Review Article

Hydrochloric Acid Hypersecretion as the Cause of Pathology in the Upper Digestive Tract: Literature Analysis

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Current literature tends to treat diseases of the upper gastrointestinal tract as separate nosologically forms, with limited exploration of their potential shared etiology and pathogenesis. In addition to diseases with organic lesions, a group of functional diseases is described, the nature of which is allegedly associated with disorders of gut-brain interaction. This study shows that to protect the body from the effects of hydrochloric acid and enzymes, nature has created an effective defense, which works at the level of myenteric reflex, including intermuscular nerve plexuses, Cajal cells, in cooperation with enzymes and hormones. This evidence leaves no room for speculation about the role of the CNS involved in this process. Some genetic features, such as lactose intolerance, as well as food allergies, overeating and obesity, destroy the defense against aggressive gastric juice, which causes damage to the mucosa, leads to an inflammatory reaction and changes the function of the intestine. Evidence suggests that many functional gastrointestinal disorders arise from inflammatory processes Hypersecretion of hydrochloric acid damages all parts of the digestive tract including the stomach, esophagus, duodenum and biliary system. Therefore, the clinical picture may include symptoms of all these organs in different combinations. Depression in these patients may be associated with chronic symptoms over extended periods. The inflammatory process in the upper digestive tract causes an increase in the tone of all parts of the digestive tract, including the colon and anal canal, which explains the occurrence of constipation in these patients. There is reason to believe that all so-called functional gastrointestinal disorders are accompanied by an inflammatory process in the intestinal mucosa because of damage to the wall by hydrochloric acid, pepsin or bile. This hypothesis, which explains the etiology and pathogenesis of acquired pathology of the upper digestive tract, is presented for discussion.

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There is no detailed description of the anatomy and physiology of the upper gastrointestinal tract in modern literature. To understand the proposed hypothesis, I dwell in detail on the anatomy and physiology of the duodenum and biliary tract. I briefly present the results of studies on the anatomy and physiology of the gastroesophageal junction and stomach, referring to previously published studies.

I. Duodenal motility

1. Anatomy of the duodenum. Duodenum is located retroperitoneally from the pyloric sphincter to the duodenojejunal sphincter and is divided into 4 parts. The 1st part features duodenal bulb, about 2 cm long. It is at the vertebral level of L1. A bulb shape is visible only on radiographs when filled with barium from the stomach. The 2nd part begins at the superior duodenal flexure. It goes inferior to the lower border of vertebral body L3. Then it is making a sharp turn to the left into the inferior duodenal flexure. The 2nd part contains the major duodenal papilla through which the pancreatic duct and common bile duct conduct pancreatic juice and bile. The 3rd part, or horizontal part of the duodenum is 10~12 cm in length. It begins at the inferior duodenal flexure and passes transversely to the left, passing in front of the inferior vena cava, abdominal aorta, and the vertebral column. The superior mesenteric artery and vein are anterior to the third part of the duodenum. The 4th part, or ascending part, passes upward, joining with the jejunum at the duodenojejunal flexure. The fourth part of the duodenum is at the vertebral level L3. Under microscopy, the duodenum has a villous mucosa, which is distinct from the mucosa of the pylorus. In the mucosa, there is Brunner's glands, which secrete mucus and bicarbonate to neutralize stomach acids[1].

2. Duodenal physiology. The duodenum is largely responsible for the breakdown of food in the small intestine, using enzymes. It also regulates the rate of emptying of the stomach via hormonal pathways. Secretin and cholecystokinin are released from cells in the duodenal epithelium in response to acidic and fatty stimuli present there. These cause the liver and gall bladder to release bile, and the pancreas to release bicarbonate and digestive enzymes such as trypsin, lipase, and amylase into the duodenum as they are needed. In lactose-tolerant people in the villous mucosa is lactase, which breaks down lactose into glucose and galactose[2].

In the literature, there is almost no information about the function of the duodenum to protect the small intestine from the aggressive effects of hydrochloric acid. The only sphincter of the duodenum is considered the sphincter of Oddi. This is because all intestinal sphincters do not have clear anatomical and histological boundaries. For example, the lower esophageal sphincter is described as a thickening of the circular layer without clear boundaries between the esophagus and the stomach. Meanwhile, all sphincters of the intestine are reduced according to a specific program, and during contraction they have clear boundaries[3].

