

**Introduction.** Gastroesophageal reflux disease (GERD) is a very common chronic progressive disease. The sooner a correct diagnosis is made and treatment is prescribed, the more likely a complete cure or slowdown of the pathological process is. For a long time, the diagnosis of GERD relied on pH-metry, which was considered the gold standard. Is it so? Some authors believe that a set of typical clinical symptoms is sufficient for a diagnosis. Recently, many researchers rely on the results of manometric studies and cross the LES, ignoring the pH-metry. Ideas about the physiology of the esophagogastric junction (EGJ) at the norm and GERD are contradictory and uncertain. We offer a case history analysis and discuss different hypotheses.

**Case Report.** An Ashkenazi Jewess of 63 years old considers herself sick from the age of 54 years when there was severe pain in the epigastrium. Antral gastritis caused by *Helicobacter pylori* was diagnosed with gastroscopy. After a course of eradication, all symptoms disappeared, and the patient considered herself healthy for 3 years. At the age of 57, when epigastric pain reappeared, a small hiatal hernia with red stripes leading to the cardia was diagnosed with gastroscopy. Gastritis was diagnosed, probably based on the fact that hernia is considered part of the stomach. Colonoscopy was normal. At the age of 61, every morning, she was worried about a painful cough and a sore throat. Several times at night, she woke up with attacks of suffocation and with a feeling of strong acid in her mouth. At the same time, pain in the epigastrium and in the left hypochondrium often bothered her. 3-4 months after the onset of symptoms, she turned to the otolaryngologist, who discovered laryngopharyngeal inflammation, which served as the basis for the diagnosis of gastroesophageal-pharyngeal reflux. She began to take 20 mg of Esomeprasol per day and stopped drinking coffee, tea, chocolate. She had an evening meal 4 hours before bedtime. She slept with a raised head end of the bed. However, there was no significant effect. Gastroscopy was performed twice with an interval of 2 months. The endoscopic diagnosis was antral gastritis

with the histologic conclusion: oxyntic mucosa showing mild chronic gastritis and focus erosion. Negative for H. pylori by immunostain. Negative for intestinal metaplasia. Negative for dysplasia. Although the clinical diagnosis was GERD, these studies did not affect treatment.

X-ray examination with the provocation of high pressure in the stomach confirmed the diagnosis of GERD. The significant improvement came after she started taking 20 mg of Esomeprazole 2 times a day and swallowed a tablet with a barium 2.2 cm diameter. After a month, all the symptoms passed and the patient gradually began to reduce the dose of PPI, until she completely abandoned it. However, she was not sure of the stability of her recovery, as sometimes after a violation of the diet or eating regimen there was a pain in the epigastrium and left hypochondrium, as well as burning and sore throat at night. She was invited to take part in a scientific study suggesting that the electrical stimulation of the lower esophageal sphincter (LES) could improve its function. She was excluded from this study since within 48 hours the pH-metry detected a pH <4 in only 3.2% of the total amount of time. For 2 months, she strictly adheres to the diet: does not eat foods that provoke the release of hydrochloric acid (dairy, coffee, citrus fruits, honey, and chocolate). She dines 4 hours before bedtime, sleeps with the elevated head end of the bed. She has no symptoms of GERD, although she does not take any medications.

Supplement: Her mother had similar symptoms for a long time: persistent sore throat, chronic cough, and attacks of laryngospasm. She was treated by an otolaryngologist without a significant effect. Gastroscopy was normal. The relief was after taking antacids.

