The motility of the esophagus and lower esophageal sphincter in normal and in gastroesophageal reflux disease. Review.

Anatomy. The esophagus is a conduit for the passage of a food bolus from the pharynx to the stomach. It starts at the upper esophageal sphincter and ends at the lower esophageal sphincter (LES), surrounded by the crural part of the diaphragm at the tenth thoracic vertebra. The length and width of the esophagus depend on the age. Bott et al showed that in healthy children the mean diameter at the cranial point of measurement was 6.75 mm at the lower weight (2.6 kg) and 14 mm at 74 kg [1]. The average width of the esophagus in healthy adults is 15 mm with small individual fluctuations [2]. The LES length according to pull-through manometry with end-hole and side-hole catheter in the control group was 34±9 mm [3], 35±4 mm [4]; 36±12 mm [5]; 37 ±1 mm [6]. The abdominal sphincter length was 23±7 mm [4, 7]. The LES pressure was well developed by 2 weeks of age. In children less than 1 year of age, mean LES pressure (43.3±2.4 mmHg) was significant greater than mean LES pressure (30.6±2.3 mmHg) children older than 1 year of age and LES sphincter length increased with age [8]. X-ray measurement of LES showed similar results **(Table 1**) [2, 8].

Table 2. Normal length of the LES in different age groups (cm)

Age	Up to 1 year	1-3 years	4-7 years	8-10 years	11-15 years	Adults
Limits	0.7-1.0	1.2-1-5	1.5 -1.8	1.9-2.3	2.3-2.0	3.2-4.2
M±m	0.86±0.03	1.40±0.02	1.72±0.07	2.10±0.05	2.45±0.11	36±0.080

Physiology After the swallowing, when the upper esophageal sphincter missed the bolus and closed, there is a contraction of the circular muscle layer of the esophagus. This impulse of contraction travels downward along the body of the esophagus without an obvious pause. It is observed after each sip only once and is not repeated. The contraction at each point continues from 3 to 4 seconds. The force of contraction is different at different points and ranges from 40 to 100 mm

Hg. Swallowing also causes contraction of the longitudinal muscle layer [9]. Underlying luminal transport in the esophagus, transport and mixing in the gut, and regulation of transport in the sphincters, is the controlled opening and closure of localized luminal segments by circularly aligned muscle fibers. Brasseur et al showed that the longitudinal muscle produced a local wave of longitudinal muscle contraction coordinated with circular muscle contraction. The presence of the longitudinal muscle layer both reduces substantially the number of muscle fibers required for peristaltic bolus transport and the energy required by the muscles involved in the transport process [10]. Thus, we are talking about the contraction of the longitudinal layer only in the zone of circular contraction. First, this zone moves along with the circular contraction and therefore the length of the esophagus cannot change during the passage of the bolus through the esophagus, sometimes increasing, sometimes shortening, as described in the article by Kahrilas et al [11]. Secondly, the shortening zone in each segment is so scanty that it does not affect the total length of the esophagus.

Esophageal motility is altered by body position and bolus consistency: Contraction amplitude, duration, percentage of multipeaked and repetitive contraction, and the resting pressure of the LES are significantly reduced and the relaxation duration of the LES is significantly prolonged in sitting as compared to the supine position. With a food bolus compared to swallows of water. Wilhelm et al found significantly higher values for the contraction amplitude and the percentage of repetitive contractions, for the duration and for the percentage of multipeaked contractions at some orifices and for the relaxation duration of the LES. Propagation velocity and the resting pressure of the lower esophageal sphincter were significantly reduced with the food as compared to the water bolus [12].

Shafik recorded the pressure response of LES to balloon distension of the esophagus and pharyngoesophageal sphincter (PES) in 14 normal volunteers. In

normal subjects, esophageal distension caused a significant decrease in LES pressure; this reflex action was reproducible and was called "esophagosphincter inhibitory reflex" (ESIR). PES distension caused insignificant LES pressure changes ($p > .05$). Distension of the anesthetized esophagus or PES did not evoke the LES pressure response [13]. The LES balloon distension with 2 mL of saline produced esophageal pressure increase to a mean of 34.2 +/- 5.3 cm H2O ($p < 0.001$). An increase of the balloon distending volume produced results similar to the 2-mL distension ($p > 0.05$). The esophageal electrical activity increased on esophageal balloon distension; the increase was like distensions of 2 mL up to 10 mL [14].

The coughing and straining effect an increase of the LES EMG activity and pressure, an action presumably mediated through a reflex. This reflex seems to be evoked during increased intra-abdominal pressure and to affect LES contraction, thus, sharing with other factors in the prevention of gastroesophageal reflux [15]. Franzi et al showed that the distension of the intact stomach, lesser curve, or proximal stomach in 12 dogs produced a progressive increase LES. Background LES pressure fell progressively with distension of the antrum but was unchanged by distension of the fundus alone. In another two dogs, truncal vagotomy performed at the time of gastric partitioning prevented the change in background LES pressure [16]. An increase in the tone of the LES in response to an increase in pressure in the stomach has become a generally accepted scientific fact [17,18]. A study by Rossiter et al indicates that excitatory and inhibitory control of LES and intragastric pressure are mediated by vagal efferent neurons located in two distinct sites in the dorsal motor nucleus of the vagus [19].

The above scientific facts describing the anatomy and physiology of the esophagus and LES have not been disputed, because they correctly reflect the function of the esophagogastric junction. However, the continuation of these studies stopped more than 10 years ago, and they are not mentioned anywhere.

The new generation of practitioners relied on the introduction of high-tech equipment and started research from scratch as if no research had been done before. Their works are based not on scientific facts, but on hypotheses which, because of numerous citations, have become generally accepted dogmas, even though there is no scientific evidence for their reliability. Moreover, these dogmas are refuted by alternative explanations. For example, Kahrilas et al studied the effect of hiatus hernia on longitudinal muscle-mediated peristaltic esophageal shortening during barium swallows using metal clips endoscopically affixed at the squamocolumnar junction [11]. The results they obtained have an alternative explanation.