A) Function of the duodenal bulb and post bulbar sphincter (PBS)

On an x-ray examination, chyme from the stomach comes in a certain volume, which is formed after the connection in one place of the peristaltic wave on the lesser and greater curvature of the stomach. Thus, a closed antral cavity is formed, and the area of contraction above it is called the antral sphincter **(Figure 1a).** When, because of contraction of the antral cavity, a threshold pressure arises in it, a reflex opening of the pyloric sphincter (PS) occurs and a bolus volume equal to the capacity of the duodenal bulb fills the bulb. When the bulb is filled with chyme, the pressure in it rises, which leads to reflex closure of the PS and relaxation of the PBS. This reaction of the PS conforms to the Bayliss-Starling gut law: - "Excitation at any point of the gut excites contraction above, inhibition below. This is the law of the intestine"[4]. It is characteristic for all sphincters, for example, an increase in pressure in the stomach causes an increase in the tone of the lower esophageal sphincter; an increase in pressure in the rectum causes an increase in the tone of the rectosigmoid sphincter, etc.[5][6].

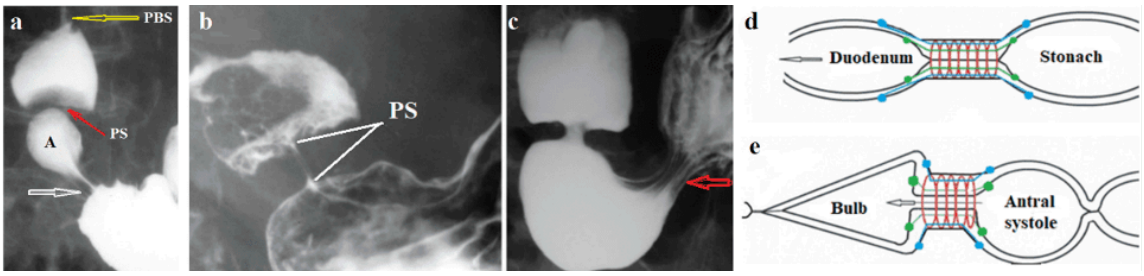

Figure 1. Radiographic studies of the gastroduodenal junction. **(a).** Peristaltic waves in the stomach met, forming the antral sphincter (white arrow). As a result, the antral chamber (A) was created, which, contracting, injects its volume into the duodenal bulb through the PS. **(b).** When the PS is closed, the bulb has its typical appearance, due to the contraction of the PBS. The base of the ampulla is equal in length and parallel to the antrum of the stomach. **(c).** The next cycle led to the opening of the PS, which turned out to be shorter than it was in the contracted state. Schemes **(d, e)** show the role of longitudinal spiral smooth muscle fibers connecting the antrum of the stomach with the bulb. During their contraction **(e),** there is a simultaneous opening of the PS with a symmetrical expansion of the base of the bulb and stomach.

The stomach is the main chemical section of the digestive tract, involved in the processing of food consumed. The mucous membrane of its walls secretes aggressive hydrochloric acid and pepsinogen, which in an acidic environment turns into pepsin. This chemical mixture destroys the proteins and is therefore dangerous for the intestinal tube. The mucous membrane of the stomach and the duodenal bulb has protection from destruction. So that other sections of the digestive tract do not suffer from chemical damage, nature created sphincters that regulate the movement of the chemical bolus. Peristaltic contractions of the body, and antral section of the stomach mix food with gastric juice. Every 3-5 wave closes, forming the antral sphincter. It is always formed in the same place, so that in the antral chamber a volume approximately corresponding to the capacity of the bulb turns out to be[3][7].

B) Sphincters of the second and third parts of the duodenum

The motility of all parts of the digestive tract follows the law of the intestine, except for the small intestine, of which the duodenum is a part. In the small intestine, contractions periodically occur not only cranial to the bolus, but also distal to it. This is probably due to the interstitial cells of Cajal of the deep myenteric plexus (ICC-DMP), which are found exclusively in the small intestine[3][8]. As soon as the chyme completely fills the bulb, the PBS contracts, the pressure in the bulb increases, which leads

to a contraction of the PS and the cessation of the flow of chyme from the stomach. After the previous bolus has passed into the jejunum, the PBS opens and the contents of the bulb penetrate the third part of the duodenum, where they are retained over the contracted sphincter.

In 1906, Ochsner during gallbladder and stomach operations drew attention to the expanded part of the duodenum with gas to a point just below the entrance of common duct, while below this it was contracted. On the anatomical material, he found a narrowing in the third part of the duodenum. It was found that the dilatation of the upper portion of the duodenum was most commonly present in patients suffering from chronic cholecystitis with sand or gallstones in the gallbladder. He concluded about the presence of a sphincter at this place whose physiological function would consist of providing for a means of retaining the chyme in the upper portion of the duodenum sufficiently long to provide for a thorough mixing with bile and pancreatic fluid. He assumed that this sphincter in the case of inflammation in this vicinity can lead to pathological conditions[9]. Since then, this sphincter has been called Ochsner's sphincter. In the second part of the duodenum, the sphincter is localized, which in the literature is called the Kapanji's sphincter[10]. Normal patterns of duodenal physiology cannot be recorded by X-ray examination because healthy people are not examined. Secondly, the sphincters are not activated by examination with barium, which does not contain acid. Below are X-rays of patients with duodenitis **(Figure 2).**

