

The Role of Hiatus Hernia in GERD

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Increased esophageal acid exposure in gastroesophageal reflux disease has several potential causes, some related primarily to physiological dysfunction of the LES and others related to anatomic distortion of the gastroesophageal junction as occurs with hiatus hernia. One attractive feature of implicating hiatal hernias in the pathogenesis of reflux disease is that, like reflux disease, axial hernias become more common with age and obesity. However, the importance of hiatus hernia is obscured by imprecise definition and an all-or-none conceptualization that has led to wide variation in estimates of prevalence among normal or diseased populations. There are at least three potentially significant radiographic features of a hiatus hernia: axial length during distention, axial length at rest, and competence of the diaphragmatic hiatus. Although any or all of these features may be abnormal in a particular instance of hiatus hernia, each is of different functional significance. Grouping all abnormalities of the gastroesophageal junction as "hiatus hernia" without detailing the specifics of each case defies logic. Mechanistically, the gastroesophageal junction must protect against reflux both in static and dynamic conditions. During abrupt increases in intra-abdominal pressure, the crural diaphragm normally serves as a "second sphincter," and this mechanism is substantially impaired in individuals with a gaping hiatus. Large, non-reducing hernias also impair the process of esophageal emptying, thereby prolonging acid clearance time following a reflux event (especially while in the supine posture). These anatomically-determined functional impairments of the gastroesophageal junction lead to increased esophageal acid exposure. Thus, although hiatus hernia may or may not be an initiating factor at the inception of reflux disease, it clearly can act as a sustaining factor accounting for the frequently observed chronicity of the disease.

INTRODUCTION

Historically, hypotheses on the pathogenesis of gastroesophageal reflux disease (GERD)^b have implicated either anatomical or physiological abnormalities of the gastroesophageal junction. Initially, esophagitis was deemed a predictable con-

sequence of hiatus hernia, but this construct became untenable with the observations that not all patients with hiatus hernias had reflux disease, that not all patients with esophagitis had concomitant hernias, and that simple repair of a hiatus hernia did not resolve GERD. With the description of the smooth muscle lower

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^b Abbreviations: GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter. tLESR, transient lower esophageal sphincter relaxations.

esophageal sphincter (LES), the pendulum swung to the opposite extreme, and the presence of hiatus hernia was viewed as simply coincidental; the primary abnormality in reflux disease being either a hypotensive LES [1] or one prone to more frequent transient relaxations [2, 3]. Subsequently, it has become apparent that the gastroesophageal junction is an anatomically complex valvular mechanism composed of both an extrinsic element (the crural diaphragm) and the smooth muscle LES, intrinsic to the esophagus [4]. An attractive feature of the two-sphincter construct is that it suggests a mechanism wherein both LES dysfunction and hiatus hernia diminish gastroesophageal junction competence.

Although incompetence of the gastroesophageal junction is a prerequisite for the development of GERD, the central hypothesis regarding the pathogenesis of esophagitis is that symptom generation and esophageal mucosal injury are proportional to the duration of time that the mucosa is acidified and by the caustic potency of refluxed fluid. Studies comparing individuals with reflux disease to disease-matched controls suggest no defining abnormality of gastric secretion within the esophagitis population [5]. However, esophagitis patients can differ from normal patients in their ability to clear the refluxate from the esophagus and re-establish normal intra-esophageal pH after a reflux event has occurred [6]. Overall esophageal acid exposure time as quantified by prolonged pH recordings is the product of the number of reflux events and the time required for restoration of the mucosal pH to a value of 4 following each reflux episode (the acid clearance time). Thus, either a markedly increased propensity to incur reflux events or markedly impaired acid clearance can be the dominant abnormality leading to the development of esophagitis. Since peptic esophagitis is most severe at the gastroe-

sophageal junction, it is logical to examine determinants of acid exposure within this region. This paper will focus on how anatomic variables of the gastroesophageal junction affect the susceptibility to incur reflux events and impair the process of esophageal acid clearance.