1) It is known that in healthy individuals there are no folds at the level of the LES and in the esophagus. Someone has suggested that the rugal-like folds above the diaphragm are folds of the stomach that has penetrated the chest. This hypothesis has no scientific confirmation. First, because of reflux esophagitis, the walls lose elasticity and folds appear both in the body of the esophagus and at the level of the LES. They differ in thickness and quantity since the pressure in the esophagus is much lower than in the LES (**Figure 1**).

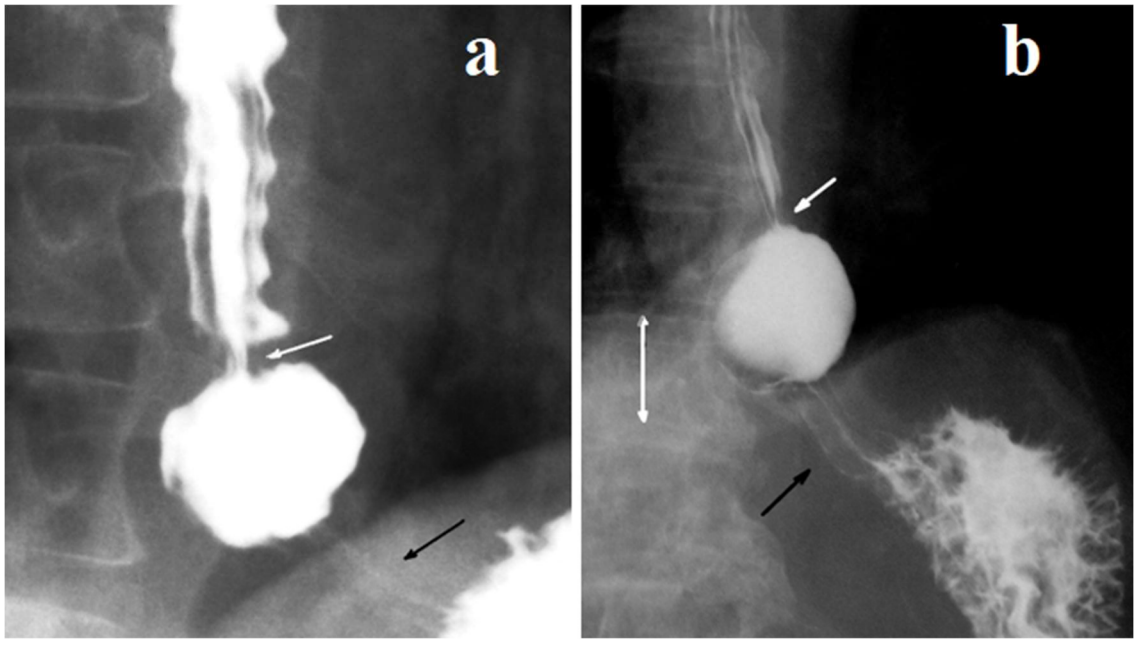

Figure 1. EGJ radiographs of two elderly patients with GERD taken in a horizontal position during abdominal compression. The length of the distal narrowing (black arrow) is equal to the height of D-10, i.e. ≈ 2 cm. The length of the upper narrowing (white arrow) is ≈ 3 mm. The round cavity between these constrictions resulted from the contraction of the distal region, which delayed the advance of the contrast agent into the stomach. After stopping the compression of the abdomen, the peristalsis of this round cavity squeezed barium into the stomach.

From the generally accepted point of view, the distal narrowing is due to the contraction of the crural part of the diaphragm, and the proximal narrowing is due to the upwardly displaced LES. However, the thickest part of the diaphragm does not exceed 0.5 cm, therefore, it cannot create a 2 cm long contraction zone. It contracts during breathing and cannot be in a contracted state for a long time. In patients with a so-called hernia, the hiatal canal wide opens, therefore, during the operation, it is sutured for hiatal closure [20]. The upper zone of contraction with a length of 3 mm cannot be LES, which is normally about 3.6 cm long. A round chamber 2.5 cm in diameter cannot be a stomach, because it is emptied by peristalsis. However, the fundal part of the stomach and upper body have not peristalsis since they do not contain intestinal cells of Cajal [21,22]. The proximal point of the circular chamber is 4.5 cm from the stomach. Such a shortening of the esophagus is not possible, since every moment of peristalsis, only the area accompanying the circular zone of contraction is shortened [10]. Conclusion: In patients with GERD during abdominal compression, only 2 cm of LES was contracted. The weak abdominal portion of the LES is open and does not participate in the antireflux function. Folds in the esophagus and LES indicate the presence of esophagitis. The circular cavity closed between two constrictions is a phrenic ampulla, which for some unknown reason is considered an ampulla up to a diameter of 2 cm, and more than 2 cm - a sliding hernia [23]. In both cases, the length of the esophagus did not change during the study, but the esophagus + LES complex became shorter by ≈ 2 cm due to the shortening of the LES.

2) The authors fixed metal clips endoscopically at the squamocolumnar junction, assuming that this is a EGJ location. However, recent studies by Chandrasoma et al reject two false dogmas that result in two widely believed fundamental errors: (1). These are the belief that cardiac epithelium normally lines the proximal stomach and (2) that the EGJ is defined by the proximal limit of rugal folds [24, 25]. They showed that "the normal state where the esophageal squamous epithelium transitions at the GOJ to gastric oxyntic epithelium with no intervening cardiac epithelium; (b) cardiac metaplasia of the squamous epithelium due to exposure to gastric juice results in cephalad movement of the squamo-columnar junction (SCJ). This creates the squamo-oxyntic gap and the dilated distal esophagus, which is distal to the endoscopic EGJ. The length of the squamo-oxyntic gap in the dilated distal esophagus is concordant with the shortening of the abdominal segment of the lower esophageal sphincter; (c) in the early stages, the gap is <5 mm and the LES retains its competence. Reflux is uncommon and patients are asymptomatic; (d) the squamo-oxyntic gap increases in length, concordant with the amount of shortening of the LES, which becomes increasingly incompetent. At a gap length of 5-15 mm, reflux is sufficient to cause symptoms, but in most patients, symptoms are controllable and the patients are normal at endoscopy. The gap is entirely within the dilated distal esophagus, which is mistaken by the present criteria for the proximal stomach. (e) The last stage of GERD is when the squamo-oxyntic gap is >15 mm. In these patients, reflux is severe with increasingly uncontrollable symptoms and columnar lined esophagus, both irreversible states" [24]. First, these studies prove the squamocolumnar junction is well above the true EGJ. Secondly, it turned out that hydrochloric acid reflux and primary damage to LES function, and shortening of its abdominal length occurs even before the acid enters the esophagus and symptoms of GERD appear.

