Gastroesophageal reflux disease is a lifelong problem

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A disease is a complex of pathological signs with a known cause (etiology), established physiological mechanisms of the onset of a disease under the influence of an etiological factor (pathophysiology) with the well-known process by which a disease develops (pathogenesis). The existing concept of gastroesophageal reflux disease (GERD), despite the large volume of publications, is confusing and contradictory, which negatively affects the pathophysiological treatment.

I. Definition.

Reflux symptoms are common, but there is a continuum of illness from infrequent heartburn through GERD to esophagitis and Barrett's esophagus. By convention, reflux symptoms become indicative of disease when they start to impair patients' health-related quality of life, or they are associated with demonstrable esophageal or extraesophageal lesions [1]. Patient surveys have shown that impairment of health-related quality of life begins with mild symptoms at least 1 day per week [2,3]. Based on these criteria, the prevalence of GERD in Western countries has been estimated to be 10-20% [4].

Symptoms considered to be related to GERD, are principally heartburn and regurgitation [5,6,7].

1. The above definition of GERD, which is the result of the Montreal consensus, is misleading by doctors and researchers. First, because consensus is not the result of scientific research, but the push of an idea by a more active group of doctors. Secondly, as the graph of the initial registration of the diagnosis of GERD shows, the peak occurs in old age (**Figure 1**) [1].

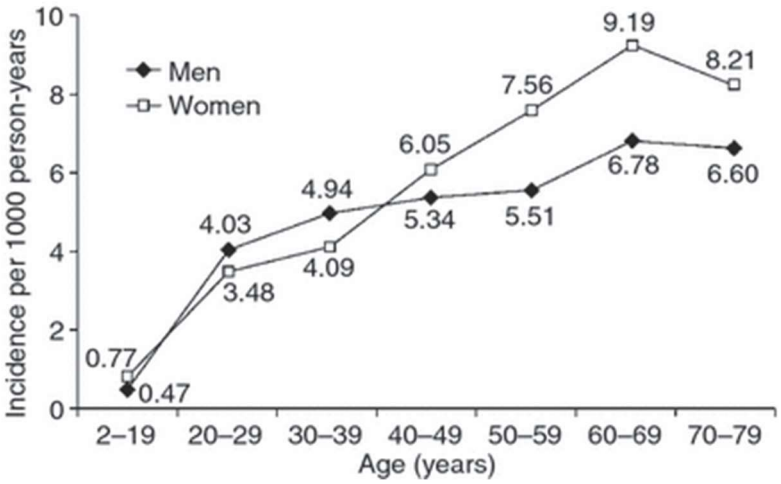

Figure 1. Incidence of gastro-esophageal reflux disease diagnosis in UK general practice (reproduced, with permission from Blackwell Publishing Ltd.).

Was it possible that these patients had GERD for the first time in old age? "These studies showed that a prior diagnosis of asthma, COPD, irritable bowel syndrome (IBS), ischaemic heart disease, peptic ulcer disease, chest pain, dyspepsia or abdominal pain was associated with a significant increase in the risk of the first diagnosis of GERD " [1]. In other words, these patients consulted doctors for a long time with symptoms of GERD, but the severity of their condition and symptoms did not meet the criteria of the Montreal consensus. The diagnosis of GERD was made very late with the presence of severe esophagitis, peptic ulcer, stenosis, or Barrett's esophagus. Thirdly, all the above-listed diseases and symptoms may be the only signs of GERD, i.e., without heartburn and regurgitation.

2. All theoretical constructs and diagnostic methods are based on the misconception that individuals who do not have the typical symptoms of GERD and who do not take drugs that suppress the secretion of hydrochloric acid do not have reflux disease. Here is an example of selection criteria for control (healthy) individuals. "Healthy controls were sought from among medical staff and patients. Exclusion criteria were prior upper gastrointestinal surgery, prior or current upper gastrointestinal or respiratory disease or symptoms, prior or current use of medications which might affect gastric acidity or motility" [9]. Several studies have shown that in GERD the total LES length reduces by shortening of its abdominal portion [10, 11,12]. In the article by Marshall et al, the authors do not comment on why the LES length in the control group is reliably shorter than in patients with GERD [9]. The only possible explanation is that the controls included patients with GERD.

This conclusion is supported by a study of healthy volunteers. So, for example, with a screening gastroscopy examination of 6,683 healthy Koreans, 14.66% had GERD diagnosed [13]. In another study, eight subjects (14%) from 57 healthy 'asymptomatic volunteers claimed intermittent reflux symptoms at the computer

interview, but they did not have more acid reflux at pH-monitoring than asymptomatic volunteers. Thirteen subjects (23%) had abnormalities at endoscopy, 3 of whom had erosion in the distal esophagus, and 12 had hiatus hernia. Subjects with hiatus hernia had increased acid reflux at 24-h pH-monitoring compared with those without hernia [14].

Approximately 30% of healthy volunteers show dilated intercellular spaces in the esophageal epithelium suggesting a functionally reduced epithelial integrity. Pauwels et al found in «a subgroup of healthy volunteers a low epithelial integrity in the distal esophagus probably due to the increased presence of physiological acid reflux" [15].

Thus, disregard for fundamental scientific methodological principles has led modern gastroenterology to chaos, as the erroneous selection of control persons has led to the following false conclusions:

A) The normal range for prolonged pH-metry leads to the erroneous exclusion of GERD in a significant percentage of patients with reflux disease, making this study meaningless.

B) From point (A) it follows that what is commonly called a hiatal hernia is not a cause, but a consequence of GERD. This means that this picture in 100% of cases indicates severe GERD.

C) Recurrent reflux of gastric contents into the esophagus and also the so-called transient lower esophageal sphincter relaxation (TLESR) are symptoms of GERD. Reflux with low epithelial integrity in the distal esophagus cannot be physiological.

Conclusion (Part I. Definition). The sooner GERD is diagnosed, and pathophysiological treatment is started, the more chances are to prevent severe complications that worsen the quality of life. This is the law of medical science, and the Montreal consensus definition contradicts it. Two methods of histological examination of the esophagus allow an accurate diagnosis in time. (a) Definition of cardiac metaplasia of the squamous epithelium due to exposure to gastric juice, that results in cephalad movement of the squamocolumnar junction [15]. (b) Definition of Dilated Intercellular Spaces [16]. A positive characteristic of this method should be considered the conclusion from the article by Kia et al "DIS is not specific to acid-induced injury, as it can also be seen with weakly acidic refluxate" [17]. This conclusion confirms that the pH-metry is not an accurate method, as it does not diagnose weakly acidic reflux.

