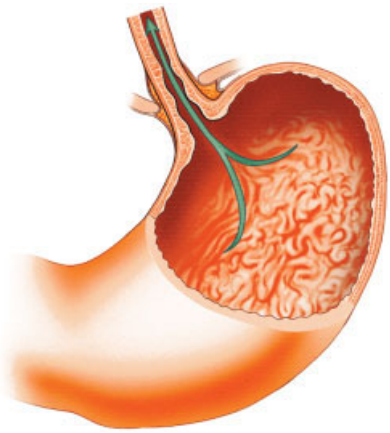

Figure 1. The gastroesophageal junction with arrow indicating gastroesophageal reflux, which is defined as passage of gastric contents from the stomach into the esophagus. Gastroesophageal reflux disease results when gastroesophageal reflux becomes excessive and damages the esophageal mucosa.

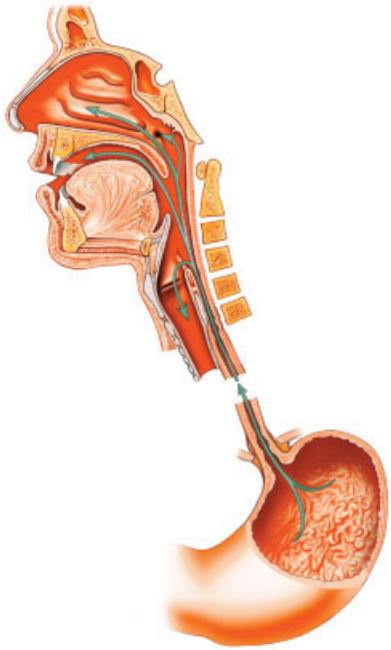

Figure 2. Regions of the head and neck with arrow indicating passage of gastroesophageal reflux proximally past the upper esophageal sphincter. Laryngopharyngeal reflux results when reflux damages the vulnerable mucosa of the pharynx, larynx, oral cavity, and nasal cavity. As few as one episode of reflux to these regions is considered excessive.

LPR has recently been described within an evolutionary perspective in studies from our laboratory (Laitman and Reidenberg, 1993; Laitman and Reidenberg, 1997). By comparing the anatomical position of the adult human larynx to human children and other mammals, the studies demonstrated that the adult human larynx's caudal shift from an intranarial position makes it unsuited to accommodate reflux to the region. The descent of the larynx during development unifies what were two largely separate pathways, namely, the respiratory tract and the digestive tract. This altered positional relationship allows the respiratory tract to be exposed to reflux reaching this level of the throat. Furthermore, the relatively unprotected posterior larynx of the adult human is inadequate to shield the laryngeal vestibule from exposure to reflux (Laitman and Reidenberg, 1997).

In recent years, major efforts have been made to gain a better understanding of the anatomical, physiological, neurobiological, and cellular mechanisms that break down to allow reflux to reach the laryngopharynx and, once there, cause disease. There are four antireflux barriers that normally exist to protect against LPR: the gastroesophageal junction, esophageal motor function and acid clearance, the upper esophageal sphincter, and pharyngeal and laryngeal mucosal resistance. The goal of this review is to present the current understanding of how these antireflux barriers must sequentially fail in order for LPR to occur.

GASTROESOPHAGEAL JUNCTION

The first antireflux barrier is the gastroesophageal junction (Fig. 3). This barrier consists of a complex sphincter with smooth muscle elements of the lower esophageal sphincter (LES) and skeletal muscle of the crural diaphragm, which combine to maintain pressure at this junction. This pressure must be kept above intra-abdominal pressure to prevent stomach contents from passing into the esophagus, whose intrathoracic location subjects it to a negative pressure. The LES is a physiological sphincter defined as the 3–4 cm area of tonically contracted smooth muscle at the distal end of the esophagus. The sphincter relaxes after swallowing to allow passage of ingested materials into the stomach. Anatomically, the zone corresponds to the most distal portion of the esophagus and is 2–3 times thicker than the proximal esophageal wall. It is divided almost in half by the insertion of the phrenoesophageal ligament, making the distal half intra-abdominal. The diaphragmatic crural fibers, whose action augments the LES at the distal esophagus, are attached to the LES by the phrenoesophageal ligament. Thus,