### **Analysis of symptoms, and methods of examination.**

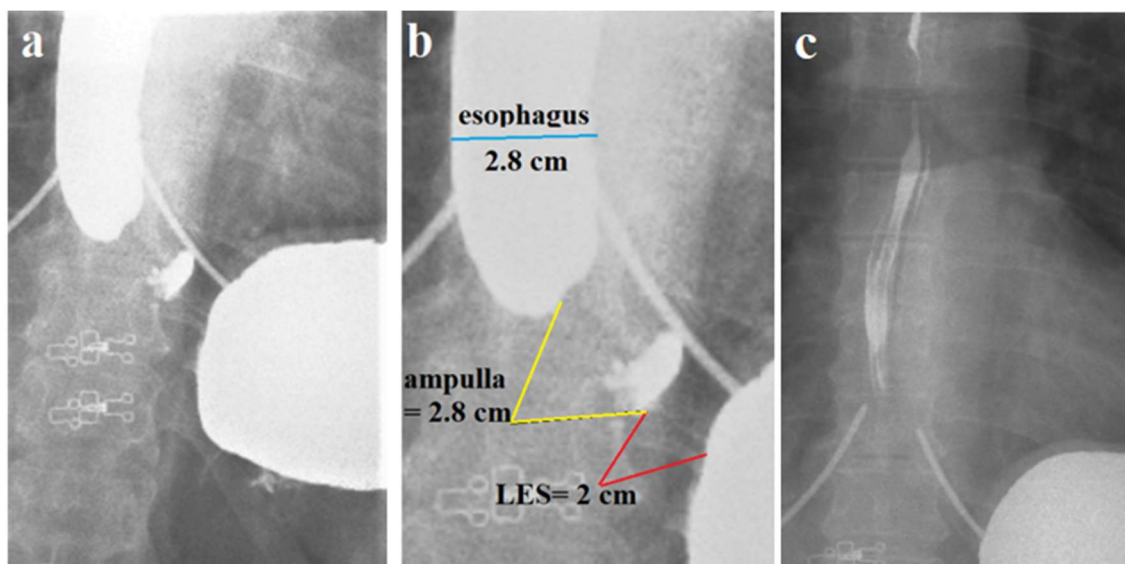
**The clinical picture** clearly indicates a severe form of GERD: epigastric pain, the sensation of acid in the mouth, chronic cough with bronchospasm, treatment effectiveness with PPI.

**Gastroscopy** was performed 4 times, which confirms the severity of the process. In 3 cases, antral gastritis was diagnosed. Only at the beginning of the disease did histological examination show the presence of *Helicobacter pylori*. One study found a small hiatal hernia with signs of inflammation. All studies were conducted during treatment with PPI treatment. No pathology was found in the esophagus, and no histological examination was performed.

**The pH-metry** for 48 hours revealed pH <4 in 3.2% of the observation time, which according to modern ideas does not confirm the diagnosis of GERD.

**X-ray examination** of the esophagogastric junction (EGJ) with provocation high pressure in the stomach was performed during a period of exacerbation of the disease.

**Method.** The patient drank 300 ml of water, and then in a horizontal position through a straw, drank 200 ml of barium suspension from a can located near her head. When the contrast agent was over, she raised her straightened legs, and at that moment the first radiograph was taken (**Figure 1.a**). The second x-ray was performed after several minutes ( $\approx 5$  minutes) also in a horizontal position at low pressure in the stomach (**Figure 1.c**).