3) During the intake of liquid contrast agents, the phrenic ampulla, regardless of its size, is formed only in a horizontal position. Therefore, it is called a slipping hernia, as it is assumed that the horizontal position facilitates the sliding of the stomach into the chest. During the formation of the ampoule, the area of its inner surface increases sharply. The mucous membrane is pulled upward to provide a covering of the ampoule. Metal clips attached to the mucous membrane move upward at a distance proportional to the volume of the ampoule. The location of the clips is not relevant to the EGJ.

4. Figure 1 shows two contracted areas: one above and the other below the phrenic ampulla, which corresponds to two pressure peaks, which are determined by a manometric study [26]. The lower segment is due to the contraction of the LES, as was shown earlier, it cannot be due to the contraction of crural part of the diaphragm.

It is known that at rest the pressure in the lower part of the esophagus is lower than in the stomach [27]. The opening of the LES, in this case, would inevitably lead to reflux of gastric contents into the esophagus. Normally, a strong peristaltic wave creates high pressure, which, firstly, causes the LES to open, and secondly, it must be higher than the gastric pressure in order to transport the bolus from the esophagus to the stomach. In reflux esophagitis, the lower part of the esophagus is dilated and the force of its contraction is weakened. To create a threshold pressure for opening the LES, a proximal sphincter (PS) arises above the ampulla, which closes the ampoule, which allows, when it contracts, to create a threshold pressure for opening the LES and inject a bolus into the stomach.

5. It is impossible to obtain new scientific information using incorrect assumptions analysis. The key to scientific progress is the precise boundaries of the norm.

Esophageal pH-metry was initially introduced in 1969 and it was considered the gold standard for the diagnosis of GERD since the 1980s [28]. The last and most recent study used the Reflux Index (RI, defined as the percentage of time that pH < 4) to determine pathological GERD (where abnormal was defined as pH < 4 for >10% for infants <1 year and 5% infants >1 year and > 4 in adults) [29]. These boundaries contradict not only the studies of Chandrasoma et al but also common sense because the presence of aggressive hydrochloric acid in the esophagus for a huge amount of time can only indicate the failure of EGJ. Analysis of the literature indicates that the reason for this error is due to the incorrect initial selection of persons to determine these boundaries. Obviously, individuals were selected without symptoms of heartburn and regurgitation, in whom endoscopy showed no sign of esophagitis. However, it is known that GERD often occurs not only without typical clinical symptoms but generally without any deviations. So, for example, with a screening gastroscopy examination of 6,683 healthy Koreans, 14.66% had GERD diagnosed [30]. On the other hand, it is known that endoscopy does not reveal pathology in non-erosive GERD [31].

As a result of this mistake, a large number of GERD patients with typical and non-typical symptoms, even in cases where improvement occurred after the use of drugs that suppress the release of hydrochloric acid, were invented different diagnoses under the general name of the functional disorders. So, for example, in the study, Morozova et al 29 (48%) of 60 patients with heartburn, belch, and epigastric discomfort pH-impedance measurement data did not differ from normal. And the authors suggested that this group of patients with functional gastroesophageal disorders [32]. Некоторые авторы придерживаются более простой формулы: "Gastroesophageal reflux (GER) is a normal physiologic process. It is important to distinguish GER from GER disease (GERD) since GER

does not require treatment" [33]. Cases of false negatives in pH measurement, which resulted in surgical treatment, are not uncommon [34,35].

I. Physiology of the esophagus and gastroesophageal junction

Esophageal motility is altered by body position and bolus consistency.

1. In the vertical position, the liquid bolus forms a pillar above the LES, the upper limit of which does not rise above the 4th thoracic vertebra (aortic arch). The pressure of this pillar causes a reflex opening of the LES, as a result of which the entire liquid bolus without delay falls into the stomach. The cleansing of the esophagus is quick and complete. The maximum width of the esophagus is no more than 1.2 cm. The functioning area of the LES is not visible. Provocative tests, including compression of the abdomen or deep breath, do not cause LES contraction and do not affect the speed of cleansing the esophagus [2]. Evacuation of a liquid bolus from the esophagus in an upright position takes about 7 seconds [9]. During this time the gravity of the bolus decreases progressively, but the evacuation of the bolus does not stop. This confirms the reflex, rather than mechanical, nature of the opening of the LES. Second, the LES not only relaxes but also opens as a result of the contraction of angled muscle fibers [36], some of which are attached to the stomach wall [37]. It is likely that such a function is characteristic of all sphincters. It is more clearly visible during the opening of the pyloric sphincter [38].

2. **In a horizontal position,** the bolus moves under the influence of a peristaltic wave. When the bolus approaches the distal part of the esophagus, the last peristaltic wave creates a threshold pressure above the LES, which leads to a reflex opening of the LES. Continuing to contract, the latter peristaltic wave injects a bolus into the stomach, because at this moment it creates the pressure higher than in the stomach. After that the LES contracts, preventing reflux into

the esophagus. When the LES is closed, the barium in the esophagus no exists, so it is not possible to differentiate the LES in healthy (**Figure 2).**

