

Chapter 129: Gastroesophageal Reflux Disease

James A. Koufman

Historical Perspective

It is likely that gastroesophageal reflux disease (GERD) was recognized in antiquity. In 1618, Fabricius described the gastroesophageal junction and attributed its name "cardia" to Galen (130-200 AD), who had coined the term because symptoms arising from the gastroesophageal junction were similar to those arising from the heart (Henderson, 1980). It was not until the twentieth century, however, that the relationship between the symptoms and the gastroesophageal reflux (GER) was established (Berenberg and Neuhauser, 1950; Winkelstein, 1935). In 1880 Jackson introduced the esophagoscope and the modern era of esophagology began. Nine years later, using a crude manometric system, Meltzer (1899) described esophageal peristalsis. Although Tiletson (1906), Mosher (1921), and Jackson (1922) described the anatomic, endoscopic, and pathologic findings of stricture and "peptic ulcer" of the esophagus, they did not consider the cause to be related to reflux of the gastric contents.

Mosher commented: "I feel that narrowing of the liver tunnel due to an inflammatory involvement of the lesser omentum will be found in the future to play a large part ... in producing these strictures. ... This shares in the inflammation, acute and chronic, of the rest of the peritoneal tissue of the abdominal cavity."

He attributed such inflammation to gallbladder disease, stomach causes, or a foreign body.

In a landmark article in JAMA, Winkelstein (1935) reported "peptic esophagitis: a new clinical entity". He reviewed the prevailing beliefs of his time that the causes of esophagitis were (1) irritative (mechanical, thermal, and chemical irritants, including alcohol and tobacco); (2) specific (syphilis, tuberculosis, actinomycosis); and (3) secondary to cardiospasm, diverticula, or neoplasm. He described in detail five patients with heartburn, dysphagia, esophagitis, stricture, and esophageal spasm and stated, "The type of substernal pain, heartburn, sour regurgitations and the hyperchlorhydria in all recall the clinical features of peptic ulcer of the esophagus". Indeed, in three of his patients there was a history of a preexisting peptic ulcer. Winkelstein's patients all responded to antireflux treatment, although four had periodic relapses and one required a gastrectomy. In addition to reviewing the symptom complex in his patients, Winkelstein reported the endoscopic and radiographic findings.

Throughout the 1940s and 1950s, hiatal hernia became equated with GERD, and surgical correction of "symptomatic sliding hiatal hernia" became the focus of treatment (Allison, 1951). The belief that the sphincteric function of the lower esophageal sphincter was created by mechanical factors was supported by the failure of anatomists and operating surgeons to demonstrate a separate anatomic muscle at the gastroesophageal junction (Allison, 1951; Henderson, 1980).

In 1950 Berenberg and Neuhauser reported "cardioesophageal relaxation (chaliasia) as a cause of vomiting in infants". Their description of GERD was the most accurate and comprehensive after Winkelstein's. Dysfunction (low resting pressure) of the lower esophageal sphincter was believed to be the sole factor responsible for reflux. However, despite the insight afforded by Berenber and Neuhauser' study, knowledge about the physiology of esophagogastric function and the mechanisms of GERD was still limited.

With the introduction of modern manometry, Fyke et al (1956) and Ingelfinger (1958) began to unravel the complex neurophysiologic events associated with swallowing and with the pathogenesis of GERD. The lower esophageal sphincter remained the primary focus of reference, but esophageal motility and dysmotility also became recognized as factors in GERD.

The presupposition of the 1940s that hiatal hernia caused reflux gave way in the 1950s to the concept of lower esophageal sphincteric incompetence as the sole cause. However, as esophageal physiology was further elucidated, a multi-factorial model of the pathogenesis of GER began to emerge.

With the introduction of the flexible fiberoptic esophagoscope (Burnett, 1962; LoPresti and Hilmi, 1964; LoPresti et al, 1962), some aspects of diagnostic esophagology moved out of the operating theater and into the gastroenterologist's laboratory. However, despite advances in diagnosis, GER research remained almost exlcusively focused on the problem of esophagitis.

In 1958 Bernstein and Baker introduced the acid perfusion test, which proved to be more sensitive than contrast radiography for the diagnosis of reflux esophagitis. These and most other diagnostic tests were for the consequences and complications of esophagitis (Jamieson and Duranceau, 1988).

In 1967 prolonged pH monitoring (pH-metry) was introduced (Miller et al, 1964; Spencer, 1969). It readily became apparent that pH-metry was both highly sensitive and specific for the reflux event itself. Over the last 20 years, this test had resulted in new insights into the pathophysiology of GERD. Perhaps because of esophageal manometry, fiberoptic esophagoscopy, and pH-metry, the body of literature on GERD since the 1960s is primarily within the specialty of gastroenterology.

Antireflux Barrier

In its elemental form, the antireflux barrier consists of four lines of defense: (1) the lower esophageal sphincter (LES); (2) esophageal acid clearance; (3) epithelial resistance; and (4) the upper esophageal sphincter (UES). In addition, salivary functions (Helm, 1986; Helm et al, 1982, 1983, 1986, 1987) and gastroduodenal functions (Di Lorenzo et al, 1987; Gill et al, 1987; Helm et al, 1983) substantially influence antireflux mechanisms. Thus the integrity of the antireflux barrier is inexorably tied to the processes of deglutition and digestion. The components of the deglutitory mechanism are shown in the box.

Components of normal swallowing mechanism

A. Oral phase

1. Oral preparation

a. Mastication

b. Salivation

c. Bolus formation

2. Initiation of the swallowing reflex

a. Central recognition (brainstem)

b. Bolus propulsion (tongue thrust)

B. Pharyngeal phase

1. Reflex inhibition of respiration

2. Velopharyngeal closure

3. Laryngeal closure and elevation

4. Pharyngeal contraction ("peristalsis")

5. Relaxation of the cricopharyngeus and opening of the upper esophageal sphincter

C. Esophageal phase

1. Primary peristalsis

2. Relaxation and opening of the lower esophageal sphincter

3. Secondary peristalsis.

Lower esophageal sphincter

Although difficult to identify anatomically, a functioning LES can be demonstrated easily both radiographically and manometrically (Henderson, 1980). The primary functions of the LES are (1) relaxation from the usual tonic state during swallowing to allow free passage of ingested material from the esophagus into the stomach and (2) maintenance of an effective high pressure zone to prevent reflux of the gastric contents back into the esophagus (Castell, 1975). LES competence and LES pressure are determined by anatomic, neural, hormonal, and life-style-related factors.

Anatomic factors

The anatomic relationships of the diaphragm to the lower esophagus vary widely; however, most commonly, the right crus dominates in the formation of a hiatus, creating a muscular sling (Henderson, 1980; Jackson, 1922). Using a dog model, Radmark and Pettersson (1989) demonstrated that excision of half of the diaphragm lowered manometrically measured LES pressure from an initial mean of 20 cm H₂O to 15 cm H₂O. In the preoperative state, "spontaneous" (provoked) reflux occurred when a gastric volume of 3200 mL was reached, whereas the volume necessary to create such reflux after removal of the diaphragm was only 1400 mL. Thus the diaphragm may be considered to contribute to up to 25% of LES competence.

Also believed to be important in maintaining LES competence is the "cardiac angle", that is, the angle of entry of the esophagus into the stomach (Henderson, 1980; Mosher, 1921). It is believed that the acute angle of entry helps to create a valve effect; however, there is a great variability in the angle in normal people, ranging from 7 degrees to 60 degrees with a mean angle of 21 degrees (Jamieson and Duranceau, 1988).

