Gastroesophageal reflux disease is the first signal of damage to the digestive tract in response to hydrochloric acid hypersecretion.

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General problems of gastroenterology

We must give credit to those scientists who took the first significant steps in the study of the normal physiology of the esophagus and the esophagogastric junction (EGJ). For this purpose, I will refer to the article by Gordon et al. «Winklestein first described gastro-esophageal reflux disease (GERD) in 1935, and Allison highlighted the association between esophagitis and hiatus hernia. For many years it was thought that a hiatus hernia had to be present for reflux to occur. In 1972, Cohen et al. drew attention to the role of a persistently hypotensive lower esophageal sphincter (LES) in patients with GERD. However, many patients with GERD were then found to have basal LES pressure within the normal range. In 1982, Dodds et al. emphasized transient lower esophageal sphincter relaxations (TLESRs) not associated with swallowing and their role in the etiology of GERD. Subsequent studies have shown that TLESRs are in fact physiological, and they underlie the majority of reflux events in healthy subjects. The pathogenesis of GERD is now recognized to be multifactorial, involving the LES, diaphragmatic crus, esophageal acid clearance, gastric acid secretion, gastric emptying, and intra-abdominal pressure. But what of the hiatus hernia?"[1].

In recent years, a huge number of articles have been devoted to this problem, but it is difficult to find among them works that meet scientific criteria.

(1) New equipment is constantly being introduced in gastroenterology, and manufacturers are motivating doctors to use it, spending huge amounts of money on it. It is tempting to become rich and famous without spending time studying the physiology of the digestive system. For example, a group of authors from the

Medical Center Groningen, Groningen, the Netherlands claim that they, using high-resolution anal manometry, first described 2 reflexes: the contraction of the puborectalis muscle and the external anal sphincter in response to rectal distension [2]. The responses of these sphincters to rectal distension are known from numerous studies with «low-resolution anal manometry" and X-ray studies, with a much deeper understanding of the role of all sphincters in fecal retention [3]. Such publications are not permissible, but if they have already appeared, they should evoke criticism from the scientific community. Unfortunately, this phenomenon takes on more and more scaled forms, as evidenced by the publication of these articles in the journal Diseases of the Colon & Rectum.

(2) The number of scientific journals increased and became part of one of the many business groups (Elsevier, Springer, Wiley, Wolters Kluwer, et al). Their business interests are closer to those of the hardware manufacturers. As a result, the low competence of reviewers leads to the publication of false information. For example, in the article, Neri et al. states that “The aortomesenteric angle is normally 25–60 ° [2, 3, 6, 7, 10-12] and the mean aortomesenteric distance of 10–28 mm [1-3, 6, 7, 10 -12]. Subjects presenting an angle <25 ° and aortomesenteric distance <8–10 mm may be affected by SMA syndrome” [4]. However, the conventional diagnosis, which supposedly confirms the diagnosis of SMAS, was erroneous. Second, the authors did not measure the aortomesenteric angle in healthy individuals of different ages and weights. Thirdly, links to articles that allegedly cite the same numbers are false, since their authors also did not carry out such research. Moreover, most of them are devoted to descriptions of single cases. As a result of this deception, many surgeons produce duodenojejunoanastomosis in patients with functional dyspepsia only based on an aortomesenteric angle less than 25º [5,6]. But the truth is that this angle decreases in people with low weight [7].

(3) Diagnostics is a comparison of a sick person with a healthy one. Poor selection of patients for determining normal parameters negates the results obtained since the error is harmful for patients and for further research. For example, the primary selection in the group of patients to determine the normal limit of prolonged (24 hours) pH-metry, included patients without complaints typical of GERD, in whom endoscopic examination did not reveal esophagitis. It is believed that the thresholds are reflux index (RI) (% proportion of time during which esophageal pH is below 4)> 10% in infants,> 7% in older children, and> 4 in adults [8]. These figures, firstly, contradict common sense since the reflux of aggressive hydrochloric acid in infants for 2.4 hours a day cannot be without serious consequences. Secondly, it is known that some findings on endoscopy and manometry can be encountered in asymptomatic individuals without GERD symptoms [9]. So, for example, with a screening gastroscopy examination of 6,683 healthy Koreans, 14.66% had GERD diagnosed [10]. Thirdly, it is known that endoscopy does not reveal pathology in non-erosive GERD [11]. Normal esophageal appearance failed to identify 79.2% of patients with histologic esophagitis [12].

The evidence presented above indicates that the normal range for prolonged esophageal pH-metry, proposed at the end of the last century [13], was developed based on misconceptions. As a result of this error, the pH-metry only detects severe forms of GERD. In scientific research, mistakes are possible, but the task of researchers is to correct them in a timely manner. Unfortunately, this has not happened. It also became a bad example for high-resolution manometry. All modern ideas about the normal and pathological physiology of the esophagus and the EGJ carry the burden of this error, i.e., they need to be reviewed. We must answer the following questions: **1.** How does GEJ function normally? **2.** Is a so-called hiatus hernia (HH) a cause or a consequence of GERD? **3.** What is the difference between phrenic ampulla and HH? **4.** How is the angle of His formed

and what does it mean? **5.** What is the pathological physiology of functional heartburn and reflux hypersensitivity? **6.** How are the esophagus and LES shortened in normal conditions and in GERD? **7.** Transient lower esophageal sphincter relaxation - is it normal or pathology?

Basic principles of scientific research. 1) Any research should not contradict common sense. The human body is an amazing example of expediency and knowledge of this principle can indicate the direction of research. **2)** If even a single reliable scientific fact contradicts a working hypothesis, this hypothesis must be revised or completely rejected. **3)** An opinion that does not have documentary support is not scientific fact and is not accepted as evidence, despite the number of supporters. **4)** Based on the previous principle, no collective statements (Rome criteria, consensus, etc.) are accepted as scientific works. **5)** Articles are judged on the quality of scientific research, not the number of papers published by these authors.

1. Anatomy and physiology of the esophagus and LES.

The esophagus is a peristaltic tube that begins caudal to the upper esophageal sphincter and ends above the LES. Even though the LES on surgery and autopsy seems to be a slightly thickened continuation of the esophagus body without a clear boundary between them, both histologically and functionally, it is an independent unit, like other anatomical sphincters (pyloric sphincter, internal anal sphincter, Oddi's sphincter, internal urethral sphincter, etc.). It obeys the same laws as other anatomical sphincters.

It is known that at rest the pressure in the lower part of the esophagus is lower than in the stomach [14]. This means that for the bolus from the esophagus to enter the stomach, the distal segment of the esophagus must create a pressure that, firstly, must correspond to the threshold pressure for opening the LES. Secondly,

it must be higher than the gastric pressure. The mechanism for creating the threshold pressure above the LES depends on the position of the body.