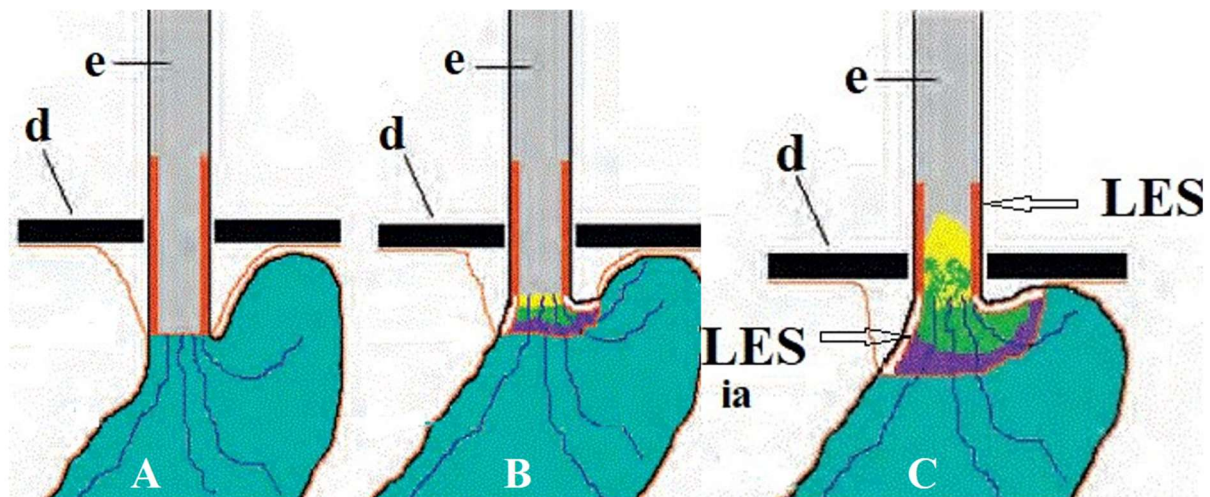
**Figure 1.** (a) X-ray of an EGJ with the provocation of high pressure in the stomach. (b) In the diagram, the length of the contracted LES (2 cm) is two times shorter than normal. At the site of the contracted LES, rough folds are visible. The folds filled with barium (white lines) are noticeably wider than the gaps between them (dark lines). Between the sharply expanded esophagus and the LES, the contraction zone of the phrenic ampulla is determined. In the lower part of the ampulla, on the left wall, a barium depot similar to a diverticulum is determined. (c) On a radiograph made after  $\approx 5$  minutes, with normal abdominal pressure, remnants of the contrast agent are visible in the folds of the esophagus. There are white lines a slightly narrower than black.

### **Description and analysis of pathological x-ray symptoms:**

**The esophagus** is significantly expanded (2.8 cm vs average 1.5 cm in the norm). There are longitudinal folds of the mucosa after emptying. The incomplete cleansing of the esophagus is determined. These symptoms indicate a chronic inflammatory process.

The normal peristaltic wave is enough strong to overcome the tone of the LES, intensified by high intragastric pressure. Therefore, in the norm, LES does not interfere with the promotion of contrast medium into the stomach, as a result, LES cannot be visualized. With GERD, the peristaltic wave of the esophagus is

weakened and cannot overcome the tone of the LES. In such cases, the LES is defined as a contraction zone, i.e. no contrast agent between phrenic ampulla and stomach. In the case under discussion, the LES contracted in response to increased pressure in the stomach and it is 2 times shorter than in norm. The scheme of the pathogenesis of GERD shows how shortening of the LES occurs (**Figure 2**).