A third anatomic factor thought to contribute to LES competence is the intraabdominal segment of esophagus. This portion of esophagus is exposed to the same pressures as the rest of the abdominal cavity; therefore increased intraabdominal pressure will tend to be transmitted to the lower esophagus as well as to the gastric cavity, tending to close the esophagus (Henderson, 1980; Jamieson and Duranceau, 1988).

Bonavina et al (1986) demonstrated that the length of the intraabdominal segment seemed to correlate well with LES pressure. They found that the longer the intraabdominal segment, the lower the pressure required to act as a barrier to reflux.

Finally, the phrenoesophageal ligament is a fibroelastic membrane that arises as a condensation of the abdominal fascia. Allison (1951) believed that this ligament was an important anatomic structure, which, when defective, gave rise to hiatal hernia. Although it is accepted that the phrenoesophageal ligament is a definable anatomic structure that inserts into the lower esophagus, the role of the ligament in promoting LES competence has not been demonstrated definitively (Jamieson and Duranceau, 1988).

Innervation

Full details of the neural control of LES function remain to be elucidated (Castell, 1975). It is clear, however, that vagotomy, whether intraabdominal or cervical, does not result in a change of resting LES pressure (Castell, 1975). Although this observation suggests that parasympathetic innervation of the LES may not be important, pharmacologic doses of cholinergic or anticholinergic substances markedly raise and lower LES pressure. Observations from animal models suggest that noradrenergic inhibitory fibers may be responsible for normal relaxation of the LES during swallowing (Castell, 1975).

Hormonal factors

In 1970 Castell and Harris demonstrated that gastrin increases LES pressure. It is now clear, however, that many hormones have a marked influence on the LES. In addition to gastrin, those that increase tone are pitressin, angiotension II, and motilin; those that decrease LES pressure are secretin, cholecystokinin, glucagon, and vasoactive intestinal peptide (Richter and Castell, 1981).

LES pressure increases with gastric alkalization (Higgs et al, 1974). However, the relationship is now believed to be more complicated than simply a response to serum gastrin. Even though the pharmacologic hormonal details have not been elucidated fully, this mechanism appears to be important in preventing postcibal reflux (Castell, 1975; Higgs et al, 1974).

Esophageal acid clearance

Helm et al (1983) demonstrated that when a 15 mL bolus of acid is instilled into the distal esophagus, a single peristaltic wave normally clears virtually all the volume of the bolus. The intraluminal pH, however, does not begin to rise until the occurrence of subsequent swallows of saliva, which buffers the acid due to its high bicarbonate content. Indeed, following instillation of the acid bolus, spontaneous swallowing occurs approximately every 30 to 60 seconds. With each swallow, there is an increase in pH back toward a neutral pH of 7. In subjects swallowing once every 30 seconds, pH returns to neutral within 3 minutes. (This forms the basis of the "standard acid clearance test".) (Helm et al, 1982, 1983).

To demonstrate the importance of salivary bicarbonate, additional experiments were performed, with aspiration (removal) of all the saliva from the oral cavity. When this was done, the intraesophageal pH remained below 4 despite secondary esophageal activity. Finally, using a third variation, the experiments were repeated in patients with impaired esophageal motility (whose primary peristalsis was defective). The authors found that it was not until volume clearance of the acid was achieved that the buffering capacity of salivary bicarbonate became effective in restoring neutral intraluminal pH (Helm et al, 1983).

Helm et al (1982) also have demonstrated that normal subjects with a salivary flow of 1.2 mL/min produce enough saliva in 5 minutes to titrate 1.0 mL of 0.1 N hydrochloric acid from a pH of 1.2 to 4.0. In addition, they have found that the concentration of bicarbonate in the saliva increases with salivary stimulation caused by instilling acid into the distal esophagus. The reflex pathway responsible for increased the bicarbonate content has been postulated to be parasympathetic, but the exact mechanism remains unproven.

Following a spontaneous "physiologic" reflux episode, it is postulated that peristalsis (after a single swallow) clears acid volume from the distal esophagus; thereafter salivary bicarbonate neutralizes the remaining intraluminal acid. These observations are supported by pH-metry results in normal subjects, which reveal that when spontaneous reflux events occur, pH is restored to greater than 4 in less than 5 minutes (Johnson, 1980). As a corollary, patients with abnormal esophageal motility and/or xerostomia are more likely to develop GERD than are normal subjects, even if LES function is normal.

Esophageal epithelial resistance

The third determinant of the degree to which esophageal injury may occur is referred to as "epithelial (tissue) resistance". Tissue resistance is not a single factor but represents a number of layered "structures" and functions that interact to form a dynamic barrier (Orlando, 1986).

Mucus, with its viscoelastic and gel properties, forms an excellent barrier to the penetration of large molecules, such as pepsin. However, mucus does not block penetration of the hydrogen ion (acid) (Orlando, 1986) - the layer below does that.

The outermost layer of protection is the mucous layer, below which is the "unstirred water layer". This layer has a relatively high bicarbonate content, which is probably derived from saliva, mucosal secretions, and serum, or is transported from epithelial cells. This unstirred water layer produces a buffering sink by creating an alkaline environment adjacent to the cell surface (Orlando, 1986).

At the epithelial level, both the cell membrane and the intracellular bridges form a barrier to penetration to both acid and pepsin. Finally, the postepithelial defenses are composed of the buffering capacity of the outer layers of the epithelium and the subepithelial blood flow. The latter removes toxic by-products, thereby providing local tissue buffering once injury has occurred. Further, when esophageal mucosa injury occurs, blood flow in the esophageal wall increases to provide additional buffering by delivering nutrients and bicarbonate to reestablish tissue acid-base balance (Orlando, 1986).

Upper esophageal sphincter

The UES, or cricopharyngeus, was first described in 1717 by Valsalva (Kirchner, 1958). Valsalva distinguished the cricopharyngeal muscle as an entity separate from the inferior constrictor. Killian ((1907) subdivided the cricopharyngeus muscle anatomically into two portions: the upper, pars obliquus, and the lower, pars fundiformis. The superior fibers of the inferior pharyngeal constrictor pass obliquely from the origin in the thyroid cartilage to be inserted on the median raphe, whereas the inferiormost fibers from the cricoid cartilage pass without interruption in a horizontal direction encircling the cricoid. The cricopharyngeus has no midline raphe. It is still controversial whether the cricopharyngeus is wholly distinct from the inferior constrictor (Reichert and Faw, 1980). However, among surgeons and anatomists there seems to be at least a consensus that the lower horizontal portion is discrete.

There are two areas of relative weakness. The first, between the two groups of muscle, the oblique and horizontal, is the area known as Killian's area, which is believed to be the exit point for Zenker's diverticula. The second is Laimer's triangle, which is situated posteriorly between the cricopharyngeus and the uppermost fibers of the esophagus. The terms *cricopharyngeus* and *UES* are used interchangeably.

The cricopharyngeus is innervated by the pharyngeal plexus, vagus, and glossopharyngeus nerves. The parasympathetic function is probably entirely vagal, and the sensory function is probably entirely glossopharyngeal. Sympathetic fibers arise from the superior cervical ganglia and also join the pharyngeal plexus. In its normal resting state, the

cricopharyngeal muscle is in a state of tonic contraction. Vagal stimulation produces relaxation.