A) In an upright position, liquid food (contrast agent) forms a vertical column with a liquid level at the height of the 3rd thoracic vertebra, the hydrostatic pressure of which opens of the LES (**Figure 1, a**).

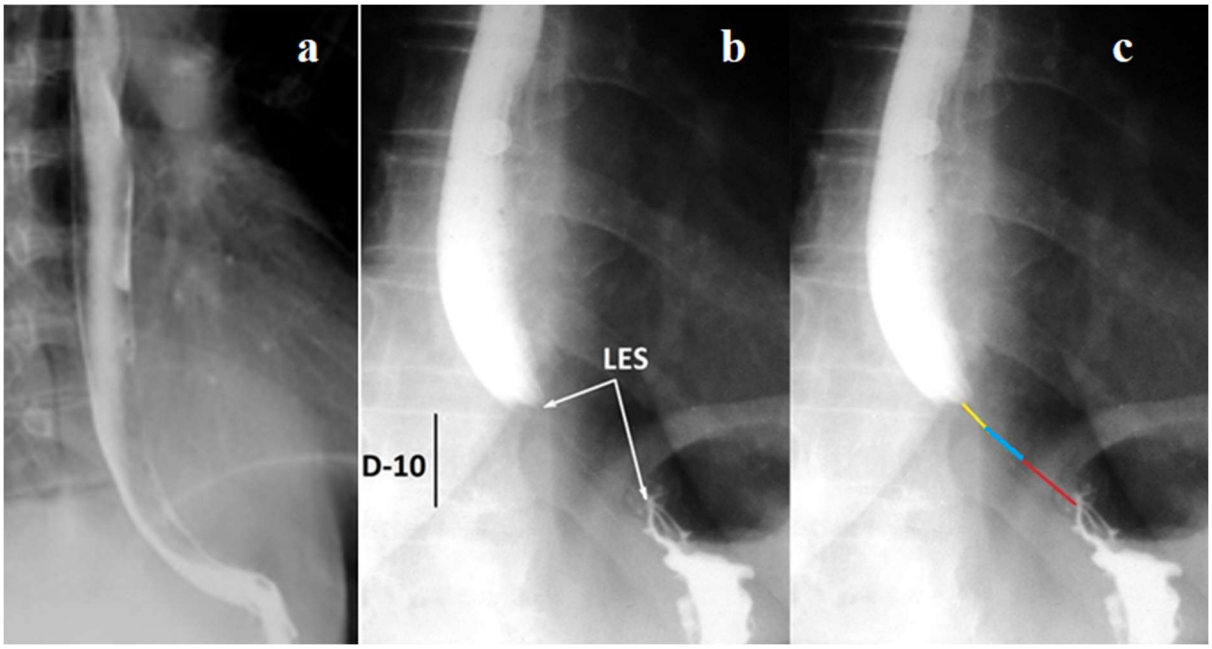

Figure 1. Radiographs of the esophagus and EGJ in an upright position of two adult patients with GERD. (a). A wide opening of the LES is determined, which remains until the esophagus is completely emptied. (b) During abdominal compression, LES contraction occurred, which stopped the advance of barium. Since the height of the 10th thoracic vertebra is approximately 2 cm, the distance between the esophagus and the stomach is 3.5 cm. It corresponds to the length of a normal LES. (c) An approximate diagram of the components of the LES. The supraphrenic part is a yellow line (≈0.5 cm), at the level of the diaphragm there is a blue line (≈1 cm), the abdominal part is a red line (≈2 cm).

In the process of emptying the esophagus (Figure 1 a), the fluid level in it quickly approached the stomach. Consequently, the hydrostatic pressure decreased progressively. Despite this, the LES continued to be open for several seconds until the esophagus was completely cleared of liquid contrast agent. This

fact is evidence that the opening of the LES is a reflex phenomenon, and not mechanical. Second, the wide opening of the LES in the absence of other muscles that could participate in its opening indicates a structural difference between the LES and the esophagus body. In 1979, Liebermann-Meffert et al, using a new method of processing anatomical specimens, described sling muscle on the greater curvature of the cardiac stomach and claps muscle on the lesser curvature, which is the abdominal part of the LES [15]. Thirdly, we see in Figure 1b that the LES is a clearly limited area distal to the esophagus, which obeys the laws inherent in all sphincters. It relaxes in response to an increase in pressure above the LES, and its tone increases with increasing pressure in the stomach [16,17]. These two reactions define the valve mechanism of the LES.

The LES has amazing abilities that are common to all sphincters. First, it is in constant contraction. Secondly, the strength of its contraction, i.e., the tone is proportional to the pressure in the stomach. This means that at rest his tone is minimal, but he has large reserves. Contraction of the muscle fibers is a "work" accompanied by energy consumption, without its renewal muscle, cannot continue to contract. Following the contraction inevitably the muscle relaxation must arise, during which the muscle restores its capacity for subsequent contraction. It is known that the sheaves of smooth muscle fibers anastomosing with each other forming a tightly knit group of fibers, which operate together. Only a part of the muscle bundles scattered throughout the sphincter is simultaneously contracted at a certain moment. When their energy supply is depleted, other bundles begin to contract, which to this time had restored the ability to contract. This process, regulated by the Cajal cells, continues in a circular motion, allowing the sphincter to contract continuously. In response to an increase in pressure in the stomach, the number of muscle bundles increases, which leads to an increase in the tone of the LES [18].

B) In a horizontal position, as well as in an upright position when eating thick food, when there is no hydrostatic pressure, the movement of the bolus is due to peristalsis. The peristaltic movement obeys the Baileys-Starling gut law. "Excitation at any point of the gut excites contraction above, inhibition below" [19]. Local circular contraction is accompanied by local longitudinal shortening. The combined physiological and mechanical consequences of local longitudinal shortening are to reduce circular muscle fiber tension and power by as much as 1/10 what would be required for peristalsis without the longitudinal muscle layer, a tremendous benefit that may explain the existence of longitudinal muscle fiber in the gut [20]. Local circular contraction does not add to each other but moves along with peristalsis and stops above the LES. Therefore, there is no reason to believe that the esophagus will be shortened during bolus movement. There is no peristalsis in the LES. It, like all other sphincters, opens simultaneously throughout the length **(Figure 2)**.