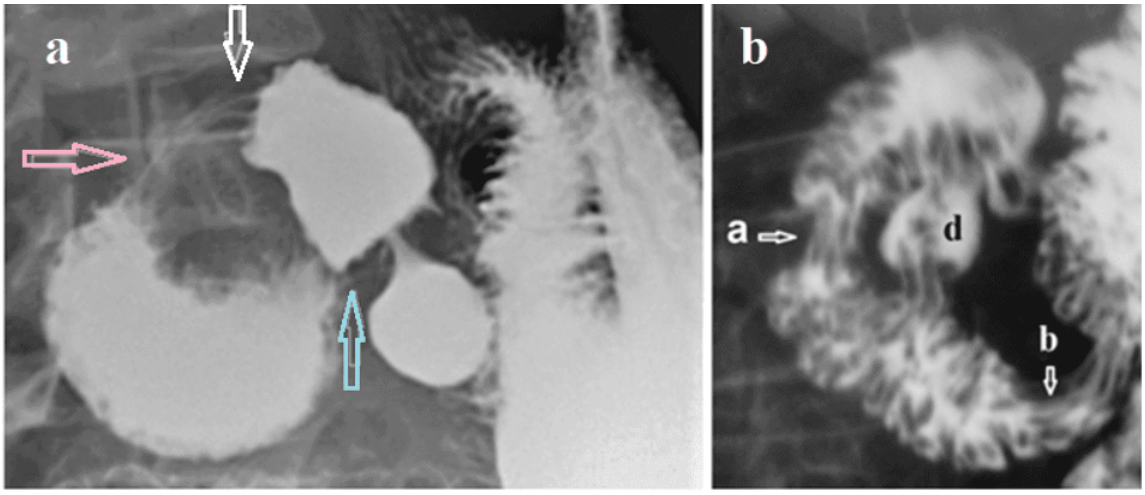

Figure 2. Radiographs of elderly patients with duodenitis and duodenal dyskinesia. (a) The duodenal bulb is expanded and deformed. Despite the large volume of contents, it continues to receive chyme, since the bulb has not reached its maximum capacity. This indicates a high tone of PBS (white arrow). A sharp expansion of the intestine is determined between the Kapanji sphincter (pink arrow) and the Ochsner sphincter (blue arrow). This expansion is due to the high pressure that occurs when both sphincters contract; (b) The duodenum was emptied, but the barium remained in deep folds because the barium-filled bowel was very wide. Two zones of contraction with longitudinal folds are visible: (a) the Kapanji sphincter, and (b) the Ochsner sphincter. The juxtapupillary diverticulum is located between them. These diverticula result from the extrusion of the mucosa between the muscular fibers. Thus, this diverticulum is evidence of high pressure that occurs during contraction between Kapanji and Ochsner sphincters dyskinesia[7].

To test the correctness of Ochsner's assumption that the sphincter of his name responds to acid by contraction, I conducted 8 studies with the addition of 3 grams of vitamin C to the barium suspension. Such a slight decrease in pH, nevertheless, contributed to the contraction of the Ochsner and Kapanji sphincters, which confirms the opinion of Ochsner about the reaction of sphincters to hydrochloric acid. Moreover, in a retrospective analysis of radiographs, the sphincter Kapandji was detected and measured in 16 cases. He was in the 2nd part of the duodenum 2-3 cm from the PBS. Its length ranged from 1 to 3 cm (2.05± 0.09 cm). The Ochsner sphincter was found on 20 radiographs. It was in the third part of the duodenum in the L-3 projection. Its length ranged from 2 to 4.2 cm (3.2 ± 0.15 cm). In all cases, these sphincters were in the same place, which excludes the possibility of registering peristaltic contraction[7][11].

C) Anatomy and physiology of the Oddi sphincter

In the duodenum, the process of digestion of food that begins in the stomach continues. The motor function of the duodenum ensures portioned processing of chemically aggressive chyme because of mixing the bolus with bile and pancreatic juice. This is facilitated by coordinated contraction of the sphincters and hormonal regulation. For example, cholecystokinin, which is synthesized and secreted by enteroendocrine cells in the duodenum, causes the release of digestive enzymes and bile from the pancreas and gallbladder, respectively. This occurs because of contraction of the gallbladder and opening of the sphincter of Oddi (SO)[12].

The sphincter of Oddi is the most studied sphincter of the duodenum. It is muscular valve responsible for controlling the flow of bile and pancreatic secretions through the ampulla of Vater into the second part of the duodenum and prevents reflux of duodenal contents into the pancreatobiliary system. It is composed of three layers of concentric smooth muscle that surrounds the common bile duct, the main pancreatic duct, and the ampulla of Vater. The papilla of Vater includes the SO and its overlying mucosa. Its length during manometry is determined as a high-pressure zone is approximately 1 cm (9.5±0.5 mm)[13]. With autopsy specimens the median intramural length of the sphincter was 14 mm (range 7-22 mm); the median length of the common channel between the common bile and pancreatic ducts was 3 mm (range 0-9 mm). The median extramural length of the sphincter was 5 mm (range 1-11 mm). No associations were found between the length of the sphincter, presence of stones in the gallbladder or the postcholecystectomy state ($p > 0.05$)[14]. It is believed that: - "The mechanism of dysfunction (SO) remains uncertain, but disruption of neural pathways involved in sphincter function seems likely"[15].