Kirchner (1958) demonstrated that sectioning the vagus nerves bilaterally (in dogs) abolished the relaxation phase and produced severe dysphagia. Electrical stimulation of the superior cervical sympathetic ganglion produced an increase in the UES pressure. Conversely, electrical stimulation of the cut vagi produced full relaxation.

Thus, in contradistinction to the LES, the UES is a clearly defined anatomic entity and its innervation has been well defined. On the other hand, cricopharyngeal physiology is poorly understood because the development of solid-state pressure transducers (not dependent on pull-through or water perfusion systems) has been recent. Further, because of the anatomic configuration of the cricopharyngeus and its relationship to the cricoid with deglutition, manometric pressures recorded in the anteroposterior diameter may be considerably higher than those measured in the side-to-side diameter. Gerhardt et al (1978), using a pull-through technique, found just such a differential in pressure: in the posterior direction the mean was $109 \pm \text{SD } 4$ mm Hg; anteriorly it was $88 \pm \text{SD } 4$ mm Hg; to the left, $48 \pm \text{SD } 2$ mm Hg; and to the right, $45 \pm \text{SD } 2$ mm Hg.

Despite the limitations of these techniques, significant physiologic events and responses of the UES have been described. Gerhardt et al (1978) demonstrated that intraesophageal infusion of 0.1 N hydrochloric acid significantly increased UES pressure and that an increase in UES pressure occurred in response to volume, rate of infusion, and pH. (Increases in infusion volume, increases in rate of infusion, and decreases in pH each produced increased UES pressure.)

Like the LES, the UES has its own diurnal cycle. The resting pressure of the cricopharyngeus has been found to decrease significantly during sleep. In a study of eight healthy volunteers (Kahrilas et al, 1987), the mean resting pressure was $40 \pm \text{SD } 17$ mm Hg during wakefulness; $20 \pm \text{SD } 17$ mm Hg during light sleep; and $8 \pm \text{SD } 3$ mm Hg during deep sleep (Kahrilas et al, 1987). In those studies it was also noted that UES pressure increased transiently with each inspiration during both wakefulness and sleep and that UES pressure after a meal was no different from before a meal.

Within the last few years, improved technology has been developed to evaluate UES function (Green et al, 1988; McConnel, 1988). As a consequence, a range of normal UES pressures has been established, but there is still significant variation from laboratory to laboratory. Kahrilas et al (1987) found mean resting UES pressures in normal subjects to be $40 \pm \text{SD } 17$ mm Hg. Green et al (1988) found values of $67 \pm \text{SD } 5.4$ mm Hg with a round catheter and $64.4 \pm \text{SD } 8.3$ mm Hg using an oval catheter.

In summary, the UES is believed to have two physiologic functions (Kahrilas et al, 1987; Logemann, 1983):

1. To prevent aerophagia (air swallowing) during respiration.
2. To act as an upper esophageal barrier to reflux and thereby prevent regurgitation of gastric contents into the upper aerodigestive tract and lungs.

Pathogenesis of Gastroesophageal Reflux Disease

No review of the factors associated with the development of GERD can ever consider every variable. Many of the known postulated etiologic factors are listed in the box.

Etiologic factors associated with GERD

A. Decreased lower esophageal sphincter pressure (LESP)

1. Hiatal hernia

2. Diet

a. Fat

b. Chocolate

c. Mints

3. Tobacco

4. Ethanol

5. Drugs

6. GERD

B. Abnormal esophageal motility

1. Neuromuscular disease

2. Laryngectomy

3. Ethanol

4. GERD

C. Abnormal or reduced mucosal resistance

1. Xerostomia

a. Sicca syndrome

b. Oral cavity XRT

c. Esophageal XRT

2. Tobacco

3. Ethanol
 4. Drugs
 5. GERD
- D. Delayed gastric emptying
1. Outlet obstruction
 - a. Ulcer
 - b. Neoplasm
 - c. Neurogenic
 2. Diet (fat)
 3. Tobacco
 4. Ethanol
- E. Increased intraabdominal pressure
1. Tight clothing (corsets, belts)
 2. Diet
 - a. Overeating
 - b. Carbonated beverages
 3. Obesity
 4. Pregnancy
 5. Occupation
 6. Exercise
- F. Gastric hypersecretion (of acid or pepsin)
1. Stress
 - a. Trauma
 - b. Surgery

- c. Life-style
2. Tobacco
3. Ethanol
4. Drugs
5. Diet.

Within this listing are factors that alone can lead to GERD, such as esophageal dysmotility, gastric outlet obstruction, and xerostomia; however, more often than not, the cause is multifactorial and related to diet, ingested substances, and life-style, as well as to constitutional factors. Further, many factors, such as smoking and drinking ethanol, have a simultaneous adverse effect on several of the antireflux mechanisms.

Diagnostic Tests for Gastroesophageal Reflux Disease

Most of the diagnostic methods used in GERD either test for complications of reflux, such as esophagitis, or qualitatively test for reflux itself. These methods each have advantages and disadvantages, and none offers 100% accuracy. The most commonly performed tests, as well as their relative sensitivities and specificities, are listed in Table 129-1.

The most clinically useful, the most sensitive, and the most specific diagnostic battery currently available is provided by ambulatory 24-hour double-probe pH-metry and barium esophagography with videofluoroscopy. These two tests are complementary and demonstrate the pattern of GER as well as the presence or absence of esophageal complications such as stricture (Koufman, 1991).

Tests for esophagitis

Barium esophagography

Barium radiography is the oldest of the diagnostic tests. It was originally used in the 1930s and 1940s to demonstrate a "sliding hiatal hernia". The association between hiatal hernia and GERD is no longer considered clinically important, in that 40% to 60% of asymptomatic adults have easily demonstrable hiatal hernias (Castell et al, 1985).

Barium esophagography with cinefluoroscopy has been used to demonstrate GER. However, in a recent review (Castell et al, 1985), the sensitivity of radiographic examination for reflux was only 33%; Ott et al (1979) found radiographic reflux in only 25% of 40 patients with endoscopic esophagitis and in 20% of 35 normal controls.

Despite its limitations, the barium esophagogram may show erosive esophagitis, Barrett's esophagus, rings, and strictures that might not be diagnosed by other methods (Ott et al, 1986). Fig. 129-1 shows the radiographic appearance of erosive esophagitis, and Fig. 129-2 shows an esophageal peptic stricture.

Acid perfusion (Bernstein) test

In 1958 Bernstein and Baker introduced the acid perfusion test as a test for esophagitis. The test is performed by placing a nasogastric tube in the distal esophagus and infusing normal saline for 15 minutes followed by 0.1 N hydrochloric acid at a rate of 6 mL/min until either symptoms are produced or 45 minutes have elapsed. Bernstein and Baker (1958) reported that the sensitivity of the test was 95% and the specificity 95%. However, in later studies, Battle et al (1973) found the sensitivity to be 32%, and Krejs et al in 1976 found it to be 54%; Sonnenberg et al (1982) found the sensitivity to be 80% and the specificity to be 59%.

The acid perfusion test is specific for neither esophagitis nor reflux. Patients with motor disorders often have a positive study even when there is no evidence of GERD (Benjamin et al, 1979). Thus it appears that a positive acid perfusion test indicates only a likelihood that the symptoms mimicked are primarily esophageal.

Acid barium test

Donner et al (1966) introduced the acid barium test. (Standard barium sulfate (100 mL) is mixed with hydrochloric acid, producing a mixture with a pH of 1.7.) Ten patients with esophagitis and 10 controls were studied. None of the controls showed any abnormality, but all 10 of the patients showed cessation of peristaltic activity and segmental nonpropulsive tertiary contractions. Benz et al (1972) carried out this radiologic assessment in a blind fashion and found a sensitivity of 83% but a specificity of only 50%.

Esophagoscopy and biopsy

Subjective evaluation of the esophageal lining is useful when esophagitis is present. Many grading systems have been proposed, but contemporary gastroenterologists tend to use a very simple scoring system: grade I, erythema; grade II, ulceration; grade III, stricture.

The endoscopic diagnosis of esophagitis does not tally with either the histologic assessment or the symptoms (Jamieson and Duranceau, 1988). Endoscopic esophagitis has been confirmed histologically in 33% to 72% of patients (Jamieson and Duranceau, 1988). Clearly when esophagitis is likely, endoscopy with biopsy is a reasonably sensitive diagnostic option.

Test demonstrating or measuring reflux

Radionuclide scanning

Radionuclide scanning was introduced by Fisher et al (1976). (The patient swallows 300 mL of saline with technetium and is placed supine under the gamma camera; abdominal pressure is applied.) Fisher et al devised a scoring system to semiquantitate the amount of reflux observed. However, Ott et al (1979) reported the sensitivity of this test to average 68%, with a range of 14% to 90%. The reported sensitivity of radionuclide scanning in otolaryngology patients with GERD was recently reported to be 11% (Kuriloff et al, 1989).

Lipid-laden macrophage test

The presence of lipoid intracellular inclusions in the macrophage has been postulated to be due to GERD. Nussbaum et al (1987) and Corwin and Irwin (1985) have shown an increase in lipid-laden macrophages in children with pulmonary complications of GERD. The potential advantage of the test is that lipid-laden macrophages may remain for days after a reflux episode has occurred, so that the test potentially offers the clinician an opportunity to "track" GERD for days after the fact. Unfortunately, the test requires tracheobronchial sampling (for example, suction aspiration), and the specificity of the test is unknown.

Short-term pH assessment

Several different techniques have been employed for short-term pH monitoring in assessment of GERD. The "standard acid reflux test" (Skinner and Booth, 1970) is most widely used. The test is performed by placing a pH catheter into the stomach and instilling 300 mL of 0.1 N hydrochloric acid. The pH electrode is then withdrawn to a point 5 cm above the LES, and the patient performs a variety of maneuvers designed to stimulate reflux, that is, deep breath, Valsalva, and cough. A fall in pH to less than 4 is positive evidence for reflux. The test is graded in a standard fashion. The average reported sensitivity of the test is 80% (range of 54% to 100%), and the average specificity is 84% (range of 70% to 95%) (Kambic and Radsel, 1984).

Prolonged pH monitoring

Since its introduction by Miller et al (1964) and Spencer (1969), prolonged pH monitoring has been used simultaneously as a research tool and as a clinical test. Whereas the previous diagnostic methods have relied on (1) demonstration of esophagitis (for example, barium esophagogram, endoscopy); (2) reproduction of symptoms by provocative testing (for example, acid perfusion test); (3) demonstration of abnormal esophageal function (for example, esophageal clearance test); and (4) nonquantitative demonstration of reflux of dysmotility (for example, radionuclide scanning, acid barium swallow study), prolonged pH-metry quantitates the event of GER itself.

Much of the credit for pioneering work in pH-metry to establish standards and to popularize the technique as a clinical tool belongs to DeMeester and Johnson. Johnson (1980) defined a reflux event with pH manometry as a drop in pH to less than 4.0. This value was chosen because Tuttle et al (1961) had shown that heartburn occurs at pH of less than 4 and because it was believed that there is minimal peptic activity at a pH above 4.0.

Boesby (1975) performed 12-hour pH monitoring in 26 normal subjects. There were 31 reflux episodes, and the percent time that pH was less than 2.3 was 0.08%; pH less than 3, 0.18%; pH less than 4, 0.46%; and pH less than 5, 1.02%. Thus there was a direct relationship between percent time and pH.

Many variables have been investigated and reported, including percent time that pH is less than 4 (usually reported in terms of percent time upright, percent time supine, and total time); number of reflux episodes; duration of longest reflux episode; episodes lasting longer than 5 minutes per hour; and episodes per hour supine, upright, and total (Ward et al, 1986).

In terms of reporting pH-metry results, percent times that pH is less than 4 supine, upright, and total have become relatively common, and these variables are considered the most reliable and most reproducible. Since these variables have become widely used, many laboratories have established normal standards. Table 129-2 lists the upper limit of normal for nine studies (of normals) for pH time less than 4 in both positions and total time. All values are expressed as the mean plus 2 SDs. The average value for upright reflux was 5.68% (time); for supine reflux, 1.91%; and total, 4.19%.

Otolaryngologic Manifestations of GERD

GERD has protean upper aerodigestive manifestations and is commonly encountered in otorhinolaryngologic (ORL) practice. It has been estimated that 10% of patients with laryngeal complaints have a primary GER-related disorder (Koufman et al, 1988). In addition, GERD has been shown to be associated with the development of life-threatening complications such as stenosis and carcinoma of the larynx, as well as with other less serious conditions, such as reflux laryngitis (with and without granuloma formation), globus pharyngeus, and cervical dysphagia. Only within the last decade have otolaryngologists, in collaboration with gastroenterologists, begun to investigate systematically these conditions using ambulatory esophageal pH monitoring (pH-metry).

Although the natural history of GERD in ORL patients is still to a great extent unknown, some important observations are emerging that suggest that the pattern of GERD in ORL patients may be somewhat different from that seen in the "typical heartburn-esophagitis" patient commonly encountered by the gastroenterologist. The principal difference is that ORL patients fall predominantly into the "atypical" GERD group, as defined by a conspicuous absence of esophagitis and its symptoms, namely, heartburn and regurgitation (Koufman, 1991). Stiegmann et al (1987) reported the incidence of primary upper aerodigestive symptoms, including hoarseness and cervical dysphagia, in 376 gastroenterology patients evaluated endoscopically for GERD. Twenty-two (6%) had predominantly upper aerodigestive complaints; of that group, only five (23%) had heartburn. In the ORL literature, Ossakow et al (1987) reported the incidence of heartburn in ORL patients with GER-related disorders to be 6% (N = 63); Toohill et al (1991), 20% (N = 207); and Koufman (1991), 43% (N = 197).

The primary symptoms of GER-associated ORL disorders are hoarseness, which may be either chronic or intermittent; chronic throat clearing and/o cough; difficulty in swallowing (cervical dysphagia) or discomfort in the throat; and the sensation of a foreign body in the throat (globus, globus pharyngeus). Many ORL patients experience several or all of these symptoms.

In addition, ORL patients seem to have a relatively low incidence of esophagitis when compared with gastroenterology patients with GERD. Wiener et al (1989) reported the diagnostic double-probe pH-metry results in 33 ORL patients with chronic hoarseness: although 79% had abnormal esophageal pH monitoring, esophagoscopy was normal in 73%.

ORL patients with GERD also have a relatively high incidence of "chronic-intermittent" GERD and medical treatment failure. (In this context, chronic intermittency implies that among patients who respond to antireflux therapy, late recurrences are common

after apparently disease-free intervals of many months or years.) Medical treatment failure in these patients implies that antireflux therapy fails to control the GER-related symptoms (as above) or the associated laryngopharyngeal lesion or lesions, such as granulomas. The incidence of both chronic-intermittent GERD and medical treatment failure in ORL patients is approximately 35% (Koufman, 1991). This pattern (chronic intermittency and the high rate of treatment failure) is seemingly different than that seen in the typical gastroenterology patient.