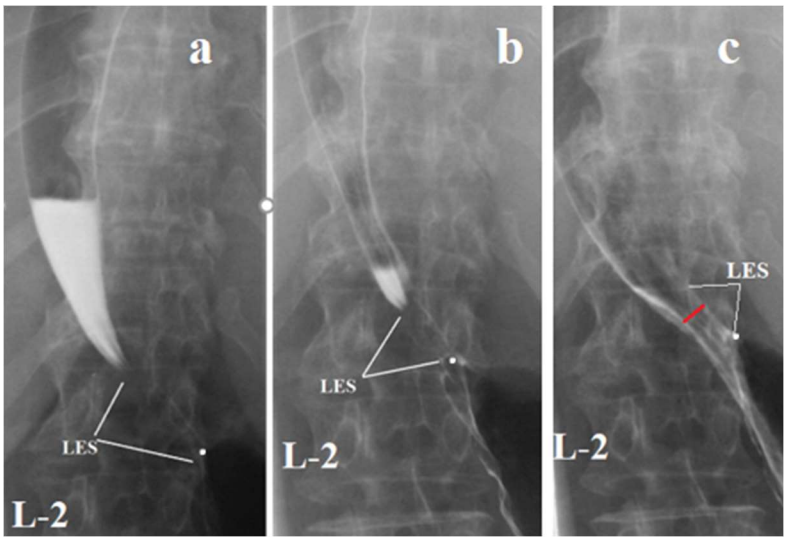

Figure 2. Consecutive radiographs after upright barium intake. The L-1 height is 2.2 cm. (a) The true length of the narrowing between the esophagus and the stomach is 3.1 cm. (c) With full opening of the LES its length became 2 times shorter - 1.6 cm. However, the upper border of the LES remained at the same level. There was a shortening of the LES due to the opening of its abdominal part.

Since the LES is an anatomical and functional unit distinct from the esophagus, the name of "esophagogastric junction" is erroneous and misleading. In fact, there is a junction of the esophagus with the LES and the connection of the LES with the stomach.

In a horizontal position in healthy individuals, the width of the esophagus does not exceed 1.5 cm and is the same throughout. A strong peristaltic wave creates such a high pressure over the LES that no provocative tests can cause the LES to contract and stop the bolus from advancing above it. Therefore, it is impossible to measure the length of the LES in a healthy person during an X-ray study. We measured the length of the LES in patients of different ages with recent emerging mild symptoms of GERD. Since these results were comparable to the length of the LES measured by manometric studies [21,22,23], we accepted them as a conditional norm [24] (**Table 1**).

Table 1. 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

Reflux of aggressive hydrochloric acid into the esophagus causes inflammation and expansion of the lumen of the lower esophagus, which leads to a weakening of the last peristaltic wave above the LES. In such cases, an increase in gastric pressure causes a contraction of the LES, because a weak peristaltic wave cannot create a threshold pressure for its opening (**Figure 3a**).

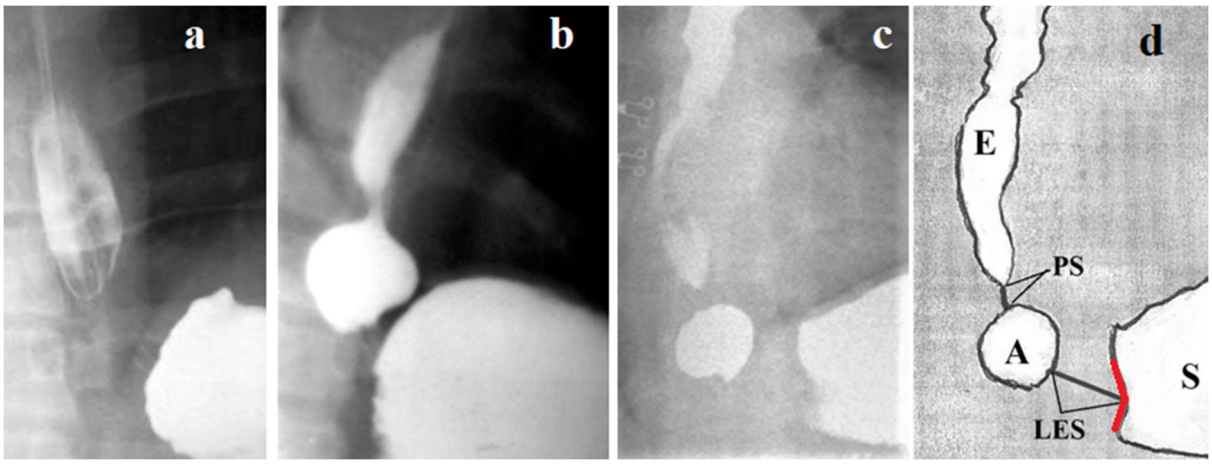

Figure 3. Evacuation of a bolus from the esophagus to the stomach in a horizontal position for GERD. (a) Contraction of LES during abdominal compression. (b-d) Formation of the esophageal ampulla over the LES. E-esophagus, S-Stomach, A-phrenic ampulla, PS - proximal sphincter.

To create higher pressure, the portion of the esophagus above the dilated part of the esophagus is contracted. At some point in peristaltic movement, a closed cavity (phrenic ampulla) is formed above the closed LES. During the peristaltic contraction of the phrenic ampulla, high pressure is created in it, which leads to the opening of the LES and the contracting ampulla injects a bolus into the stomach (**Figure 4**).

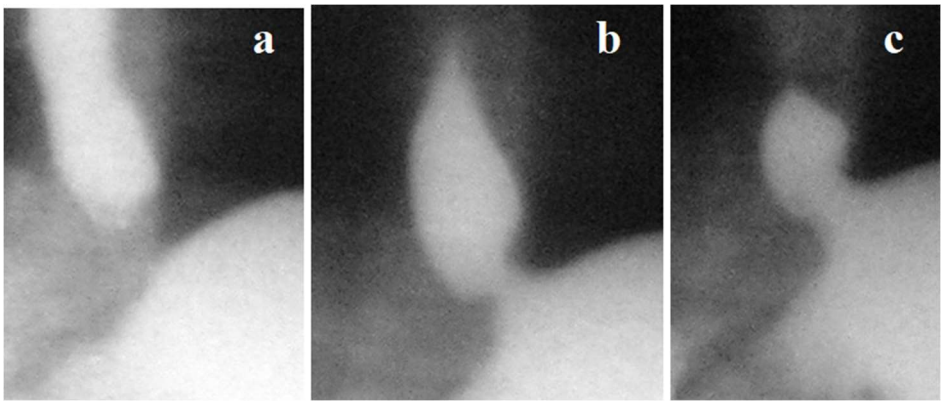

Figure 4. Sequential video graphic footage of esophageal emptying to form an ampulla, which injects a bolus through a wide-open LES.