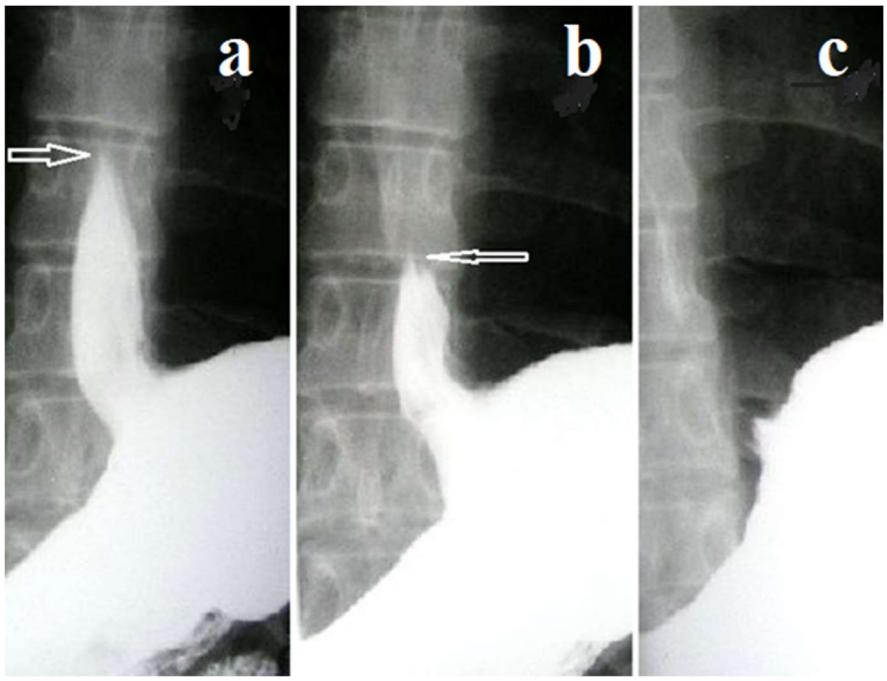

Figure 2. Elderly patient with GERD. A series of pictures taken during the reception of barium without provocative tests. It is known that at rest the pressure in the lower esophagus is lower than in the stomach [4]. For the bolus to penetrate the stomach during the opening of the LES, the last peristaltic wave must create a pressure higher than in the stomach. The arrow shows the exceptional importance of the force of contraction of the last peristaltic wave.

In healthy people, the true width of the esophagus in a horizontal position does not exceed 1.5 cm. Normally, the use of provocative tests does not lead to barium reflux from the stomach into the esophagus. Despite the compression of the abdomen during the passage of barium through the EGJ, the contrast agent passes into the stomach without delay, since the force of contraction by the last peristaltic wave overcomes the increased tone of the LES. The cardiac part of the stomach always has a rounded configuration. The contours of the esophagus have always smooth. There are no folds in the esophagus or in the area of the EGJ.

Obviously that food, which stretches of the esophageal wall and cannot create hydrostatic pressure above the LES in the upright position of the patient, moves along the esophagus due to peristalsis.

Based on the analysis of the literature, the radiological signs of the normal function of the esophagus and EGJ are as follows: (1) the true mean width of the esophagus, i.e., with a correction for projection magnification, is 12 mm in the vertical position and 15 mm in the horizontal position, and it is the same for all over the esophagus; (2) Provocative tests with an increase in pressure in the stomach do not lead to a contraction of the LES, do not interfere with the rapid and complete cleansing of the esophagus from the contrast medium.

II. Pathological physiology of gastroesophageal reflux disease

The generally accepted concept of the pathophysiology of GERD is reflected in the following excerpt from Herregods et al: "Even today, the pathophysiology of GERD is not fully understood but it is now recognized to be a multifactorial disease. Among the factors that have been shown to be involved in the provocation or increase of reflux, are sliding hiatus hernia, low lower esophageal sphincter pressure, transient lower esophageal sphincter relaxation, the acid pocket, obesity, increased distensibility of the esophagogastric junction, prolonged esophageal clearance, and delayed gastric emptying. Moreover, multiple mechanisms influence the perception of GERD symptoms, such as the acidity of the refluxate, its proximal extent, the presence of gas in the refluxate, duodenogastroesophageal reflux, longitudinal muscle contraction, mucosal integrity, and peripheral and central sensitization. Understanding the pathophysiology of GERD is important for future targets for therapy as proton pump inhibitor-refractory GERD symptoms remain a common problem" [39].

Analysis of the literature allows us to differentiate the etiology and pathogenesis of GERD.

Etiology of GERD. The etiology of GERD includes two main factors: (a) aggressiveness of gastric juice; (b) high load for the antireflux function of the LES.

a) The aggressiveness of gastric juice depends on the amount and concentration (pH) of hydrochloric acid. The amount of trypsin and bile acids (with duodenogastric reflux) is probably less important. Provocateurs of hypersecretion are lactose intolerance [40,41], allergic conditions in which histamine is released [40, as well as histamine intolerance [42]. The consumption of meat and fat also increases the secretion of gastric juice and slows down the evacuation from the stomach.

b) Any conditions that lead to prolonged increases in pressure in the stomach, including overeating, chronic constipation, delayed gastric emptying, etc., contribute to reflux.

Pathogenesis of GERD Although the literature does not describe a direct relationship between GERD and lactose intolerance, there is still ample evidence of such a relationship. For example, Pérez Lara et al showed that lactose intolerance may account for the symptoms presented by a significant number of patients with gas bloat syndrome following antireflux surgery; these patients help a lactose-free diet [43]. However, based on the materials of this article, it can be concluded that these patient patients underwent surgery as they suffered from severe GERD due to lactose intolerance. Heine et al found pathological GERD in 18% of children with persistent crying. Pathological GERD was defined as a fractional reflux time > 10% (with an esophageal pH of less than 4) [44]. Most pediatricians (consensus) do not recognize GERD as the cause of infantile colic, because the use of PPI not reduce the frequency and duration of colic [40,45]. This estimate is all the more strange since inadequate response to proton pump inhibitor therapy in adult patients with gastroesophageal reflux disease is reported in up to 40% [46]. Lack of consensus is due to the destructive role of works that

do not follow the methodology of scientific research (pH-metry, and breath tests) as well as the decisions of congresses that suppress dissent as if voting can solve scientific problems. As shown above, GERD was definitely in those 82% infants where pH-metry revealed acid reflux with pH <4, not only with fractional reflux time> 10% but also 5,4, and 1%. This means that 82% of children with GERD were diagnosed with functional gastrointestinal disorders and they did not receive pathogenetic treatment.