Although it has been postulated that GER-related upper aerodigestive symptoms (for example, laryngeal "irritation", hoarseness, cough, and dysphagia) may occur as a result of vagally mediated reflexes (for example, cough) secondary to distal esophageal reflux or as a result of direct exposure of laryngopharyngeal structures to the gastric contents, the available data support the latter mechanism as the primary one in ORL patients. When a second pH probe is placed in the pharynx simultaneously with the intraesophageal probe for pH-metry, many ORL patients demonstrate actual pharyngeal acid exposure, and some even demonstrate such exposure despite "normal" intraesophageal acid exposure times (Koufman, 1991).

The six clinical conditions that are the most common GER-associated ORL disorders are laryngeal carcinoma; laryngeal stenosis; reflux laryngitis, with or without granuloma formation; globus pharyngeus; cervical dysphagia; and chronic cough. GERD may also be associated with other conditions encountered in ORL practice, including laryngospasm, laryngomalacia, pachydermia laryngis, cricoarytenoid fixation, and chronic pharyngitis.

Case example

In 1981, a 55-year-old clergyman presented with a recurrent granuloma on the laryngeal surface of his epiglottis. He was otherwise healthy, and his only symptoms were the sensation of a lump in the throat, chronic throat clearing, cough, and hoarseness. He denied heartburn, regurgitation, and a sour taste on eructation.

Six months and again 3 months earlier, he had undergone endoscopic removal of the lesion, but it had recurred. Pyogenic granuloma had been found histologically on both occasions. A third excision using the CO₂ laser was performed, but within 10 days the lesion had recurred. An epiglottectomy was then performed, but within 1 week, granulation tissue had begun forming in the base of the tongue at the surgical site.

A barium esophagogram was obtained and was normal. Nevertheless, because of the intractability of the disease and the possibility of GER contributing to the disorder, the patient was started on antireflux regimen, which included cimetidine, 300 mg QID. Within 3 weeks (1 year after his initial presentation), the lesion had healed.

This case illustrates that GERD in ORL patients may produce upper aerodigestive symptoms or complications without producing the symptoms considered typical of the "primary disease", namely heartburn and regurgitation. In 1985 Koufman et al (1988) began to employ pH monitoring as a primary diagnostic test in such patients. Throughout the rest of this chapter, unless otherwise stated, the data (figures and tables) presented are adapted from Koufman (1991). The clinical studies were performed in accordance with a protocol, the

key elements of which are summarized below.

Diagnosis

After an overnight fast, each patient underwent esophageal manometry, and the UES and LES resting pressures and positions were determined. After several months of single-probe study, double-probe pH-metry was introduced using a second probe piggybacked onto the esophageal probe. By January of 1988, two separate pH probes were no longer being used but had been replaced by a Synectics Monocrystant special pH catheter (Synectics Medical, Inc, Irvin, Tx). These catheters are available with the dual probes 18, 20, 22, 24, and 26 cm apart.

The presence of acid was documented, and the pH probes were positioned 2 cm above the UES and 4 to 5 cm above the LES. Patients were instructed to abstain from all non-essential drugs known to modify LES pressure or gastric secretion for at least 24 hours before and during the test. Patients were asked to follow a diet consisting principally of foods with a pH of greater than 5; carbonated beverages and coffee were restricted to mealtimes. An event marker was used to record mealtimes, bed and rising times, and symptoms.

Normative data (controls)

Thirty-two asymptomatic adult subjects served as controls to establish normative intraesophageal data. The percent time the pH was less than 4.0 was as follows: upright, $1.71 \pm \text{SD } 2.07$; supine, $0.35 \pm \text{SD } 0.73$; total, $1.27 \pm \text{SD } 1.56$. The upper limit of normal was defined as the mean value plus 2 SDs. Thus the upper limit values for time pH was less than 4.0 were as follows: upright, 5.85%; supine, 1.81%; and total, 4.39%. (These values are similar to those reported from other centers; see Table 129-2.)

In addition, 20 normal subjects underwent double-probe pH monitoring. None had any evidence of pharyngeal reflux.

Treatment

All patients were treated with dietary and life-style modifications as well as with ranitidine, 150 mg BID. If symptoms had not improved after 8 weeks of therapy, the dose of ranitidine was increased to 300 mg BIT or TID. All patients were treated medically for a minimum of 6 months.

Patients in whom medical treatment failed, because of persistent symptoms, findings, or both, underwent repeat pH-metry while receiving antireflux therapy. If the results of this study were abnormal, the patient was referred for Nissen fundoplication.

Follow-up

Sixty-eight percent (123/182) of the patients were available for follow-up. The mean duration of follow-up was 11.6 ± 12.7 months.

Symptoms and manifestations of GERD in OTOHNS patients

The symptoms of 182 ORL patients with GER-related conditions were carefully elicited. The most common symptom experienced by the patients was hoarseness (71%). The remaining symptoms in decreasing order of occurrence were chronic cough (51%), globus pharyngeus (47%), heartburn/regurgitation (43%), chronic throat clearing (42%), and difficulty in swallowing (35%). Notably, 57% of patients denied ever having had heartburn and/or regurgitation. Of those who did have gastrointestinal symptoms, 40% had fewer than three occurrences per week; 40% had an average of one episode daily; and only 20% had frequent daily symptoms. Indeed, 75% of the patients either denied having any gastrointestinal symptoms or had them only once or twice per week.

For years, otolaryngologists have realized the limitations of the standard diagnostic tests for GERD (for example, barium esophagography, acid perfusion test, and radionuclide scan) in ORL patients and have relied, as in the preceding case example, primarily on clinical diagnosis (Olson, 1986). Although the specificity of many of the standard tests for GERD is reasonably good, the sensitivity is often poor (Jamieson and Duranceau, 1988). Ambulatory 24-hour pH-metry is by far the most sensitive and specific test for GERD currently available, but at this time there are relatively few reports that present pH-metry data on ORL patients with GER-related conditions (Koufman et al, 1986; Ossakow et al, 1987; Rosman et al, 1988; Wiener et al, 1986, 1989).

Despite these diagnostic limitations, GER has been postulated to be associated with or responsible for an array of upper aerodigestive conditions. Some GER-related ORL syndromes have been well described, including the vocal process granuloma and posterior laryngitis (red arytenoids and piled-up interarytenoid mucosa); however, there is some disagreement on the role played by GER. Posterior laryngitis, for instance, which is considered by many otolaryngologists to be virtually pathognomonic for GER, is not always associated with demonstrable GER (Wilson et al, 1989).

It now seems likely that GER may affect any part of the upper aerodigestive tract. Table 129-3 lists some of the landmark reports in the ORL literature. Many of these GER-related conditions appear to have been "discovered" only recently. Interestingly, few of these reports have suggested that GER-related upper aerodigestive tract conditions may result from occult or intermittent GERD.

Technique and interpretation of double-probe (simultaneous esophageal and pharyngeal) ambulatory 24-hour pH monitoring

Using a specially designed pH catheter, it is possible to perform simultaneous esophageal and pharyngeal pH monitoring. The technique of catheter positioning has been reported (Koufman, 1991; Koufman et al, 1988) and is shown in Fig. 129-3. A few articles report data from studies using this technique in ORL patients (Koufman et al, 1988; Wiener et al, 1989), but normative data, as well as the advantages, disadvantages, and limitations of the technique, remain essentially unreported (Koufman, 1991).