An analysis of the radiographs in Figures 3 and 4 indicates that the ampoule creates high pressure due to the strong contraction of the short section of the

esophagus above it. We measured the length of this segment, which functions as a sphincter n 20 patients. It, depending on age, ranged from 0.5 to 0.7 cm [24]. It is likely that this functional sphincter occurs when the esophagus expands and the peristaltic wave is weakened. We called it the proximal sphincter (PS). It turned out that ampullar expansion and a similar narrowing above it occurs with dysfunction of other anatomical sphincters **(Figure 5).**

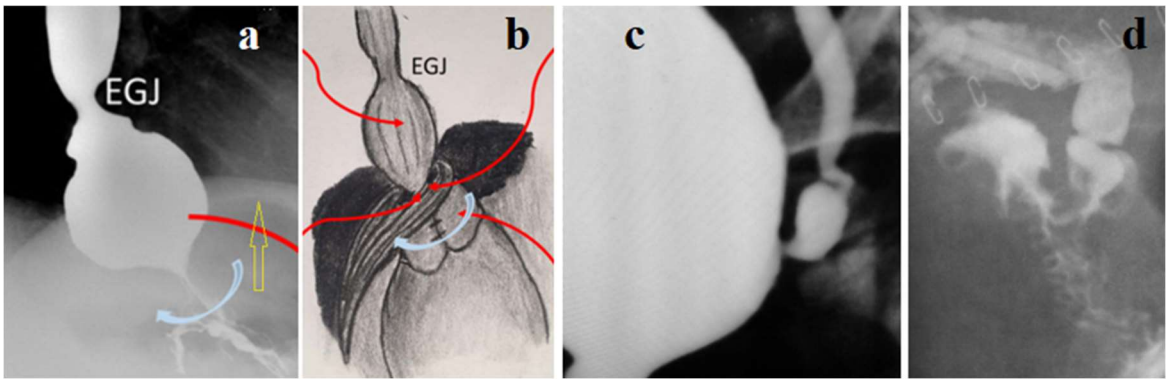

Figure 5. (a-b) Examples of ampulla formation elsewhere. (a). Appearance of the ampulla after fundoplication from article of Yadlapati et al [25]. The cuff (yellow arrow) severely squeezed the area between the esophagus and stomach, causing impaired esophageal emptying (blue arrow). As a result, there was an expansion of the esophagus in the form of an ampoule. The authors mistakenly assumed that the stomach could leak through this constriction. A zone marked as EGJ is a functional sphincter. **(c).** Ampullar expansion of the ureter over the vesicoureteral sphincter and the functional sphincter above it. **(d)** Ampullar dilatation of the common bile duct over the sphincter of Oddi and the functional sphincter above it.

An analysis of the X-ray examination performed concurrently with the high-resolution manometry from the article Pandolfino et al [26] supports the above evidence **(Figure 6).**

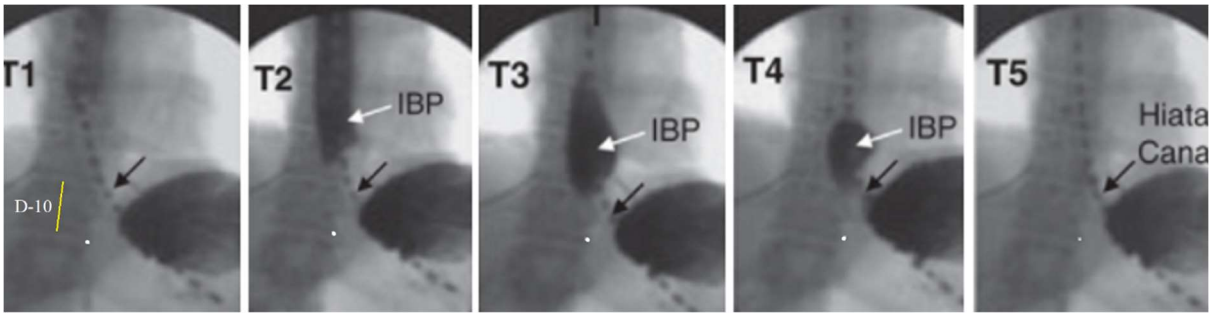

Figure 6. (Authors' explanation) T1, when the leading edge of the bolus first entered the distal oesophagus; T2, when the bolus was first compartmentalized in the oesophagus between the contractile front and the closed OGJ; T3, when the compartmentalized bolus began transitioning from a sharpened pencil shape to a globular form; T4, when barium emptying through the OGJ began; and T5, when barium emptying through the OGJ was completed (or ended). The position of the hiatal canal is indicated on the fluoroscopic images by the black arrow and on the OPT plots by the black line at the 30 cm sensor. The white arrow (images) or dots (OPT plots) indicates the location at which intrabolus pressure (IBP) was measured. Note that a dominant determinant of bolus transit from T3–T5 is descent of S4 back to its native position within the hiatus, which occurs as the oesophageal shortening associated with peristalsis is reversed.

(My analysis). The study was performed in a horizontal position, but there is no peristalsis in T2, which indicates esophagitis. The contraction of the LES between the esophagus and the stomach supports this conclusion. The length of the LES is 2.5 cm, which is less than the minimum age norm (3.2 cm). During the formation of the ampoule (T3-T4), the distance between the ampoule and the lower-left corner of L-10 (white point) decreased markedly, and the distance from this point to the angle that appeared above the stomach increased. As shown in Figures 1c. and 2 s, this is due to the opening of both the supraphrenic part of the LES at the top and the abdominal part of the LES at the bottom. Conclusion: GERD, severe damage to the LES function, esophagitis. The length of the esophagus did not change. The LES has become shorter, due to the full disclosure of its abdominal part.

The shortening of the LES due to the opening of its abdominal portion is a well-known scientific fact [27,28,29]. However, in many patients with a severe form of GERD, which is detected by pH-metry, the length of the LES does not go beyond the normal range. This is explained, firstly, by the fact that the normal limit was determined based on previously erroneously determined normal limits for pH-metry. Secondly, manometry, as a rule, is performed without provocative tests. Since the degree of damage to the LES function in each case is different, it can be differentiated using different provocative tests (**Рисунок 7**).

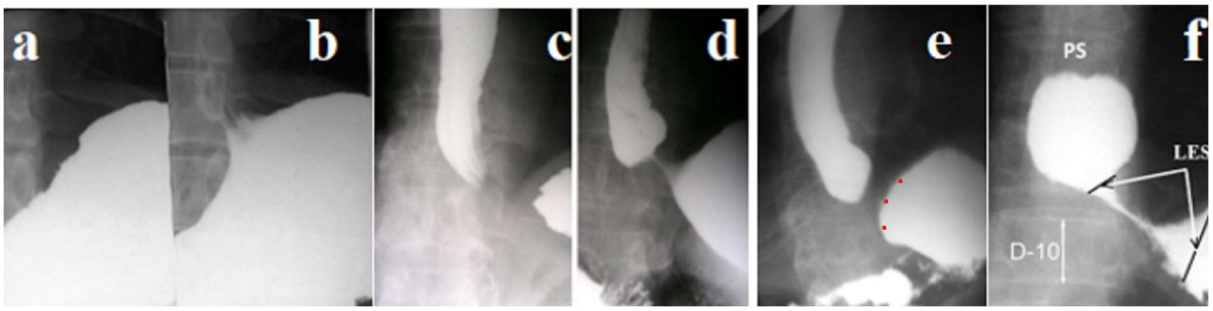

Figure 7. Definition of LES weakness using different provocative tests in a horizontal position. **(a-b).** During the use of the water-siphon test, the abdominal part of the LES appeared in the form of an angular deformity of the stomach. **(c-d)**. During abdominal compression, the LES contracted. **(c)**. It was originally shorter than the norm - less than 2 cm **(d).** In the process of pressure, the LES became shorter than 1 cm. **(e).** Valsalva test. Only a part of the LES located at the level of the diaphragm (at least 1 cm) is in a contracted state. The abdominal part has permanently become part of the stomach wall (red dots). **(f).** During abdominal compression, the LEC contracted, but its weak abdominal portion opened up at an angle. The proximal sphincter (PS) closed the ampulla of the esophagus to create high pressure.