ANATOMIC FACTORS INFLUENCING GASTROESOPHAGEAL JUNCTION COMPETENCE

Under normal circumstances, gastroesophageal reflux is prevented by a competent gastroesophageal junction. The antireflux barrier is an anatomically complex zone whose functional integrity has been attributed to intrinsic LES pressure, extrinsic compression of the LES by the crural diaphragm, the intraabdominal location of the LES, integrity of the phrenoesophageal ligament, and maintenance of an acute angle of His (the angle of entry of the esophagus into the stomach). Quite possibly, the antireflux barrier depends upon more than one of these factors, and incompetence becomes increasingly severe as more antireflux mechanisms are compromised. Even more likely, several, if not all, of these factors are interdependent and susceptible to compromise with the development of hiatus hernia.

The complexity of the antireflux barrier at the gastroesophageal junction discussed above has led investigators to focus on different potential mechanisms of reflux. Three dominant theories of pathogenesis attribute gastroesophageal junction incompetence to: 1) transient lower esophageal sphincter relaxations without any accompanying anatomic abnormality; 2) simply a result of a hypotensive LES, without any accompanying anatomic abnormality; or 3) a result of anatomic disruption of the gastroesophageal junction probably associated with a hiatus hernia.

Undoubtedly, individuals can be found exemplifying each mechanism; however, the proportion of the overall GERD population attributable to each remains a hotly debated issue. Recent evidence suggests that the dominant mechanism may vary as a function of disease severity with transient LES relaxation predominating with mild disease and mechanisms associated with a hiatus hernia and or weak sphincter dominating with more severe disease [7].

Transient lower esophageal sphincter relaxations

There is compelling evidence that transient lower esophageal sphincter relaxations (tLESRs) account for the overwhelming majority of reflux events in normal individuals (“physiologic reflux”) and in patients with a normal LES pressure at the time of reflux [2, 3, 8]. Compared to swallow-induced LES relaxations, tLESRs occur without an associated pharyngeal contraction, are unaccompanied by esophageal peristalsis, and persist for longer periods (more than 10 seconds) than do swallow-induced LES relaxations [9]. However, not all tLESRs are accompanied by reflux. The likelihood of reflux during a tLESR is influenced by both the circumstances of the recording and the temporal proximity to a meal, with different investigators reporting reflux during as many as 93 percent or as few as 9 to 15 percent [8, 10]. What has become clear is the role of tLESRs in belching [11, 12]. The frequency of tLESRs is greatly increased by distention of the stomach by gas or by assuming an upright as opposed to supine posture [13]. Although, recent investigations have also suggested that tLESRs can be elicited in response to pharyngeal stimulation, perhaps being manifestations of “sub-threshold swallows,” this relationship continues to be enigmatic [14]. It seems likely that some of the con-

fusion stems from a lack of appreciation that tLESRs are integrated motor responses involving not only LES relaxation, but also crural diaphragmatic inhibition and contraction of the costal diaphragm [15]. As such, tLESRs promote gas venting from the stomach, and this complex integrated response has not been convincingly demonstrated in response to pharyngeal stimulation of any kind. In view of the circumstances in which they appear, it seems most likely that tLESRs are a physiologic response to gastric distention by food or gas and are the mechanisms responsible for gas venting of the stomach; acid reflux is an inconstant associated phenomenon.

Hypotensive lower esophageal sphincter

Gastroesophageal reflux can occur with a diminished LES pressure either in the setting of a completely atonic LES or when a hypotensive LES is overcome and “blown open” by an abrupt increase of intra-abdominal pressure [3]. Prolonged manometric recordings suggest that these mechanisms of reflux are relatively unusual, operant mainly when the LES pressure is less than 4 mmHg [16]. However, these studies were not controlled for the presence of a hiatus hernia (see below) and may introduce artifact because of the activity-restricting effect of the required instrumentation (recumbent subjects reading or watching television with a manometric assembly and a pH probe in their nose). It is possible that if subjects were classified as to hernia status and data were obtained with patients subjecting themselves to conditions that are more provocative of heartburn, a different profile of mechanisms would be observed.