The anatomic configuration of the pharynx differs from that of the esophagus in ways that suggest several potential and real technical problems in pH monitoring. First, the pharynx is a relatively cavernous space that does not collapse around the pH probe in the resting state. Thus, in comparison with the esophagus (particularly during sleep when swallowing is infrequent), pharyngeal mucus may dry out around the pH sensor, rendering the device nonfunctional. Second, the probe may be suspended in the pharynx in such a way that it is not in contact with the mucosa. And third, the probe may not necessarily record small quantities of pharyngeal reflux; that is, the qualitative threshold for pharyngeal probe response (positivity) is unknown.

Nevertheless, pharyngeal pH monitoring has been shown to be reasonably sensitive for pharyngeal reflux events, and the incidence of pharyngeal probe malfunction with the newer double probes (described above) seems to be lower than previously encountered. Although upper esophageal placement (just below the UES) of the second probe seems an obvious alternative to pharyngeal probe placement, interpretation of the resulting data using that technique would remain forever uncertain unless (1) data were collected using simultaneous probes just above and just below the UES, and (2) the effectiveness of the UES itself as a barrier to laryngopharyngeal reflux could be assessed by another method.

Fig. 129-4 demonstrates the characteristic features of true pharyngeal reflux, namely, (1) a sharp drop in pH measured by the pharyngeal probe preceded by a sharp drop in pH measured by the esophageal probe and (2) a similar pattern of "recovery" (return to normal pH) as measured in each of the probes. The first event at approximately 10:38 PM demonstrates a sharp drop in the esophageal pH to less than 2.0 followed within seconds by a sharp drop in the pharyngeal pH to 3.5. Within 1 minute there is a significant increase toward normal as measured by both pH probes. The second pharyngeal reflux event (at approximately 10:48 PM) is similar but is even shorter in duration. The third (10:50 PM) event, however, demonstrates drops in pH in both probes, which are similar in pattern and last 3 to 4 minutes. (This recording is part of the upright pH record of an ORL patient with carcinoma of the larynx. Other than hoarseness and chronic throat clearing, he had no GER-related symptoms.)

Fig. 129-5 demonstrates a phenomenon usually designated "pseudopharyngeal reflux". In this instance, the drop in the pharyngeal pH is gradual (over a 6-minute period) and has a rapid upward recovery. In addition, it is unassociated with a significant prior esophageal reflux event and the patterns of the two probes are quite dissimilar. (This tracing was taken from a patient with a normal pH study.)

Most, but not all, cases are easily interpreted. An example is Fig. 129-6, which shows a portion of the supine pH record of an ORL patient who complained of chronic cough and globus pharyngeus. By UES manometric study, he was found to have very prolonged UES relaxation in association with a high UES resting pressure (177 mm Hg). The pH-metry is difficult to interpret. At 12:30 AM, there is an intraesophageal drop to pH 2 followed by a slow rise back to pH 6. At 1:30 AM, there is a more severe pH drop. At that point, the intrapharyngeal pH begins to drop, but it is not until almost 20 minutes later (when the intraesophageal pH probe has recovered to 4) that the pharyngeal pH drop precipitously below 4. This episode may reflect abnormal upper esophageal function and may be a real pharyngeal reflux event, or it may be another example of pseudopharyngeal reflux. In either case, the

pattern is unusual.

As experience with double-probe pH-metry in ORL patients increases, it is apparent that much remains to be investigated about the relationship or relationships between upper and lower esophageal function. It is important to note, however, that, at present, not a single bona fide pharyngeal reflux event has been observed in controls and that abnormal pharyngeal pH studies seem to be clustered within a few groups of ORL patients (as discussed in the next section).

Results of diagnostic pH-metry in otolaryngology patients

pH-metry data from 182 consecutive ORL patients with suspected GER-related disorders are presented in Table 129-4, and the inclusion criteria (indications for pH-metry) are presented in the box. Sixty-two percent (113/182) of the patients had abnormal pH studies (Table 129-4). The pH results by diagnostic subgroup reveal (in decreasing order of positivity (abnormality)): stenosis, 78%; carcinoma, 71%; laryngitis, 60%; globus pharyngeus, 58%; cough, 52%; and dysphagia, 45%.

If one considers just the patients with abnormal pH studies, 65% had upright reflux and 65% had supine reflux, but in only 38% did both upright reflux and supine reflux occur. A notable exception was the globus group, in which both upright reflux and supine reflux were observed 72% of the time. The highest incidence of supine reflux were seen in the globus, laryngitis, and dysphagia groups (86%, 72%, and 70%, respectively), and the highest incidences of upright reflux were seen in the globus, carcinoma, and stenosis groups (78%, 77%, and 72%, respectively).

Of the patients undergoing double-probe pH-metry, 30% (44/147) demonstrated pharyngeal reflux events; however, the finding of pharyngeal reflux was clustered; that is, it was most frequently seen in the carcinoma and stenosis group, in which pharyngeal pH studies were positive in 58% and 56%, respectively. Pharyngeal probe positivity for the other groups was as follows: globus, 28%; cough, 22%; laryngitis, 17%; and dysphagia, 10% (Table 129-4). In 11% of the patients, the pharyngeal probe was positive (abnormal), even though the acid exposure time of the esophageal probe was within normal limits.

Results of antireflux treatment

After 6 months of antireflux treatment, 85% of the patients had resolution of their symptoms; the remaining 15% had recalcitrant symptoms despite aggressive therapy consisting of life-style and dietary modifications and ranitidine (see preceding section). Of the patients who responded to treatment, approximately half responded within 3 weeks to 3 months, and the other half had responded by 6 months. All patients underwent medical treatment for at least 6 months.

Over the 5 years of the study, nearly 50% of the patients had relapses. (If therapy was discontinued before 6 months, the recurrence rate was even higher.) Once a relapse occurred, the chance of subsequent medical treatment failure was more likely than that of primary (initial) treatment failure.

Medical treatment failure was documented by repeat pH-metry with the patient still on the therapeutic regimen. Patients in whom medical treatment failed were referred for Nissen fundoplication. Medical treatment failed in a total of 35% of the patients: in 15% during the first 6 months of treatment and in another 20% subsequently. Notably, the stenosis group had a 55% medical treatment failure rate. The medical treatment failure rates and fundoplication rates by subgroup are shown in Table 129-5.

Since the introduction of omeprazole in October of 1989, most of the patients in whom medical treatment with H2 blockers failed were treated with omeprazole, 20 mg OD or BID, for a period of 6 months in lieu of referral for fundoplication. (Almost all GER patients respond to this treatment.) After 6 months of treatment with omeprazole, treatment was switched to an H2 blocker, and if the medical treatment again failed, fundoplication was recommended. (In the future, "pulsed" or "alternating" therapy, for example, 6 months of omeprazole, 6 months of H2 blocker, 6 months of omeprazole, and so on, may prove to be an effective alternative to surgery in high-risk patients with intractable GERD, particularly in ORL patients with life-threatening complications.)

Animal Studies: Effects of Intermittent Reflux Following Mucosal Injury on Subglottic Larynx

Virtually all experimental studies of GER have employed perfusion techniques. Usually, the target organ, for example, the esophagus, is perfused with combinations of hydrochloric acid at various pH levels and with gastroduodenal enzymes for various periods of time. Indeed, it has been demonstrated that hydrochloric acid and pepsin in combination have the most injurious effects and that injury increases in severity as the pH decreases, as the pepsin concentration increases, and/or as the duration of perfusion increases (Gaynor, 1988; Johnson and Harmon, 1986; Lilemoe et al, 1982).

Koufman reported a series of experiments to evaluate the effects of acid and pepsin in producing subglottic injury in a canine model. Unlike most previous experiments, these were specifically designed to mimic the effects of intermittent reflux on the larynx following mucosal injury (Koufman, 1991; Little et al, 1985).

On the first day of each experiment, the mucosa of the subglottis was abraded using a diamond burr, thereby creating a standard reproducible injury. The animal subglottic regions were then "painted" three times weekly (Monday, Wednesday, Friday) for 2 weeks with a test substance. Four days after the last painting, each animal was sacrificed and the larynx harvested and subsequently examined by a pathologist who did not know which "test" substances had been used. (An inflammation score was adapted from that used to study a previously reported feline esophagitis model (Katz et al, 1988)).

Group I dogs (N = 8) were the controls; the larynges in these animals were painted with saline or neutralized acid and/or pepsin to pH 7.0. Larynges in group II dogs (N = 6) were painted with hydrochloric acid at pH 1.5, 2.5, and 4.0 (2 dogs each). In group III dogs (N = 6), larynges were painted with hydrochloric acid and porcine pepsin (0.3 mg/mL) at pH 1.5, 2.5, and 4.0 (2 dogs each).

The group I (control) mean inflammation score was $5.75 \pm \text{SD } 1.83$. For group II (acid only), the mean was $7.67 \pm \text{SD } 2.88$. There was no significant difference between the inflammation scores for groups I and II ($p = 0.28$). For group III (acid and pepsin) the mean score was $11.33 \pm \text{SD } 1.03$. The difference between group III and the controls was statistically significant ($p < 0.0002$). Surprisingly, three of the group III dogs had frank ulceration of the cricoid cartilage and the degree of damage was comparable at all three levels (1.5, 2.5, and 4.0).

Thus pepsin was the primary injurious component of the refluxate, and if there was prior mucosal injury, significant subglottic injury occurred even at pH 4.0. In a related experiment, it was found that three "paintings" per week of normal larynges with acid (pH 1.5) and pepsin (0.3 mg/mL) was not sufficient to cause mucosal breakdown. Therefore it appears that intact laryngeal mucosa offers more resistance to peptic injury than the underlying perichondrium and cartilage.

The potential clinical implications of these animal experiments are as follows:

1. The threshold for subglottic nonhealing and progressive laryngeal injury (inflammation, ulceration, granulation, and chondritis) is probably very low (three reflux episodes per week) when a prior mucosal injury exists, so that the threshold for laryngeal damage from reflux may be considerably lower than the threshold for GER-related esophageal injury.

2. A single laryngopharyngeal reflux episode, as seen on double-probe pH-metry, probably has great clinical significance.

3. Significant subglottic injury can occur at pH 4, suggesting a possible explanation for the high medical treatment failure rate in the stenosis group. (The pH of the refluxate of patients treated with H2 blockers is probably greater than 4 at the therapeutic nadir.)

4. Omeprazole in a dose of 20 mg BID may be drug of choice for the initial treatment of patients with laryngopharyngeal reflux, particularly for those with laryngeal carcinoma and stenosis.

Significance of Pharyngeal Probe Positivity (Is Pharyngeal pH-Metry Necessary in Otolaryngology Patients?)

Experimentally, instillation of acid into the esophagus has been shown to increase UES resting pressure, and the UES pressure increases inversely with pH (Gerhardt et al, 1978). Thus, in normal subjects, the UES probably acts as an effective barrier to laryngoesophageal reflux. The presupposition that "high esophageal reflux", as measured by a monitoring probe in the region just below the UES, may be equated with pharyngeal reflux is therefore debatable.

The available data do suggest, however, that laryngopharyngeal reflux does not occur in normal subjects and that intermittent and relatively infrequent laryngeal exposure to GER can produce significant peptic upper aerodigestive tract injury (Koufman, 1991). Within this

context, patients in our study with severe laryngeal disease, namely, carcinoma and stenosis, did have a high incidence of pharyngeal probe positivity. In addition, it should be recalled that 11% of the study patients had normal esophageal pH-metry, yet evidence of pharyngeal reflux. Although, at first glance, this appears to be a relatively small proportion of the patients, the significance of this finding cannot be overemphasized. Were it not for the pharyngeal probe, these patients would have been falsely presumed to be normal. The pharyngeal probe is therefore an important part of pH-metry in ORL patients with GER-related disorders, because a single positive event may outweigh all other negative findings.

Indications for Double-Probe pH-Metry and Other Clinical Implications (by Diagnostic Subgroup)

Carcinoma of larynx

Carcinoma of the larynx is the most common site of upper aerodigestive tract cancer, and 96% of the lesions are of the squamous cell type (Cann et al, 1985). It has been estimated that the greatest single risk factor for the development of laryngeal carcinoma is cigarette smoking (Wynder and Stellman, 1977). Alcohol (ethanol) abuse by itself is also associated with an increased incidence of laryngeal carcinoma. However, there appears to be a synergistic interaction between tobacco and alcohol, which elevates the risk of developing laryngeal carcinoma above that which would be expected if these two risks were purely additive. This synergistic interaction in heavy drinkers/smokers is manifest both in the incidence of laryngeal cancer and in a propensity for synchronous multiple tumor site presentations, that is, field cancerization. Second synchronous primary squamous cell tumors occur in approximately 20% of head and neck cancer patients, and cancer of the esophagus is the most common second site (McGuirt et al, 1982).

Cigarette smoking has been shown to decrease LES pressure, reduce mucosal resistance, delay gastric emptying, and stimulate gastric hypersecretion (Dennish and Castell, 1971; Stanciu and Bennett, 1972). Ethanol has been shown to decrease LES pressure, promote esophageal dysmotility, impair mucosal resistance, delay gastric emptying, and stimulate gastric hypersecretion (Vitale et al, 1987). Thus tobacco and alcohol adversely modify almost all of the physiologic defenses against GERD.

The high incidence of abnormal pH-metry observed in the patients with carcinoma of the larynx (total, 71%; pharyngeal probe, 58%) suggests the possibility that GERD is a major, previously unidentified, cofactor in the carcinogenic process. Indeed, in the series presented above, the incidence of GER exceeded the incidence of tobacco consumption and there were six lifetime nonsmokers in the group, all with documented abnormal GER by pH-metry (Koufman, 1991).

With advances in microbiology, especially the advent of the polymerase chain reaction and the availability of viral DNA probes, it now appears that the papilloma virus may also be a significant factor in the development of aerodigestive carcinoma (Eisenstein, 1990; Jarrett et al, 1978; Kiyabu et al, 1989).

Thus a multifactorial theory of aerodigestive carcinogenesis can be postulated in which mucosal injury (by tobacco, alcohol, and reflux) may be followed by viral penetration or

reactivation with viral malignant transformation as the final common pathway.

Are there specific carcinogenic substances within the refluxate? Are two or more factors, such as reflux and virus, or smoking and reflux, necessary for malignancy to develop? What are the roles of each of the carcinogenic factors, and how are they interrelated? These and other questions remain to be explored. In the meantime, 24-hour double-probe pH-metry should be considered part of the evaluation in every patient with carcinoma of the laryngopharynx unless it is medically contraindicated because of the threat of airway obstruction or hemorrhage from the tumor.