II. Etiology

All authors reiterate that «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 hiatal hernia, low lower esophageal sphincter pressure, transient lower esophageal sphincter relaxation, the acid pocket, obesity, increased distensibility of the esophageal junction, prolonged esophageal clearance, and delayed gastric emptying" [18].

"Gastroesophageal reflux disease (GERD) may also be promoted by associated motility disturbances. Primary motility disorders consist of achalasia, diffuse esophageal spasm (DES), "nutcracker esophagus," hypertensive lower esophageal sphincter, and nonspecific esophageal motility dysfunction (NEMD)" [19]. Obviously, the above factors in different associations are found in GERD. If they are provocateurs, i.e., cause reflux disease, the question arises: what caused their appearance? The question of the etiological factor is not raised.

1. Hydrochloric acid is a cause of GERD

It is known that hydrochloric acid, penetrating from the stomach into the esophagus, causes irritation and inflammation. Chandrasoma and DeMeester shows the beginning of this process. Under the influence of gastric juice, which in the early stages penetrates only the abdominal part of the LES, cardiac metaplasia of the squamous epithelium occurs. This creates the squamo-oxyntic gap and the dilated distal esophagus, which is distal to the endoscopic gastroesophageal junction (GEJ). Gradually the squamo-oxyntic gap increases in length, concordant with the amount of shortening of the LES, which becomes increasingly incompetent [16]. Similar results were obtained by Csendes et al, who assessed esophageal body length indirectly by endoscopic measurement of the position of the distal LES. They found no change in LES position with increasing reflux disease, although they did observe proximal migration of the squamocolumnar junction [20]. These results also correspond to manometric studies with an open catheter, which showed that in GERD, the LES is shortened by opening the abdominal part of the LES [10,21]. X-ray studies are also consistent with this mechanism of exposure to hydrochloric acid **(Figure 2)** [22].

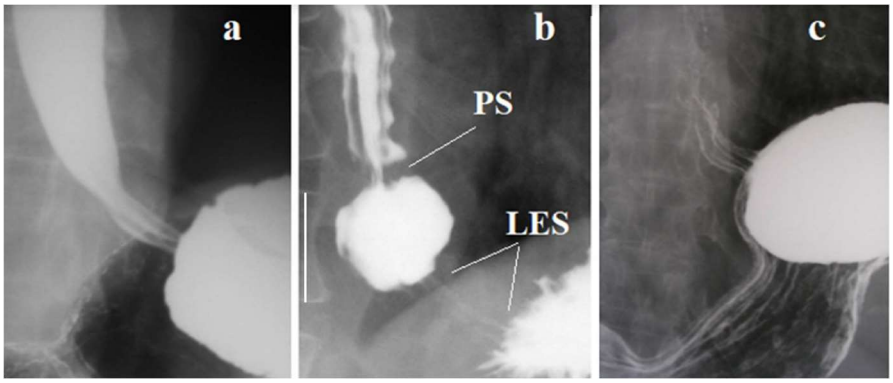

Figure 2. The EGJ radiographs of patients with GERD during abdominal compression. **(a)** Longitudinal folds in the zone of LES contraction between the esophagus and the stomach indicate an inflammatory process. **(b)** Reflex contraction of the LES in response to increased pressure in the stomach. Its length (1.7 cm) is 2 times shorter than the normal LES (3.4-4.0 cm). This is the result of the opening of the abdominal part of the LES. Longitudinal folds are visible both at the level of the LES and proximal to the phrenic ampulla. Different forms of folds are due to different pressures. **(c)** After the intake of barium, its traces were preserved in the longitudinal folds of the LES. PS - proximal sphincter. It is a functional sphincter that arises in the last peristaltic wave to create high pressure in the phrenic ampulla to open the LES and evacuate the bolus from the esophagus to the stomach.

These studies prove that GERD begins with damage to the LES by hydrochloric acid, which leads to its shortening since the damaged abdominal part of the LES opens and ceases to perform an antireflux function. Two widely believed fundamental errors prevent timely diagnosis of GERD. "These are the belief that cardiac epithelium normally lines the proximal stomach (1) and that the gastroesophageal junction (GOJ) is defined by the proximal limit of rugal folds (2)" [16]. The above evidence is neither verified nor refuted. They are ignored because they refute all the invented constructions of the pathophysiology of GERD. So, for example, from these studies, it follows that LES in GERD does not change its position, and therefore the stomach does not penetrate the chest. And what is called a hiatal hernia is a phrenic ampulla, regardless of its size.

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

Why does only approximately in 20% of the US population develop symptoms of GERD?

A) Hypersecretion of hydrochloric acid is a property of the body of patients with GERD that distinguishes these 20% of the population in Western countries from the rest 80%. For example, of 150 patients with symptoms suggestive of gastroesophageal reflux disease in 22 (15%) had gastric acid hypersecretion [basal acid output level > 5 mmol/h (19 patients) or maximum acid output level > 30 mmol/h (13 patients)]. They were compared to 25 consecutive patients with normal gastric acid secretion. The authors conclude that patients with gastric acid hypersecretion have more acid reflux, esophagitis, and cervical dysphagia [23].

B) Differential diagnosis between hypersecretion of hydrochloric acid in GERD and in Zollinger-Ellison disease (gastrinoma) consists in the detection of hypergastrinemia in Zollinger-Ellison disease on fasting examination and after temporary cessation of PPI intake (PPI use leads to hypergastrinemia in up to 80-100% of normal subjects as well as patients with idiopathic GERD or PUD due

to the hypo-/achlorhydria induced by its long-term use) [24]. It follows from this that, unlike Zollinger-Ellison disease, in which hypergastrinemia does not depend on food intake, in GERD there is a factor in food that causes hypergastrinemia, which leads to temporary hypersecretion of hydrochloric acid. Thus, in a disposable study of patients with GERD, the secretion of hydrochloric acid may be normal if the patient did not eat an ingredient that stimulates hypersecretion. C) Our studies have shown that in all cases of severe GERD there was a genetically determined lactose intolerance. Most patients over the age of 60 were aware that milk sharply exacerbates their reflux symptoms. Those patients who did not suspect anything, drank milk after a long period of refusal of it. This provocation caused heartburn and/or abdominal pain. We do not exclude that there may be other provocateurs of hydrochloric acid hypersecretion. But only in one case was histamine intolerance found, which does not exclude lactose intolerance, since the patient's mother and aunt suffered from severe complications from GERD and lactose intolerance.