All studies of SO, including radiological ones **(Figure 3),** were performed in sick individuals, as evidenced by the large variation in SO length and the absence of differences in length between those who had pathology of the biliary tract and those who did not. Therefore, the given figures for SO length cannot be considered normal. The study of duodenal motility allows us to determine with a high degree of reliability the cause of the disorder of the motor function of SO and biliary tract.

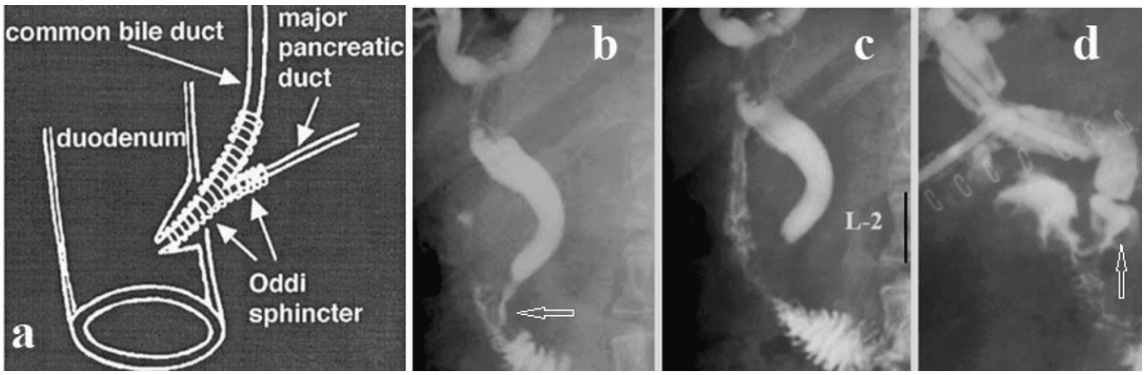

Figure 3.(a). Scheme of duodeno-choledochal junction. **(b-c).** Endoscopic retrograde cholangiopancreatography (ERCP) in a patient with obstructive jaundice. It is known that the true height of L-1 is 2.2 cm. However, it turned out to be impossible to accurately determine the height L-1 on the radiograph. We measured the L-2 height, assuming it to be 2.3 cm. The length of the non-contrasting gap between the common duct and the duodenum (arrow) is approximately 1.3 cm. This is the contracted SO. **(d)** A significant expansion of the common bile duct is combined with a shortening of SO. Its upper part looks like an ampulla. The authors of the article mistakenly called this picture normal[16].

II. New concept of normal duodenal motility

Figure 4 shows a diagram of the sphincters associated with the function of the duodenum. The locations of the sphincters are marked with a maroon line. These are not places of constant constriction. Normally, the sphincters contract with a certain pattern, which will be discussed below. The abbreviations to Figure 4 provide the length of the sphincters, if it has been described in the literature. The contraction of the pyloric sphincter (PS), which is determined by X-ray examination, does not correspond to the anatomical formation described under this name.

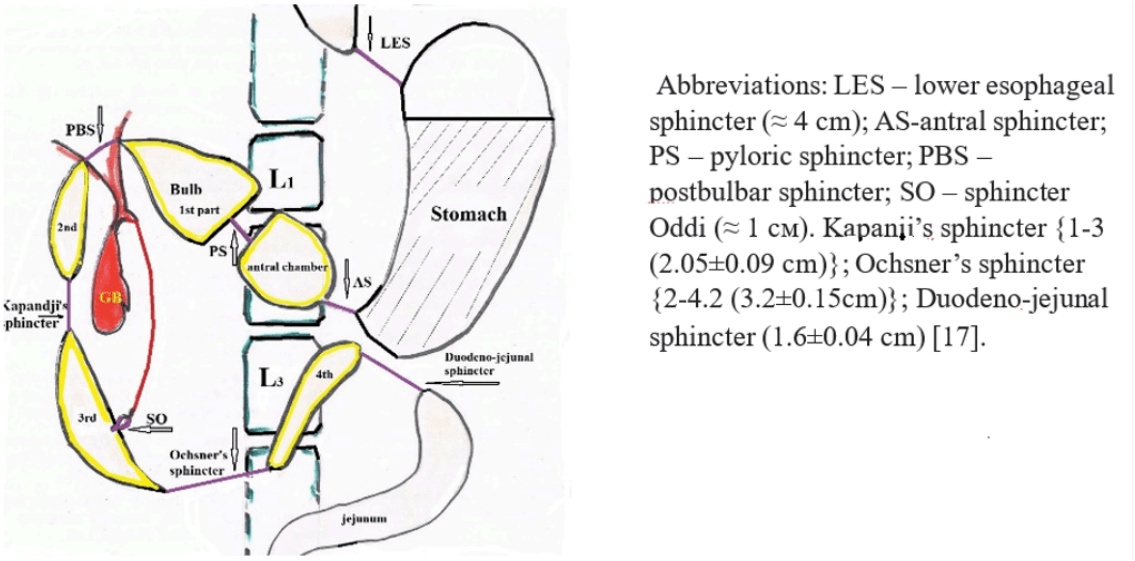

Figure 4. Diagram of the location of the sphincters of the stomach and duodenum.

Peristalsis is observed only in the body and anal part of the stomach. It mixes food with hydrochloric acid and pepsinogen, which are secreted by the gastric mucosa. In an acidic environment, pepsinogen is converted to pepsin. This is how the digestive process begins. Every 3-5 peristaltic waves on the greater and lesser curvatures of the stomach meet in the antrum and completely block its lumen. Since this always happens in the same place, this muscular zone is called the antral sphincter (AS). The closed chamber between the AS and the PS is called the antral chamber. Its volume is approximately equal to the capacity of the duodenal bulb. When the antral chamber contracts, the pressure in it rises, which leads to the opening of the PS and the chamber injects chyme into the bulb. This mechanism plays a dual role. (1) It promotes portioned evacuation of chyme, which protects the duodenum from massive exposure to chemically aggressive substances. (2) Food evacuation occurs under high pressure, which does not extend to other parts of the stomach, which facilitates the antireflux function of the LES. Opening of the PS together with the evacuation of chyme causes contraction of the PBS. When the volume of chyme in the bulb reaches its capacity, the pressure in the bulb reaches a threshold level, which causes contraction of the PS. At this moment, a standard portion of chyme is retained in the bulb between the PS and the PBS. From this time on, cholecystokinin begins to be synthesized and secreted by enteroendocrine cells of the duodenum. When the previous bolus leaves the duodenum, the PBS opens, and the bolus enters the third part of the duodenum. There, in response to high acidity, the Ochsner sphincter contracts and throws the bolus cranially. In the second part, it is

met by the contracted Kapandji sphincter, because of which the bolus is thrown back to the Ochsner sphincter. Multiple repetitions of this movement, which is described in the literature as pendulum-like, are accompanied by contraction of the gallbladder and opening of the SO, because of the action of cholecystokinin. Bile and pancreatic juice secreted into the duodenum, which have an alkaline pH, cause an increase in the pH of the contents. In response to this, the Ochsner sphincter relaxes and passes the bolus into the jejunum. This process is repeated until all the chyme has disappeared from the stomach.

III. Discussion

The above hypothesis of duodenal motility does not contradict known scientific facts but unites them into a rational system that shows how the rationalism of nature protects the digestive tract from the inevitable evil in the form of a mixture of hydrochloric acid and pepsin. Most acquired diseases of the digestive tract are caused by a breakthrough in this natural defense. Without touching on the etiology of this phenomenon, it can be said with confidence that inflammatory diseases of the stomach and duodenum (ulcers, gastritis, duodenitis and gastroesophageal reflux (GER) are a consequence of hypersecretion of hydrochloric acid. The effectiveness of treating these syndromes with drugs that reduce acid secretion, as well as antacids and prorectors that protect the mucous membrane of organs from contact with acid, is convincing evidence of the role of hypersecretion of hydrochloric acid in the pathogenesis of these disorders. Below are examples of how the new concept of duodenal motility is changing our understanding of the pathophysiology of some diseases.

1. Superior mesenteric artery syndrome (SMAS)

According to the suggestion of Professor Carl von Rokitansky (1842), the cause of SMAS is considered to be compression of the duodenum in the angle between the aorta and the superior mesenteric artery. Analysis of this hypothesis, based on which most of these patients undergo surgical treatment, does not stand up to criticism[7][11][17][18][8]. The assertion that in thin people, fatty tissue disappears from the aorto-mesenteric angle, which leads to a decrease in the angle and to compression of the intestine between the vessels, contradicts scientific facts. Firstly, because in some patients the BMI is within normal limits, and sometimes higher than normal. Secondly, millions of thin people with a narrow angle do not have obstruction in the third part of the duodenum. Thirdly, the length and location of

the narrowing of the duodenum cannot be caused by compression in the aorto-mesenteric angle **(Figure 5).**

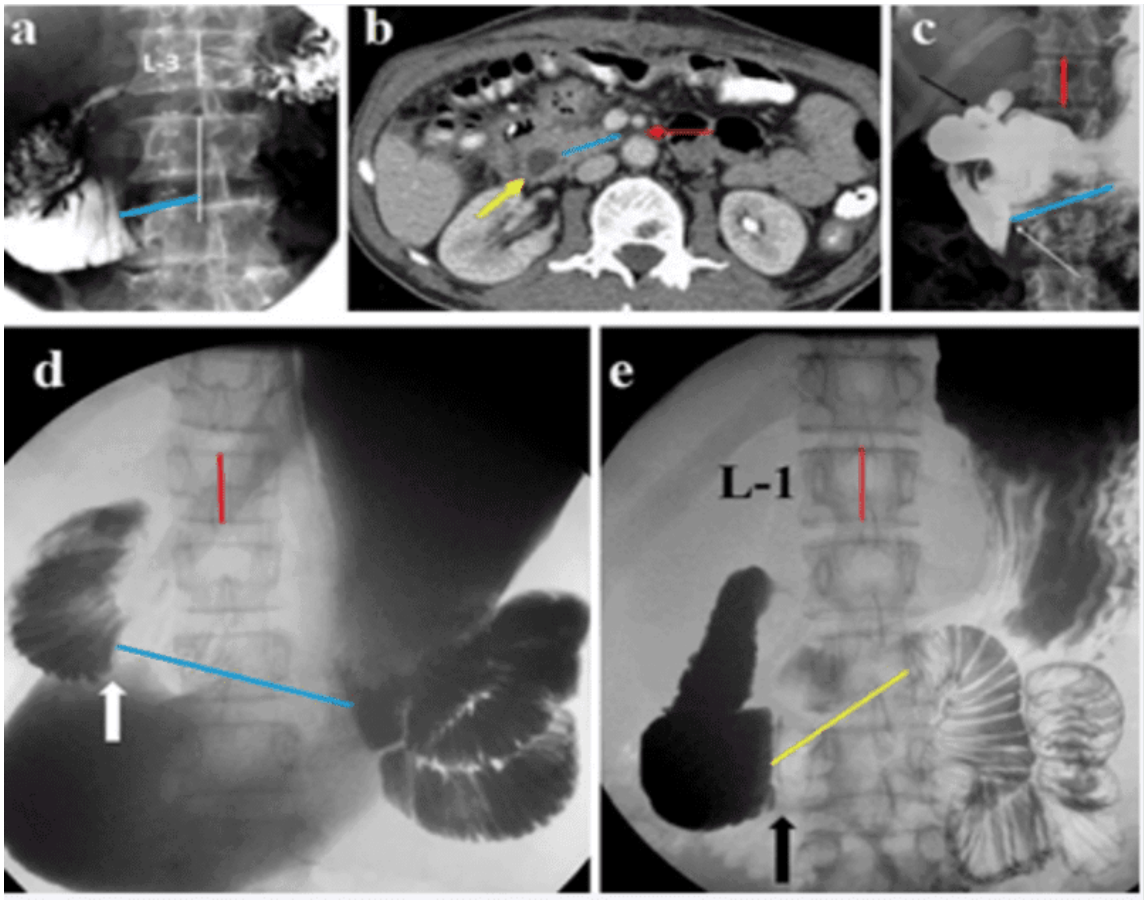

Figure 5. X-ray examinations of patients with a "diagnosis" of SMAS. **(a)**. A patient after laparotomy. The beginning of the narrowed segment of the duodenum (blue line) is located 3.2 cm from the midline L-3. His CT **(b)** shows that the narrowed segment is located far from the aorto-mesenteric angle (AMA) (red line). **(c)**. In a patient with a bulb ulcer (black arrow), the narrowed segment of the duodenum begins to the right of L-3 (white arrow) and ends to the left of L-3. Its length is 4.6 cm. **(d)**. The distance from the duodenum to the jejunum is 6.5 cm. **(e).** In this patient the narrowed segment of the duodenum begins to the right of L-4 and ends to the left of the midline of L-3. Its length is 4.9 cm.

Since the true diameter of the abdominal aorta at this location is 2 cm, and that of the superior mesenteric artery (SMA) is 1 cm, the compression of the intestine between these vessels cannot be longer than 2 cm, and even more so it cannot be located far from the midline of the vertebra where these vessels are located. I measured the distance from proximal points the sharp contraction in the

3rd part of the duodenum to the location of the SMA, i.e., up to the middle of the 3rd lumbar vertebra (L3) on 35 radiographs, CT, and MRI, published in PubMed and PMC. In 29 (83%) cases on X-ray examination or on CT and MRI, the length of the narrowed segment of the duodenum ranged from 2.5 to 4.6 cm (3.30 ± 0.15 cm) and always started a few centimeters to the right of L-3. In 6 cases, the length from the beginning of the narrowing to the midline of the vertebra was about 2 cm, but I was unable to detect its continuation to the left of the midline L3.

Thus, the narrowing of the duodenum in SMAS in length (3.30 ± 0.15 cm) and location completely corresponded to the length (3.2 ± 0.15 cm) ($p > 0.05$) and location of Ochsner's sphincter. These data confirm Ochsner's research that hypersecretion of hydrochloric acid causes persistent contraction (dyskinesia) of Ochsner's sphincter, which in severe cases leads to obstruction of the duodenum.

2. Pathogenesis of acquired diseases of the biliary tract

Currently all authors agree that the etiology of sphincter of Oddi dyskinesia (SOD) is unknown. However, Ochsner's study has shed light on this issue. During operations on the gall bladder and stomach, he found that "in many cases the duodenum is distended by gas to a point just below the entrance to the common duct, while below it is contracted, and on elevating the transverse colon and finding the beginning of the jejunum, this part of the bowel will also be found in a contracted state"[9]. As shown in Figure 2, the dilation of the bowel between the hypertensive sphincters of Kapandji and Ochsner, as well as the juxtapupillary diverticulum, indicate that a high pressure occurs between these sphincters. Thus, the sphincter of Oddi opens into the chamber with pathologic high pressure in it.

Based on the analysis of the literature and our own research, the following conclusions can be drawn. (a). Hypersecretion of hydrochloric acid, which causes acid-related diseases (esophagus, stomach, and duodenum), leads to dyskinesia of the duodenum, including the Kapanji and Ochsner sphincters with hypertrophy of their walls; (b). In the duodenum between the Kapanji and Ochsner sphincters, where the SO opens, pressure increases. (c). An increase in pressure in the chamber into which the SO opens leads to a disruption of its function (dyskinesia), which causes to a delay in the outflow of bile and pancreatic juice, an increase in pressure in the ducts and contributes to the periodic reflux of an acidic bolus into the ducts. (d). With a significant expansion of the CBD, a shortening of the SO occurs with the formation of ampulla and a functional sphincter above it. (f). Duodeno-biliary reflux increases pressure in the biliary system, which leads to disruption of liver function tests, chronic pancreatitis, the formation of gallstones and acute cholecystitis, after contamination of

microorganisms. (f). The pathology of the biliary system, including SOD, is an acid-dependent disease and therefore is always combined with other acid-dependent diseases. Their differential diagnosis can be difficult since many symptoms of different diseases are the same. The ontogenesis of the disease begins from the dyskinesia with the subsequent development of inflammatory, sclerotic, and anatomical changes, including the formation of ampulla, SO stenosis, metaplasia, which can lead to the tumor. Thus, SOD is one of the possible stages in the development of pathology caused by hypersecretion of hydrochloric acid[19].

3. Functional Dyspepsia

It is currently believed that "Functional dyspepsia (FD) is a disorder of gut-brain interaction (DGBI) with an estimated prevalence of 10-40% in Western countries and 5-30% in Asia"[20]. This hypothesis has no evidence. Moreover, the authors contradict the obvious facts. On the one hand, they claim "absence of structural gastrointestinal tract abnormalities", even though "recent reports have highlighted the existence of low-grade duodenal inflammation, including intramucosal eosinophilia and elevated mast cell density within the duodenum"[20].

1. Functional gastrointestinal disorders (FGIDs), according to Rome IV criteria, are defined as variable combinations of chronic or recurrent gastrointestinal signs and symptoms[20]. FD is categorized into two distinct subgroups based on the pattern of symptoms. The first subgroup is postprandial distress syndrome (PDS), characterized by the presence of bothersome early satiation and/or postprandial fullness. The second subgroup is epigastric pain syndrome (EPS), characterized by bothersome epigastric pain and/or burning. This classification has changed as compared to the previous Rome III classification[21].

A. **Rome IV criteria** were adopted by a vote, in which the recommendations were accepted by a majority and which, as you can see, have been updated for the third time. No science accepts recommendations adopted by a vote. If the Theory of Probability were put to a vote, then 90% of university professors would reject it, and we would live in a different world. For this reason alone, the Rome IV criteria do not have scientific status and should not be considered in scientific papers.
B. The above symptoms are characteristic of any disease caused by hypersecretion of hydrochloric acid. Symptoms of gastroesophageal reflux disease overlap with FD more than expected by chance[22]. The study of overlapping FD, gastroesophageal reflux disease (GERD), irritable bowel

syndrome with constipation (IBS-C), and chronic idiopathic constipation (CIC) showed: Of 2641 respondents, 60.3% had one condition; 31.5% had two; and 8.2% had three; 57.3% of 1690 FD, 54.6% of 1337 GERD, 82.6% of 328 IBS-C, and 62.5% of 552 CIC respondents had condition overlap[23]. It follows that the proposed Rome IV criteria, which divide FD into two syndromes, as well as other functional disorders, do not have clear definitions.

2. Diagnosis. It is believed that the utility of endoscopy in all patients with typical symptoms is minimal; its use should be restricted to people aged 55 years and older, or to those with concerning features, such as weight loss or vomiting[24]. Miwa et al recommend doing endoscopy only in cases where organic disease is suspected[25]. This generally accepted recommendation is contrary to common sense, because the diagnosis of FD based on clinical manifestations is impossible. All symptoms of FD are non-specific and are observed in all acid-related diseases, which are always, to one degree or another, combined, since they are caused by one cause.

3. Treatment of functional disorders includes the administration of hydrochloric acid suppressors (Level of evidence 1). The effectiveness of PPI in FD is less than in GERD, but this is not a reason to consider these diseases to be of different origin, since the symptoms of GERD are not always controlled by PPI. Dietary treatment involves the exclusion of triggers of the inflammatory process of allergic origin, disaccharides (lactose) and other products that cause worsening of symptoms. Medicines that are prescribed in accordance with the physiological disorders and mental state of patients (Level of evidence 2) include: Prokinetic; Centrally acting drugs; Miscellaneous therapy; Selective serotonin reuptake inhibitors; Selective norepinephrine reuptake inhibitors; Antacids, Sucralfate, Bismuth[22].

4. What are functional gastrointestinal disorders?

A. GERD is a chronic, progressive, recurrent disease. There is overlap between GERD and various functional gastrointestinal disorders (FGIDs)[21]. During ontogenesis, the symptoms of GERD change. As a disease caused by hypersecretion of hydrochloric acid, GERD is always accompanied by damage to the stomach, duodenum and bile ducts, because of which typical and non-esophageal symptoms are combined with symptoms of damage to other parts. For example, hunger pains and their disappearance after eating are known symptoms of damage to the duodenum. The presence of constant abdominal pain, heartburn, postprandial bloating, early satiety and constipation in patients over many years cannot but affect their psychological state.

This is an axiom! Wang et al showed that significant factors for the risks of FD are «Genetically predicted GERD, less years of education and depression. However, the conclusions do not correspond to the results: - -«comprehensive MR study demonstrated that depression and lower educational attainment were causal factors for FD at the genetic level»[26].

First, there are no known genes that are responsible for GERD. The authors had in mind a causal relationship. Secondly, the authors omitted from the conclusion the connection between FD and GERD. Thirdly, the results do not allow us to consider that depression causes FD, and not vice versa.

B. Functional dyspepsia is defined as persistent symptoms of postprandial bloating, early satiety, or pain in the center of the upper abdomen, without findings on upper endoscopy such as peptic ulcer disease to explain these symptoms[20][23][24][25][27]. Firstly, there is no logic in this definition, given the recommendation to perform endoscopy in cases where an organic cause is suspected in elderly people. Secondly, it is known that endoscopy only detects complications in the esophagus (erosions, stenosis, Barrett's esophagus and tumors). The inflammatory process in the esophagus in the so-called nonerosive reflux disease is determined based on a histological examination of the mucosa, by the presence of eosinophils[28], by the width of the intercellular space[29], by the presence of cardiac epithelium[30]. Therefore, based on endoscopy without histology, it is impossible to judge the absence of an inflammatory, i.e. organic process in the duodenum.

C. However, recent studies have indicated that the pathogenesis of FD involves impaired duodenal epithelial barrier function and low-grade inflammation[20][31][32], impaired duodenal barrier integrity and immune cell infiltration[33], often combined with eosinophilic infiltration[34]. Walker et al showed that the inflammation of the duodenum is characterized by internal inflammation, an eosinophil infiltrate in the duodenum in FD. Emphasizing their adherence to Rome IV criteria, they conclude that "Thus functional is becoming inflammatory"[34], instead of the obvious conclusion that what was considered functional is in fact organic in nature. Vanheel et al, proved that «Duodenal hyperpermeability and low-grade inflammation in functional dyspepsia is potentially related to duodenal acid exposure"[35]. Walker et al reanalyzed duodenal biopsy by eosinophil counts in five high power fields that had previously been assessed as normal. In patients "without predominant UGI symptoms" duodenal eosinophilia was in 22.5%, in postprandial distress syndrome the prevalence of duodenal eosinophilia (47.3%, $P < 0.04$)

were significantly higher. Duodenal eosinophilia was significantly associated with allergy ($P < 0.001$)[36]. These scientific data are beyond doubt. They indicate that FD is not a functional process. It occurs because of damage to the duodenal mucosa by hydrochloric acid, which causes an inflammatory reaction and may be accompanied by eosinophilia in response to an allergy.

D. Surprisingly, the updated definition acknowledged the crucial role of the gut-brain axis and the bidirectional communication between the enteric nervous system and central nervous system in DGBI pathophysiology[37]. This statement, found in many articles on FD, need in scientific validation.

   1. More than a third of patients suffer from psychological comorbidities. However, almost 2/3 of patients do not suffer. