Gastroesophageal reflux disease (etiology, pathogenesis, diagnosis, treatment).

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Part II. Anatomy and physiology of the esophagus and EGJ in healthy and gastroesophageal reflux disease

The esophagus is a peristaltic tube that begins caudal to the upper esophageal sphincter (UES) and ends above the lower esophageal sphincter (LES). Immediately after closing of the UES, contraction of the esophageal muscle occurs, which travels down the esophagus as a peristaltic wave to the LES. This contraction impulse progresses without an apparent pause after each sip. The speed of caudal progression is different in different parts of the esophagus and is between 1 and 4 cm/sec, and the pressure at different points varies from 40 to 100 cm H2O [1]. This complies with the law of the intestine by Bayliss and Starling - «Excitation at any point of the gut excites contraction above, inhibition below". Cannon later proposed the term "myenteric reflex" for the phenomenon [2].

There are two types of bolus movement in the esophagus. In a horizontal position, it always occurs due to peristalsis. In the vertical position, a solid bolus passes with the help of peristalsis, but the liquid (barium suspension) quickly fills the esophagus in the form of a column with a liquid level near the fourth thoracic vertebra, after which barium enters the stomach by jet. During the evacuation of barium from the esophagus, the fluid level drops. The EGJ remains open until the esophagus is empty. Bott et al measured the diameter of the esophagus on x-ray between the second and third rib. It was proportional to the weight of the child. The mean diameter at the cranial point of measurement was 6.75 mm at the lowest weight (2.6 kg) and 14 mm at 74 kg [3]. The true diameter of the esophagus, i.e., adjusted for projection magnification, in healthy adults, according to our data, is 1.5 cm and in the vertical position, it is the same along the entire length of the esophagus [4].

In normal subjects, inflating the balloon in the upper esophagus increases the tone of the UES [5, 6]. Esophageal distension above LES causes a significant decrease in LES pressure [6, 7]. An increase in the gastric pressure causes an increase in the tone of the LES [8, 9, 10]. At rest, i.e., outside of swallowing, the pressure over the LES is lower than in the stomach [11, 12].

The lower esophageal sphincter (LES) surrounded by the crural part of the diaphragm (CD) at the tenth thoracic vertebra. Unlike the esophagus and stomach, it is in a state of constant contraction. Its length increased with age. In adults,

the LES length according to pull-through manometry with end-hole and side-hole catheter in the control group ranged from 34±9 mm [13], to 4.1 cm [14]. The length of its abdominal part was 2.1 cm [14] and 23±7 mm [15]. Manometric studies have reliably established that in GERD, the LES tone is lower, and its length is shorter than in healthy individuals. The shortening of the LES occurs due to the opening of its abdominal part [13, 16, 17].

Based on the physiology of the EGJ described above, I performed X-ray studies, creating compression of the patient's abdomen while he was drinking barium. The compression of the abdomen caused an increase in pressure in the stomach, which should have increased the tone of the LES. To eliminate the effect of CD, I continued to press on the stomach for about 30 seconds. Shafik study found that the striated muscle of the diaphragm quickly gets tired. "The CD response disappeared when straining was sustained for more than 15–18 seconds (mean 16.8 ± 1.2) and was not evoked after frequent successive straining" [18].

X-ray examination is the simplest and most visual method for studying the function of the EGJ. At the same time, unlike other methods, tubes are not introduced into the digestive canal, which, by stretching the wall, distorts its true reaction. In a study with abdominal compression, in a proportion of our patients who developed heartburn or chest pain a few weeks ago, barium entered the stomach without delay, just as it did without compression. In other patients, abdominal compression resulted in the contraction of the EGJ between the esophagus and stomach, which prevented the evacuation of barium from the esophagus [19] **(Figure 1)**.

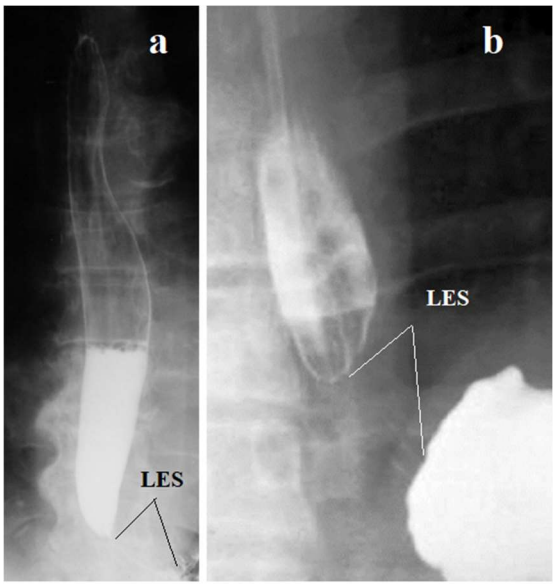

Figure 1. Radiographs of patients with GERD. Two options for bolus evacuation from the esophagus to the stomach. **(a). In an upright position**, during abdominal compression, the LES contracted and the fluid level stopped to sink. A column of gas and liquid with an aortic depression on the left is visible between the UES and LES. (**b). In the horizontal position**, the bolus advances in a peristaltic wave. Abdominal compression led to a contraction of the LES. Mucosal folds are visible both at the level of the LES and in the esophagus.

First, the studies with abdominal compression confirmed previous manometric that an increase in gastric pressure causes an increase in LES tone. Secondly, it turned out to be possible to measure the length of the LES. Thirdly, an increase in the tone of the LES in response to abdominal compression indicates that an additional amount of muscle fibers joined the number of contracted muscle fibers that provided the tone of the LES at rest.

I took the group of patients in whom compression did not affect the progression of barium into the esophagus as a conditional norm, but they did not have the opportunity to measure the LES length. Of those patients who had a contraction of the LES, I selected those with minimal clinical symptoms that appeared recently, assuming that their LES had not yet had time to noticeably change. The results of measuring the length of the NPS are shown in Table 1.

Table 1. Normal length LES in different age groups

	Length of lower esophageal sphincter (cm)					
Age	Up to 1 year	1–3 years	4–7 years	8–10 years	11–15 years	21–65 years
Limits	0.7 – 1.0	1.2 – 1.5	1.5– 1.8	1.9 – 2.3	2.3 – 2.9	3.2 – 4.2
M± м	0.86±0.03	1.40±0.02	1.72±0.07	2.10±0.05	2.45±0.11	3.60±0.08

We have described the LES length for children of different ages for the first time. The length of the LES in adults practically coincides with the data of a manometric study. However, for adults, the difference between the minimum and maximum limits is too large. Obviously, both X-ray and manometric studies included patients with GERD in the group of healthy people, in whom we erroneously did not associate abdominal pain, anemia or non-intestinal problems with GERD. Probably, the real norm is closer to the maximum limit. Unfortunately, there is still no generally accepted methodology for excluding GERD. I think that the absence of cardiac epithelium on histological examination can provide strong evidence for the absence of GERD [16]. The data in this table should be considered as a relative norm and used for lack of more accurate ones.

Mapping of esophagogastric junction

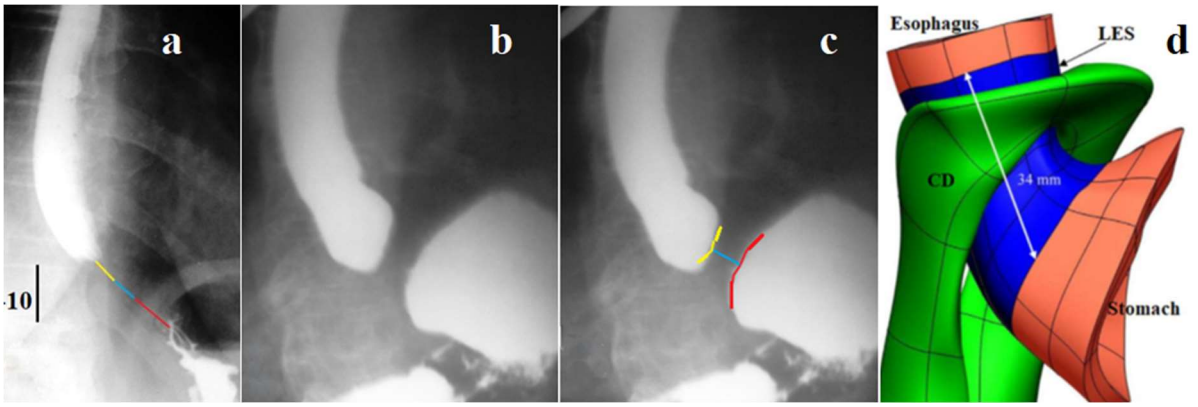

Figure 2. **(a).** Radiograph of a patient with GERD in an upright position taken during abdominal compression. The zone without contrast agent between the esophagus and stomach is the contracted LES. Since the actual height of D-10 is ≈2 cm, the actual length of the LES is ≈3.3 cm. Diagram of the LES parts: red - the abdominal segment, blue - inside the diaphragm, yellow - above the diaphragm. **(b, c).** The same patient during abdominal compression in a horizontal position. A sharp shortening of the LES is determined due to the disclosure of the intra-abdominal (red line) and supradiaphragmatic (yellow line) parts. Only a part of the LES 1 cm long located at the level of the diaphragm is in a contracted state. **(d)** Three-Dimensional Model of the Esophageal Gastro Junction [20]. The length of the LES is 3.4 cm (blue). Its abdominal part is ≈2 cm. About 1 cm is located at the level of the CD and 0.4 cm above the diaphragm.

In all cases, the minimum contraction zone was 1 cm. Thus, X-ray, manometric and CT studies created a general picture of the state of EGJ. The total LES length is about 4 cm. It consists of three parts: (a) the supra-phrenic part, 0.8–1.0 cm long; (b) inside the diaphragmatic part 1 cm long, where CD is located around the LES; and (c) an abdominal part about 2 cm long.

The mechanism of the passage of the bolus from the esophagus to the stomach in healthy individuals.

If at rest the pressure in the esophagus over the LES is less than in the stomach, then the opening of the LES under such conditions would inevitably lead to reflux of gastric contents into the esophagus. Obviously, for the passage of the bolus from the esophagus to the stomach through the open LES, the pressure in the esophagus must be higher than in the stomach.

In the upright position, the hydrostatic pressure of the liquid column, firstly, provides a positive pressure gradient. Second, it causes the EGJ to open, which remains open until the esophagus is completely empty of contents. Obviously, the

opening of the EGJ is a reflex. Since the opening continues even at the stage when the fluid level is near the LES, i.e., the hydrostatic pressure is very low, therefore, the opening does not occur because of mechanical stretching, but the active contraction of the muscles of the LES. The mechanism of this opening is explained by the location of muscle fibers in the LES. Manometric 3D images and histological studies of the lower esophageal high-pressure zone showed a marked radial and longitudinal asymmetry. Radial pressures peaked were highest toward the left posterior direction. The anatomic evaluation showed an asymmetric thickening of the muscular layer at the gastroesophageal junction that mirrored the manometric image. Muscle thickness was highest toward the greater curvature side corresponding to the gastric "sling" fibers and toward the lesser curvature corresponding to the semicircular "clasp" fibers [21, 22].

In the horizontal position, the last peristaltic wave with a high tone at the proximal point at point creates a closed cavity between the proximal point and the LES. Since the proximal point of the peristaltic wave moves towards the LES, then in this closed cavity, the pressure is understood to the threshold level, which leads to the opening of the LES. As the proximal point is progressively advanced, the peristaltic wave injects the bolus into the stomach **(Figure 3).**

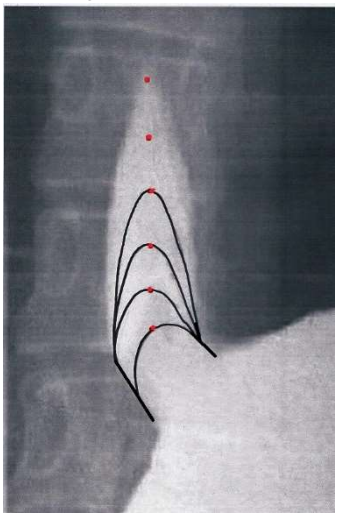

Figure 3. Diagram of bolus evacuation with the last peristaltic wave in a patient with GERD. In a healthy individual, it is not possible to stop the peristaltic wave. It flows instantly and without stopping. The red dots show the movement of the proximal high-pressure point, which ensures the tightness of the chamber and the high pressure in it.

The mechanism of the passage of the bolus from the esophagus to the stomach in GERD.

With GERD, the EGJ changes occur under the influence of hydrochloric acid. It causes mucosal damage and an inflammatory reaction first in the LES and then in the esophagus, with gradual progression from the lower to the upper

esophagus. The antireflux capacity of the LES is deteriorating both due to a decrease in its tone and because of its shortening.

Shortening of the LES occurs due to the disclosure of its intra-abdominal part. This process is constantly progressing. For example, at low pressure in the stomach, the length of the LES during X-ray examination may be within the normal range, and with an increase in load, it is shortened depending on the magnitude of gastric pressure, its continuous duration and on the degree of damage of the LES.

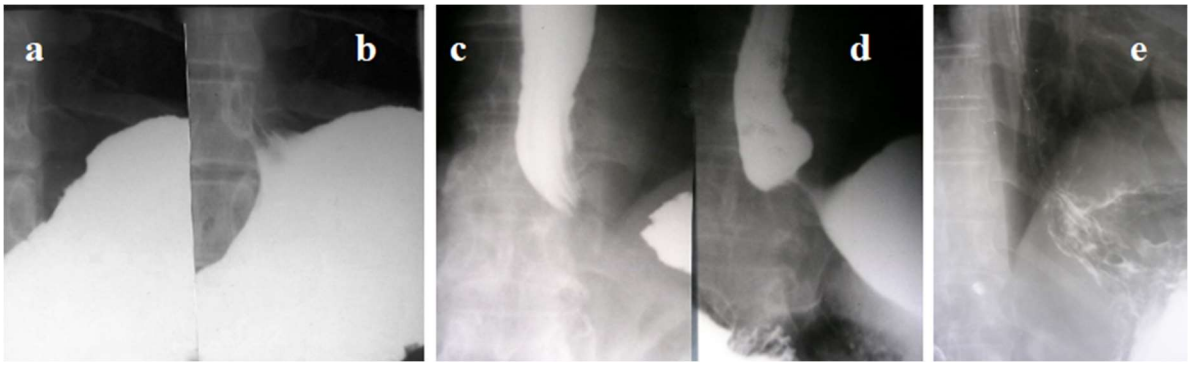

Figure 4. Radiographs of the EGJ in patients with GERD. **(a).** Before provocation. **(b).** During the water-siphon test, the LES opened (the angle of His became obtuse). **(c)** Short LES contracted during abdominal compression (2 cm vs 4 cm). **(d)** Continued compression resulted in LES shortening to 1 cm. (e) The opening of the LES in the form of a beak of the stomach is seen without provocation (Angle of His obtuse).

Figure 5 shows how the shortening of the LES leads to an increase in the His angle and a decrease in the volume of the gas bubble of the stomach.

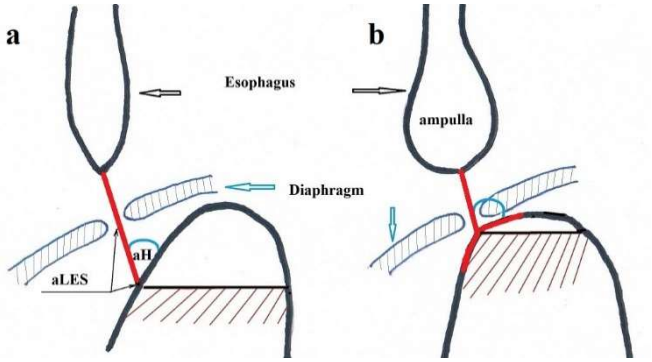

Figure 5. Scheme of the opening of the abdominal part of the LES in GERD. **(a).** The EGJ in normal. aLES - abdominal part of the LES. aH – the angle of His. **(b).** As a result of the opening of the abdominal part of the LES, the angle of His increased and the volume of the gastric bubble decreased.

The above data indicate that an increase in the angle of His is not one of the causes of GERD, but its symptom.

The inflammatory process in the lower part of the esophagus, above the diaphragm, causes weakness of the last peristaltic wave. In many cases, but not always, there is an expansion of the esophagus at this site, which is called the phrenic ampulla.

Phrenic ampulla forms in a horizontal position above the LES only in GERD. The idea that it may be normal is due to the erroneous selection of supposedly healthy individuals to determine the normal range for pH monitoring. Since GERD may be asymptomatic, GERD patients were selected in the control group.

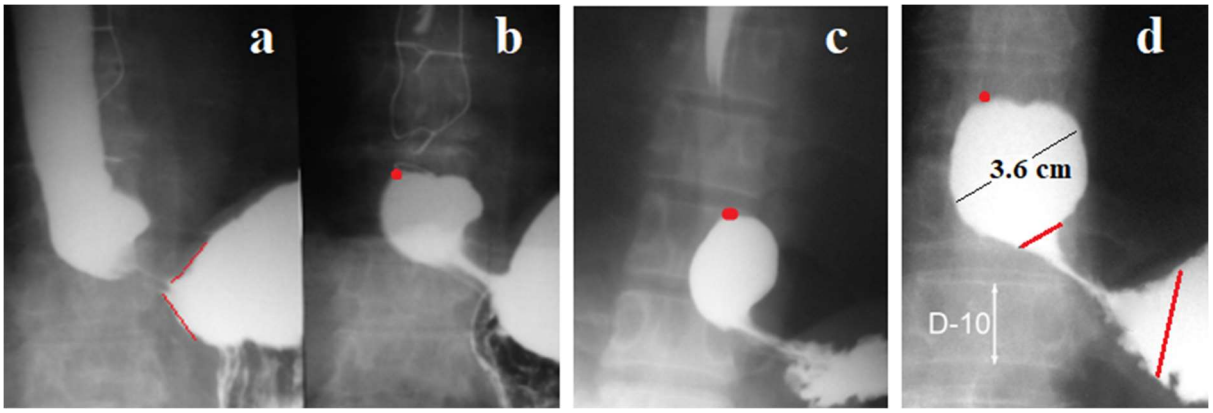

Figure 6. Examples of the phrenic ampulla formation of the esophagus. In all cases, LES is almost 2 times shorter than normal. (a, b, c). The last peristaltic wave closes proximally (red dot). During its contraction, it creates a high pressure that opens the LES, after which the ampoule injects a bolus into the stomach. (d). Since the height of D-10 is about 2 cm, the width of the ampulla is 3.6 cm. The true length of the LES is limited by red lines, but only the diaphragmatic part contracted during abdominal compression.

In fact, the ampulla is the last peristaltic wave that must create high pressure to open the LES and inject the bolus into the stomach. An important role in this process is played by the esophagus, which closes the ampulla proximally and prevents the penetration of barium from the ampulla into the proximal section. In Figure 7 an example of the weakness of this department is shown, and barium penetrated the proximal esophagus.

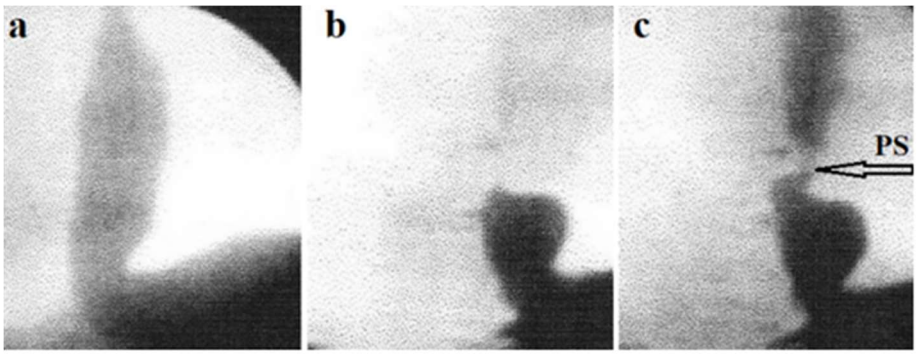

Figure 7. Video footage showing the functioning of the ampoule in a patient with GERD. When the ampulla created a high pressure and began to squeeze the bolus into the stomach, the proximal area could not withstand this pressure and opened. The pressure in the ampulla dropped and barium from the stomach began to flow into the ampoule and into the proximal esophagus. Figure 7.c shows that the ampoule was closed by a certain area of the esophagus (PS).

To seal the ampulla and create a threshold pressure in it for opening the LES in conditions of esophagitis, when the lumen of the esophagus is expanded and the wall tone is weakened, a functional sphincter appears above the ampulla. I measured the length of this acquired sphincter, which I named the proximal sphincter (PS). Its length ranges from 5 to 7 mm **(Figure 8).**

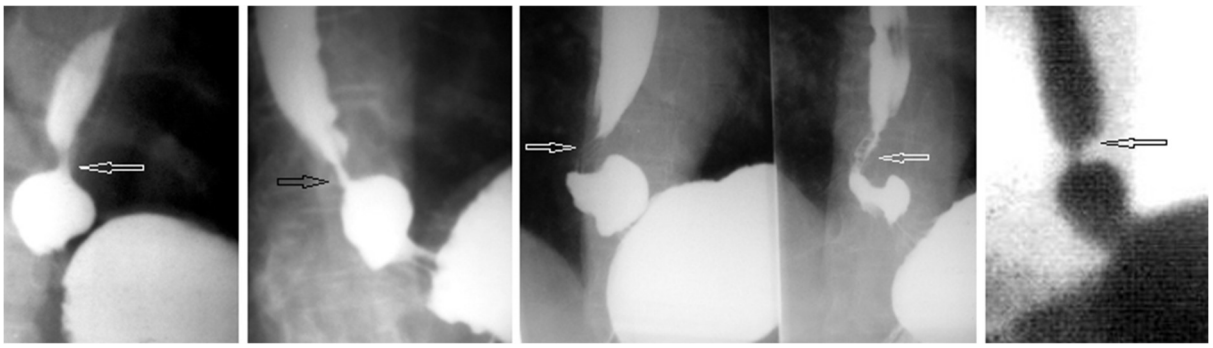

Figure 8. Examples to measure the functional "proximal sphincter" (PS) that arises for seal of the ampulla seal (arrows).

The discovery of PS is neither an accident nor a feature characteristic of the esophagus. Such sphincters occur in the different peristaltic organs (colosigmoid, rectosigmoid in colon) [21,22]), in the common bile duct and ureter etc.

Hiatal Hernia

Modern ideas about hiatal hernia (HH) are presented in the article Roman et al "Hiatus hernia is a condition in which elements of the abdominal cavity herniate through the esophageal hiatus into the mediastinum. Displacement of the lower esophageal sphincter (LES) above the crural diaphragm (CD) creates a pouch of stomach between the two sphincters and this corresponds to a sliding hernia (Type I). which is the most common type of hernia. Although the defining features of hiatus hernia pertain to the EGJ, there are also obligatory changes in the esophageal body associated with the axial displacement: the esophagus shortens and/or develops a tortuous configuration" [23].

The following information is known about hiatal hernia, which conflict with the above concept:

1. The HH is also called a sliding esophageal hernia because it does not show upright on X-ray. It is believed that it appears in a horizontal position, since this position facilitates the sliding of the stomach into the chest cavity.

However, this explanation is refuted by the fact that the ampulla of the esophagus is also detected only in a horizontal position.

2. It is believed that a rounded expansion of the esophagus up to 2 cm in diameter is an ampulla, and more than 2 cm is a hiatal hernia. However, Lin et al показали, что "As such, a normal phrenic ampulla is analogous to a small reducing hiatal hernia" [24]. Obviously, there is no scientific logic in this explanation, because there is no reasonable explanation for how a 1.9 cm wide ampulla of the esophagus, after expanding to 2.1 cm, becomes part of the stomach.

3. It is considered, that “Only some patients with hiatal hernia suffer from GERD, defined by pathological 24-h-ph-metry, while almost all patients with GERD do have hiatal hernia [25]. The statement that HH can be without GERD is false. Because "Although ambulatory pH monitoring is considered the most sensitive test for diagnosing gastro-oesophageal reflux disease (GORD), its optimal utilisation in that context remains controversial" [26].

4. Basseri et al, using high-resolution manometry, showed that "resting pressures in the HH are greater than in the subdiaphragmatic stomach. Here, the green hue within the HH, represents higher pressure than the more blue color below the CD. This is supported by our observation that pressure measured in the HH by the eSleeve is greater than subdiaphragmatic intragastric pressure" [27].

First, if HH was the part of the stomach displaced into the chest, then the pressure in it would be equal to the pressure in the stomach. Secondly, such high pressure can only exist if HH is located between two sphincters. This is exactly how the ampulla of the esophagus functions. It closes proximally PS. Its peristalsis increases the pressure between the LES and the RS, and when it reaches a threshold level, the LES opens, and the ampoule injects a bolus into the stomach.

5. It is believed that in case of HH, along with the stomach, the LES moves into the chest, while the CD remains in the same place, and it alone performs an antireflux function. How true this is will help us to analyze the "typical case of HH" (**Figure 9)**.

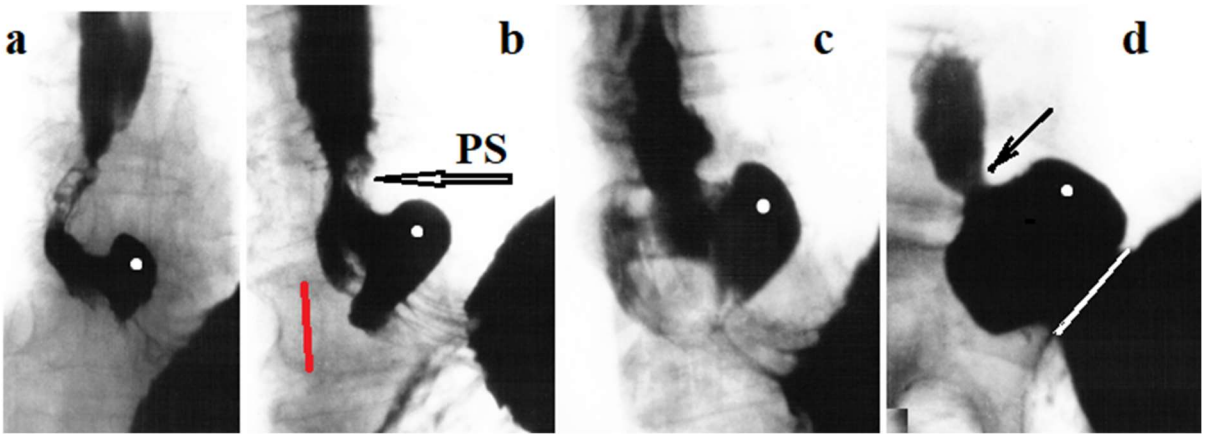

Figure 9. Sequential radiographs of the examination of GEJ in a patient with GERD. After the patient drank about 100 ml of barium in a horizontal position, abdominal compression was performed, which caused a contraction of the LES. Since the height of the 10th thoracic vertebra is approximately 2 cm (red line), the length of the contracted LES is 2 cm. The patient continued to drink barium, which filled the dilated part of the esophagus. The contracted LES prevented the passage of barium from the stomach into the esophagus. In figure **(d),** the LES could not withstand the stress and opened to a diameter of 2.5 cm, because of which barium penetrated from the stomach into the ampulla, and from the ampulla through the opened PS (arrow) into the upper esophagus.

The expansion of the lower esophagus (a, b, c) occurs because of the intake of additional sips of barium. The LES is almost 2 times shorter than the norm, since its abdominal part (cardiac), about 2 cm long, is open and serves as the wall of the stomach. However, this shortened sphincter cannot be CD, because, firstly, because the length of CD is 1 cm, i.e., it cannot create a contraction zone of 2 cm in length. Secondly, as Shafik studies have established, although CD contracts reflexively in response to an increase in gastric pressure, its striated fibers quickly tire and stop contracting after an average of 18 seconds [18]. Thirdly, in this observation, the role of CD in the antireflux function is unlikely, since with a width of the hiatus canal of 2.5 cm, the diaphragm pedicles are not able to block the lumen of the EGJ.

It is important to add that the phrenic ampulla of any size is emptied by a peristaltic wave that pushes the bolus into the stomach. However, the fundal part of the stomach and upper body have not peristalsis since they do not contain intestinal cells of Cajal [28, 29]. Thus, what is commonly called HH is in fact the phrenic ampulla.

The assertion that rugal folds proximal to the stomach are gastric folds has no evidence. Moreover, serious scientific studies state that "The reasons why there is a failure of pathologic diagnosis (GERD) are two false dogmas that result in two widely believed fundamental errors. These are the belief that cardiac

epithelium normally lines the proximal stomach (1) and that the gastroesophageal junction (GOJ) is defined by the proximal limit of rugal folds (2)" [16]. X-ray studies indicate that the inflammatory process in the LES, as well as in the esophagus, is accompanied by the formation of folds, the appearance of which depends on intraluminal pressure **(Figure 10)**.

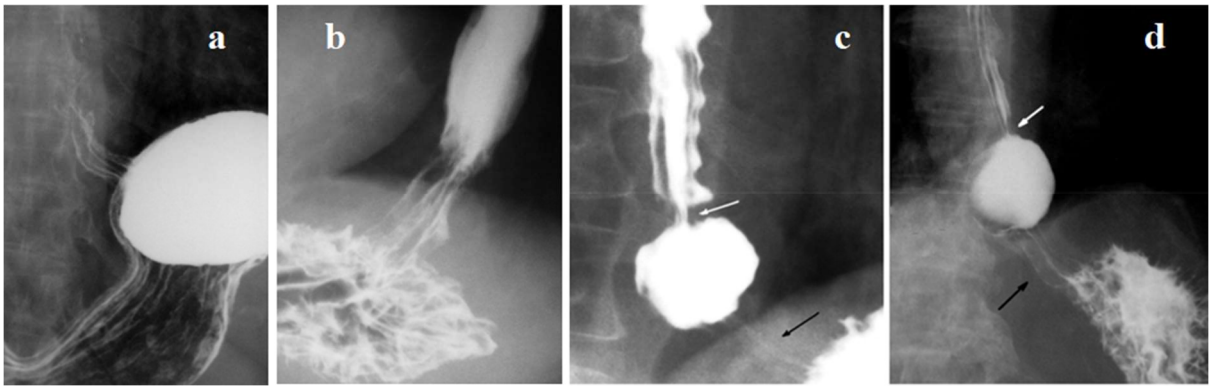

Figure 10. X-rays of EGJ patients with GERD. (a, b). The LES is represented by longitudinal folds. It's hard to imagine that these folds are in the stomach. (c, d). During abdominal compression, there was a contraction of the LES (black arrows), the length of which is approximately equal to the body height D-10 (≈ 2 cm). It is almost 2 times shorter than the norm since the abdominal part of it does not function. White arrows show the PS no more than 5 mm long, which cannot possibly belong to the LES. Mucosal folds are seen in both the esophagus and LES. They differ in shape due to the different tone of these parts.

The above evidence indicates that the formation, which is commonly called HN, is an esophageal ampulla more than 2 cm wide. The function of the LES is weakening, including due to the opening of its abdominal part. The esophagus does not shorten, but the esophagus + LES complex becomes shorter by about the 2 cm that the LES shortens.

I propose to evaluate the results of a simultaneous X-ray study with high-resolution manometry in a supposedly normal subject. Since the terminology of HRM has no physiological sense, I will focus on the radiological part (**Figure 11**).

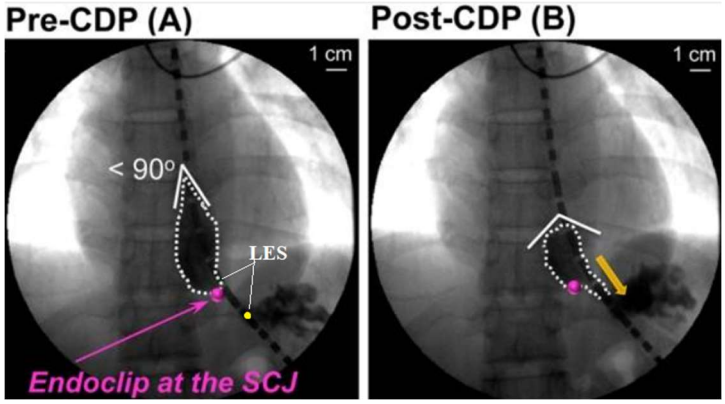

Figure 11. X-ray examination of the EGJ from Kwiatek et al [30]. This subject has all radiographic features of GERD: the presence of a phrenic ampulla, an obtuse angle of His, and a short LES (2 cm versus 4 cm). The endoclip was not attached to the EGJ, which I marked with a yellow dot, but to the end of the rugal folds. Therefore, there were longitudinal folds at the LES level, which confirms the presence of inflammation.

There is no reason to believe that the EGJ contraction is due to CD contraction. Interestingly, the authors did not measure any of the parameters of the putative sphincters, could not correctly localize the EGJ, and determine the diagnosis of GERD, but nevertheless, the following conclusions were made (with my comments).

"In conclusion, the phrenic ampulla is a transient structure that assists bolus clearance into the stomach once the peristaltic contraction reaches at the CDP (Not CD). Somewhat paradoxically, the ampulla is a manifestation of both proximal longitudinal muscle contraction of the adjacent esophagus and longitudinal muscle elongation within the LES yield zone that occurs in conjunction with the LES circular muscle effacement. (This statement is paradoxical in that it cannot be proven, either by X-ray studies or by HRM. No conclusions can be drawn from a false statement). Consequently, the phrenic ampulla seen fluoroscopically is most likely comprised of the stretched, effaced, and axially displaced LES (unreasonable assumption). The subsequent post-CDP contractility empties the bolus contained within the ampulla as the circular muscle of the LES contracts. The likely elongation of the LES during formation of the ampulla and narrowing to its native length after ampullary emptying (unreasonable assumption) suggest that reduction in the resting tone of the longitudinal muscle within the LES segment is a previously unrecognized component of LES relaxation" (it is an assumption based on two unproven assumptions).

This conclusion includes made-up claims and unproven assumptions that, if repeated many times, may appear scientific. But this is the destruction of physiology as a science. Everything that the physiology of EGJ has achieved is turned into ruins of lies and uncertainties. In this article, known structures (phrenic ampulla and lower esophageal sphincter) are mixed into a chaotic something without length and tone.

Conclusion

Currently, there is no reliable method for selecting healthy individuals to determine the exact limits of the norm. As a result of the fact that many patients

with GERD do not consider themselves ill, patients with GERD were included in the control groups to determine the limits of the norm for pH monitoring and HRM. This is the reason why the results of these studies cannot be considered accurate, scientific, and therefore diagnostic.

The function of the LES, like all other sphincters, obeys the law of the intestine. An increase in pressure above the LES causes relaxation of the LES, and an increase in pressure in the stomach causes an increase in the tone of the LES.

X-ray examination with abdominal compression allows visually, in normal physiological conditions (without anesthesia, without introducing instruments into the digestive system), to study the physiology of the EGJ, to measure the elements involved in the anti-relux function and to map the EGJ.

GERD causes expansion of the esophagus and weakening of the LES, including its shortening, due to the opening of the abdominal part. For efficient emptying of the dilated esophagus, the last peristaltic wave is closed by an acquired functional sphincter, which we call the proximal sphincter (PS). He closes the ampoule to create high pressure in it. What is commonly called a hiatal hernia is an ampulla of the esophagus, regardless of size. From this, it follows that the ampoule is a reliable symptom of GERD. The wider the ampoule, the more severe the disease.

The LES plays a decisive role in the anti-reflux function of the EGJ. It never shifts but can shorten up to 1cm. The body of the esophagus does not shorten. The esophagus + LES complex is shortened by the shortening of the LES.

In GER, there are often parallel folds in the LES that are not related to the stomach and cannot be used to judge the location of the EGJ.

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In this chapter, to study the function of EGJ in normal and GERD, I did not use any assumptions, but only scientific facts that are not contradictory when assessing histological, manometric and radiological studies. To save gastroenterology as a science, false assumptions must be eliminated from use. Then science will serve the benefit of the patients, and not the companies that produce diagnostic equipment.

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