Esophageal achalasia in the historical aspect.

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Esophageal achalasia (EA) is still considered a rare disease, but over the past 50 years, there has been a sharp increase in the frequency of EA. For example, the frequency EA increased from 0.03 to 32.58 per 100,000 population (in one of the districts of Chicago) per year [1], i.e. increased more than in 1000 times. As the analysis of the literature shows, this happened because of a change in the understanding of EA pathophysiology. Instead of a disease called idiopathic or classical EA with known characteristics of pathogenesis, manometry, and histology, EA has become a manometric syndrome. This study is devoted to the analysis of this transformation.

I divide the history of the studies into three periods: (1) before about 1980, when fundamental science was engaged in research, (2) from 1980 to 2008, when high-resolution manometry was introduced into widespread practice, and (3) from 2009 year when the Chicago Classification first appeared.

I. Idiopathic or classical achalasia of the esophagus

Until 1980, scientists were investigating an exceedingly rare disease called idiopathic achalasia of the esophagus. It was called idiopathic because although the pathological physiology of the disease was well studied, the etiological factor was not known.

The clinical picture is characterized by dysphagia, regurgitation, and chest pain. This is because the LES does not relax in response to the threshold hydrostatic pressure of the food. Normally, the hydrostatic threshold pressure is created by the pillar when the food level reaches D-4. This hydrostatic pressure in the esophagus over the LES causes reflex relaxation of the LES, which continues until all the food has entered the stomach [2]. With EA, the LES is mechanically stretched under higher pressure, which is created by the fluid level up to the upper esophageal sphincter and by the contraction of the esophageal walls. Only liquid food passes through the narrow channel that forms in the LES, and when the liquid level in the esophagus drops, the LES closes again. Stagnation of food and high-pressure lead to the expansion of the esophagus.

X-ray picture. According to Shafik, the radiographic evidence of EA include absent primary peristalsis, dilated body of the esophagus and a conically narrow cardioesophageal junction" [3]. All authors write about 'bird's beak' as a typical

symptom of EA. However, as a rule, the characteristics of this symptom and its difference from the X-ray image of LES in GERD are not given. Second, 'bird's beak' is not the only symptom of classic or idiopathic EA.

With EA, after the evacuation of a small bolus, when the fluid level in the esophagus decreases and the esophageal pressure drops, the evacuation of barium stops. Therefore, air from the esophagus never enters the stomach. Thus, the absence of a gas bubble in the stomach is one of the symptoms of EA. The LES is usually smooth in outline and normal length of about 4 cm (in adults).

In normal subjects, it is impossible to see the LES during X-ray examination since a strong peristaltic wave conducts barium from the esophagus into the stomach without stopping. In GERD, provocative tests cause a contraction of the LES and it is defined between the esophagus and the stomach, as a zone without a contrast agent **(Figure 1.a).** As the analysis of radiographs and the medical history of different patients show, only a combination of radiological symptoms allows the diagnosis of achalasia to be established.

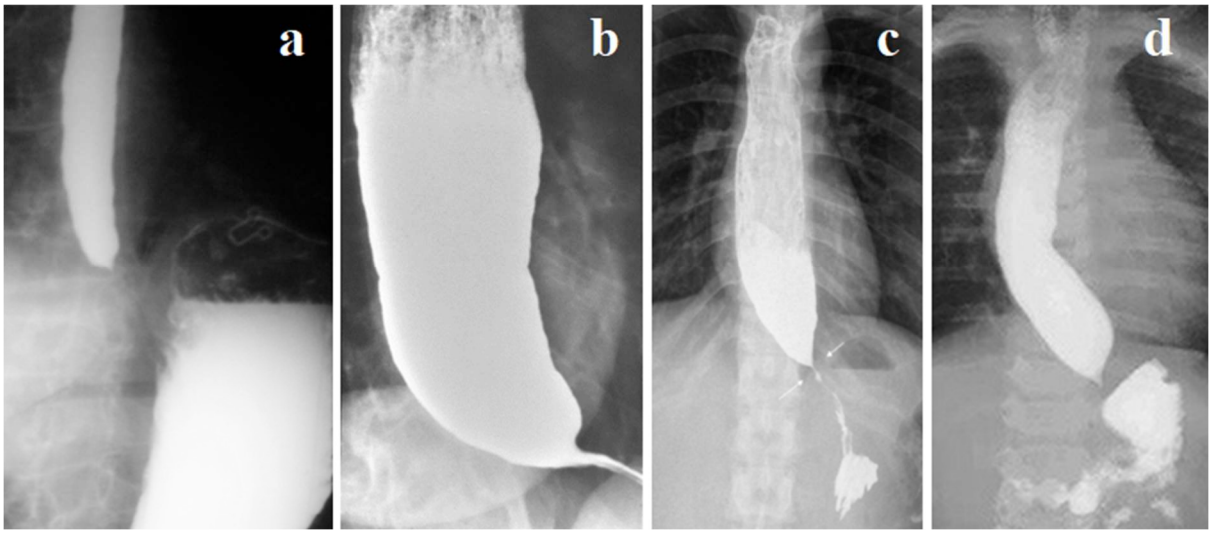

Figure 1. Radiographs with 'bird's beak' symptom. **(a)** Radiograph of an elderly patient with GERD in an upright position. Narrow esophagus with not even contours. A conical entrance to the LES that like a 'bird's beak'. The LES is in a contracted state. **(b)** The classic 'bird's beak' symptom. Unfortunately, the length of the LES is not known, and whether there is no gas in the stomach. **(c, d)** Radiographs of children with GERD who were erroneously diagnosed with EA. **(c)** In the upright position, a sharp shortening of the LES with a local narrowing in the abdominal part of the LES is determined. There is probably peptic stenosis in the abdominal part of the LES. **(d)** In a horizontal position in the dilated esophagus, the phrenic ampulla is not closed by the proximal sphincter. To create high pressure to open the short LES, this pressure is created throughout the

esophagus between the upper and lower esophageal sphincters. This is a typical picture of GERD.

In this series, only (b) is a likely snapshot of EA. Scientific research must be evidence-based. This means that if EA is suspected, images should be taken with the level of barium in the esophagus, length of EGJ, and the fundus of the stomach. The description of the radiographs should include important clinical findings and explanations for the radiological signs. Unfortunately, these rules have been lost.

Manometric study. In normal subjects, esophageal distension causes a significant decrease in LES pressure. Distension of the anesthetized esophagus does not evoke an LES pressure response. In EA patients, the resting LES pressure is significantly higher than normal ($p < .01$). Upon esophageal distension, the LES pressure is not decreased but increased [4].

If in normal subjects an increase in the gastric pressure causes an increase in the tone of the LES [5,6,7], then in patients with EA with an increase in the gastric pressure the tone of the LES does not change [8]. The LES pressure was 50.5 ±4.6 mm Hg in patients with achalasia as compared with 19.4 ±1.3 mm Hg in the normal group [8].

Normal LES function is consistent with the Bayliss-Starling's law of the gut, which states that "Excitation at any point of the gut excites contraction above, inhibition below" [9]. All sphincter zones function in accordance with this law. For example, an increase in pressure in the pharynx causes relaxation of the upper esophageal sphincter and stretching of the esophagus causes it to contract. An increase in pressure in the antrum of the stomach causes the pyloric sphincter to open, and an increase in pressure in the duodenal bulb causes a contraction of the pyloric sphincter, etc.

LES in EA behaves like an internal anal sphincter in Hirschsprung's disease, i.e., like a denervated gut.

Histological examinations. Achalasia of the cardia is known to de due to a destructive lesion of the myenteric plexus in the esophagus and gastro-esophageal segment. The loss of myenteric neurons is often extensive and may be complete. There are reports that neurons have been found in biopsies taken at cardiomyotomy. However, the ganglion cells which are left are argyrophobe and therefore do not contribute either to peristalsis or esophageal reflexes [3, 10, 11]. At the distal end of the esophagus ganglia cells were absent in 91% of cases as well as in the middle third of the stomach (20%). The Auerbach's plexuses were normal in the jejunum and colon. Some studies suggest that denervation of the

esophagus in patients with achalasia, which is a constant finding in several previous reports may extend beyond the esophagus to the stomach in nearly half the cases [12].

Biochemistry. The patients with achalasia, pre- and postpneumatic dilatation, showed a supersensitivity to exogenous intravenous gastrin as compared with normal" [13]. Suppression of gastrin release by acidification of the antrum with hydrochloric acid reduced the pressure of LES, but less markedly in the normal subjects than in patients with achalasia, thus suggesting that these patients had more gastrin or were more sensitive [14]. To determine the pathogenesis of this finding, the LES was tested to a cholinesterase inhibitor, edrophonium chloride. Edrophonium chloride significantly increased the LES pressure both in normal subjects and in patients with achalasia. The preservation of this response in the presence of denervation supersensitivity suggested intact postganglionic cholinergic nerves and, thus, a preganglionic site of denervation in achalasia [15].

The effect of glucagon on the pressure inside the LES in conscious human subjects and anaesthetized dogs was investigated using the continuous withdrawal method. Glucagon causes a decrease in sphincteric resting pressure in both man and dog and antagonizes the pentagastrin-induced pressure increase of the LES. The elevated pressure in patients suffering from achalasia is significantly reduced by glucagon [16].

Lower esophageal sphincter response to infusion of graded doses (0.003--0.050 microgram kg-1min-1) of pentagastrin was evaluated in four antrectomies patients as well as in six healthy subjects and seven achalasia patients in whom inhibition of antral gastrin release was maintained by continuous acidification (HC1 0.1 N) and aspiration of gastric antrum. In normal subjects and in antrectomies patients doses of pentagastrin required for half-maximal gastric acid secretion (0.012 microgram kg-1min-1) produced statistically significant increases of LES pressure. In achalasia patients, the infusion of pentagastrin did not affect LES pressure. These data seem to indicate that gastrin plays, at least in some degree, a physiological role in the regulation of LES tone. Insensitivity of LES to pentagastrin in achalasia suggests that the raised sphincter pressure in this disorder cannot be attributed to gastrin [17].

Etiology and pathogenesis. Etiology and pathogenesis. Thus, EA is an acquired disease with the loss of argyrophilic cells in the muscular-intestinal plexus. The LES denervation leads to a paradoxical contraction of the sphincter instead of reflex relaxation in response to stretch or increase in intraluminal pressure in the ampulla. This is accompanied by a hypertrophy of the muscle of the sphincter region which will increase the obstructive element, although of course the

sphincter is not closed, and the food can still enter the stomach under gravity if the column is high enough. Some authors have described a vagal lesion in achalasia and if this is established, it implies that it is a process involving primary and secondary neurons. This would narrow the field of etiology to a system degeneration or viral infection. Some writers have described an inflammatory infiltration of the plexus which might make a virus the more likely cause [10]. Complement fixation tests were performed on sera from 18 patients with achalasia and 12 age- and sex-matched controls against several bacterial and viral agents to ascertain any association with previous infection or any evidence of an altered immune response. There was a statistically significant increase of antibody titer against measles virus in the sera of 21 patients with achalasia compared with age- and sex-matched controls and this was confirmed by hemagglutination inhibition [18]. Herpes simplex 1 virus, cytomegalovirus, and varicella zoster virus all attack the esophagus but rarely attack the remainder of the gut. A search for these viruses in the myenteric plexus of the esophagus, using DNA hybridization, showed positivity for varicella zoster DNA in 33% of biopsy specimens taken at the time of cardiomyotomy but all tissue samples from non-achalasia controls proved negative [19].

In parallel with scientific research, many articles appeared in the literature, written by medical practitioners, where the diagnosis of EA was established based on any sign resembling a typical symptom of achalasia. And although in each article a phrase was quoted about a rare disease, in fact, it was already talking about a real epidemic. Below are the radiographs of patients diagnosed with EA **(Figure 2).**

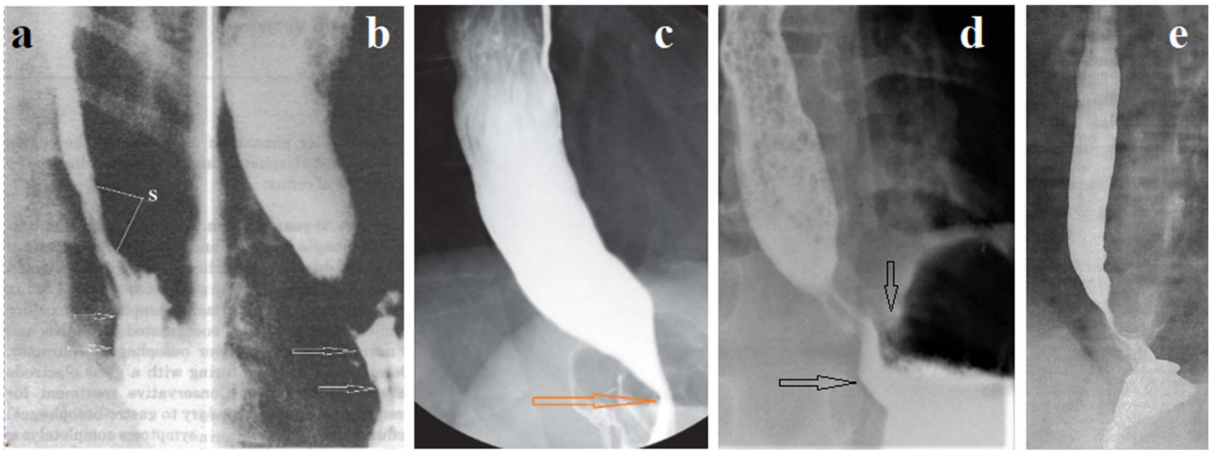

Figure 2. (a) In a patient with a gaping LES, i.e., with chalasia of the cardia (arrows), a sharp narrowing of the esophagus is visible, especially above the ampulla (s). **(b)** After 10 years, the lumen of this zone was sharply reduced, which led to the expansion of the proximal part of the esophagus. Conclusion: GERD

with esophageal contraction over the ampulla. **(c)** GERD with local narrowing in the LES. **(d)** The LES is short due to the opening of the intra-abdominal part of the LES (arrows). Good evacuation of barium from the esophagus to the stomach. Conclusion: GERD. **(e)** Narrow esophagus. A short LES is a typical GERD pattern in the horizontal position.

It is important to understand the reason why EA was diagnosed in these patients with GERD. Hypersecretion of hydrochloric acid, as the root cause of the disease, ultimately leads to reflux of aggressive gastric contents into the esophagus. The chemical effect causes an inflammatory process - esophagitis. Endoscopy allows the diagnosis of esophagitis only if there is hyperemia or erosion. It is a widely known scientific fact that esophagitis is diagnosed much more often on the basis of histological examination. The inflammatory process leads to two changes in the wall of the esophagus: a thickening of the wall and an increase in its tone. Different образцы of manometric study in patients with GERD depend on the length of the inflammatory process, as well as on the prevalence of wall hypertrophy or increased tone. So, for example, with eosinophilic esophagitis, wall thickening prevails. Thus, the absence of peristalsis and the increase in pressure are due to reflux-esophagitis.

Second, the same changes that occur in the esophagus are often seen in the LES. Its walls thicken, and its response to stimulation decreases.

Thirdly, the inflammatory process can lead to ulceration and stenosis, both in the esophagus and in the LES.

Fourth, from the point of view of etiology, pathophysiology, and pathogenesis, two diseases should be distinguished: as before a rare classical EA, which is treated only by dissection of the LES; and GERD for the treatment of which it is necessary to exclude the intake of a provocateur of the release of hydrochloric acid, the periodic use of drugs that suppress the release of hydrochloric acid and to observe a special diet. Moderate sometimes repeated stretching of the LES reduces symptoms and improves LES function. Stretching the pyloric sphincter improves gastric evacuation and reduces the load on the LES. To do this, I prescribe tablets with a diameter of 2 to 3 cm. Peristalsis pushes them through the sphincters and stretches them [20].

II. The second stage

It began with the release of an expensive manometric device, which is still being modernized. It was not ordered by physiologists but imposed by equipment manufacturers, who began to advertise their products among practitioners to expand sales.

In a typical article of practicing physicians, the authors reported "5 patients in whom confirmed gastro-oesophageal reflux, usually associated with hiatal hernia, progressed to typical achalasia, confirmed by radiology and manometry, after an interval of 2-10 years" [21].

An analysis of the radiographs presented in the article shows a typical picture of the reflux-esophagitis. Radiographs of one of them are shown in Figure 2.a,b, where the constriction is localized above the ampulla, i.e. significantly higher than LES. The survey results are described as follows: "A barium swallow showed a dilated oesophagus with no relaxation of the cardia. At endoscopy, there was no organic obstruction. Motility studies revealed no normal relaxation of the lower oesophageal sphincter on swallowing and complete lack of normal coordinated peristalsis. The diagnosis of achalasia having been confirmed" [21].

1) The authors described 5 patients with GERD, which was complicated by peptic constriction, and not always at the level of the LES. "Three of the 5 had a demonstrable hiatal hernia". If there is a so-called hiatal hernia, then the narrowing of the esophagus is not related to the LES, i.e. it is located in the lower part of the esophagus.

A). In the preface, the histological signs of classical EA are given in combination with manometric and radiological signs that do not correspond to the classical EA.

B). In at least 3 patients with a so-called hernia, the constriction was above the ampulla, i.e. had no relation to the LES.

C). The LES relaxes in response to the threshold pressure, generated above it. In patients with a wide esophagus, the bolus volume must be larger for threshold pressure to occur. At the same time, the threshold pressure, and therefore the opening of the LES also depends on the functioning of the proximal sphincter, which closes the ampoule. X-ray and manometric picture for GERD is the same as in patients with chronic constipation and megarectum. To increase the relaxation of the internal anal sphincter (rectoanal inhibitory reflex) in patients with megarectum, it is necessary to inflate a rectal balloon with a larger diameter than normal. At the same time, the depth of relaxation is less than normal, and it is not always easy to determine.

Thus, the examination of all patients with the same number of swallows is an error, and the results of such examination are not reliable.

D). The manometric study identifies areas of high pressure, but their mapping is erroneous, since they are based on false ideas about the shortening of the esophagus, sliding of the LES, and part of the stomach into the chest. As the

analysis of X-ray patterns combined with manometric examination [22,23] shows, the LES does not shift under any conditions. The upper zone of high pressure corresponds to the contraction of the proximal sphincter (PS) [24], **(Figure 4).**

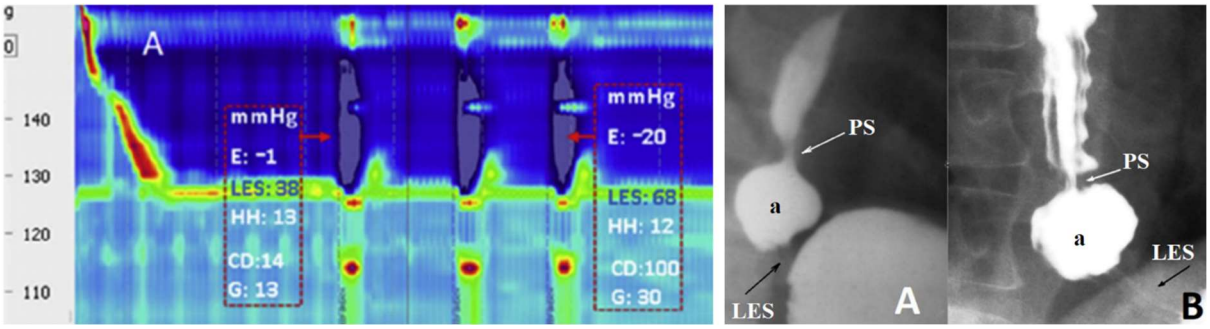

Figure 4. Manometric graph from the article of Mittal et al [25]. The two high-pressure zones (brown spots) do not have specific characteristics based on which anatomical affiliation could be accurately established. The length and extent of the upper zone are less than that of the lower one. A hiatus hernia (HH) is between them. Since there is no mixing of the LES, and what has considered HH is in fact the phrenic ampulla, the lower zone of high pressure is due to the contraction of the LES and the crural diaphragm (CD), and the upper zone is due to the contraction of the proximal sphincter (PS). (b) Radiographs of patients with GERD. (A) Child. (B) An elderly person. The designations are the same, [a] - ampulla.

In conclusion, the authors of the article came to the paradoxical conclusion that "It is suggested that the autonomic damage eventually leading to achalasia may in its initial phases cause gastro-oesophageal reflux" [21].

Even before the publication of the 1st Chicago classification, some optimists became believed that esophageal "manometry is the gold standard for the diagnosis of achalasia" [26]. To come to this conclusion, it was necessary to compare the results of manometry with the already known signs of EA: X-ray, clinical, histological and manometric when using an open catheter.

A) X-ray signs of EA, “diagnosed” by the new manometric apparatus (Figure 5.a), had nothing to do with the idea of idiopathic esophageal achalasia (Figure 5.b).

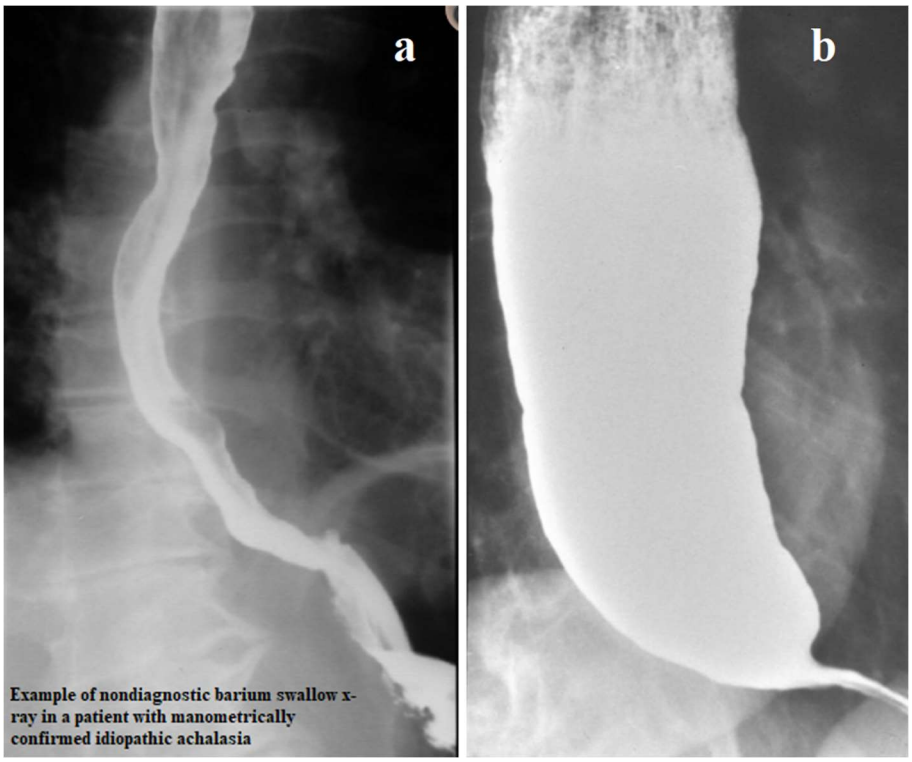

Figure 5. (a). From an article by El-Takli et al signed by the authors [26]. This X-ray does not show any of the signs of EA: the esophagus is not dilated, the LES is not contracted, evacuation to the stomach is not disturbed, and there is a large gas bubble in the stomach. In contrast, the esophagus is unevenly narrowed with irregular contours, which is strong evidence of esophagitis. **(b).** Typical picture of idiopathic achalasia.

El-Takli et al diagnosed idiopathic achalasia based on "the typical manometric features of achalasia, including complete aperistalsis and either absent or markedly impaired (less than 50%) swallow-induced LES relaxation" [26]. First, in this case complete aperistalsis of the esophagus is caused by esophagitis, which is expressed in the thickening of the esophageal wall and an increase in its tone. Secondly, the x-ray image shows swallow-induced LES relaxation, which indicates the low reliability of the manometric study. Thirdly, manometric symptoms are not only unreliable, but, in principle, are not a diagnosis.

This article, although it repeats numerous misconceptions of other authors, convincingly showed the absence of a correlation between manometric and radiological signs of EA. The purpose of this article is visible in the conclusion: «However, it is clear that classic x-ray features may not be present in some patients. Thus, to avoid misdiagnosing patients with a readily treatable disease, manometry should be performed in all patients with persisting esophageal-type dysphagia but negative endoscopy and radiological examinations» [26]. This is an advertisement for a manometric device and nothing more.

B). **All clinical symptoms** attributed to EA are characteristic of GERD, including those that are in principle impossible with EA. For example, heartburn was found in 52% of patients with EA [27]. For these patients, it is speculated that achalasia develops in the setting of underlying GORD [28]. From the physiology of EGJ, it is known that normally an increase in pressure in the stomach leads to an increase in the tone of the LES, which prevents reflux into the esophagus and cannot be accompanied by heartburn. With EA, the LES tone is increased and does not change in response to an increase in pressure in the stomach, which does not contribute to reflux. And only with GERD, an increase in pressure in the stomach leads to reflux and heartburn. Thus, an expanded understanding of EA is due to GERD and clinical symptoms cannot confirm the validity of a manometric study.

C) The denervation of LES in GERD, supposedly turning into EA, has not been confirmed, since practical doctors do not do such research.

D) Manometric studies with high-resolution instrumentation do not detect the EGJ reflexes that were established with open catheter manometry. This can be explained either by the fact that medical practitioners are not familiar with research from previous generations or by the fact that HRM does not have ability to identify these reflexes. It follows from this that an open catheter manometric study cannot confirm the validity of HRM.

Conclusion. The conclusion about the importance of HRM in the diagnosis of EA was made based on the general impression of a huge number of articles carried out without scientific evidence.

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