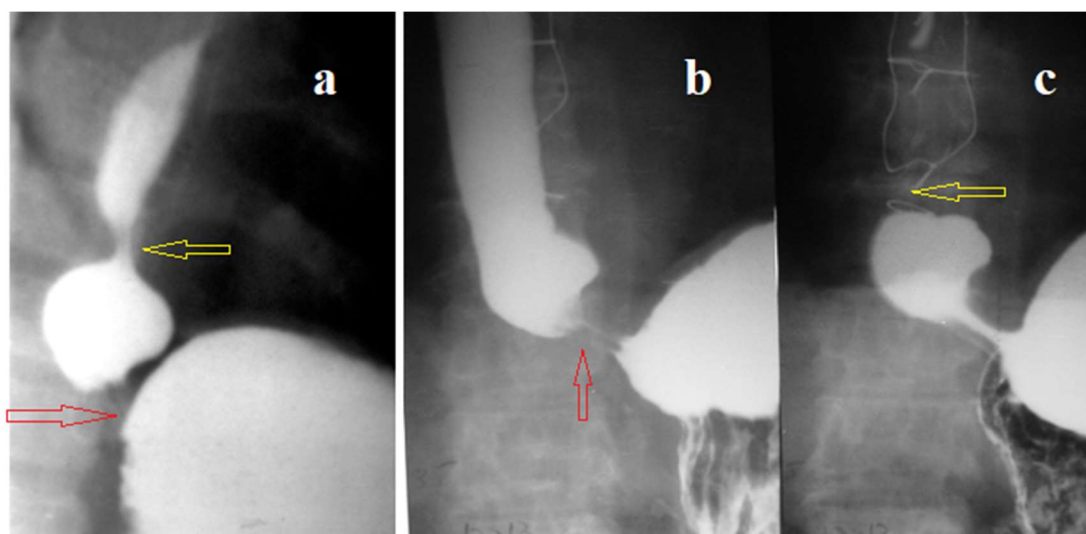


**Figure 2.** The scheme of the pathogenesis of GERD. (A) Norm. LES (brown line) is located both above and below the diaphragm (d). The part of the LES located below the diaphragm is slightly longer than the rest one. (B) Reflux of aggressive gastric juice (yellow) initially starts only within the abdominal part of the LES. In this case, a weakening of some part of the LES occurs. It expands, ceases to fulfill the antireflux function and becomes the wall of the stomach (white line). (C) In more severe cases, the reflux agent penetrates the esophagus. The inflammatory process affects the entire intraabdominal part of the LES (LES ia), and this part ceases to function as a sphincter. In the inflamed and extended part of the LES, folds appear. In the process of development of GERD, the angle of His increases and the esophagus expands.

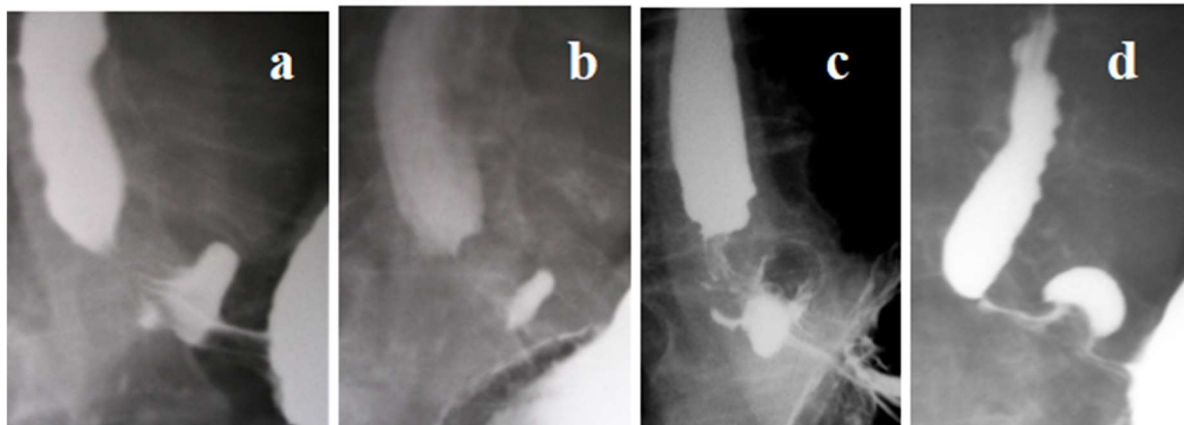
In this observation, we see only that part of the LES ( 2 of 4 cm) that is located inside the diaphragm and above it. The abdominal part of the LES expanded and became the wall of the stomach. The rough folds in the functioning part of the LES differ from the folds in the esophagus because they are in the contracted gut, the wall of which is somewhat thicker than in the esophagus. Thus, a contracted

LES in response to increased pressure in the stomach, shortening of the sphincter and the presence of folds indicates the advanced GERD.

**The phrenic ampulla** is a pathological expansion of the esophagus over the LES. It functions as a pump. It is known that the pressure in the esophagus is lower than in the stomach. Normally, a strong peristaltic wave creates a high (threshold) pressure over the LES, which causes the opening of the LES. The peristaltic wave in accordance with the law of the gut closes proximally and injects the bolus into the stomach. With GERD, the esophagus is dilated, and the peristaltic wave is weakened. The phrenic ampulla is the last peristaltic wave in the dilated and weakened part of the esophagus. It is closed proximally by a functional proximal sphincter (PS), as a result of which, during a bolus advancement, at some point, a closed cavity appears between the PS and the LES. During its contraction, a threshold pressure arises in it, which leads to the opening of the LES and a contracting ampulla injects a bolus into the stomach (**Figure 3**). In the present observation, the x-ray recorded the moment when the ampulla contracted. The barium collection on the left side of the ampulla in the form of a pseudo diverticulum is a typical pattern that results from the weakness of the wall at the base of the ampulla (**Figure 4**). A pseudo diverticulum has never been found on the right side of an ampulla.



**Figure 3.** Radiographs of the EGJ of patients with GERD, in which a functioning phrenic ampulla is fixed. **(a)** The moment of formation of a closed cavity between the PS (yellow arrow) and the LES (red arrow) was recorded. **(b-c)** The wide esophagus is filled with barium without signs of peristalsis **(b)**; the last portion of barium is injected into the stomach with a contracting ampoule. The pressure in it is maintained due to the contraction of PS **(c)**.



**Figure 4.** Radiographs of EGJ, which recorded different stages of contraction of the phrenic ampulla. In all cases, the weakness of the left wall of the base of the ampoule is determined. After complete contraction, a contrast agent remains in this pocket. The picture resembles a false diverticulum.

Thus, the detection of a false diverticulum over the LES indicates the functioning of the esophagus ampoule with a weak left wall, which confirms the advanced stage of GERD. On the same day, after a study of the EGJ with increased pressure in the stomach, the patient swallowed a large pill and began to take 20 mg PPI twice a day. After a month, when all the symptoms of GERD disappeared, the patient gradually reduced the dose of PPI until it was completely canceled. Over the past two months, she has not taken medicine. She strictly adheres to a diet and remains free from symptoms.

## Discussion.

The patient is sick for at least 9 years. The clinical picture is beyond doubt - it is GERD, which is progressing, despite treatment. We are faced with three questions:

(1) Why were none of the 4 gastroscopies diagnosed with GERD? (2) Why was GERD not detected by pH-metry? (3) Why did the symptoms disappear after treatment and did not resume after stopping PPI?

Histologic markers of reflux-induced mucosal injury are demonstrable in patients with nonerosive GERD. Dilated intercellular spaces (DIS) distinguishes GERD from functional heartburn. However, the authors believe that DIS is not specific to acid-induced injury, as it can also be seen with weakly acidic refluxate [1,2]. Chandrasoma and DeMeester showed that the normal state where the esophageal squamous epithelium transitions at the EGJ to gastric oxyntic epithelium with no intervening cardiac epithelium. Cardiac metaplasia of the squamous epithelium due to exposure to gastric juice results in the cephalad movement of the squamo-columnar junction. This creates the squamo-oxyntic gap and the dilated distal esophagus, which is distal to the endoscopic EGJ. In the early stages, the gap is <5 mm and the LES retains its competence. Reflux is uncommon and patients are asymptomatic [3]. Thus, at the early stage of GERD (see Figure 2.B), the contents of the stomach do not enter the esophagus, which means that the diagnosis cannot be established by pH-metry. Secondly, a pH <4 on an ongoing basis in a healthy person cannot be at all. Biopsies of the squamocolumnar junction that show microscopic intestinalization of metaplastic cardiac mucosa in endoscopically normal patients are predictive of future visible Barrett's esophagus, and an indicator of GERD progression [4]. The authors do not refer to a correlation with the pH-metry, since the pH-metry reveals only severe forms of GERD [5].

de Bortoli et al studied how many cases of laryngopharyngeal reflux suspected by Laryngoscopy are gastroesophageal reflux disease-Related? MII-pH (24-h multichannel intraluminal impedance) analysis confirmed GERD diagnosis in less than 40% of patients with the previous diagnosis of laryngopharyngeal reflux, most likely because of the low specificity of the laryngoscopic findings



[6]. However, this conclusion is questionable because, all patients underwent an upper endoscopy, stationary esophageal manometry, 24-h multichannel intraluminal impedance and pH (MII-pH) after a 16-d wash-out from PPIs. It is noteworthy that hypersensitive esophagus patients had a positive association with typical GERD-related symptoms. Obviously, these authors made a conclusion, considering the pH monitoring to be a golden test. In any case, they should have explained the alternative origin of laryngopharyngeal inflammation.

Based on current notions, «a diagnosis of GERD might be confirmed by evident signs of erosive esophagitis and the finding of pH or multichannel intraluminal impedance-pH tests, such as more than 6%. The 'Lyon Consensus' panel of experts confirmed that positive indices of reflux-symptom association, without other altered parameters, represent reflux hypersensitivity" [7].

This formulation is contrary to scientific evidence and common sense. First, GERD can progress in the absence of clinical symptoms [2-5]. Secondly, the determination of the normal boundary for pH meter has no scientific justification. It proceeded from erroneous assumptions: that the absence of typical symptoms of GERD (heartburn, dysphagia, regurgitation) in combination with the absence of visible changes in the esophagus during gastroscopy exclude GERD. Therefore, a portion of patients with GERD was selected into the group of supposedly healthy individuals. Enough scientific evidence has now accumulated to claim that pH-metry is not the gold standard. Consensus accepted by voting is not a scientific method. As a result of the primary error in the choice of individuals to determine the normal range, the pH-metry determines only severe cases of GERD. So, the idea of reflux hypersensitivity came about. These are patients with typical clinical symptoms of GERD who need pathophysiological treatment, but they are denied this because of the defective method of pH-metry.

### **Purpose and results of treatment**

The purpose of treatment depends on the degree of impaired function of the LES. If the sphincter contracts in response to increased pressure in the stomach, the goal of the treatment is to fight esophagitis, since the inflammatory process in the esophagus worsens the function of EGJ. If the LES does not close, or it is very short and does not contract in response to increased pressure in the stomach, or the treatment does not allow PPI to be abandoned, the goal of treatment is to control the symptoms of GERD.

Treatment of esophagitis includes the appointment of high doses of PPI (40 mg x2 for 8 weeks, followed by a gradual dose reduction, until it is completely canceled); exclusion of food provocateurs that enhance the release of hydrochloric acid (allergens, products containing lactose, citrus fruits, honey, chocolate, alcohol); swallowing tablet with a diameter of  $\approx 2$  cm, what improves the function of the LES and to improve evacuation from the stomach [8]. It is necessary to reduce the volume of a single meal, so as not to provoke high pressure in the stomach. An early dinner without meat and fat to go to bed with an empty stomach. Antacids and enveloping agents must be taken 30 minutes after eating and at bedtime.

As can be seen from the above observation, which reflects our experience in treating patients with GERD, a decrease in reflux episodes and decreases aggression of the reflux agent allows us to abandon the continuous use of PPI. This can only be explained by a decrease in inflammation in the esophagus, which leads to an improvement in the antireflux function of EGJ. From this, it follows that the results of pH-metry depend on the conditions under which this study was performed, i.e. before or after treatment. Before treatment, the pH-metry indicates GERD, and after treatment, it turns out that it is a hypersensitive esophagus.

## **Conclusion**

We have described a case of chronic progressive disease with typical GERD symptoms. Expansion of the esophagus and shortening of the LES indicate a chronic inflammatory process and a weakened function of the LES. Based on pH meter (pH <3.2%), this case was regarded as a hypersensitive esophagus. The patient received empirical treatment, which was not effective. The treatment of acute esophagitis led to an improvement in the antireflux function of EGJ, which made it possible to abandon the continuous use of PPI. This case and the numerous scientific facts cited to prove the falsity of the modern concept of the pathophysiology of GERD due to the low sensitivity of pH-metry.

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