D) In many people with GERD, the disease begins soon after birth as infantile colic.

(a) In those cases where this could be established, it turned out that our patients were restless babies. Kanabar et al showed that "pre-incubation of the feed with lactase resulted in breath hydrogen levels and total crying time which were both at least 45% lower than figures with placebo treatment, in 26% of the full trial group with infant colic. The remainder did not respond to the same extent" [25].

(b) The review of Hjern and al showed moderately strong evidence that the administration of Lactobacillus reuteri DSM 17938 can shorten the crying duration in infants with infantile colic. However, no effect of effect of Lactobacillus reuteri DSM 17938 on infants with colic in Australia [26]. Meanwhile, it is known that Lactobacillus converts lactose in the milk to lactic acid, converting the milk into curd. This method of treatment of the infantile colic cannot be effective, since the transformation process takes a long time, while a painful reaction in patients with lactose intolerance occurs 15-30 minutes after taking milk.

c) In infants' colic, the resting pressure of the LES was 0.1-6.7 (2.7+/-0.2 mm Hg). It was less than in control group ($p<0.001$). In 11 of 12 cases the LES pressure was decreased at least in one of three air inflations into the stomach. After inflation of an air into the stomach the pressure in the stomach was higher than the LES pressure in all patients [27].

d) Heine et al found pathological GERD in 18% of patients with persistent crying. Pathological GERD was defined as a fractional reflux time > 10% (with an esophageal pH of less than 4). Pathological GERD was more common in infants under 3 months [28]. This figure is significantly less than the true state since the normal limit described in the study by Vandenplas et al [29] is erroneous. The reflux time <10% (9% and even 3%) cannot be the norm, because, firstly, contrary to common sense. Second, as shown above, the selection of control individuals was based only on the absence of symptoms of GERD.

e) A study by Loots et al showed that proton-pump inhibitors with left lateral position was most effective in reducing GER episodes and esophageal acid exposure [31]. However, although PPl significantly reduced esophageal acid exposure, it does not affect the infant's irritability. Therefore, some authors do not support the use of PPI to decrease infant crying and irritability [32,33].

f) X-ray examination of patients with infantile colic determines the failure of the EGJ (**Figure 3)** [27].

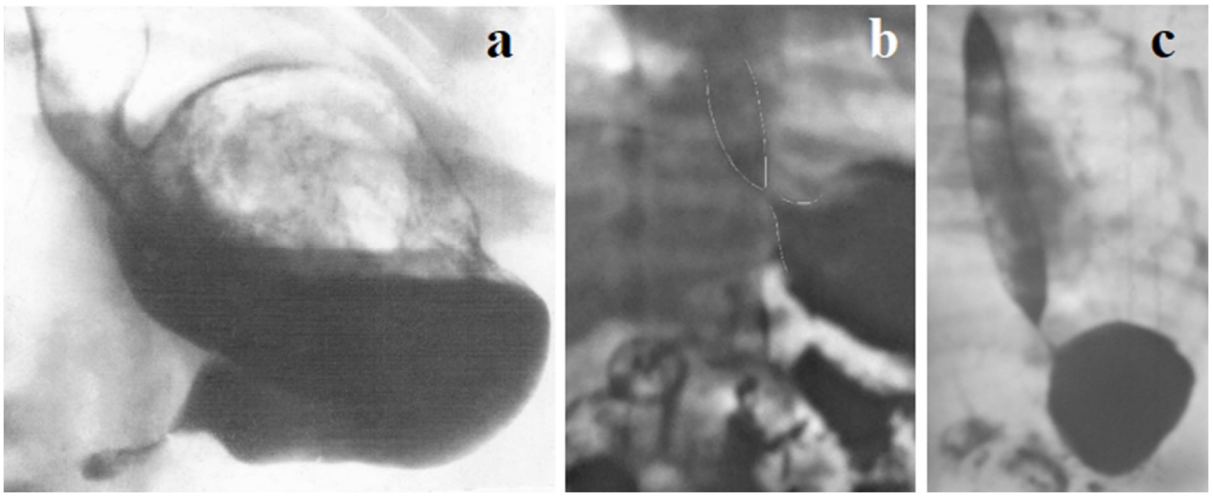

Figure 3. The radiographs of the EGJ of restless babies with x-ray evidence of GERD. **(a)** Liquid level in the stomach above the barium level and level in the esophagus. The LES opened but the body of the stomach is not expanded, and the contracted antrum is located below the gastric body, which excludes pyloric stenosis. **(b)** The abdominal part of the LES is opened and reflux into the esophagus is visible. **(c)** In a horizontal position, abdominal compression caused the LES to contract. There is no peristalsis in the esophagus between the upper and lower sphincters.

g) According to Søndergaard et al, the cumulated incidence of infantile colic was 10.9%. Low birth weight babies (< 2500 g) had more than twice the risk of infantile colic [34]. Meanwhile, GERD is more common in infants with a history of prematurity due to the failure (immaturity) of the LES [35].

As shown above (a-g), infant colic is a serious condition. Hypersecretion of hydrochloric acid caused by lactose intolerance leads to reflux of aggressive gastric juice into the esophagus and causes damage to LES function.

III. Pathological physiology of GERD

1. Pathological physiology of GERD in infants.

A baby is born with a small stomach. For normal development, he must consume a large amount of milk. When the baby begins to suck greedily the stomach is stretched, and the baby regurgitates excess milk. Since milk does not need to be treated with hydrochloric acid, hydrochloric acid normally is not excreted during breastfeeding and regurgitation of a large volume of gastric contents does not cause pain and harm to the child. With hypersecretion of hydrochloric acid, the ingress of aggressive contents into the esophagus causes severe pain and gradually leads to dysfunction of the LES and the esophagus. The baby calms down by 4 months, because by this time the volume of feeding corresponds to the volume of the stomach, i.e., no excess food and no regurgitation.