In newborns with lactose intolerance, GERD occurs 2-4 weeks after birth and proceeds as infant colic. The pain syndrome disappears in about 6 months of age, but by this time irreversible changes occur in some patients: the weakening of the LES and expansion and weakness of peristalsis of the distal part of the esophagus. These changes lead to a resurgence of the disease at a later age with different symptoms. The provocateurs of hypersecretion and high pressure in the stomach can be different (lactose intolerance allergy, and intolerance others substances) but the pathogenesis of the GERD is the same type **(Figure 3).**

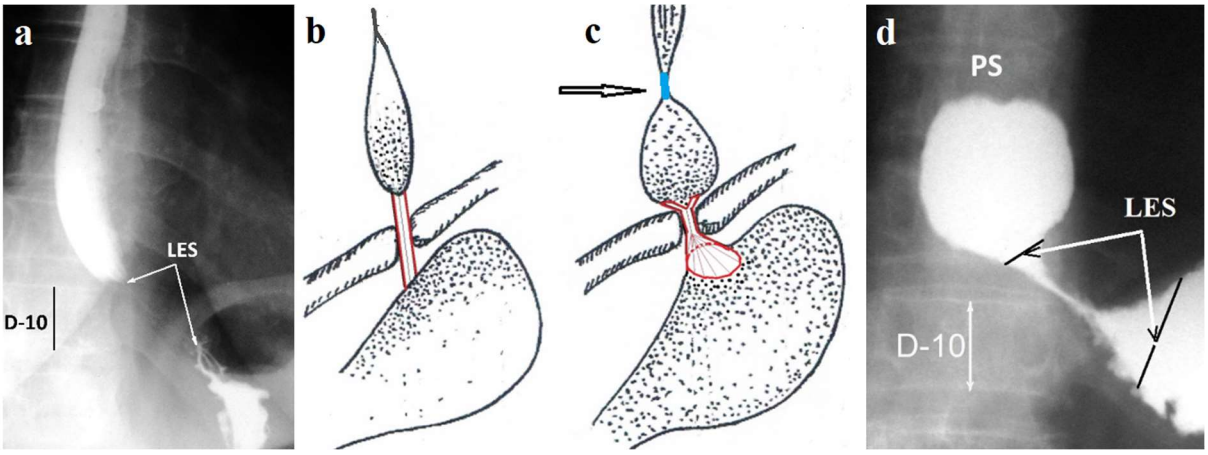

Figure 3. Radiographs and diagrams of the EGJ for GERD in vertical (a-b) and horizontal (c-d) positions during abdominal compression. The actual height of the D-10 is ≈ 2 cm. (A-b). In a patient with pronounced esophagitis (uneven and indistinct left wall of the esophagus), during compression of the abdomen in an upright position, there was a contraction of LES. Its length is 3 cm. (C-d). During the abdominal compression, only the central portion of the LES 1.4 cm in length contracted out of the total length of 4.0 cm (red). The abdominal part of the LES

opened in the form of an angular deformity of the stomach (≈ 1.8 cm). The supraphrenic part of the LES (0.8 cm) also opened. The circular chamber above the diaphragm with a diameter of 3.5 cm is an ampulla, the lumen of which is blocked from above as a result of the contraction of the proximal sphincter (PS) (blue, arrow). This allows the ampoule to generate high pressure during contraction to open the LES and inject the bolus into the stomach.

Analysis of the literature shows that the numerous factors that were considered as provocateurs or enhancers of GERD are a manifestation of the pathogenesis of this disease.

1. Manometric and X-ray 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 [3, 24, 38, 40, 47], which is better revealed with an increase in the gastric pressure. Weakness of the LES is not the cause of GERD, but the result of the damaging effects of gastric juice on the esophagus and LES.

2. The length of the esophagus between the upper and lower esophageal sphincters does not change either in healthy people or in patients, regardless of provocative tests (**Figure 4).**

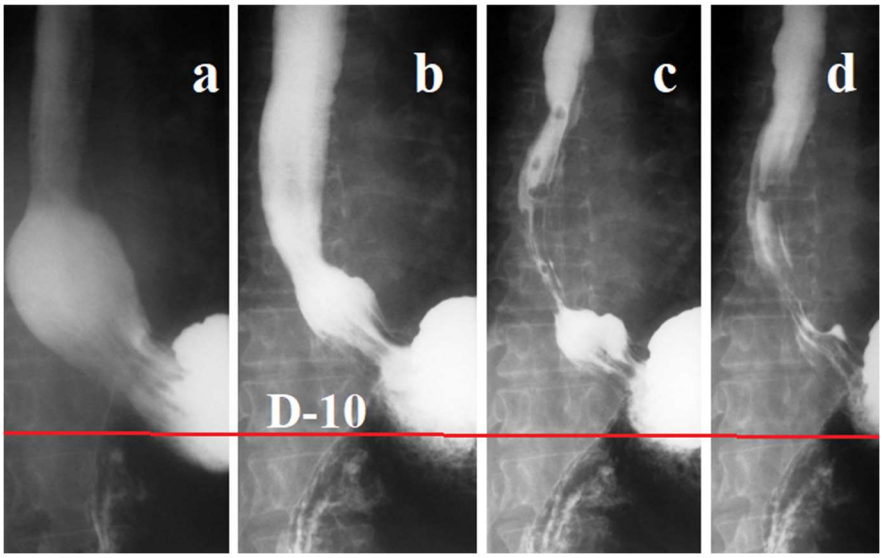

Figure 4. A series of images of a GERD patient while taking barium in a horizontal position during abdominal compression. The diameter of the hiatal canal (Figure 4.a) is 2 cm. The abrupt shortening of the LES, which is located between the stomach and the ampulla, is due to the opening of the abdominal portion of the LES. Folds of the mucosa are visible both at the level of the LES and in the esophagus. The LES proximal point is at the same place relative to D-10 on all radiographs.

Thus, the EGJ does not change its position. Only with GERD, the esophagus-LES complex is shortened by the shortening of the LES.

3. What is considered to be a sliding hiatal hernia is the phrenic ampulla, the size of which is proportional to the severity of the esophagitis. Hence, the phrenic ampulla is the result, not the cause, of GERD.