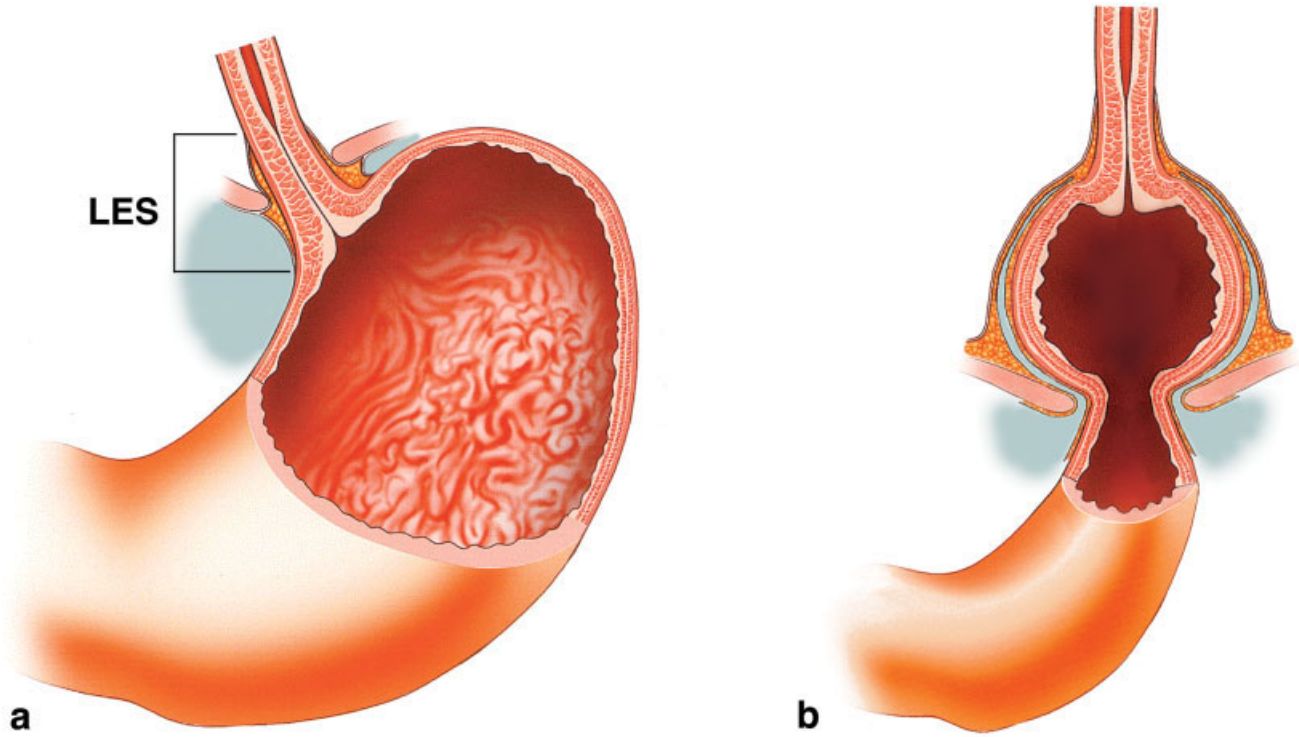

Figure 3. The gastroesophageal junction indicating (**a**) the normal anatomy of this region with the functional tonically contracted region of the LES indicated with a bracket and (**b**) anatomic disruption of the junction as occurs with a sliding hiatal hernia. Physiologic phenomena such as hypotension of the lower esophageal sphincter and transient lower esophageal sphincter relaxations result in the passage of reflux into the esophagus. When they occur in conjunction with a hiatal hernia, this reflux is accentuated.

while diaphragmatic contraction causes an increase in intra-abdominal pressure (as occurs with inspiration or Valsalva maneuver), it simultaneously prevents the reflux of gastric contents into the esophagus by superimposing its muscular tone onto the esophagus to raise junctional pressure.

Three theories have emerged to explain how reflux crosses the gastroesophageal junction: transient LES relaxations (TLESRs), the failure to maintain substantial pressure at the LES (i.e., LES hypotension), and anatomic disruptions associated with hiatal hernia. Investigation of LES function frequently uses manometry, a clinical test where a transducer measures intraluminal pressures created by muscular tone. Physiologically, reflux into the esophagus can occur multiple times a day without causing disease; it is an established pattern of reflux that determines the manifestations of disease. GERD patients usually have numerous and prolonged periods of reflux exposure, usually in the recumbent position. LPR patients tend to have more infrequent upright reflux of short duration that reaches the laryngopharynx without causing esophageal damage (Koufman et al., 2002). It is with these patterns in mind that mechanisms of reflux across the gastroesophageal junction should be considered.

The first theory, TLESR, involves a physiologic phenomenon in which there is a sudden drop in pressure at the LES, which is accompanied by crural diaphragmatic inhibition and not preceded by swallowing. TLESRs typically last longer than relaxations after swallowing and are primarily triggered by gastric fundus distention after a meal. The vagus nerve serves as both the afferent and efferent arc of the mechanism, resulting in release of nitric oxide and vasoactive intestinal peptide to mediate muscle relaxation (Hornby and Abrahams, 2000).

Abnormal levels of reflux are thought to be attributed to either an increased frequency of TLESRs or an increased frequency of acid reflux during a TLESR, since not all transient relaxations are accompanied by reflux. No study has yet shown a relationship between reflux to the laryngopharynx and TLESRs, but conclusions can be drawn from experiments using GERD patients. There has not been consistent evidence that there is an increased frequency of TLESRs in GERD patients compared to a healthy cohort of individuals (i.e., the control group) (Trudgill and Riley, 2001). However, the frequency of TLESRs has been found to be position-dependent. Patients with GERD had an increased rate of TLESRs compared to the control group with all subjects lying on their right side, whereas no difference in frequency was noted when subjects sat upright (Sifrim and Holloway, 2001). Since patients with LPR frequently reflux while upright, it is unlikely that an increased frequency of TLESRs would explain the abnormal reflux in these patients. Instead, it is possible that LPR patients could have an increased frequency of acid reflux during a TLESR. Although the percentage of TLESRs that result in reflux in patients with GERD varies widely in the literature, from 9% to 93% (Kahrilas, 1998), most reports confirm that these patients have a greater rate of reflux with each

TLESR than the control group (Sifrim and Holloway, 2001). Based on these results, it is likely that increased frequency of acid reflux during TLESR may be the more important contributor to the genesis of LPR than an increased frequency of TLESRs.

Hypotension of the LES is the second theory of how dysfunction of the gastroesophageal junction promotes reflux. LES function in LPR patients was measured during reflux episodes to the proximal esophagus versus the distal esophagus. Findings showed that TLESR was the primary mechanism in distal reflux events, but a hypotensive LES was the primary mechanism in proximal reflux events (Grossi et al., 2001). Since reflux to the proximal esophagus is more likely to reach the laryngopharynx than reflux to the distal esophagus (Shaker et al., 1995), hypotension of the LES likely plays a pivotal role in contributing to LPR.

Two studies measured basal LES pressures in patients with LPR and found them to have pressures comparable to the control group (Shaker et al., 1995; Ylitalo et al., 2001). It is possible that due to the intermittent nature of the reflux associated with LPR, these studies failed to capture the LES response during a reflux event. Therefore, the role of LES hypotension is unclear, but its role in proximal reflux events likely makes it a cause of LPR.

The third theory implicates a sliding (i.e., type 1) hiatal hernia as the cause of reflux. A sliding hiatal hernia is an anatomical defect where the distal esophagus and the gastric cardia herniate upward through the esophageal hiatus of the diaphragm, thus shifting the LES into the thoracic cavity. It is the most common type of hiatal hernia and is usually an acquired condition that is often associated with no sequelae. The hernia is associated with widening of the muscular hiatal tunnel and laxity of the normally elastic phrenoesophageal ligament (Kahrilas, 2001) and, most importantly, results in uncoupling the combined effect of the diaphragmatic crural fibers and LES in maintaining basal tone at the gastroesophageal junction. This uncoupling leaves LES tone as the sole contributor to maintaining pressure, making TLESR and hypotensive LES more likely to allow reflux to pass into the esophagus. Hypotension of the LES in patients with a hiatal hernia is thought to occur for two reasons. First, as mentioned previously, the pressure imparted by crural fibers is no longer imparted over the LES. Second, the high-pressure zone of the distal esophagus becomes shortened. This shortening is attributed to the loss of the intra-abdominal segment of the esophagus. Normally, any positive intra-abdominal pressure would exert an equal force on both the stomach and the intra-abdominal segment of the esophagus. Therefore, minimal tone in the esophagus would be sufficient to prevent reflux. However, herniation into the thoracic cavity exposes the entire esophagus to negative pressures, which counters the positive pressure created by the LES. Consequently, reflux meets less resistance at the gastroesophageal junction when intra-abdominal pressure increases. Therefore, any patient with a hiatal hernia would be more likely to reflux into the esophagus during TLESRs or hypotension of the LES than if the gastroesophageal sphincter was in its normal anatomic position.

More studies that measure LES function when reflux reaches the laryngopharynx would be useful to better characterize the precise gastroesophageal junction deficiency encountered in LPR. Since GER is a prerequisite for both GERD and LPR, a combination of these theories, well studied in patients with GERD, is likely to account for the reflux that causes LPR. Based on the evidence presented, hypotension of the LES leading to proximal reflux and an increased frequency of reflux during TLESR are both likely to be important factors in LPR. The concurrent presence of these two phenomena with a hiatal hernia exacerbates the disease.

ESOPHAGEAL MOTOR FUNCTION AND ACID CLEARANCE

The second antireflux barrier is the normal motor function of the esophagus (Fig. 4). Boluses of food and water are pushed by a strong coordinated peristaltic wave from the pharyngoesophageal junction down past the gastroesophageal junction and into the stomach. Peristaltic waves are either primary (i.e., triggered by a pharyngeal swallow) or secondary (i.e., triggered by direct simulation of the esophageal mucosa). These peristaltic sequences are important in clearing any reflux back into the stomach. Reflux remaining in the esophagus is then neutralized by swallowed saliva delivered during primary peristalsis. Any disturbance in normal esophageal motility increases the likelihood that reflux could travel the full length of the esophagus into the laryngopharynx. Indeed, manometric measurements of esophageal peristalsis in LPR patients revealed abnormal motility in 75% of subjects (Knight et al., 2000). This study looked exclusively at primary peristalsis and found that the most common motility disorder was ineffective esophageal motility, an abnormality characterized by occasional low contraction strength, contraction that fails to be transmitted along the whole length of the esophagus, and incomplete LES relaxation.

The finding of abnormal esophageal motor function was confirmed by another study, which compared esophageal acid clearance time in patients with LPR and the control group (Postma et al., 2001). Esophageal acid clearance time is the amount of time necessary to return the esophagus to a neutral pH following an acidic reflux event. This time is affected by both overall esophageal motor function and salivary neutralization. Since the authors of the study assume that the latter component is constant among subjects, esophageal acid clearance time becomes a good measure of esophageal motor function. The study found that patients with LPR had significantly longer clearance times than the control group, but the times were not as long as in patients with GERD.

Secondary esophageal peristalsis has also been examined in patients with LPR (Ulualp et al., 2001). Stimulation of the esophagus via abrupt injections of air volumes invokes a peristaltic wave. The threshold to trigger the peristalsis was comparable between LPR patients and the control group. Additionally, the parameters of the pressure wave (amplitude, duration, and velocity) were similar between the two groups as well.

Thus, abnormalities in primary

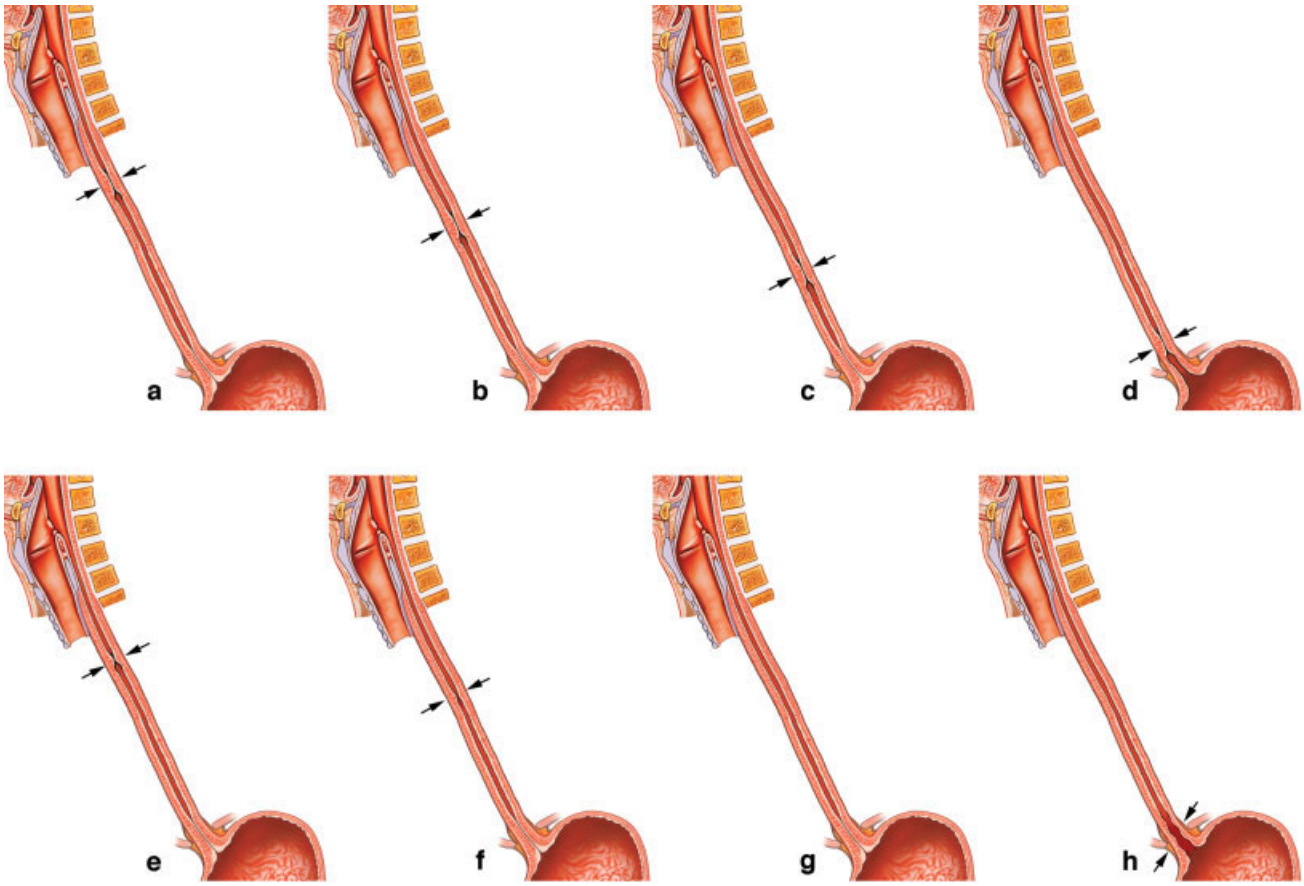

Figure 4. a–d: The esophagus exhibiting normal progression of the primary peristaltic wave from the proximal esophagus to the distal esophagus, ending in lower esophageal sphincter relaxation. This mechanism clears reflux back to the stomach and delivers saliva to neutralize any remaining reflux. **e–h:** The esophagus exhibiting ineffective esophageal motility, the most common abnormality of the primary peristaltic wave that occurs in laryngopharyngeal reflux. This disorder is characterized by occasional low contraction strength (e and f), loss of contraction as the peristaltic wave is transmitted along the length of the esophagus (e–g), and incomplete LES relaxation (h), which, in combination, increases the chance that reflux reaches laryngopharynx once in the esophagus, as occurs in LPR. Secondary peristalsis is normal in LPR.

peristalsis but not secondary peristalsis characterize the esophageal dysmotility found in patients with LPR. These results are not surprising given that the pharyngeal swallow and the resulting primary peristaltic wave are considered to be the predominant mechanism in returning reflux back to the stomach (Bremner et al., 1993). Moreover, the defect in primary esophageal function associated with LPR is not as severe as that found in GERD (Postma et al., 2001). This conclusion reinforces the fact that GERD is characterized by excessive exposure of reflux to the esophagus, whereas the sequelae of this excessive contact is usually lacking in LPR patients. Reflux in LPR must travel rapidly through the esophagus on the way to the laryngopharynx, where the problems of the disease manifest.

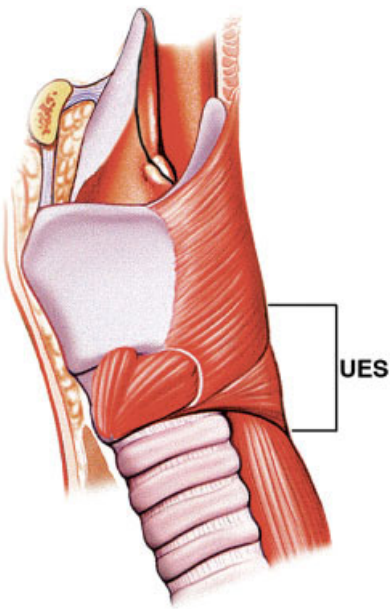

Figure 5. The larynx with the functional tonically contracted region of the UES indicated with a bracket. Abnormal response of reflexes that prevent the passage of reflux to the laryngopharynx is thought to contribute to laryngopharyngeal reflux.

UPPER ESOPHAGEAL SPHINCTER

The third antireflux barrier is the upper esophageal sphincter (UES; Fig. 5). It is the deficiency in this mechanism that makes LPR unique from GERD. The UES is defined as a high-pressure zone that is tonically constricted at the pharyngoesophageal junction. Like the LES, it relaxes to allow the passage of food or liquid boluses during swallowing. The UES is made up of the most distal fibers of the inferior pharyngeal constrictor (i.e., the cricopharyngeus muscle) and the most proximal portion of the esophagus. The cricopharyngeus

muscle makes the largest contribution to pressure at the UES in all physiologic states (Lang and Shaker, 1997). The pressure of the UES demonstrates a wide range of variation. For example, pressures decrease significantly during sleep, periods of calmness, and even expiration (Kahrilas et al., 1987). Pressures have also been shown to be lower in the elderly (Fulp et al., 1990).

The main functions of the UES are to prevent air from entering the esophagus during respiration and to prevent gastric secretions from entering the pharynx during reflux events. An aberration in accomplishing this second function is believed to be the primary defect in LPR, since its manifestations result from reflux abnormally breaching this sphincter to reach the laryngopharynx.

Manometric studies have been used to see if hypotension of the UES has any role in allowing reflux into the laryngopharynx. Average pressures of the UES at rest were similar between patients with LPR and the control group (Shaker et al., 1995; Ulualp et al., 1998). Electrophysiologic measurements of the cricopharyngeus muscle confirmed these findings and showed no abnormality in its tonic activity or activity during swallowing in patients with LPR (Celik et al., 2005). As with studies of the LES, these studies may be missing measurement of intermittent sphincteric dysfunction around the time of reflux events. Studies evaluating UES pressures during reflux yielded conflicting results. Two studies in adults demonstrated no change in the UES pressure during esophageal reflux events in patients with GERD or the control group (Kahrilas et al., 1987; Vakil et al., 1989), though lack of response could be a result of the methodology used. In both studies, pressures at the UES were measured during a reflux event, and the average pressure was compared to the average pressure measured during an equal interval prior to the reflux event. Therefore, the experiments may have failed to detect a short lasting change in UES pressures that may have occurred at the onset of the reflux event.

In contrast to the above studies, Torrico et al. (2000) found that nearly all reflux events resulted in an increase in UES pressure regardless of whether the reflux occurred in GERD patients or the control group. This response to esophageal stimulation has been termed the "esophago-UES contractile reflex" (Creamer and Schlegel, 1957). The increase in pressure was not significantly different between GERD patients and the control group, but the duration of the pressure increase was nearly double in the control group (25 vs. 15 sec). If a similar response were to be found in patients with LPR, it stands to reason that while the longer contraction may be sufficient to restrict normal GER to the esophagus in healthy individuals, the sphincter's premature relaxation may allow reflux to pass into the laryngopharynx in LPR.

The opposite of the esophago-UES contractile reflex is the belch reflex. The venting of gastric gas through the mouth starts with gastric distention leading to a relaxation of the LES. The gas pressure leads to esophageal distention triggering complete UES relaxation (Kahrilas et al., 1986). Thus, belching while reflux is in the proximal esophagus may allow the reflux to pass into the laryngopharynx. Patients with LPR have been shown to have more episodes of distal reflux reaching the proximal esophagus than patients with GERD or the control group. Additionally, 30% of reflux events in the laryngopharynx were associated with belching (Shaker et al., 1995).

Artificial elicitation of the belch reflex showed that the rapidity and pattern of esophageal distention determine if the UES relaxes, constricts, or remains unchanged (Kahrilas et al., 1986). Both air boluses injected into the esophagus and balloon dilation resulted in relaxation, while injected fluid boluses resulted in constriction or no change in UES tone. Likewise, abrupt GER could also cause esophageal distention and elicit UES relaxation as occurs in the belch reflex (Williams et al., 1999). This abrupt and forceful episode of GER accompanied by UES relaxation may explain why LPR patients exhibit reflux in the upright position, when it must overcome the effects of gravity, which normally resists reflux. Evidence that gastric reflux triggers UES relaxation was reported in children (Willing et al., 1993), while the opposite response, UES contraction, was found in adults (Torrico et al., 2000). Clearly, a complex interplay exists between the belch reflex and the esophago-UES contractile reflex, and similarly to the LES, UES pressures must be measured during reflux events that reach the laryngopharynx in order to better understand the precise UES defect associated with LPR.

Reflexes resulting in UES contraction have also been described when regions proximal to this sphincter are stimulated, namely, the laryngeal and pharyngeal mucosa. An example of this is the laryngo-UES contractile reflex, which is elicited by stimulation of mechanoreceptors of the larynx. The internal division of the superior laryngeal nerve acts as the afferent arc and the vagus nerve as the efferent arc of this reflex. A second example is the pharyngo-UES contractile reflex, which is elicited by stimulation of mechanoreceptors of the posterior pharyngeal wall. The glossopharyngeal nerve acts as the afferent arc and the vagus nerve as the efferent arc of this reflex. Although speculative, these reflexes are thought to play a role in preventing reflux from passing the UES. Reflux contacting the pharyngeal or laryngeal mucosa stimulates the reflex arc leading to augmentation of the UES basal resting tone. This increase in sphincter tone would then prevent further passage of reflux into the laryngopharynx.

The integrity of the pharyngo-UES contractile reflex in patients with LPR was investigated using water stimulation (Ulualp et al., 1998). Both patients and the control group demonstrated an increase in the UES pressure at a certain threshold volume of water injection. However, LPR patients required twice the amount of water volume to evoke the reflex compared to the control group, suggesting a dysfunctional afferent sensory arc, possibly at the level of the pharyngeal receptors. The laryngeal sensory deficiency in LPR was found to be due to the damaging effect on the mucosa from exposure to reflux (Aviv et al., 2000). This loss of mecanosensitivity was confirmed by infusing acid into the laryngopharynx of healthy controls to achieve diminished mucosal sensation (Phua et al., 2005). This causal relationship was supported by

the ability to reverse the sensory defect with aggressive therapy against LPR (Aviv et al., 2000).

Therefore, a defect of the UES may cause a vicious cycle of events at the laryngopharynx in patients with LPR. First, the UES fails to sustain a prolonged contraction when the esophagus is stimulated by a reflux event. Once an initial reflux event reaches the laryngopharynx, it causes an inflammatory reaction that disrupts normal sensation of the pharyngeal and laryngeal mucosa. This disruption leads to a diminished pharyngo-UES contractile reflex that normally would have prevented further reflux from reaching the laryngopharynx and perpetuates more damage to the mucosa.

PHARYNGEAL AND LARYNGEAL MUCOSAL RESISTANCE

Once reflux passes the UES and reaches the laryngopharynx, it diffuses along the aqueous mucosal environment to reach adjacent regions of the head and neck (Westcott et al., 2004). At this point, the only antireflux barrier left to prevent inflammation and damage is the inherent mucosal resistance of the pharynx and larynx to the corrosive components of the reflux (Fig. 6).

It is widely accepted that the mucosa in this region is poorly suited to resist damage from components of reflux in comparison with the esophageal mucosa (Koufman et al., 2002). Although as many as 50 reflux episodes a day into the esophagus is considered to be within a normal physiologic range, some researchers believe that a single acidic event in 24 hr in the laryngopharynx could cause LPR (Postma et al., 2001). In experimental dog models, as few as three reflux episodes per week caused significant damage to the laryngeal mucosa (Little et al., 1985; Koufman, 1991). Electron microscopy has demonstrated that pepsin compromises cell membrane integrity by disrupting the intercellular junction complex and increasing the intracellular space (Axford et al., 2001).

One extrinsic mechanism to protect the mucosa is salivary bicarbonate neutralization of acid. In the esophagus, normal intermittent swallowing

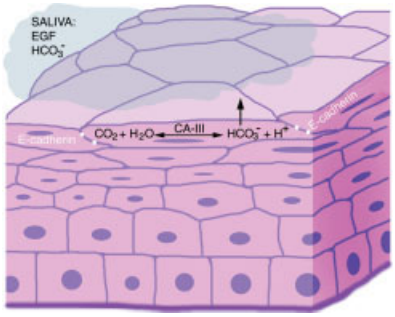

Figure 6. The stratified squamous epithelial layer of mucosa in the head and neck. Intrinsic resistance to reflux is from salivary delivery of bicarbonate ions (HCO_3^-) and epidermal growth factor (EGF), integrity of intracellular junctions by E-cadherin (represented by white squares), and luminal secretion of intracellular bicarbonate ions produced in a reaction catalyzed by CA. Cellular changes that promote laryngopharyngeal reflux include lack of contact with saliva, decreased salivary epidermal growth factor, loss of E-cadherin, and downregulation of CA III.

not only leads to a peristaltic wave that clears reflux back to the stomach, but also delivers bicarbonate-rich saliva to neutralize any residual acid (Helm et al., 1982). The laryngeal mucosa, however, does not normally come into contact with saliva and hence is not buffered by salivary bicarbonate. This poor acid neutralization leads to increased contact time between the acidic reflux and laryngeal mucosa leading to tissue damage.

The lack of extrinsic buffering from saliva heightens the importance of mucosal secretion of bicarbonate ion as an intrinsic defense to resist the local effects of reflux. This bicarbonate secretion depends on the epithelial cell expression of carbonic anhydrase (CA) isoenzymes. These enzymes function to catalyze the reversible hydration of carbon dioxide to bicarbonate ion, which is then actively pumped into the extracellular space. This reaction is vital in buffering and maintaining a neutral pH on the luminal surface of the mucosa. Esophageal mucosa expresses CA isoenzymes I to IV. In patients with GERD, the expression on CA III increases and is thought to be a protective mechanism to increase the cellular buffering capacity of mucosa exposed to reflux. Endogenous bicarbonate secretion from the esophageal epithelium can increase the pH of reflux from 2.5 to a more neutral pH, where pepsin loses most of its activity (Tobey et al., 1989). In an analysis of laryngeal epithelium expression of CA III, patients with LPR failed to show a similar upregulation of CA III expression as seen in GERD patients (Johnston et al., 2003, 2004). In fact, all patients with detectable levels of pepsin in laryngeal epithelium samples had an absence of CA III protein in vocal fold and laryngeal ventricle tissue biopsies, whereas laryngeal tissue from the control group expressed CA III at high levels (Johnston et al., 2004). The levels of the enzyme in the posterior commissure were not significantly different between the two groups. The lack of mucosal bicarbonate secretion after pepsin injury, in conjunction with the absence of salivary bicarbonate, leaves the laryngeal mucosa unable to neutralize reflux. This allows for particularly prolonged contact with pepsin within the acidic range where pepsin is most damaging.

Johnston et al. (2003) also measured the levels of expression of the adhesion molecule E-cadherin and secreted mucin MUC5AC. Adhesion molecules in the esophageal mucosa form intracellular bridges that create a barrier to penetration of both acid and pepsin (Orlando, 2000). Both E-cadherin and MUC5AC were found to have diminished expression in the laryngeal tissue of patients with LPR (Johnston et al., 2003; Gill et al., 2005). The loss of E-cadherin indicates a defect in the epithelial barrier in the larynx, although the importance of mucin proteins in mucosal resistance to reflux is less clear.

All of these findings demonstrate the mucosa's susceptibility to damage from reflux, but an additional factor determining the severity of disease is the mucosa's ability to heal after the damage is done. Six months may be needed to allow adequate time to reverse mucosal injury (Belafsky et al., 2001). An important mediator in this repair process is salivary epidermal growth factor, which is involved in the rapid epithelial regeneration of the gastrointestinal mucosa. The concentration of salivary epidermal growth factor was found to be significantly diminished in patients with LPR compared to the control group (Eckley et al., 2004). A deficiency of this protein

could explain the long period of time required for the mucosa to heal fully.

Although it is unclear if these changes are a consequence of reflux or a primary defect, these studies investigating the molecular biology of the laryngeal mucosa in LPR demonstrate why this region is so sensitive to refluxed gastric secretions. The downregulation of CA, E-cadherin, mucin MUC5AC, and salivary epidermal growth factor combine to cause a disruption of the basic mucosal barrier and accounts for the chronic inflammation found in LPR. It is this inflammation that leads to symptoms of the disease (Table 1). If untreated, the inflammation continues and may eventually cause the life-threatening conditions of subglottic stenosis, laryngospasm, and, most importantly, cancer.

CONCLUSION

The sibling diseases of gastroesophageal reflux disease and laryngopharyngeal reflux are a modern-day plague. Their increasing prevalence in our population has led to an undeniable burden on society, from the patients who suffer from them to the exponentially rising costs of treatment. Although GERD and LPR may often present as only mild disturbances, their association with severe alterations in quality of life, and even with life-threatening conditions, makes a detailed and precise understanding of their respective etiology imperative for proper treatment.

In order for reflux to travel from the stomach to the laryngopharynx, there must be a breach in delicate synergistic function of four anatomically, neurologically, and physiologically distinct antireflux barriers. This article has sought to examine the precise mechanisms that fail when gastric reflux is allowed to enter such distant and vulnerable regions in the head and neck. As the impact of LPR becomes more widely recognized, it is likely that research will focus on further characterizing the multifactorial defects that promote it. Much of our current understanding is drawn from the more extensively studied condition GERD. However, it is becoming dramatically apparent that GERD and LPR are on different ends of a spectrum of diseases caused by gastric reflux. Due to the different anatomy of these diseases, it stands to reason that advances in diagnosis and treatment will likely follow distinct paths as well.

LITERATURE CITED

Altman KW, Stephens RM, Lyttle CS, Weiss KB. 2005. Changing impact of gastroesophageal reflux in medical and otolaryngology practice. Laryngoscope 115: 1145–1153.

Aviv JE, Liu H, Parides M, Kaplan ST, Close LG. 2000. Laryngopharyngeal sensory deficits in patients with laryngopharyngeal reflux and dysphagia. Ann Otol Rhinol Laryngol 109:1000–1006.

Axford SE, Sharp N, Ross PE, et al. 2001. Cell biology of laryngeal epithelial defenses in health and disease: preliminary studies. Ann Otol Rhinol Laryngol 110: 1099–1108.

Belafsky PC, Postma GN, Koufman JA. 2001. Laryngopharyngeal reflux symptoms improve before changes in physical findings. Laryngoscope 111:979–981.

Belmont JR, Grundfast K. 1984. Congenital laryngeal stridor (laryngomalacia): etiologic factors and associated disorders. Ann Otol Rhinol Laryngol 93:430–437.

Bremner RM, Hoeft SF, Costantini M, Crookes PF, Bremner CG, DeMeester TR. 1993. Pharyngeal swallowing: the major factor in clearance of esophageal reflux episodes. Ann Surg 218:364–369.

Celik M, Alkan Z, Ercan I, et al. 2005. Cricopharyngeal muscle electromyography in laryngopharyngeal reflux. Laryngoscope 115:138–142.

Cherry J, Margulies SI. Contact ulcer of the larynx. 1968. Laryngoscope 78:1937–1940.

Creamer B, Schlegel J. 1957. Motor responses of the esophagus to distention. J Appl Physiol 10:498–504.

Demeter P, Pap A. 2004. The relationship between gastroesophageal reflux disease and obstructive sleep apnea. J Gastroenterol 39:815–820.

Eckley CA, Michelsohn N, Rizzo LV, Tadokoro CE, Costa HO. 2004. Salivary epidermal growth factor concentration in adults with reflux laryngitis. Otolaryngol Head Neck Surg 131:401–406.

El-Serag HB, Hepworth EJ, Lee P, Sonnenberg A. 2001. Gastroesophageal reflux disease is a risk factor for laryngeal and pharyngeal cancer. Am J Gastroenterol 96:2013–2018.

Fulp SR, Dalton CB, Castell JA, et al. 1990. Aging-related alterations in human upper esophageal sphincter function. Am J Gastroenterol 85:1569–1572.

Gill GA, Johnston N, Buda A, et al. 2005. Laryngeal epithelial defenses against laryngopharyngeal reflux: investigations of E-cadherin, carbonic anhydrase isoenzyme III, and pepsin. Ann Otol Rhinol Laryngol 114:913–921.

Grossi L, Ciccaglione AF, Marzio L. 2001. Transient lower oesophageal sphincter relaxations play an insignificant role in gastro-oesophageal reflux to the proximal oesophagus. Neurogastroenterol Motil 13:503–509.

Hanson DG, Kamel PL, Kahrilas PJ. 1995. Outcomes of antireflux therapy for the treatment of chronic laryngitis. Ann Otol Rhinol Laryngol 104:550–555.

Harding SM, Richter JE. 1997. The role of gastroesophageal reflux in chronic cough and asthma. Chest 111:1389–1402.

Havas TE, Priestley J, Lowinger DS. 1999. A management strategy for vocal process granulomas. Laryngoscope 109:301–306.

Helm JF, Dodds WJ, Hogan WJ, Soergel KH, Egide MS, Wood CM. 1982. Acid neutralizing capacity of human saliva. Gastroenterology 83:69–74.

Hornby PJ, Abrahams TP. 2000. Central control of lower esophageal sphincter relaxation. Am J Med 108(Suppl 4A):90S–98S.

Irwin RS, French CL, Curley FJ, Zawacki JK, Bennett FM. 1993. Chronic cough due to gastroesophageal reflux: clinical, diagnostic, and pathogenetic aspects. Chest 104:1511–1517.

Jindal JR, Milbrath MM, Shaker R, Hogan WJ, Toohill RJ. 1994. Gastroesophageal reflux disease as a likely cause of "idiopathic" subglottic stenosis. Ann Otol Rhinol Laryngol 103:186–191.

Johnston N, Bulmer D, Gill GA, et al. 2003. Cell biology of laryngeal epithelial defenses in health and disease: further studies. Ann Otol Rhinol Laryngol 112: 481–491.

Johnston N, Knight J, Dettmar PW, Lively MO, Koufman J. 2004. Pepsin and carbonic anhydrase isoenzyme III as diagnostic markers for laryngopharyngeal reflux disease. Laryngoscope 114:2129–2134.

Kahrilas PJ, Dodds WJ, Dent J, Wyman JB, Hogan WJ, Arndorfer RC. 1986. Upper esophageal sphincter function during belching. Gastroenterology 91:133–140.

Kahrilas PJ, Dodds WJ, Dent J, Haeberle B, Hogan WJ, Arndorfer RC. 1987. Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper esophageal sphincter pressure in normal human volunteers. Gastroenterology 92:466–471.

Kahrilas PJ. 1998. GERD revisited: advances in pathogenesis. Hepatogastroenterology 45:1301–1307.

Kahrilas PJ. 2001. Supraesophageal complications of reflux disease and hiatal hernia. Am J Med 111(Suppl 8A):51S–55S.

Kahrilas PJ, Lee TJ. 2005. Pathophysiology of gastroesophageal reflux disease. Thorac Surg Clin 15:323–333.

Kerr P, Shoenut JP, Millar T, Buckle P, Kryger MH. 1992. Nasal CPAP reduces gastroesophageal reflux in obstructive sleep apnea syndrome. Chest 101:1539–1544.

Knight RE, Wells JR, Parrish RS. 2000. Esophageal dysmotility as an important co-factor in extraesophageal manifesta-

tions of gastroesophageal reflux. Laryngoscope 110:1462–1466.

Koufman JA. 1991. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 101:1–78.

Koufman JA, Amin MR, Panetti M. 2000. Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. Otolaryngol Head Neck Surg 123: 385–388.

Koufman JA, Aviv JE, Casiano RR, Shaw GY. 2002. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the american academy of otolaryngology-head and neck surgery. Otolaryngol Head Neck Surg 127:32–35.

Kuhn J, Toohill RJ, Ulualp SO, et al. 1998. Pharyngeal acid reflux events in patients with vocal cord nodules. Laryngoscope 108:1146–1149.

Laitman JT, Reidenberg JS. 1993. Specializations of the human upper respiratory and upper digestive systems as seen through comparative and developmental anatomy. Dysphagia 8:318–325.

Laitman JT, Reidenberg JS. 1997. The human aerodigestive tract and gastroesophageal reflux: an evolutionary perspective. Am J Med 103:2S–8S.

Lang IM, Shaker R. 1997. Anatomy and physiology of the upper esophageal sphincter. Am J Med 103:50S–55S.

Little FB, Koufman JA, Kohut RI, Marshall RB. 1985. Effect of gastric acid on the pathogenesis of subglottic stenosis. Ann Otol Rhinol Laryngol 94:516–519.

Loughlin CJ, Koufman JA. 1996. Paroxysmal laryngospasm secondary to gastroesophageal reflux. Laryngoscope 106: 1502–1505.

Maceri DR, Zim S. 2001. Laryngospasm: an atypical manifestation of severe gastroesophageal reflux disease (GERD). Laryngoscope 111:1976–1979.

Nebel OT, Fornes MF, Castell DO. 1976. Symptomatic gastroesophageal reflux: incidence and precipitating factors. Am J Dig Dis 21:953–956.

Nielson DW, Heldt GP, Tooley WH. 1990. Stridor and gastroesophageal reflux in infants. Pediatrics 85:1034–1039.

Orlando RC. 2000. Mechanisms of reflux-induced epithelial injuries in the esophagus. Am J Med 108(Suppl 4A):104S–108S.

Ormseth EJ, Wong RK. 1999. Reflux laryngitis: pathophysiology, diagnosis, and management. Am J Gastroenterol 94: 2812–2817.

Parsons DS. 1996. Chronic sinusitis: a medical or surgical disease? Otolaryngol Clin North Am 29:1–9.

Phua SY, McGarvey LP, Ngu MC, Ing AJ. 2005. Patients with gastro-oesophageal reflux disease and cough have impaired laryngopharyngeal mechanosensitivity. Thorax 60:488–491.

Postma GN, Tomek MS, Belafsky PC, Koufman JA. 2001. Esophageal motor function in laryngopharyngeal reflux is superior to that in classic gastroesophageal reflux disease. Ann Otol Rhinol Laryngol 110:1114–1116.

Qadeer MA, Colabianchi N, Vaezi MF. 2005. Is GERD a risk factor for laryngeal cancer? Laryngoscope 115:486–491.

Schroeder PL, Filler SJ, Ramirez B, Lazarchik DA, Vaezi MF, Richter JE. 1995. Dental erosion and acid reflux disease. Ann Intern Med 122:809–815.

Shaker R, Milbrath M, Ren J, et al. 1995. Esophagopharyngeal distribution of refluxed gastric acid in patients with reflux laryngitis. Gastroenterology 109:1575–1582.

Sifrim D, Holloway R. 2001. Transient lower esophageal sphincter relaxations: how many or how harmful? Am J Gastroenterol 96:2529–2532.

Smit CF, van Leeuwen JA, Mathus-Vliegen LM, et al. 2000. Gastropharyngeal and gastroesophageal reflux in globus and hoarseness. Arch Otolaryngol Head Neck Surg 126:827–830.

Stein JH, et al. 1998. Internal medicine. St. Louis, MO: C.V. Mosby. chap 329.

Tasker A, Dettmar PW, Panetti M, Koufman JA, Birchall J, Pearson JP. 2002. Is gastric reflux a cause of otitis media with effusion in children? Laryngoscope 112: 1930–1934.

Thach BT. 2000. Sudden infant death syndrome: can gastroesophageal reflux cause sudden infant death? Am J Med 108(Suppl 4A):144S–148S.

Tobey NA, Powell DW, Schreiner VJ, Orlando RC. 1989. Serosal bicarbonate protects against acid injury to rabbit esophagus. Gastroenterology 96:1466–1477.

Torrico S, Kern M, Aslam M, et al. 2000. Upper esophageal sphincter function during gastroesophageal reflux events revisited. Am J Physiol Gastrointest Liver Physiol 279:G262–G267.

Trudgill NJ, Riley SA. 2001. Transient lower esophageal sphincter relaxations are no more frequent in patients with gastroesophageal reflux disease than in asymptomatic volunteers. Am J Gastroenterol. 96:2569–2574.

Ulualp SO, Toohill RJ, Kern M, Shaker R. 1998. Pharyngo-UES contractile reflex in patients with posterior laryngitis. Laryngoscope 108:1354–1357.

Ulualp SO, Toohill RJ, Hoffmann R, Shaker R. 1999. Pharyngeal pH monitoring in patients with posterior laryngitis. Otolaryngol Head Neck Surg 120:672–677.

Ulualp SO, Gu C, Toohill RJ, Shaker R. 2001. Loss of secondary esophageal peristalsis is not a contributory pathogenetic factor in posterior laryngitis. Ann Otol Rhinol Laryngol 110:152–157.

Vakil NB, Kahrilas PJ, Dodds WJ, Vanagunas A. 1989. Absence of an upper esophageal sphincter response to acid reflux. Am J Gastroenterol 84:606–610.

Ward PH, Hanson DG. 1988. Reflux as an etiological factor of carcinoma of the laryngopharynx. Laryngoscope 98:1195–1199.

Westcott CJ, Hopkins MB, Bach K, Postma GN, Belafsky PC, Koufman JA. 2004. Fundoplication for laryngopharyngeal reflux disease. J Am Coll Surg 199:23–30.

Wiener GJ, Koufman JA, Wu WC, Cooper JB, Richter JE, Castell DO. 1989. Chronic hoarseness secondary to gastroesophageal reflux disease: documentation with 24-h ambulatory pH monitoring. Am J Gastroenterol 84:1503–1508.

Williams RB, Ali GN, Wallace KL, Wilson JS, De Carle DJ, Cook IJ. 1999. Esophagopharyngeal acid regurgitation: dual pH monitoring criteria for its detection and insights into mechanisms. Gastroenterology 117:1051–1061.

Willing J, Davidson GP, Dent J, Cook I. 1993. Effect of gastro-oesophageal reflux on upper oesophageal sphincter motility in children. Gut 34:904–910.

Ylitalo R, Lindestad PA, Ramel S. 2001. Symptoms, laryngeal findings, and 24-hour pH monitoring in patients with suspected gastroesophago-pharyngeal reflux. Laryngoscope 111:1735–1741.