2. Throughout the person's life, two problems remain: (a) lactose intolerance and impaired EGJ function. The duration of the asymptomatic interval depends on the degree of damage to the antirelux function of the EGJ, the amount of lactase produced, and the amount of lactose consumed.

Figure 1 shows only episodes of the disease that worsened of health-related quality of life. They forced doctors to use different examination methods to diagnose GERD. These included recurrent pneumonia and recurrent vomiting in children, persistent heartburn, bronchospasm, noncardiac chest pain, and unexplained abdominal pain. However, patients over the age of 40 who were first diagnosed with GERD, in previous years had of health problems that were not promptly diagnosed as GERD. In children in their early years of life, pain caused by reflux wakes them up at night, and children fall asleep after drinking, as the liquid flushes acid from the esophagus. Anemia in such cases is common. Chronic cough or asthma caused by reflux is often treated symptomatically. Abdominal pain, gastritis, duodenitis, gastric ulcer, cholelithiasis and irritable bowel syndrome, which, like GERD, are caused by hydrochloric acid hypersecretion, precede the diagnosis of severe damage to the esophagus and EGJ.

The sharp increase in the number of patients with GERD in the second half of life is explained by two factors. First, in the LES and in the esophagus, the pathological process progresses with age, despite the "low-symptom" course of the disease. Secondly, the older the patient is, the less amount of lactose provokes hypersecretion of hydrochloric acid. In some patients over 70 years old, yogurt

or a sandwich with butter provoked severe heartburn. This phenomenon can be explained by the fact that GERD in the elderly is always combined with duodenitis. It is likely that the inflammatory process in the duodenum damages the cells that produce lactase.

It should be noted that patients rarely associate the onset of GERD symptoms with dairy products. This is due to two reasons. First, some sufferers drink milk to relieve heartburn. The effect of milk is since it has an alkaline pH and therefore neutralizes acid. Lactase causes hypersecretion hydrochloric acid after a sometime after eating. Therefore, the patient does not associate the aggravation with milk intake. Secondly, there is no scientific evidence in the literature on the effect of lactose on the pathogenesis of GERD. An example would be the case histories of two doctors from the same family (**Figure 4**).

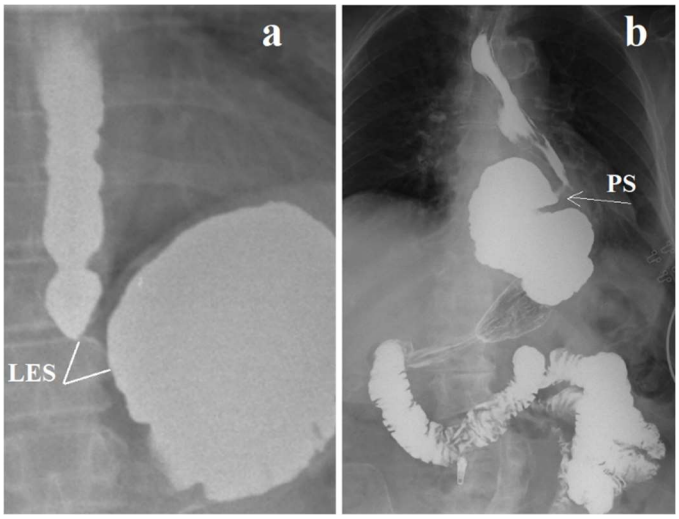

Figure 4. X-ray examination of EGJ. **(a)** Study with high pressure in the stomach (during lifting of straightened legs after ingestion of 200 ml of barium). The high pressure in the stomach caused a reflexive contraction of the LES. Its length is 1.4 cm (norm 3.4-4.0 cm). The width of the esophagus in the lower part is 1.8 cm, and in the middle part it is 2.4 (the normal maximal limit is 1.5 cm). The walls of the esophagus are uneven, indicating esophagitis. Reflux index - the ratio of the width of the esophagus to the length of the LES is 1.3. Normal RI <1. Conclusion: GERD, esophagitis. **(b).** X-ray of another patient 5 minutes after high pressure was created. S-shaped esophagus after a failed Nissen fundoplication. Sharp expansion of the esophagus below the proximal sphincter (PS). Conclusion: Severe GERD with gaping EGJ. The sigmoid esophagus.

Figure 4a shows a radiograph of a 53-year-old woman. For many years, she has had often abdominal pain with recurrent heartburn. After multiple endoscopies, helicobacter pylori eradication, removal of the polyp from the stomach, the condition did not improve. About 10 years ago, she stopped drinking milk because it was causing her condition to deteriorate, but she continued to consume dairy products. PPI 40 mg twice daily had no significant effect. The condition

improved dramatically on a lactose-free diet, except for cheeses. The patient is currently taking PPI 20 mg once a day and has no symptoms.

Figure 4b shows a radiograph of her 83-year-old mother. After the Nissen fundoplication, an S-shaped esophagus developed. She took a PPI of 40 mg twice a day but was constantly bothered by abdominal pain and heartburn. During heartburn, she drank a glass of milk, which triggered instant relief. After stopping the use of foods containing lactose, there was a dramatic relief, which allowed the PPI dose to be reduced to 20 mg per day.

Pathological physiology of GERD. (Conclusion). Hypersecretion of hydrochloric acid is an etiological factor in the development of GERD. It is triggered by lactose in people with genetically determined lactose intolerance. In most cases, the disease begins in the first weeks of life in the form of infant colic, the symptoms of which disappear at about 4 months of age. The frequency of manifestation and the severity of the development of this chronic progressive disease depends on the degree of damage to the LES and the esophagus during infant colic. In most cases, clinical presentation of GERD becomes severe after the age of 40.

IV. Pathogenesis

Most studies in humans have shown that the healing or amelioration of esophagitis does not result in increased LES tone or pressure of the esophagus [36,37]. This factor of pathogenesis, firstly, explains the absence of symptoms of GERD, despite impaired function of the LES and esophagus. Secondly, this suggests that each exacerbation of esophagitis leaves behind irreversible changes in the LES and esophagus, which defines GERD as a chronic, recurrent, progressive disease. These facts were known long before the Montreal consensus, the decision of which is contrary to this scientific evidence.

The mantra that many authors have cited about pathophysiology, which is "complex and multi-factorial", is surprising in its lack of evidence and common sense. Because if these factors (listed below), which supposedly cause or aggravate GERD, they too must have arisen for some reason. It is surprising that this topic is not discussed in the literature.

1. Decreased of the LES resting pressure and shortening of its length is not the cause of GERD, but the result of exposure to hydrochloric acid.

2. The extension of the esophagus above the LES, called the phrenic ampulla, is caused by the action of hydrochloric acid, which irritates and inflames the esophageal wall, and as a result reduces the force of contraction of the last

peristaltic wave. Gradually, the ampulla increases in size, which is unreasonably called a hiatal hernia.

a) The esophagus is not shortened. The LES shortened by opening of its abdominal part.

b) Exposure to hydrochloric acid causes inflammation of its wall, which leads to the formation of longitudinal folds. These folds are not related to the stomach. It follows from this that the LES does not change its position under any physiological and pathological conditions.

c) Oral displacement of the cardiac epithelium is due to hydrochloric acid exposure and not by displacement of the LES [16].

3) A stretched and weak ampulla of the esophagus cannot create high enough pressure to open the LES and push the food bolus into the stomach, where the pressure is greater than in the esophagus. A functional sphincter (proximal sphincter) appears cranial to the ampulla. Its contraction allows creating in the ampulla high pressure. It also contracted during reflux, preventing the passage of acid cranially.

4) The increased number of transient lower esophageal sphincter relaxations is due to the weakness of the LES. If in healthy individuals an increase in pressure in the stomach causes an increase in the tone of the LES, in GERD, an increase in the gastric pressure causes a relaxation of the LES [38].

5) The article by Kahrilas et al talks about discovery of the “acid pocket”, an area of unbuffered gastric acid that accumulates in the proximal stomach after meals and serves as the reservoir for acid reflux in healthy individuals and gastroesophageal reflux disease (GERD) patients. "The nadir esophageal pH of reflux observed during pH monitoring in the postprandial period is often more acidic than the concomitant intragastric pH "[39]. The findings of this article are based on misconceptions about the normal physiology of EGJ and pathological physiology of the GERD.

a) It is known that the stomach works as an effective mixer due to the activity of the musculature. Therefore, there can be no difference in acidity in its different departments. The difference in acidity indicates that the contents with different acidity are in two different separate cavities.

b) The schematic, overlaid on the scintigraphy image, does not match the original image. On the scintigraphy, between the stomach and the phrenic ampulla, a contracted LES (marked by me) is visible, in the folds of which radioactive material was retained. (**Figure 5 a)**.

c) Based on two erroneous dogmas, the authors call the phrenic ampulla a hiatus hernia. First, the proximal end of the longitudinal folds is the proximal, not the distal end of the LES. Secondly, the oral movement of the cardiac epithelium is because of hydrochloric acid, and not the movement of the LES. In fact, the authors describe a well-known symptom of the pathogenesis of GERD - impairing esophageal clearance, which is due to the weakness of the ampulla contraction. The wider the ampoule, the more acid is retained in it after reflux. For the same reason, the food remains in the ampulla after eating, the decay of which causes the symptom of putrid breath. (**Figure 5b, c)**.

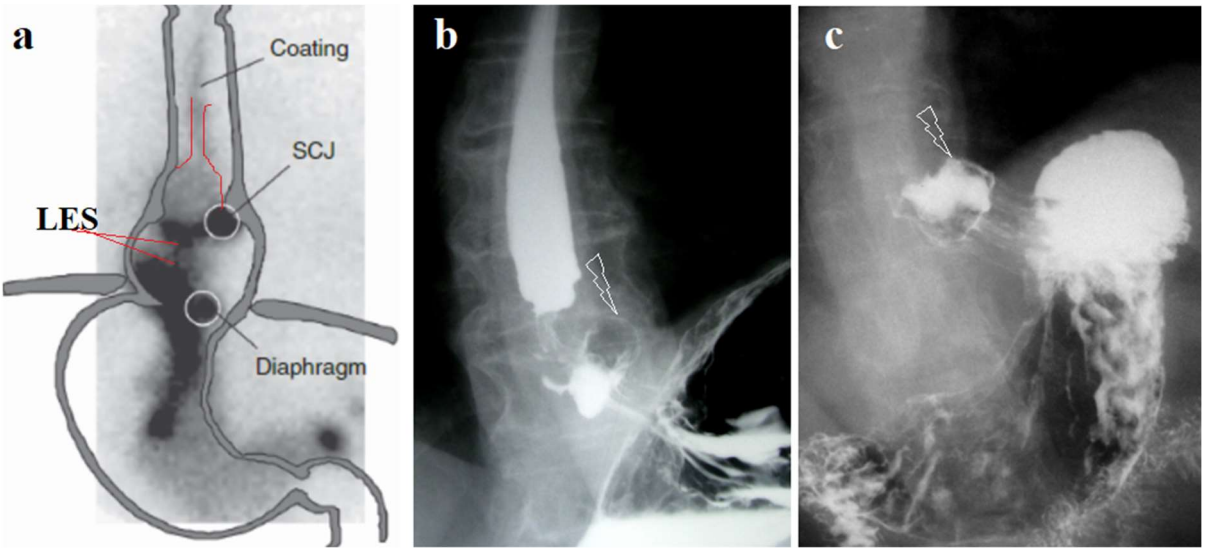

Figure 5. The various studies of the EGJ. (a) Scintigraphy image from Kahrilas et al [39]. The diagram is drawn at random. The scintigraphy clearly shows the stomach and the ampulla of the esophagus. A narrow isthmus is visible between them, where a radioisotope is stuck in the folds of the LES (my correction in red). (b) Barium remained in the ampulla after contraction. (c) Barium stayed in the phrenic ampulla above the sharply shortened LES (≈2 cm long). The longitudinal folds are visible in the LES because of its contraction.

Thus, firstly, the so-called “acid pocket” symptom is the well-known “impairing esophageal clearance” symptom. Secondly, it becomes apparent that we are talking about two chambers separated from each other by the contraction of the LES, which is further confirmation that the stomach does not penetrate the chest. What is commonly called a hiatal hernia is a wide phrenic ampulla.

6) Delayed gastric emptying is due to the hypersecretion of hydrochloric acid. GERD is only one of the clinical manifestations of HCl hypersecretion. For example, it is known that patients owe their ulcer to gastric hypersecretion of hydrochloric acid [40]. That is why it is sometimes impossible to differentiate what is the source of abdominal pain: esophagitis or duodenitis. It can be assumed

that the pain reaction and heartburn in the elderly occur in response to the intake of a scanty amount of lactose because, because of damage to the mucous membrane by hydrochloric acid, the formation of lactase gradually decreases with age. “The overproduction of acid and the associated illnesses linked to hypersecretion have a lifetime prevalence of 25-35% in the United States” [41]. Figure 6 shows a diagram of the pathogenesis of GERD.

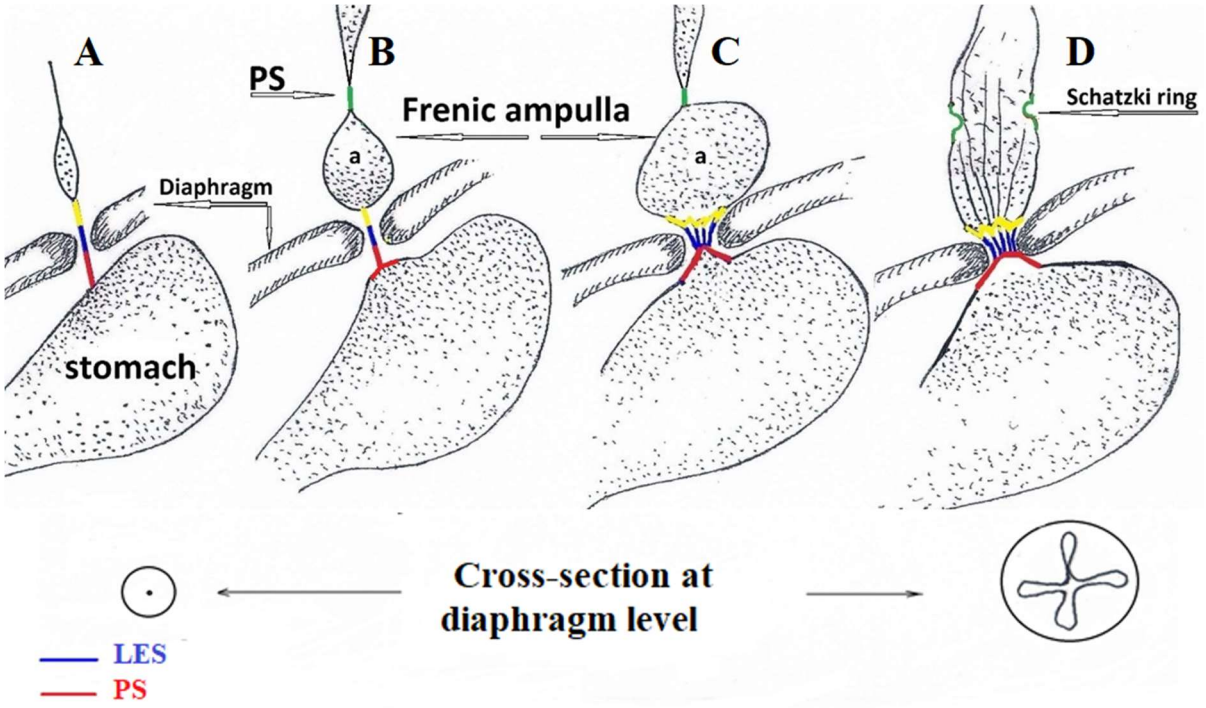

Figure 6. A diagram of the change of GEJ in the process of GERD pathogenesis. (A). The normal EGJ. The esophagus is not dilated, and the length of the LES is in the normal range. (B). The initial stage of GERD. During the abdominal compression, there was a short-term contraction of the LES and a phrenic ampulla appeared. 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). The LES is very short without provocation test. The proximal sphincter is not functioning. In its place, a rigid fibrous ring appears (Schatzki ring). Symptoms of severe esophagitis.

Discussion

As a result of repeated pressure on the participants in the discussion, 90% of them came to a consensus that GERD is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications [42].

In the discussion, as a result of repeated pressure on the participants, 90% of them came to a consensus that GERD is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications [42].

As can be seen from the present study, GERD in most cases begins in infancy and progresses with age. It has several features. First, at different periods of life, it can occur with different clinical manifestations (infant colic, restless sleep, anemia, bronchospasm, non-cardiac chest pain, abdominal pain of different localization, etc., and only in some cases with so-called typical symptoms - with heartburn and regurgitation). Secondly, the disease can proceed with long (many years) periods without obvious clinical manifestations. Therefore, in most cases, patients with GERD undergo a detailed examination only at the age of over 40 years with "troublesome symptoms and/or complications", when a third of patients with conventional PPI treatment is not effective [43]. Thus, the definition of GERD adopted by the Montreal consensus leads to late diagnosis and delayed treatment.

All decisions made by voting have no scientific basis. Not only the Montreal consensus, but also the Rome foundation, and the Lyon consensus, and the Chicago classification [44] are not scientific achievements and should not be used in medical practice. As you can see from the Montreal definition of GERD, this can be dangerous for patients. I did not find a single article of those scholars (10%) who disagreed with the definition of GERD during consensus-pushing. I realized that their works do not accept journals because they do not conform to consensus. It's like the medieval dictatorship of the Jesuits!

Obviously, based on non-scientific assumptions, it is impossible to create something scientific, and therefore useful. Katzka et al merge the three major consensuses (the Montreal Consensus, The Rome Foundation, and the Lyon Consensus), developing the concept that what has come to be known as GERD is actually a family of syndromes with a complex matrix of contributing pathophysiology. They state without proof, "it is becoming clear that many presentations of GERD represent distinct phenotypes with unique predisposing cofactors and pathophysiology outside of this paradigm" [41].

A phenotype is the set of observable characteristics or traits of an organism. Phenotype (clinical medicine), the presentation of a disease. The phenotype implies persistent characteristics of the disease that distinguish one disease from another. In the article by Katzka et al «Reflux chest pain syndrome" and "Barrett's esophagus" are treated as different phenotypes. However, first, many patients with Barrett's esophagus complain of heartburn and/or chest pain. Secondly, all

patients at some stage in the development of the disease suffered from pain in the chest. Obviously, we are not talking about phenotypes, but about different stages of pathogenesis.

I first drew attention to the relationship of GERD with hypersecretion of hydrochloric acid caused by lactose intolerance. This connection is not in doubt, since we are talking about complete coincidence, judging by the significant and immediate improvement in 100% of patients who switched to a lactose-free diet. Since different patients have different amounts of lactose provoking symptoms of GERD, treatment should begin with the exclusion of all products made from milk (butter, yogurt, cheese, etc.). After a significant improvement in symptoms, cheese, butter, etc., can be gradually added to determine the level of lactose tolerance. Every practitioner can easily verify the correctness of my statement.

Conclusion

1. **Etiology.** GERD is a chronic, recurrent, progressive disease that in many cases begins in infancy because of lactose intolerance.

2. **Pathological physiology.** Lactose, which has not undergone hydrolysis, causes hypersecretion of hydrochloric acid, which, penetrating the abdominal part of the LES, causes inflammation and reduces its tone. Gradually, the opening of the abdominal part of the LES occurs, which weakens its antireflux function and leads to reflux into the esophagus.

3. **Pathogenesis.** The weakness of the LES leads to the periodic penetration of aggressive gastric contents into the esophagus, causing inflammation and expansion, mainly of the supraphrenic esophagus (phrenic ampulla). In the cranial part of the ampulla, a functional (proximal) sphincter (PS) arises, the contraction of which allows the ampulla to create pressure to open the LES and inject a bolus into the stomach. Contraction of the PS during reflux prevents chyme from flowing into the proximal esophagus. Over time, the ampulla increases in size and the PS does not close the esophageal lumen. The PS gradually turns into a rigid ring of different diameters. At this stage, the chyme penetrates the proximal esophagus and can damage the function of the upper esophageal sphincter, resulting in extraesophageal symptoms (bronchospasm, chronic laryngitis, bronchitis, etc.). If the ampoule is large, then the force of contraction of it is weakened. Therefore, after each reflux episode, an acid bolus is retained in it, which at different periods of life can cause erosion, ulcers, and Barrett's esophagus. When PS ceases to function, the inflammatory process and complications are observed throughout the esophagus.

4. GERD is one of several manifestations of hydrochloric acid hypersecretion. Therefore, with gallstone disease, duodenitis, gastritis, and ulcers, there is inevitably GERD. If there are symptoms of GERD, then the likelihood that the stomach, duodenum, and gallbladder are simultaneously affected increases with age.

5. **Diagnosis of the GERD.** Since the normal range for pH-metry was developed based on an erroneous selection of control individuals, this technique diagnoses GERD only in severe cases. Therefore, pH-metry is not only meaningless but also dangerous, since the diagnosis is not confirmed in a significant number of patients with GERD. Initial diagnosis and initiation of treatment should be based on clinical symptoms. In doubtful and severe cases and in those cases when the treatment is not effective, an endoscopic examination with obligatory histology at the level of the LES, the ampulla of the esophagus, and in the proximal esophagus is necessary. X-ray examination can be useful in primary diagnosis, as the most simple и accessible method.

References

1. El-Serag H, Hill C, Jones R. Systematic review: the epidemiology of gastro-oesophageal reflux disease in primary care, using the UK General Practice Research Database. Aliment Pharmacol Ther. 2009 Mar 1;29(5):470-80. doi: 10.1111/j.1365-2036.2008.03901.x.
2. Wiklund I, Carlsson J, Vakil N. Gastroesophageal reflux symptoms and well-being in a random sample of the general population of a Swedish community. Am J Gastroenterol. 2006 Jan;101(1):18-28. doi: 10.1111/j.1572-0241.2005.00343.x.
3. Ronkainen J, Aro P, Storskrubb T, et al. Gastro-oesophageal reflux symptoms and health-related quality of life in the adult general population--the Kalixanda study. Aliment Pharmacol Ther. 2006 Jun 15;23(12):1725-33. doi: 10.1111/j.1365-2036.2006.02952.x.
4. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005 May;54(5):710-7. doi: 10.1136/gut.2004.051821.
5. De Giorgi F, Palmiero M, Esposito I, et al.Pathophysiology of gastro-oesophageal reflux disease. Acta Otorhinolaryngol Ital. 2006 Oct;26(5):241-6.
6. Boeckxstaens GE. Review article: the pathophysiology of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2007 Jul 15;26(2):149-60. doi: 10.1111/j.1365-2036.2007.03372.x.

7. Clarrett DM, Hachem C. Gastroesophageal Reflux Disease (GERD).Mo Med. May-Jun 2018;115(3):214-218.
8. Armstrong D, Marshall JK, Chiba N, et al. Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults - update 2004. Can J Gastroenterol. 2005 Jan;19(1):15-35. doi: 10.1155/2005/836030.
9. Marshall RE, Anggiansah A, Anggiansah CL, et al. Esophageal body length, lower esophageal sphincter length, position and pressure in health and disease. Dis Esophagus. 1999;12(4):297-302. doi: 10.1046/j.1442-2050.1999.00060.x.
10. 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.
11. 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.
12. 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.
13. 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.
14. Stål P, Lindberg G, Ost A, et al. Gastroesophageal reflux in healthy subjects. Significance of endoscopic findings, histology, age, and sex. Scand J Gastroenterol. 1999 Feb;34(2):121-8. doi: 10.1080/00365529950172952.
15. Chandrasoma P, DeMeester T. 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.
16. Pauwels A, Broers C, Vanuytsel T, et al. A reduced esophageal epithelial integrity in a subgroup of healthy individuals increases with proton pump inhibitor therapy. United European Gastroenterol J. 2018 May;6(4):511-518. doi: 10.1177/2050640617749115.
17. Kia L, Pandolfino JE, Kahrilas PJ. Biomarkers of Reflux Disease.Clin Gastroenterol Hepatol. 2016 Jun;14(6):790-797. doi: 10.1016/j.cgh.2015.09.014.
18. Herregods TV, Bredenoord AJ, Smout AJ. Pathophysiology of gastroesophageal reflux disease: new understanding in a new era.

Neurogastroenterol Motil. 2015 Sep;27(9):1202-13. doi: 10.1111/nmo.12611.
19. Nelson JB, Castell DO. Esophageal motility disorders. Dis Mon. 1988 Jun;34(6):297-389. doi: 10.1016/0011-5029(88)90021-1.
20. Csendes A, Maluenda F, Braghetto I, Csendes P, Henriquez A, Quesada M S. Location of the lower esophageal sphincter and the squamous columnar mucosal junction in 109 healthy controls and 778 patients with different degrees of endoscopic oesophagitis. Gut. 1993 Jan;34(1):21-7. doi: 10.1136/gut.34.1.21.
21. Ackermann C, Rothenbühler JM, Martinoli S, Muller C. Esophageal manometry prior to and following anti-reflux surgery. Schweiz Med Wochenschr. 1991 May 25;121(21):797-800.
22. Levin MD, Korshun Z, Mendelson G. Pathological physiology of gastroesophageal reflux disease. Hypothesis (Review). Eksp Klin Gastroenterol. (Moscow) 2013; 5: 72-88.
23. Singh S, Hinder RA, R Naspetti R, et al. Cervical dysphagia is associated with gastric hyperacidity. J Clin Gastroenterol. 1993 Mar;16(2):98-102. doi: 10.1097/00004836-199303000-00004.
24. Ito T, Igarashi H, Uehara H, Jensen RT. Pharmacotherapy of Zollinger-Ellison syndrome. Expert Opin Pharmacother. 2013 Feb;14(3):307-21. doi: 10.1517/14656566.2013.767332.
25. Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. J Hum Nutr Diet. 2001 Oct;14(5):359-63. doi: 10.1046/j.1365-277x.2001.00304.x.
26. Hjern A, Lindblom K, Reuter A, Silfverdal SA. A systematic review of prevention and treatment of infantile colic.Acta Paediatr. 2020 Sep;109(9):1733-1744. doi: 10.1111/apa.15247.
27. Misharev OS, Troian VV, Levin MD, et al. Diagnosis and surgical treatment of gastroesophageal reflux in children. Vestn Khir Im I I Grek. 1989 Jun;142(6):71-6.
28. Heine RG[1], Jordan B, Lubitz L, et al. Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress. J Paediatr Child Health. 2006 Mar;42(3):134-9. doi: 10.1111/j.1440-1754.2006.00812.x.
29. Vandenplas Y[1], Goyvaerts H, Helven R, Sacre L. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. Pediatrics. 1991 Oct;88(4):834-40.
30. Vandenplas Y[1], Benninga M[2], Broekaert I[3], et al. Functional gastro-intestinal disorder algorithms focus on early recognition, parental

reassurance and nutritional strategies. Acta Paediatr. 2016 Mar;105(3):244-52. doi: 10.1111/apa.13270.
31. Loots C[1], Kritas S, van Wijk M, et al. Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. J Pediatr Gastroenterol Nutr. 2014 Aug;59(2):237-43. doi: 10.1097/MPG.0000000000000395.
32. Moore DJ[1], Tao BS, Lines DR, et al. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. J Pediatr. 2003 Aug;143(2):219-23.
33. 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. Epub 2014 Dec 30.
34. Søndergaard C, Skajaa E, Henriksen TB. Fetal growth and infantile colic. Arch Dis Child Fetal Neonatal Ed. 2000 Jul;83(1):F44-7. doi: 10.1136/fn.83.1.f44.
35. Lopez RN, Lemberg DA. Gastro-oesophageal reflux disease in infancy: a review based on international guidelines. Med J Aust. 2020 Jan;212(1):40-44. doi: 10.5694/mja2.50447.
36. Herregods TV, Bredenoord AJ, Smout AJ. Pathophysiology of gastroesophageal reflux disease: new understanding in a new era. Neurogastroenterol Motil. 2015 Sep;27(9):1202-13. doi: 10.1111/nmo.12611.
37. Allen ML, McIntosh DL, Robinson MG. Healing or amelioration of esophagitis does not result in increased lower esophageal sphincter or esophageal contractile pressure. Am J Gastroenterol. 1990 Oct;85(10):1331-4.
38. Levin MD. Pathophysiology of gastroesophageal reflux disease. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2F4d90110e-2e9f-4032-b658-72b6d84114fd.filesusr.com%2Fugd%2F4d1c1d_08f14bcf63bc42e1acca211e481aad70.pdf&clen=1533900&chunk=true
39. Kahrilas PJ, McColl K, Fox M, et al. The acid pocket: a target for treatment in reflux disease? Am J Gastroenterol. 2013 Jul;108(7):1058-64. doi: 10.1038/ajg.2013.132.
40. Hobsley M, Tovey FI, Holton J. Controversies in the Helicobacter pylori/duodenal ulcer story. Trans R Soc Trop Med Hyg. 2008 Dec;102(12):1171-5. doi: 10.1016/j.trstmh.2008.04.035.

41. Kirchhoff P, Socrates T, Sidani S, Duffy A, e al. Zinc salts provide a novel, prolonged and rapid inhibition of gastric acid secretion. Am J Gastroenterol. 2011 Jan;106(1):62-70. doi: 10.1038/ajg.2010.327.
42. Vakil N, Veldhuyzen van Zanten S, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastro-esophageal reflux disease (GERD)—a global evidence-based consensus. Am J Gastroenterol. 2006;101(8):1900–20.
43. Katzka DA, Pandolfino JE, Kahrilas PJ. Phenotypes of Gastroesophageal Reflux Disease: Where Rome, Lyon, and Montreal Meet.Clin Gastroenterol Hepatol. 2020 Apr;18(4):767-776. doi: 10.1016/j.cgh.2019.07.015.
44. Levin MD. Esophageal achalasia in Chicago Classification. https://4d90110e-2e9f-4032-b658-72b6d84114fd.filesusr.com/ugd/4d1c1d_06a08986e633470ab2310c5b027f8b73.pdf
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