4. Kim et al found that transient lower esophageal sphincter relaxation (TLESR) events did not differ between the GERD and control groups [53]. This conclusion was made because the control group, selected according to the pH-metry data, consisted of a large number of patients with GERD. If the PS does not withstand the pressure during the contraction of the phrenic ampulla and opens at the time of the opening of the LES, then the pressure in the ampoule drops sharply and the chyme from the stomach is thrown into the esophagus. Thus, TLESR is not a cause, but a result of GERD, and it cannot be in healthy people.

Over time, the force of contraction of the PS weakens, and in some cases a rigid Schatzki ring forms in its place [54]. It is not always narrow. However, since it does not overlap the proximal lumen of the ampulla, evacuation occurs only when the threshold pressure for opening the LES occurs in the esophagus between the upper and lower esophageal sphincters. Until the esophagus is completely filled, TLESRs will follow one after the other after each swallow.

5. Since the contraction force of the phrenic ampulla is sharply weakened, this leads to incomplete emptying of the ampulla, as a result of which, after its

contraction, acid refluxate often remains in it. Thus, the acid pocket is not a cause but a consequence of GERD.

Conclusion. Analysis of the literature leads to an unambiguous understanding that the main patterns of the esophageal physiology and LES, as well as the pathological physiology of GERD, were established 40 years ago. Since then, practical doctors, using modern equipment (pH-metry, gas analyzers, high-resolution manometry, etc.), neglecting the principles of scientific research and ignoring the scientific achievements of previous generations, have made a counterrevolution not only in scientific but also in ethical plan. Not surprisingly, 40 years later, doctors know less. This is the generally accepted conclusion: “Even today, the pathophysiology of GERD is not fully understood ...” [39]. The current state of the raised issues is characterized by the absence of precise boundaries of the norm, a mass of diagnoses without understanding pathological physiology with borders that overlap, contradictory statements called theories. Forty years ago, every new study was discussed in journals The high level of analysis was perceived as a gift and as a stimulus for the development of science. Currently, we are learning about the decisions taken on the lobbies of the congresses. Attempts at discussion in journals are perceived as an insult. For example, in my letter to the editor, I noticed that the authors of the article determined the standards for a new high-resolution manometry apparatus in healthy volunteers, not observing the scientific principles of selection. [8]. The authors of this article took my analysis as an insult and tried to respond accordingly [50]:

"First, individuals that volunteered to both studies were indeed selected by the absence of symptoms. This was justified by two reasons: (1) we considered not necessary or ethical to submit these individuals to upper endoscopy and (2) the mathematics for the determination of cut-off values consider the chance to accidentally include sick individuals".

-- Individuals who say they have not had typical GERD symptoms in the past 6 months cannot be considered healthy. The authors' excuses do not make sense. Either they are doing scientific work or spam.

"Moreover, the same methodology was applied in the landmark studies that defined normal values worldwide accepted, such as the Richter et al. study that defined values for conventional manometry, the Northwestern studies that defined the Chicago classification, and the Johnson and DeMeester study that defined normality for pH monitoring".

-- It is known from the example of Galileo Galilei that not everything that is worldwide accepted is scientific. Particularly revealing is the reference to pH monitoring, the results of which set science back 40 years.

"In regards to histological analysis, the routine biopsy of the esophagus in negative endoscopy is not recommended by any consensus including the Montreal, Lyon, and Porto".

-- Scientific research is not routine, like diagnostic research. But the authors did not do either endoscopic or histological studies. But the authors did not do either endoscopic or histological studies.

The authors of the article received the following standards related to LES: LES basal pressure: 4.89-37.16 (mmHg), total length - cm 3.82 ± 0.95 (1.6-5.7), abdominal length - cm 2.19 ± 0.97 (0-5). Although the average indicators are comparable with the results of manometric studies with one catheter and X-ray data, the scatter of individual characteristics indicates the low accuracy of the study and the impossibility of using them in practice. For example, in the human body, there is not any structure, which differed 3.5 or 5 times in different persons. A dilemma arises: either HRM is a poorly reliable method, or the method of selecting healthy individuals has had such an effect. The authors cite

landmark studies and consensus, which are not scientific evidences, but the stone has been thrown.

I invite all forum participants to take part in the discussion of this review

References

1. Bott TS, von Kalle T, Schilling A, et al. Esophageal Diameters in Children Correlated to Body Weight. Eur J Pediatr Surg. 2019 Dec;29(6):528-532. doi: 10.1055/s-0038-1675776. (PubMed).
2. Levin MD, Korshun Z, Mendelson G. [Pathological physiology of gastroesophageal reflux disease. Hypothesis (Literature review)]. Eksp Klin Gastroenterol. 2013;(5):72-88.PMID: 24501951 Review. Russian. . (PubMed).
3. Rådmark T, Pettersson GB. Lower esophageal sphincter pressure in normal individuals and patients with gastroesophageal reflux. A comparison between end-hole and side-hole recording techniques. Scand J Gastroenterol. 1989 Sep;24(7):842-50. doi: 10.3109/00365528909089224. . (PubMed).
4. Shaker R, Dodds WJ, Kahrilas PJ, et al.Relationship of intraluminal pH and pressure within the lower esophageal sphincter. Am J Gastroenterol. 1991 Jul;86(7):812-6. . (PubMed).
5. Narawane NM, Bhatia SJ, Mistry FP, et al. Manometric mapping of normal esophagus and definition of the transition zone. Indian J Gastroenterol. 1998 Apr;17(2):55-7. . (PubMed).
6. Gómez R, Moreno E, Seoane J, et al. Esophageal pH monitoring of postprandial gastroesophageal reflux. Comparison between healthy subjects, patients with gastroesophageal reflux and patients treated with Nissen fundoplication.Dig Dis. 1993 Nov-Dec;11(6):354-62. doi: 10.1159/000171427. (PubMed).
7. Chen MH, YanK, Wang B.[Manifestation of abdominal segment of esophagus by body surface ultrasonography and determination of normal values]. Zhonghua Yi Xue Za Zhi. 1994 Jul;74(7):410-2, 454-5. [Article in Chine]. (PubMed).
8. Levin MD. Reaction to articles on high resolution manometry, the length of the lower esophageal sphincter and the diagnosis of gastroesophageal reflux disease. Arq Gastroenterol. 2019;56(2): 209-210. . (PubMed).Open access.
9. Esophageal motility. F.J. Christensen and D.J.de Carle. In book Scientific Basis of Gastroenterology/ Edited by HL. Duthie, KG. Wormsley. Churchill Livingston, Edinburg.1979.p. 4224-439. (PubMed).