A consistent clinical observation supporting the importance of tLESRs as a mechanism of reflux is that only a minority of individuals with GERD have an LES

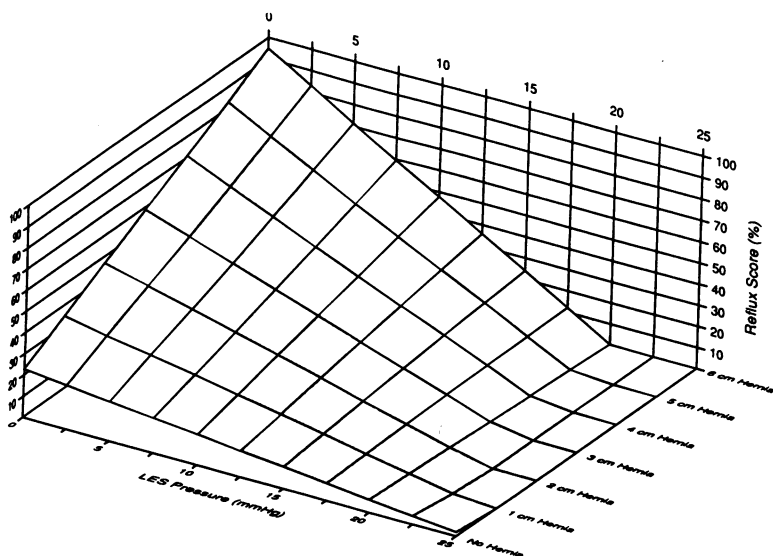


Figure 1. Model of the relationship between lower esophageal sphincter (LES) pressure, size of hernia, and the susceptibility to gastroesophageal reflux induced by provocative maneuvers as reflected by the reflux score on the Z axis. The overall equation of the model is: $\text{reflux score} = 22.64 + 12.05 (\text{hernia size}) - 0.83 (\text{LESP}) - 0.65 (\text{LESP} \times \text{Hernia size})$. The hernia size is in cm, and the LES pressure is in mmHg. The multiple correlation coefficient of this equation for the 50-subject data set was 0.86 ($R^2 = .75$). Thus, the susceptibility to stress reflux is dependent upon the interaction of the instantaneous value of the LES pressure and the size of hiatus hernia. With progressive increase in the axial dimension of hiatus hernia, individuals are increasingly dependent upon the LES as an antireflux barrier and, hence, increasingly vulnerable to foods, habits, etc., that diminish the LES pressure. From [23] with permission.

pressure of less than 10 mmHg when determined by isolated fasting measurements [17]. This observation can be somewhat reconciled with the proposed role of a weak sphincter in reflux when one considers the dynamic nature of LES pressure. An isolated fasting measurement of LES pressure is probably only useful to identify patients with a grossly hypotensive LES. However, there is undoubtedly a larger group of patients with mild or moderate GERD susceptible to reflux from increased intra-abdominal pressure when their LES pressure has been temporarily

diminished as a result of specific foods, drugs, or habits [7, 10].

Hiatus hernia and the diaphragmatic sphincter

Recent physiologic investigations in humans and animals have advanced the "two sphincter hypothesis" of gastroesophageal junction competence, suggesting that both the smooth muscle LES and the crural diaphragm encircling the LES serve a sphincteric function [4, 18-20]. Manometric recordings from the gastroesophageal junction are often characterized

by inspiratory augmentation. These inspiratory increases result from contraction of the diaphragmatic crus that encircles the LES. The respiratory oscillations correlate with crural diaphragm EMG activity, increase with respiratory effort, and are eliminated by manual hyperventilation [21]. Furthermore, a persistent gastroesophageal junction high-pressure zone can be manometrically demonstrated in patients following oncologically-prompted surgical removal of the distal esophagus and proximal stomach, which presumably removed the smooth muscle LES [22].

The clinical significance of gastroesophageal junction pressure attributable to the crural diaphragm and hiatus canal pertains to a condition potentially associated with its anatomic disruption: hiatus hernia. Observations of the antireflux mechanism during stress maneuvers such as leg raising and abdominal compression sug-

gest a "pinchcock effect" of crural contraction that augments the antireflux barrier. Thus, under these conditions, both the diaphragm and the LES contribute to gastroesophageal sphincter competence. Susceptibility to reflux under such circumstances of abrupt increases of intraabdominal pressure as occur during bending or coughing depends upon both the instantaneous LES pressure and the diaphragmatic sphincter [23]. Patients with hiatus hernia exhibit progressive disruption of the diaphragmatic sphincter proportional to the extent of axial herniation. Therefore, although neither condition in and of itself (hiatus hernia or hypotensive LES) results in severe incompetence, the two conditions interact with each other as evidenced by the statistical modeling of gastroesophageal junction competence depicted graphically in Figure 1 [23]. This model is consistent

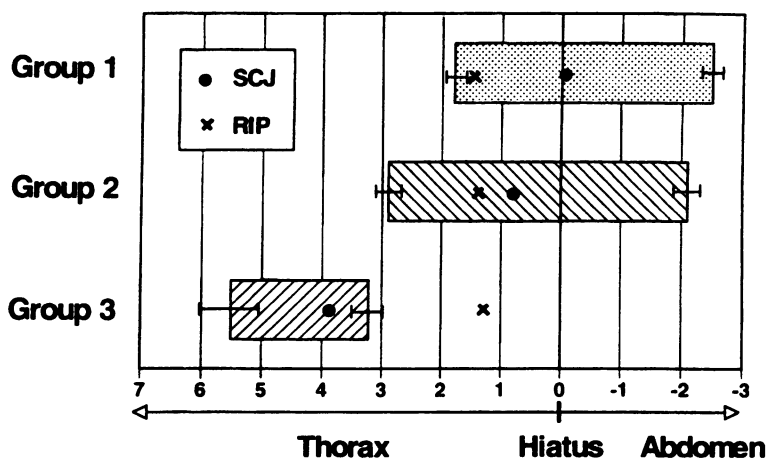


Figure 2. Length and position of gastroesophageal junction high pressure zone relative to the diaphragmatic hiatus among subject groups. The squamocolumnar junction was marked with a metal clip, and the position of the high pressure zone was determined during concurrent manometry and fluoroscopy. Group 1 patients were characterized by having the squamocolumnar junction at or below the hiatus. Group 2 and group 3 patients were characterized by having the squamocolumnar junction 0 to 2 cm and > 2 cm above the hiatus, respectively. The horizontal bars depict the average limits of the high pressure zone within each subject group (mean \pm SE cm). The position of the respiratory inversion point (RIP) is constant among subject groups while the position of the squamocolumnar junction is progressively more cephalic in groups 2 and 3. The high pressure zone is significantly shorter in the group 3 subjects compared to both groups 1 and 2. From [25] with permission.

with the clinical experience that exercise, tight fitting garments, and activities involving bending at the waist exacerbate heartburn, especially after having consumed meals that reduce LES pressure.

A further twist in the interrelationship between hiatus hernia and the LES is that a hernia in and of itself may diminish LES pressure. In experiments on dogs, surgical division of the phrenoesophageal ligament led to a decreased LES pressure that was then restored by reanastomosing the ligament [24]. The condition of a large non-reducing hiatus hernia is probably similar to that of a ruptured phrenoesophageal ligament. Figure 2 illustrates the effect of non-reducing hiatus hernia on the length and position of the gastroesophageal junction high-pressure zone relative to the diaphragm [25]. The group 3 subjects in Figure 2 were defined by having the squamocolumnar junction (marked with a metal mucosal clip) more than 2 cm proximal to the hiatus. This defect is associated with loss of the distal aspect of the high-pressure zone. Anatomically, the lost sphincteric segment corresponds to the collapsed columnar-lined distal segment described by Lieberman-Meffert extending to the gastric sling fibers [26]. The group 2 patients in Figure 2 represent an intermediate group with migration of the squamocolumnar junction above the diaphragm, but not to the extent that it distorts the sphincter profile.

Conceptually, this could continue to be the case until the extent of herniation exceeds the length of the "submerged segment" as it does with the group 3 patients. The reader is referred to a scholarly review of Friedland for more detail on the subtleties of this anatomy [27].

COMPROMISE OF ACID CLEARANCE RELATED TO HIATUS HERNIA

The normal process of esophageal acid clearance is a two-step process; virtually all fluid volume is emptied from the esophagus by esophageal peristalsis, leaving only a minimal residue that sustains an acidic pH in the esophageal mucosa until it is neutralized by swallowed saliva [28]. It takes about 7 ml of saliva to neutralize 1 ml of 0.1 N HCl, with 50 percent of this neutralizing capacity attributable to salivary bicarbonate [29]. Thus, in individuals without impaired esophageal emptying, the acid clearance time is solely dependent upon the rate of salivation. However, an impaired ability to empty fluid from the esophagus can vastly prolong acid clearance.

Prolonged esophageal acid clearance among patients with hiatus hernia and symptomatic gastroesophageal reflux was demonstrated along with the initial description of the acid clearance test [30]. Similarly, in 24-hour distal esophageal pH recordings of more than 100 patients with reflux disease, the mean acid clearance time of "supine refluxers" was markedly prolonged compared to the values of control subjects [31]. Subsequent investigations have demonstrated heterogeneity within the patient population such that although the mean acid clearance time value among patients with symptomatic reflux was greater than that of controls, only about half of reflux patients have prolonged values [6]. Heterogeneity within the GERD population was also confirmed by review of a large data set on 24-hour esophageal pH monitoring. These investigators also made the observation that individuals with known hiatus hernias tended

to have the most prolonged recumbent acid clearance times [32].

As discussed above, the two major potential mechanisms of prolonged acid clearance are impaired fluid emptying and impaired salivary function. A series of recent investigations have demonstrated that hiatus hernias compromise fluid emptying from the distal esophagus. Mittal used concurrent pH recording and scintiscanning to examine the efficacy of fluid emptying and acid clearance in a group of

patients with hiatus hernia (with or without esophagitis) and compared them to a group of esophagitis patients without hernias [33]. Irrespective of the presence of esophagitis, 15 of the 20 hiatus hernia patients had impaired acid clearance because there was "rereflux" from the hernia sac during swallowing. Sloan and Kahrilas further analyzed the impact of hiatus hernia on esophageal emptying using simultaneous videofluoroscopy and manometry in 22 patients with axial hiatus

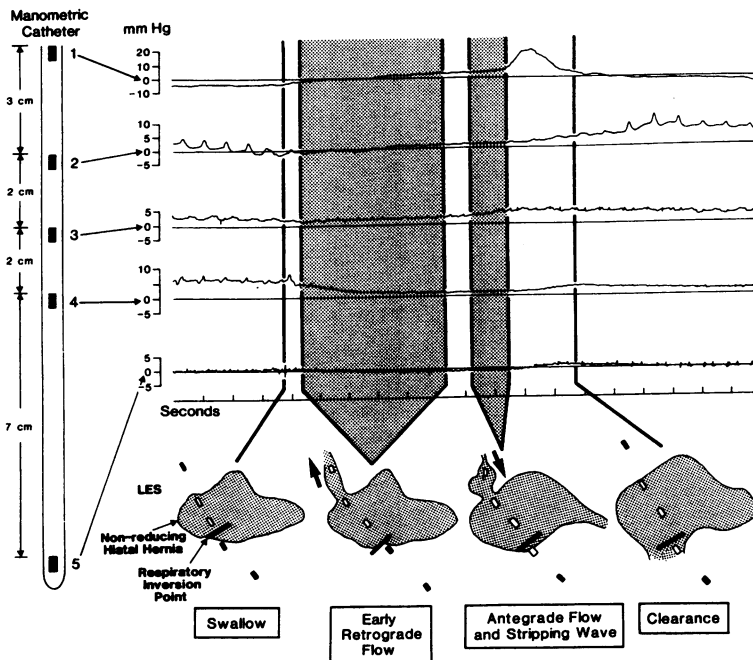


Figure 3. Concurrent manometric and fluoroscopic recording of a 10 ml barium swallow with early retrograde flow in a subject with a non-reducing hiatus hernia. Tracings below the manometric record correspond to the times on the manometric tracings intersected by the vertical lines. The schematic diagram to the left depicts the relative spacing of the pressure sensors whose tracings are depicted. The arrows next to the video image indicate the direction of barium flow. The first video image to the far left shows a barium filled hiatus hernia at the time the swallow is initiated with sensor #1 in the distal esophagus, sensor #2 in the LES, sensor #3 within the hernia, sensor #4 measuring crural contractile activity, and sensor #5 within the abdominal stomach. The second image, taken one second after the swallow, depicts the onset of retrograde flow; intrahernial pressure was 2 mmHg and LES pressure was 0 mmHg. Retrograde flow continued for 5 seconds until the peristaltic contraction reached the distal esophagus. The third image depicts antegrade flow with the stripping wave progressing down the esophagus and LES pressure increasing to equal intrahernia pressure (approx. 4 mmHg). The final image at the far right shows barium cleared from the esophagus with the LES pressure now exceeding intrahernial pressure. From [34] with permission.

hernias compared to 14 normal subjects [34]. Hernia subjects were subdivided into those that reduced between swallows and those that did not reduce between swallows. Each subject performed ten barium swallows, and the outcome of each in terms of esophageal emptying was noted. Possible outcomes were of complete clearance, minimal clearance because of failed peristalsis, late retrograde flow of barium from the ampulla back up the tubular esophagus, or early retrograde flow from the ampulla occurring coincident with LES relaxation, analogous to rereflux in Mittal's study (Figure 3). Overall efficacy of esophageal emptying was significantly impaired in both hiatus hernia groups, but it was especially poor in the group with non-reducing hernias that exhibited complete emptying in only one-third of test swallows and early retrograde flow, a phenomenon unique to this group, in almost half.

Observations on normal subjects suggest that impaired esophageal emptying with hiatus hernias is a consequence of loss of the subdiaphragmatic segment of esophagus. Normally, sphincter (ampullary) opening is not evident until it is distended by the bolus being propelled by esophageal peristalsis, an event that occurs 5 to 10 seconds after the swallow [35, 36].

Mechanistically, for opening to occur, pressure acting on the lumen of the sphincter must exceed the pressure surrounding the sphincter. However, the anatomical considerations detailed above suggest that the normal position of the distal esophagus is intra-abdominal. Hence, intragastric pressure acting to open the sphincter is negated by the external pressure of equal magnitude acting on the same esophageal segment. The effect of eliminating this intra-abdominal segment was evident in the non-reducing hernia group. During early retrograde flow events, the LES was

opened from below immediately following swallow-induced LES relaxation. For this to occur, intragastric pressure within the sphincter must exceed the extrasphincteric pressure, indicating that the extrasphincteric pressure was less than intra-abdominal pressure (i.e., closer to intrathoracic pressure) in these individuals. The importance of an extrasphincteric mechanism in preventing reflux has also been supported in an animal model. During reflux testing in monkeys fitted with pressure sensors both within the LES and within the abdominal cavity external to the LES, reflux was observed only when the external LES pressure was lower than intraluminal LES pressure [37].

Another mechanism promoting gastroesophageal junction competence during esophageal emptying is the crural diaphragm [34]. In normal individuals the esophageal ampulla fills from above as the bolus is propelled ahead of the peristaltic contraction. As the peristaltic contraction arrives at the distal esophagus, intra-ampullary pressure increases to about 10 mmHg, at which time ampullary emptying began. During emptying, the diaphragmatic crura functioned as a one-way valve. During expiration, at which time the esophageal-gastric pressure gradient favors antegrade flow, the crus is relaxed and visibly open. However, during inspiration, when intra-abdominal pressure increases, the crura contract and close, thereby preventing gastroesophageal flow. The valvular effect of the crural diaphragm is grossly impaired with non-reducing hernias because a gastric pouch persists above the diaphragm, thereby disabling this one-way valve function.

CONCLUSIONS

The gastroesophageal junction is anatomically and physiologically complex

and vulnerable to dysfunction by several mechanisms. The unifying theme of mechanisms of reflux disease is that they result in increased esophageal acid exposure. Evidence suggests that hiatus hernia is a significant factor in many instances. However, the importance of hiatus hernia is obscured by imprecise definition and all-or-none thinking; it is more accurate to view hiatus hernia as a continuum of progressive disruption of the gastroesophageal junction. There are at least three potentially significant features of a hiatus hernia: axial length during distention, axial length at rest, and competence of the diaphragmatic hiatus. Although any or all of these features may be abnormal in a particular instance of hiatus hernia, each is probably of different significance. Large hernias are of greater significance than "borderline" hernias. Presumably, the phrenoesophageal membrane, which is stretched during each peristaltic contraction and challenged during each episode of increased intra-abdominal pressure, gradually loses its elastic recoil with the years.

Mechanistically, the gastroesophageal junction must protect against reflux both in static and dynamic conditions. In static conditions, unless extremely hypotensive, the smooth muscle LES has adequate tone to protect against reflux. In this circumstance, reflux can only occur by tLESR. However, during dynamic stresses such as swallowing or abrupt increases in intra-abdominal pressure, gastroesophageal junction competence is dependent upon both the LES and the diaphragmatic sphincter. During abrupt increases in intra-abdominal pressure, the crural diaphragm normally serves as a "second sphincter," and this mechanism is substantially impaired in individuals with a gaping hiatus. During swallowing, the crural diaphragm functions as a one-way valve, permitting flow only during expiration when the pressure gradient favors ante-

grade flow to the stomach. Large hernias impair the process of esophageal emptying thereby prolonging acid clearance time (especially while in the supine posture). Thus, although hiatus hernia may or may not be involved at the inception of reflux disease as an initiating factor, it clearly can be a significant contributor to the chronicity of disease, acting as a sustaining factor.

REFERENCES

1. Cohen, S. and Harris, L.D. Does hiatus hernia affect competence of the gastroesophageal sphincter? *N. Engl. J. Med.* 284:1053-1056, 1971.
2. Dent, J., Dodds, W.J., Friedman, R.H., Sekiguchi, T., Hogan, W.J., Arndorfer, R.C., and Petrie, D.J. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. *J. Clin. Invest.* 65:256-267, 1980.
3. Dodds, W.J., Dent, J., Hogan, W.J., Helm, J.F., Hauser, R., Patel, G.K., and Egide, M.S. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N. Engl. J. Med.* 307:1547-1542, 1982.
4. Mittal, R.K., Rochester, D.F., and McCallum, R.W. Electrical and mechanical activity in the human lower esophageal sphincter during diaphragmatic contraction. *J. Clin. Invest.* 81:1182-1189, 1988.
5. Hirschowitz, B.I. A critical analysis, with appropriate controls, of gastric acid and pepsin secretion in clinical esophagitis. *Gastroenterology* 101:1149-1158, 1991.
6. Stanciu, C. and Bennett, J.R. Oesophageal acid clearing: one factor in production of reflux esophagitis. *Gut* 15:852-857, 1974.
7. Barham, C.P., Gotley, D.C., and Alderson, D. Precipitating causes of acid reflux episodes in ambulant patients with gastroesophageal reflux disease. *Gut* 36:505-510, 1995.
8. Mittal, R.K., Holloway, R.H., Penagini, R., Blackshaw, L.A., and Dent, J. Transient

- lower esophageal sphincter relaxation. *Gastroenterology* 109:601-610, 1995.
9. Holloway, R.H., Penagini, R., and Ireland, A.C. Criteria for objective definition of transient lower esophageal sphincter relaxation. *Am. J. Physiol.* 268:G128-G133, 1995.
 10. Kahrilas, P.J. and Gupta, R.R. Mechanisms of acid reflux associated with cigarette smoking. *Gut* 31:4-10, 1990.
 11. Kahrilas, P.J., Dodds, W.J., Dent, J., Wyman, J.B., Hogan, W.J., and Amdorfer, R.C. Upper esophageal sphincter function during belching. *Gastroenterology* 91:133-140, 1986.
 12. Wyman, J.B., Dent, J., Heddl, R., Dodds, W.J., Toouli, J., and Downton, J. Control of belching by the lower esophageal sphincter. *Gut* 31:639-646, 1990.
 13. Martin, C.J., Patrikios, J., and Dent, J. Abolition of gas reflux and transient lower esophageal relaxation by vagal blockade in the dog. *Gastroenterology* 91:890-896, 1986.
 14. Mittal, R.K., Chiareli, C., Liu, J., and Shaker, R. Characteristics of lower esophageal sphincter relaxation induced by pharyngeal stimulation with minute amounts of water. *Gastroenterology* 111:378-384, 1996.
 15. Martin, C., Dodds, W.J., Liem, H., Dantas, R., Layman, R., and Dent, J. Diaphragmatic contribution to gastroesophageal competence and reflux in dogs. *Am. J. Physiol.* 263:G55 I-G557, 1992.
 16. Dent, J., Dodds, W.J., Hogan, W.J., and Toouli, J. Factors that influence induction of gastroesophageal reflux in normal human subjects. *Dig. Dis. Sci.* 33:270-275, 1988.
 17. Kahrilas, P.J., Dodds, W.J., Hogan, W.J., Kem, M., Amdorfer, R.C., and Reece, A. Peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 91:897-904, 1986.
 18. Boyle, J.T., Altschuler, S.M., Nixon, T.E., Tuchman, D.N., Pack, A.I., and Cohen, S. Role of the diaphragm in the genesis of lower esophageal sphincter pressure in the cat. *Gastroenterology* 88:723-730, 1985.
 19. Boyle, J.T., Altschuler, S.M., Nixon, T.E., Pack, A.I., and Cohen, S. Responses of feline gastroesophageal junction to changes in abdominal pressure. *Am. J. Physiol.* 253:G315-G322, 1987.
 20. Mittal, R.K. and Fisher, M.J. Electrical and mechanical inhibition of the crural diaphragm during transient relaxation of the lower esophageal sphincter. *Gastroenterology* 99:1265-1268, 1990.
 21. Mittal, R.K., Rochester, D.F., and McCallum, R.W. Sphincteric action of the diaphragm during a relaxed lower esophageal sphincter in humans. *Am. J. Physiol.* 256:G139-G144, 1989.
 22. Klein, W.A., Parkman, H.P., Dempsey, D.T., and Fisher, R.S. Sphincterlike thoracoabdominal high pressure zone after esophagogastrectomy. *Gastroenterology* 105:1362-1369, 1993.
 23. Sloan, S., Rademaker, A.W., and Kahrilas, P.J. Determinants of gastroesophageal junction incompetence: hiatus hernia, lower esophageal sphincter, or both? *Ann. Int. Med.* 117:977-982, 1992.
 24. Michelson, E. and Siegel, C.I. The role of the phrenico-esophageal ligament in the lower esophageal sphincter. *Surg. Gynecol. Obstet.* 118:1291-1294, 1964.
 25. Kahrilas, P.J., Wu, S., Lin, S., and Poudroux, P. Attenuation of esophageal shortening during peristalsis with hiatus hernia. *Gastroenterology* 109:1818-1825, 1995.
 26. Lieberman-Meffert, D., Allgöwer, M., Schmid, P., and Blum, A.L. Muscular equivalent of the lower esophageal sphincter. *Gastroenterology* 76:32-38, 1979.
 27. Friedland, G.W. Historical review of the changing concepts of lower esophageal sphincter anatomy. *Am. J. Roentgenol.* 131:373-388, 1978.
 28. Helm, J.F., Dodds, W.J., Pelc, L.R., Palmer, D.W., Hogan, W.J., and Teeter, B.C. Effect of esophageal emptying and saliva on

- clearance of acid from the esophagus. *N. Engl. J. Med.* 310:284-288, 1984.
29. Helm, J.F., Dodds, W.J., Hogan, W.J., Soergel, K.H., Egide, M.S., and Wood, C.M. Acid neutralizing capacity of human saliva. *Gastroenterology* 83:69-74, 1982.
 30. Booth, D.J., Kemmerer, W.T., and Skinner, D.B. Acid clearing from the distal esophagus. *Arch. Surg.* 96:731-734, 1968.
 31. DeMeester, T.R., Johnson, L.F., Joseph, G.J., Toscano, M.S., Hall, A.W., and Skinner, D.B. Patterns of gastroesophageal reflux in health and disease. *Ann. Surg.* 184:459-470, 1976.
 32. Johnson, L.F. 24-hour pH monitoring in the study of gastroesophageal reflux. *J. Clin. Gastroenterol.* 2:387-399, 1980.
 33. Mittal, R.K., Lange, R.C., and McCallum, R.W. Identification and mechanism of delayed esophageal acid clearance in subjects with hiatus hernia. *Gastroenterology* 92:130-135, 1987.
 34. Sloan, S. and Kahrilas, P.J. Impairment of esophageal emptying with hiatus hernia. *Gastroenterology* 100:596-605, 1991.
 35. Lin, S., Brasseur, J.G., Poudroux, P., and Kahrilas, P.J. The phrenic ampulla: distal esophagus or potential hiatus hernia? *Am. J. Physiol.* 268:G320-G327, 1995.
 36. Poudroux, P., Ergun, G.A., Lin, S., and Kahrilas, P.J. Esophageal bolus transit imaged by ultrafast computerized tomography. *Gastroenterology* 110:1422-1428, 1996.
 37. Chambers, C.E., Zarins, C.K., Skinner, D.B., and Jones, E.L. External compression of the cardia related to gastroesophageal reflux. *Surg. Forum* 23:396-398, 1972.