Laryngeal stenosis

Laryngeal and tracheal stenosis have two basic patterns at presentation: mature and immature. Mature stenoses are those in which airway obstruction is caused by firm, well-established scar tissue with thin overlying epithelium. Immature stenoses are those in which obstruction is caused by massive soft-tissue edema or granulation tissue or both. Ongoing GER is invariably an important etiologic factor in perpetuating the inflammatory process in immature stenoses, whereas, in mature stenoses, GERD is either in remission or under control with antireflux treatment

In patients with immature stenoses, attempted surgical repair is often unsuccessful unless the GER is controlled before surgery. On the other hand, repair of the stenosis is almost always possible following successful antireflux treatment. The situation is analogous to the esophageal stricture: in the face of continued severe reflux, dilatation of esophageal strictures is unlikely to result in relief of obstruction. Although the pH data on laryngeal stenosis presented herein have not yet been substantiated by other investigators, the finding of a very high proportion of patients with documented laryngopharyngeal reflux who have successful stenosis repair after successful antireflux treatment seems to make validation of the above observations almost inevitable.

pH-metry is strongly recommended as a vital part of the workup of all patients with laryngeal or tracheal stenosis or both, particularly those with immature stenoses. In addition, repeat pH-metry may be indicated during or after antireflux treatment to ensure long-term control of GERD in this patient group.

Reflux laryngitis

Hoarseness is a common symptom, but most patients with vocal abnormalities do not have discrete, demonstrable vocal cord lesions. Indeed, "nonspecific laryngitis" is a common diagnosis in such patients, particularly those with long histories (several years) of chronic, intermittent hoarseness. Many of these patients have "peptic" laryngitis, whether or not they have typical reflux-related symptoms.

There are several points in the patient's history and findings on physical examination that should alert the clinician to the possibility that GER may be responsible for the hoarseness. In addition to inquiring about heartburn and regurgitation, the clinician should determine whether the patient has other reflux-associated symptoms, such as difficulty in swallowing, the sensation of a lump in the throat, chronic throat clearing, and cough. Any

patient who is found to have a granuloma or granulation tissue of the larynx should also be considered to have reflux until proved otherwise. Likewise, when the arytenoids are red and there is obvious hypertrophy of the interarytenoid mucosa, so-called "posterior laryngitis", GER should be suspected. Finally, even in the absence of the above, GER should be considered in the differential diagnosis of any patient with otherwise unexplained hoarseness; double-probe pH-metry is the diagnostic procedure of choice.

Because it is not uncommon for patients with vocal cord granulomas to have a foreign body sensation in the larynx, in addition to antireflux therapy, it is often necessary to modify simultaneously the vocal behavior of these patients with voice therapy. Even when adequately treated medically, vocal cord granulomas require an average of 8 months to resolve; rarely is surgical removal indicated.

Globus pharyngeus

A foreign body sensation in the throat (globus pharyngeus) may be from a variety of causes in addition to GERD, including mechanical, inflammatory, and neoplastic causes. A review of the differential diagnosis is beyond the scope of this chapter. The evaluation of a patient with globus should include a complete head and neck examination, trans-nasal fiberoptic examination of the pharynx and larynx, and barium swallow/esophagogram with videofluoroscopy. If no cause for the globus pharyngeus is found and if the patient has symptoms or laryngeal findings that suggest possible GER, then double-probe pH-metry should be performed. Finally, if available, pharyngeal and UES manometric studies should be performed (Castell et al, 1990).

The role of GERD as an etiologic factor in the development of globus pharyngeus is controversial, although most authors would agree that GERD may be one of its causes (Weisskop, 1981). Three separate mechanisms for the development of GER-related globus pharyngeus have been proposed and are presented below, each with an illustrative case example:

1. Actual inflammation and swelling of laryngopharyngeal structures as a result of direct laryngopharyngeal exposure to the gastroesophageal refluxate.

Case Example

A 65-year-old man present with a 2-year history of globus pharyngeus associated with hoarseness and chronic throat clearing but had no other symptoms. His medical history was unremarkable and he was a nondrinker and nonsmoker.

Examination of the larynx showed intense erythema of the arytenoids and overhanging hypertrophic posterior commissure mucosa, that is, severe "posterior laryngitis".

Barium examination showed a hiatal hernia and a lower esophageal mucosal ring. The results of double-probe pH-metry were abnormal (upright, 32%; supine, 13%; total, 26%), and there were 24 episodes of pharyngeal reflux, half upright and half supine. Pharyngeal manometry and UES manometry were normal; esophagoscopy was unremarkable. Antireflux therapy was helpful in alleviating the symptoms and findings of GERD.

2. Referred discomfort (foreign body sensation) from esophagitis in the absence of direct laryngopharyngeal reflux.

Case Example

A 58-year-old, previously healthy man presented with a 1-year history of globus pharyngeus. He had no other symptoms and was a nondrinker and nonsmoker.

The laryngeal examination yielded normal findings, as did a transnasal fiberoptic examination of the pharynx and larynx. Barium examination showed a hiatal hernia, esophagitis, and a patulous lower esophageal sphincter.

The patient underwent double-probe pH-metry. The results with the esophageal probe were abnormal (upright, 9.8%; supine, 5.9%; total, 7.5%); however, there were no episodes of pharyngeal reflux recorded. Pharyngeal propulsion and coordination were normal, and the UES resting pressure was 56 mm Hg (normal, 45 to 107 mm Hg). Endoscopy showed moderately severe distal esophagitis.

3. Reflex hypotonicity of the UES from esophageal reflux.

Case Example

A 53-year-old, previously healthy man presented with a 3-year history of globus pharyngeus and chronic cough. He was a nonsmoker and drank wine socially. His past medical history was noncontributory.

Laryngeal examination showed findings compatible with mild posterior laryngitis. A barium swallow study was not obtained; 24-hour pH-metry was abnormal (upright, 3.3%; supine, 8.8%; and total, 5.7%), and there were many episodes of pharyngeal reflux (some of which were difficult to interpret; see Fig. 129-6).

Pharyngeal propulsion and coordination were normal, but the UES relaxation phase was prolonged and the UES resting pressure was 177 mm Hg (normal, 45 to 107 mm Hg). Endoscopy was unremarkable. After 3 months of antireflux therapy, the patient was asymptomatic, and UES manometry showed a normal UES resting pressure (102 mm Hg).

Cervical dysphagia

A relationship between cervical dysphagia and GERD has been demonstrated, but the criteria for pH study are less well established than for the other groups. Of particular note, however, is the observation that 43% of the patients in this group had lower esophageal rings, strictures, or both. Therefore barium swallow/esophagography should be the initial diagnostic test in this group. Otherwise, the evaluation should be similar to that recommended for the globus pharyngeus group.

Chronic cough

Like globus pharyngeus and dysphagia, chronic cough is a symptom, rather than a specific clinical entity. Patients in this group who were found to have reflux and who responded to therapy were common. Double-probe pH-metry should be considered as part of the diagnostic evaluation for patients with unexplained chronic cough who have previously undergone an otherwise complete diagnostic workup.

Summary

Otolaryngology patients seem to have a pattern of GERD that is distinctly different from that typically seen in the gastroenterology patients. Most ORL patients deny heartburn and regurgitation, and the rate of medical treatment failure is high (35%).

GERD may be a major factor in the development of laryngeal carcinoma and laryngeal stenosis. These two groups demonstrated a very high incidence of pharyngeal reflux on double-probe pH-metry (58% and 56%, respectively).

Double-probe (simultaneous esophageal and pharyngeal) pH-metry is likely to become the diagnostic "gold standard" in ORL patients with suspected GER-related disorders.