10. Brasseur JG, Nicosia MA, Pal A, and Miller LS. Function of longitudinal vs circular muscle fibers in esophageal peristalsis, deduced with mathematical modeling. World J Gastroenterol. 2007 Mar 7; 13(9): 1335–1346. doi: 10.3748/wjg.v13.i9.1335
11. Kahrilas PJ, Wu S, Lin S, Pouderoux P. Attenuation of esophageal shortening during peristalsis with hiatus hernia. Gastroenterology. 1995 Dec;109(6):1818-25. doi: 10.1016/0016-5085(95)90748-3. (PubMed).
12. Wilhelm K, Frieling T, Enck P, J Lübke H. [Effect of body position and food composition on esophageal motility in healthy probands][Article in German]. Z Gastroenterol. 1993 Sep;31(9):475-9. (PubMed).
13. Shafik A. Esophago-sphincter inhibitory reflex: role in the deglutition mechanism and esophageal achalasia. J Invest Surg. Jan-Feb 1996;9(1):37-43. doi: 10.3109/08941939609012458. (PubMed).
14. Shafik A, Shafik I, El-Sibai O, Mostafa R. Effect of lower esophageal sphincter distension and acidification on esophageal pressure and electromyographic activity: the identification of the "sphinctero-esophageal excitatory reflex". Ann Thorac Surg. 2005 Apr;79(4):1126-31; discussion 1131. doi: 10.1016/j.athoracsur.2004.09.052. (PubMed).
15. Shafik A, El-Sibai O, Shafik AA, et al. Effect of straining on the lower esophageal sphincter: identification of the "straining-esophageal reflex" and its role in gastroesophageal competence mechanism. J Invest Surg. Jul-Aug 2004;17(4):191-6. doi: 10.1080/08941930490471948. (PubMed).
16. Franzi SJ, Martin CJ, Cox MR, Dent J. Response of canine lower esophageal sphincter to gastric distension. Am J Physiol. 1990 Sep;259(3 Pt 1):G380-5. doi: 10.1152/ajpgi.1990.259.3. G380. (PubMed).
17. Attig D, Petermann J, Klöckner H, Rosenbaum KD.[Computer-assisted analysis of the pressure behavior of the esophagogastric junction during increase in intragastric pressure]. Z Exp Chir Transplant Kunstliche Organe. 1990;23(1):40-2. [Article in German] . (PubMed).
18. Shafik A, Shafik AA, El Sibai O, Shafik IA. The effect of gastric overfilling on the pharyngo-esophageal and lower esophageal sphincter: a possible factor in restricting food intake. Med Sci Monit. 2007 Oct;13(10):BR220-4. (PubMed).
19. Rossiter CD, Norman WP, Jain M, et al. Control of lower esophageal sphincter pressure by two sites in dorsal motor nucleus of the vagus. Am J Physiol. 1990 Dec;259(6 Pt 1):G899-906. doi: 10.1152/ajpgi.1990.259.6.G899. (PubMed).
20. Zhang W, Tang W, Shan C-X, et al. Dual-sided composite mesh repair of hiatal hernia: Our experience and a review of the Chinese literature World J Gastroenterol. 2013 Sep 7; 19(33): 5528–5533. doi: 10.3748/wjg.v19.i33.5528. (PubMed).

21. Hanani M. Intestinal cells of Cajal – the pacemaker of the gastrointestinal system. Harefuah.1999;136(4):307-12. (PubMed).
22. Goyal RK, Guo Y, Mashimo H. Advances in the physiology of gastric emptying. Neurogastroenterol Motil. 2019 Apr; 31(4): e13546. doi: 10.1111/nmo.13546. (PubMed).
23. Kahrilas PJ, Kim HC, Pandolfino JE. Approaches to the Diagnosis and Grading of Hiatal Hernia. Best Pract Res Clin Gastroenterol. 2008; 22(4): 601–616. doi: 10.1016/j.bpg.2007.12.007. (PubMed).
24. Chandrasoma P[1,2], DeMeester T[3]. A New Pathologic Assessment of Gastroesophageal Reflux Disease: The Squamo-Oxyntic Gap. Adv Exp Med Biol. 2016;908:41-78. doi: 10.1007/978-3-319-41388-4_4. (PubMed).
25. Chandrasoma P. How the pathologist can aid in the assessment of gastroesophageal reflux disease. Curr Opin Gastroenterol. 2018 Apr 27. doi: 10.1097/MOG.0000000000000446. (PubMed).
26. Weijenborg PW, van Hoeij FB, Smout AJP, Bredenoord AJ. Accuracy of hiatal hernia detection with esophageal high-resolution manometry. Neurogastroenterol Motil. 2015 Feb;27(2):293-9. doi: 10.1111/nmo.12507. (PubMed).
27. Del Grande LM, Herbella FAM, Katayama RC, et al. THE ROLE OF THE TRANSDIAPHRAGMATIC PRESSURE GRADIENT IN THE PATHOPHYSIOLOGY OF GASTROESOPHAGEAL REFLUX DISEASE. Arq Gastroenterol. 2018 Nov;55Suppl 1(Suppl 1):13-17. doi: 10.1590/S0004-2803.201800000-39. (PubMed).
28. Lupu VV, Marin Burlea M, Nicolai Nistor N, et al. Correlation between esophageal pH-metry and esophagitis in gastroesophageal reflux disease in children. Medicine (Baltimore). 2018 Sep;97(37):e12042. doi: 10.1097/MD.0000000000012042. (PubMed).
29. Rosen R, Vandenplas Y, Singendonk M, et al. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2018 Mar; 66(3): 516–554. doi: 10.1097/MPG.0000000000001889. (PubMed).
30. Yoo SS, Lee WH, Ha J, Choi SP, Kim HJ, Kim TH, Lee OJ. The prevalence of esophageal disorders in the subjects examined for health screening. Korean J Gastroenterol. 2007 Nov;50(5):306-12. (PubMed).
31. Parikh ND, VianaA V, Shah S, Laine L. IMAGE-ENHANCED ENDOSCOPY IS SPECIFIC FOR THE DIAGNOSIS OF NON-EROSIVE GASTROESOPHAGEAL REFLUX DISEASE. Scand J Gastroenterol. 2018 Mar; 53(3): 260–264. Published online 2018 Jan 25. doi: 10.1080/00365521.2018.1430847. (PubMed).