In the literature, it is generally accepted that the proximal end of the rugal folds determines the location of the esophagogastric junction. In the radiographs below, the folds of the mucosa, similar to the folds of the stomach, clearly have nothing to do with the stomach **(Figure 8)**. The 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 [30, 31]. Thus, it has been shown radiographically endoscopically, and histologically that rugal folds appear throughout the LES as a result of the inflammatory process caused by irritation of hydrochloric acid. As shown by Chandrasoma et al, the abdominal part of the LES is the first to be attacked by the gastric juice, and therefore it opens up, turning into the cardiac part of the stomach [31].

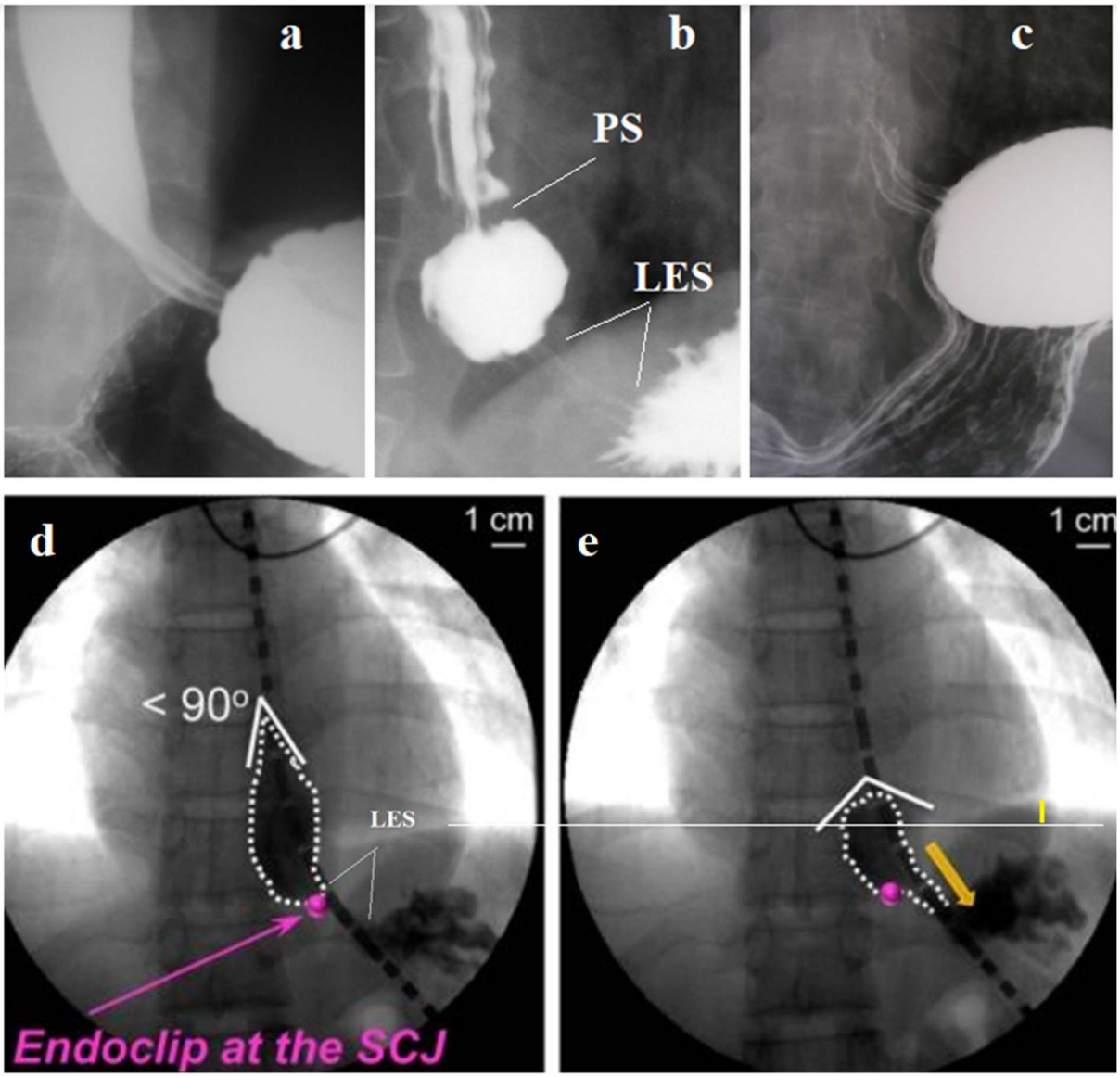

Figure 8. Folds of the mucosa at the level of the LES mistakenly considered folds of the stomach. (d-e). From Kwiatek et al [32]. LES tagged by me.

Radiographs (Figure 8 a, b, c) show wide folds proximal to the stomach, which appear to be consistent with the concept of the rugal fold. However, it is even impossible to imagine that they have anything to do with the stomach. These are folds of the inflamed and edematous wall of the LES. On radiograph (b), the contracted segment between the stomach and the ampulla is more than 2 cm. The crural diaphragm cannot create a narrowing longer than 1 cm. This is a contraction of the short LES. Above the ampoule, a zone of contractility of the PC with a length of 0.5 cm is determined. The folds of the mucous membrane in

the stomach differ in shape from the folds in the LES, due to the pressure difference in these segments.

Since the authors believe that the endoclip (Figure 8 d,e) is located at the border of the esophagus and stomach, there is no room for LES on the x-ray. However, in Figure (d) we see a contraction area around the probe between the endoclip and the stomach, which is 1.5 cm. This is a noticeably short LES. In Figure (e) the LES has opened and the ampulla injects a contrast agent into the stomach through the opened LES. Endoclip has not changed its position. It is located at the lower-left corner of D-10 and has slightly risen because of exhalation - the dome of the left diaphragm has risen slightly. Thus, the diagnosis of GERD with serious impairment of the LES function is beyond doubt. This observation confirms the above evidence that rugal folds cannot determine the location of the stomach.

All the phenomena associated with GERD can be explained based on the above evidence.

1. Please note that on all radiographs of patients with GERD, the **His angle** is greater than 90. Figure 9 shows the mechanism for increasing the angle of His in GERD **(Figure 9).**

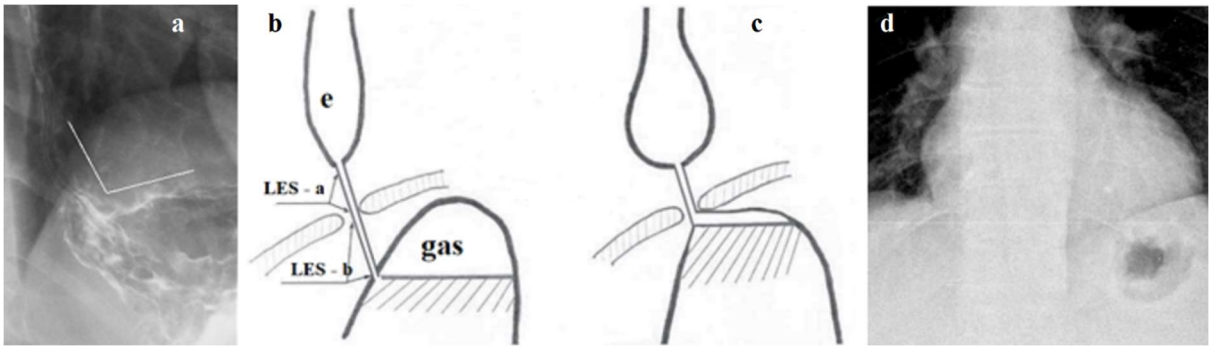

Figure 9. The mechanism of the increase of the angle of His. (**a-c**). The His angle became obtuse because of the opening of the abdominal part of the LES (LES-b), and this is accompanied by a decrease in the volume of the gas bubble (**d**). e - esophagus; LES-a above the diaphragmatic part of the LES; LES-b - abdominal

part of the LES; between them, the section of the LES located at the level of the diaphragm; gas - gas bubble of the stomach.

Thus, the weakness of the abdominal part of the LES leads to its opening on a permanent basis. This is accompanied by an increase in the angle of His and a decrease in the gas bladder of the stomach. Belching, heartburn, or regurgitation are clinical symptoms of GERD due to a decrease of the LES length. It is quite obvious that the obtuse angle of His is not a cause, but a consequence of GERD.

2. **What is phrenic ampulla and how is it different from hiatal hernia?**

A. The **phrenic ampulla** is an extended lower part of the esophagus caused by hydrochloric acid damage to the esophagus. It is found only during the LES contraction. Its function is to create a threshold pressure above the LES for opening the LES and to inject a bolus into the stomach. Let me remind you that normally the width of the esophagus is the same throughout, and the LES does not close until the bolus enters the stomach. Thus, normally the phrenic ampulla cannot be seen. **If it is visible, this is a symptom of GERD.**

B. The statement that the expansion of the esophagus to 2 cm is an ampoule, and more than 2 cm it turns into a hiatal hernia is contrary to common sense and is based on erroneous ideas. As shown above, the **esophagus is not shortened** either at rest or during swallowing. Shortening is recorded only in GERD due to the shortening of the LES. Two methodological errors are responsible for this misconception: (1) pH-metry detects only severe forms of GERD, (2) LES is considered the esophagus. As can be seen in Figure 8, with a slight expansion of the ampoule, the endoclip does not change its position. With large ampoules, the clips attached to the mucous membrane rise, since during the formation of a large cavity, the area of its inner surface increases sharply, and the mucous rises together with the clip to cover the entire area.

C. As shown above, the statement that the proximal border of the rugal folds determines the location of the EGJ is inconsistent with radiographic and histological examination. The name itself contains a mistake since there is an LES between the stomach and the esophagus. GERD begins with reflux of aggressive gastric juice only within the abdominal portion of the LES [30,31]. In this preclinical period, acid does not penetrate the esophagus, which means that the diagnosis is not available for pH-metry and there can be no transient lower esophageal sphincter relaxation (TLESR). I have found no histological studies to contradict those of Chandrasoma et al. **Thus, the so-called rugal folds are the result of an inflammatory process (expansion of the lumen and edema of the wall) at the level of the LES and are a reliable symptom of GERD. Secondly, TLESR can only be present in GERD.**

D. The lower esophageal high-pressure zone is believed to consist of the intrinsic LES and the diaphragmatic sphincter. In patients with a hiatal hernia, these constituents are supposedly separated. The distance between the two peaks pressure is larger in patients with a large hernia [33]. Shafik et al showed the sphincter-like crural diaphragm (CD) action which mediated through the esophago-crural inhibitory and the gastro-esophageal excitatory reflexes, respectively [34,35]. They showed that the CD consists of striated muscle fibers that are easily fatigable and cannot remain contracted for long periods (15–18 seconds (mean 16.8 ± 1.2) [34].

Please note that the minimum distance between the esophagus and the stomach with a contracted gap between them was always about 1 cm (see Figures 7 d, e; 10 c, d, f). This means that the length of the hiatus canal is ≈1 cm. Thus, if the length of the contraction significantly exceeds 1 cm, therefore, the contracted LES is involved in this. On radiographs (Figures 3b; 7f; 8b), where the ampulla is more than 2 cm wide (longer than the L-10 height), the length of the narrowing between the ampulla and the stomach is significantly longer than the hiatus canal.

This is evidence that there is a normally located LES between the phrenic ampulla and the stomach, and therefore **there is no displacement of the stomach into the chest cavity (Figure 10).**