32. Morozova LN, Pogromov AP, Mnatsakanian MG. [24-hour combined pH-impedance measurement in differential diagnosis of non-erosive reflux disease and functional gastroesophageal disorders]. Eksp Klin Gastroenterol. 2013;(12):39-43. [Article in Russian] (PubMed).
33. Mousa H, Hassan M. Gastroesophageal Reflux Disease. Pediatr Clin North Am. 2017 Jun;64(3):487-505. doi: 10.1016/j.pcl.2017.01.003. (PubMed).
34. Angulo JM, Tovar JA, Eizaguirre I. False negatives in pH measurement. A retrospective study of 12 surgical cases. Cir Pediatr. 1990 Jan;3(1):3-7. (PubMed).
35. Tovar JA, Angulo JA, Gorostiaga l, Arana J. Surgery for gastroesophageal reflux in children with normal pH studies. J Pediatr Surg. 1991 May; 26(5): 541-545. (PubMed).
36. Vegesna AK, Chuang KY, Besetty R, et al. Circular smooth muscle contributes to esophageal shortening during peristalsis. World J Gastroenterol. 2012 Aug 28;18(32):4317-22. doi: 10.3748/wjg.v18.i32.4317. (PubMed).
37. Liebermann-Meffert D, Allgöwer M, Schmid P, Blum AL. Muscular equivalent of the lower esophageal sphincter. Gastroenterology. 1979 Jan;76(1):31-8. (PubMed).
38. Levin MD, Korshun Z, Mendelson G.[Duodenal motility in norm and in some diseases. Hypothesis]. Ter Arkh. 2016;88(4):68-74. doi: 10.17116/terarkh201688468-74.[Article in Russian] (PubMed).
39. Herregods TVK, Bredenoord AJ, M Smout AJP. Pathophysiology of gastroesophageal reflux disease: new understanding in a new era. Neurogastroenterol Motil. 2015 Sep;27(9):1202-13. doi: 10.1111/nmo.12611. (PubMed).
40. Levin MD. Pathophysiology of infantile colic. https://4d90110e-2e9f-4032-b658-72b6d84114fd.filesusr.com/ugd/4d1c1d_194b76c5d27c40a8a3f5cc9bb5171a8e.pdf
41. Levin MD, Arinzon Z. The history of the development of gastroesophageal reflux disease in the Ashkenazi Jewish family. https://4d90110e-2e9f-4032-b658-72b6d84114fd.filesusr.com/ugd/4d1c1d_b20f340cfb78436f9f1894bc1f721a7f.pdf
42. Wantke F, Götz M, Jarisch R. The red wine provocation test: intolerance to histamine as a model for food intolerance. Allergy Proc. Jan-Feb 1994;15(1):27-32. doi: 10.2500/108854194778816599. (PubMed).
43. Pérez Lara FJ, Jose Manuel Hernández Gonzalez JMH, Fernández JD, et al. Prospective Study of Lactose Intolerance as a Potential Cause of Gas Bloat Syndrome in Patients Treated Surgically for Gastroesophageal

Reflux. Surg Innov. 2020 Apr;27(2):160-164. doi: 10.1177/1553350619891351. (PubMed).
44. Heine RG[1], Jordan B, Lubitz L, et al. Clinical predictors of pathological gastrooesophageal reflux in infants with persistet distres s. J Paediatr Child Health. 2006 Mar;42(3):134-9. doi: 10.1111/j.1440-1754.2006.00812.x. (PubMed).
45. Gieruszczak-Białek D[1], Konarska Z[1], Skórka A[1],et al. No effect of proton pump inhibitors on crying and irritability in infants: systematic review of randomized controlled trials. J Pediatr. 2015 Mar;166(3):767-70.e3. doi: 10.1016/j.jpeds.2014.11.030. (PubMed).
46. Kandulski A, Peitz U, Mönkemüller K, et al. GERD assessment including pH metry predicts a high response rate to PPI standard therapy. BMC Gastroenterol. 2013 Jan 16;13:12. doi: 10.1186/1471-230X-13-12. (PubMed).
47. Pustorino S, Migliorato D, Ianni G, et al.[Changes in mechanical and functional processes of the lower esophageal sphincter in patients with reflux esophagitis]. Recenti Prog Med. 1990 Jun;81(6):429-34.[Article in Italian]. (PubMed).
48. Kim HI, Hong SJ, Han JP, et al. Specific Movement of Esophagus During Transient Lower Esophageal Sphincter Relaxation in Gastroesophageal Reflux Disease. J Neurogastroenterol Motil. 2013 Jul; 19(3): 332–337. doi: 10.5056/jnm.2013.19.3.332
49. Levin MD, Mendel'son G.[Schatzki ring as a symptom of gastroesophageal reflux disease]. Vestn Rentgenol Radiol. Jan-Feb 2015;(1):5-15. [Article in Russian]. (PubMed).
50. Herbella FAM, da Silva RMB, Del Grande LM. IN DEFENSE OF FOUR DECADES OF ESOPHAGEAL FUNCTION TESTS. REPLY TO REACTION TO ARTICLES ON HIGH RESOLUTION MANOMETRY, THE LENGTH OF THE LOWER ESOPHAGEAL SPHINCTER AND THE DIAGNOSIS OF GASTROESOPHAGEAL REFLUX DISEASE. Arq Gastroenterol. 2019 Aug 13;56(2):211-212. doi: 10.1590/S0004-2803.201900000-40.