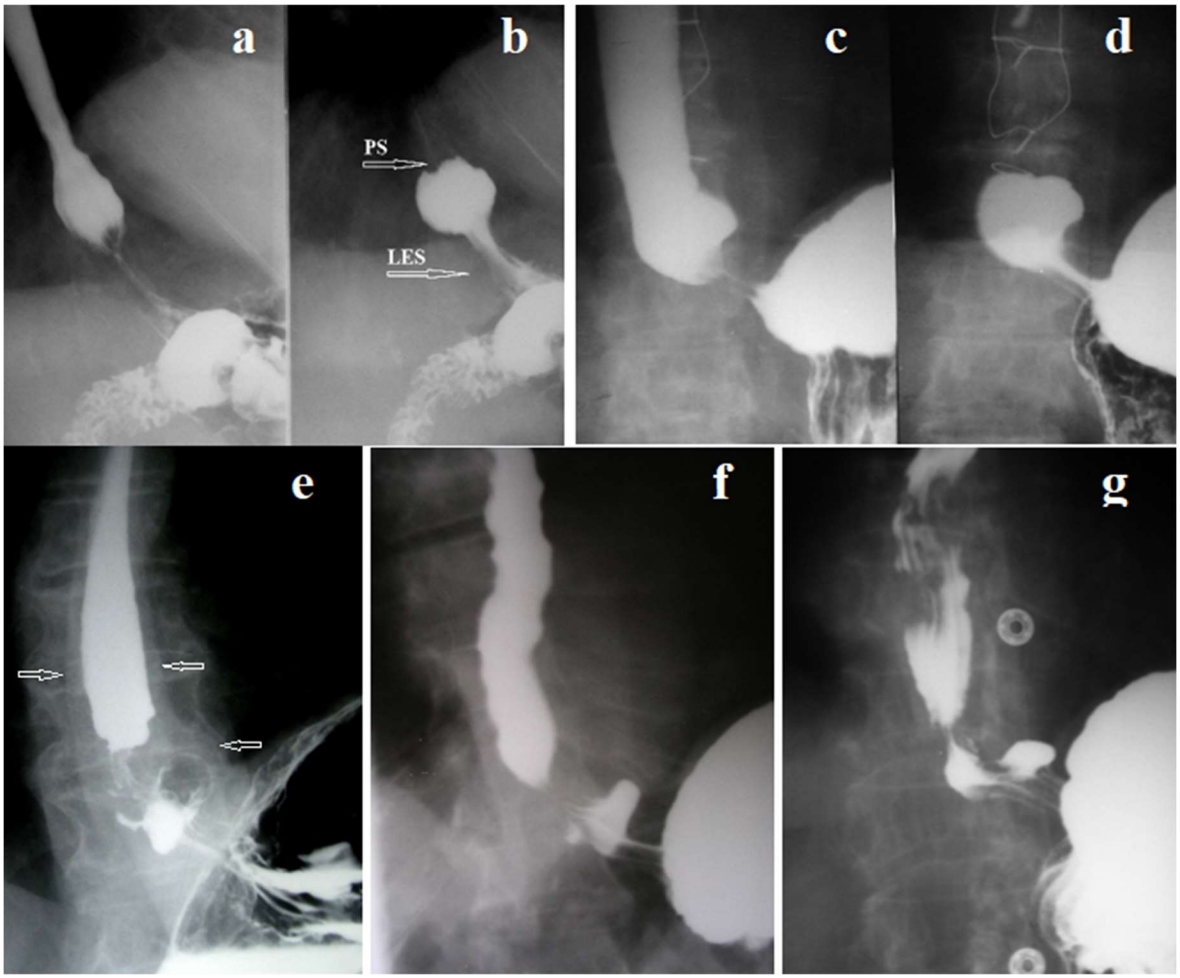

Figure 10. (a-d) EGJ with ampoules of different sizes. (**c-d**) The asymmetric ampulla was formed because of PS contraction. The asymmetry is due to the weakness of the left wall. The LES looks short because its segments have opened, both above the diaphragmatic and in the abdominal (angular deformity of the stomach and obtuse angle of His). (**e-g**) EGJ in patients with severe esophagitis, after contraction of the ampoule, the contrast agent remains in it. In each case, the asymmetry is due to the weakness of the left wall.

A. **Double-peaked high-pressure** zone at the esophagogastric junction occurs only with GERD. The lower peak is due to the contraction of the LES, and the upper peak is caused by the contraction of the PS, the contraction force of which must withstand the high pressure in the ampoule. Force of closure and circular

muscle tension increased with larger probe diameter [36], which outside swallowing provokes PS contraction.

As a result of prolonged mechanical contraction against the background of the inflammatory process, smooth muscle fibers of the PS are gradually replaced by fibrous tissue, which can narrow the lumen to 1.3 cm, which creates an obstacle for the passage of food. This is how the Schatzki ring appears [37].

B. The acid pocket and prolonged esophageal clearance are not the provocateurs of pathological reflux, but the results of severe reflux and is reliable radiographic symptoms of GERD.

3. Hypersecretion of hydrochloric acid is the main cause of GERD.

All factors that are considered to be involved in the provocation or increase of reflux, including sliding hiatus hernia, low lower esophageal sphincter pressure, transient lower esophageal sphincter relaxation, the acid pocket, increased distensibility of the esophagogastric junction, prolonged esophageal clearance, delayed gastric emptying, etc., are actually the result of excess hydrochloric acid production. GERD, gastritis, duodenitis, stomach, and duodenal ulcers, as well as irritable bowel syndrome, are not just concomitant diseases, but results of the same aggressor.

A. Provocateurs and their mechanism of action.

Certain foods are known to cause or increase the symptoms of GERD. These include honey, citrus fruits, red wines (histamine intolerance), lactose intolerance, gluten intolerance, and allergies to certain foods. It is a well-known scientific fact that histamine is a mediator of allergy. One of the many mechanisms of its action is the stimulation of the release of hydrochloric acid. If about 1% of the population suffers from gluten intolerance, then lactose intolerance is found from

10% of the population of northern Europe to almost 100% in China [38]. Analyzing the literature, we came to the conclusion that lactose provokes the release of histamine from the intestinal mast cells, which leads to an excessive release of hydrochloric acid [39]. Recently, Aguilera-Lizarraga et al reported that following oral ingestion of the respective dietary antigen, an IgE- and mast-cell-dependent mechanism induced increased visceral pain. This aberrant pain signaling resulted from histamine receptor H1-mediated sensitization of visceral afferents. Moreover, injection of food antigens (gluten, wheat, soy, and milk) into the rectosigmoid mucosa of patients with irritable bowel syndrome induced local edema and mast cell activation. [40].

Identifying a provocateur is not an easy, but very important problem, since the treatment of GERD cannot be effective without its elimination. The most common cause of GERD is lactose intolerance. Lactose intolerance is due to the absence or deficiency of the enzyme lactase in the small intestines to break lactose down into glucose and galactose. While the infant is breastfeeding, the amount of lactase is sufficient to break lactose. As soon as he begins to receive food that requires splitting it with hydrochloric acid, his intestines begin to work according to a different program: hydrochloric acid begins to be released and the excretion of lactase decreases. Excess lactose stimulates the release of histamine from the intestinal mast cells, which leads to a sharp increase in the acidity of gastric juice. For several months of life, the infant at each feed consumes a volume of food that exceeds the volume (capacity) of the stomach. This is necessary for its development and increase in the volume of the stomach. However, this physiological process is accompanied by the regurgitation of excess food. If refluxate contains aggressive hydrochloric acid, it burns the esophagus, causing an inflammatory process that clinically manifests itself as infantile colic. By about 6 months of age, when the volume of a one-time feed corresponds to the capacity of the stomach, the baby calms down, but by this time irreversible

changes in the LES and esophagus may develop. Typically, symptoms of GERD reappear after varying amounts of asymptomatic years. At the age of over 30-40 years, even a small amount of lactose can aggravate the disease. Probably, this is due to the fact that as a result of duodenitis caused by hydrochloric acid, the production of lactase in it completely stops.

4. A lifestyle that causes an increase in intragastric pressure (overeating, physical activity after eating, tight belt, etc.) or provokes a prolonged maximum contraction of LES (eating before bedtime, abundance of meat, and fatty foods) also provokes the development of GERD. However, if this is not combined with the provocateurs of histamine release, in such cases the clinical picture is less severe.

5. Eosinophilic esophagitis

Numerous supporters of this disease describe this pathology as follows: Esophageal eosinophilia was initially considered a manifestation of GERD solely. However, in the mid-1990s, clinicians identified esophageal eosinophilia in both adults and children with neither the clinical symptoms nor the histologic changes responded to acid suppression and antireflux surgery, which suggested that the condition was distinct from GERD. The studies showed the resolution of esophageal eosinophilia in response to therapy with an elemental-formula diet suggested that eosinophilic esophagitis was a unique entity. The dominant antigens that mediate this disease appear to be food-based. Diagnosis is based on histological examination if esophageal mucosal eosinophilia of at least 15 eosinophils per high-power field is present. However, GERD may be difficult to rule out. Ambulatory pH monitoring definitively distinguishes GERD from eosinophilic esophagitis [41].

Two theses (immunological response to food ingredients, and poor response to treatment by acid suppression) support the importance of food provocateurs as

described above. In cases where the clinical symptoms correspond to GERD and drugs that suppress the secretion of lactic acid do not have a therapeutic effect, there is no need to perform pH-metry, HRM, and surgical interventions. It is necessary to eliminate the food provocateur of hydrochloric acid hypersecretion. But we cannot agree that this disease is not related to GERD. First, the borderline of differential diagnostics by histological analysis (at least 15 eosinophils per high-power field is present) has no scientific basis. Second, it is a mistake to say that pH monitoring can diagnose or exclude GERD.

In order not to be unfounded, I will cite several serious studies. Of the 46 consecutive patients presenting with heartburn, and other GER symptoms ineffective esophageal motility (IEM) identified, 19 (41%) had normal esophageal acid exposure and 27 (59%) patients, evidence of pathologic acid reflux (total time with esophageal pH <4 exceeded 4.2%). HRM did not discriminate symptomatic patients with IEM and either normal or abnormal esophageal acid exposure [42]. In another study, 50 (53.8%) of 93 patients had GERD symptoms, 49 (52.7%) had esophagitis and 33 (35.5%) had a positive pH-test. Among patients with GERD symptoms, 18% had normal pH-test and no esophagitis, while 34.9% of patients without GERD symptoms had positive pH-test, esophagitis, or both [43]. It is time to finally abandon studies for which the boundaries of the norm were incorrectly defined, which have no physiological meaning, and the results of which contradict common sense. So-called eosinophilic esophagitis is proof of GERD in the presence of a food provocateur.

6. Functional heartburn and reflux hypersensitivity

Recent studies allegedly have shown that most patients with refractory heartburn or other typical GERD symptoms, often do not have GERD as the underlying cause. The commonly implicated mechanisms include functional heartburn and reflux hypersensitivity [44]. This is an example of the use of unreliable research methods, which led to an absurd result.

GERD is a chronic, progressive process. The loss of EGJ antireflux function is irreversible. That is why it is so important to make the correct diagnosis as early as possible and identify the provocateur of hydrochloric acid hypersecretion. Pathogenetic treatment not only relieves the patient from suffering but also slows down or stops the progression of GERD **(Figure 11).**

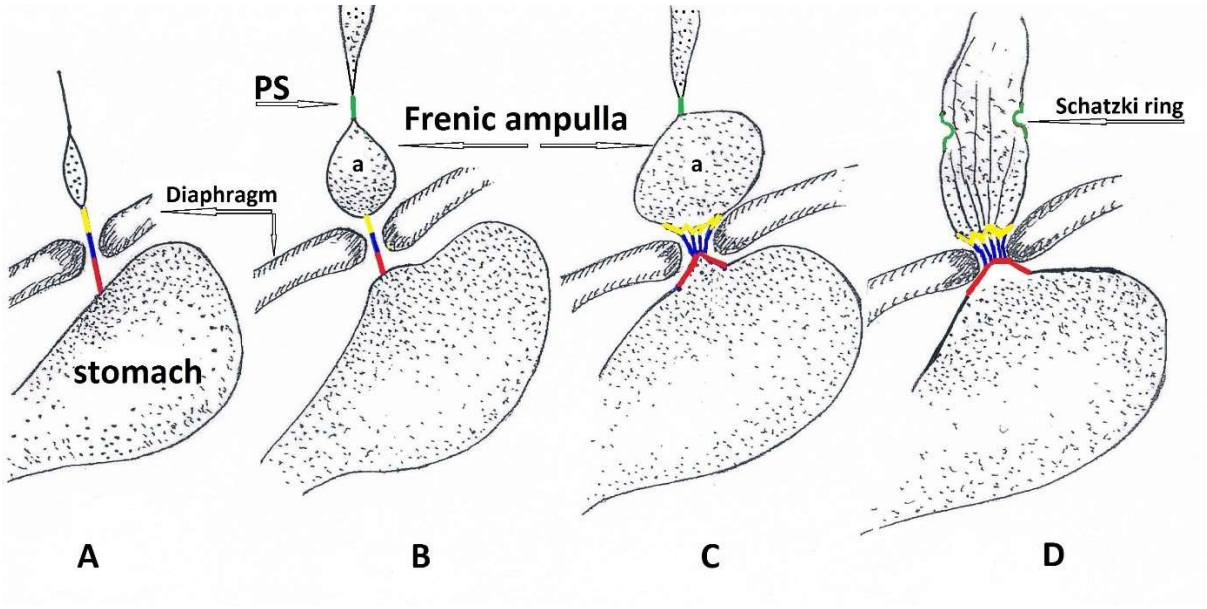

Figure 11. A diagram of the change of GEJ in the process increasing of the GERD severity. (A). Norm. The esophagus is not dilated, and the length of the LES in the normal range. (B). The initial stage of GERD. During the compression of the abdomen, there was a short-term contraction of the LES and a phrenic ampulla appeared. Perhaps a slight shortening of the LES, due to the disclosure of the distal portion of its abdominal segment (red). (C). Severe GERD. Expansion of the esophagus with the formation of ampulla wider than 2-3 cm. Significant shortening of the LES during abdominal compression, widening of the hiatus canal, and appearance of folds at the LES level. The proximal sphincter (PS - green) is functioning. (D). Short LES without the use of provocation tests. The proximal sphincter is not functioning, or in its place appears a rigid fibrous ring (Schatzki ring). Symptoms of severe esophagitis.

Conclusion. As a result of natural selection, the human body, including its digestive system, is arranged very rationally. The stomach is a chemical reactor, for the normal functioning of which you need to follow the rules of use. In case of violation exploitation, aggressive hydrochloric acid affects all parts of the

digestive system: from the tongue, which turns white, to the large intestine, in which histamine is released from mast cells. Knowledge of the normal physiology of different parts of the digestive system is necessary to understand pathological processes. X-ray functional studies, together with endoscopy and histological examination, make it possible to make a correct diagnosis in time and apply pathophysiological treatment.

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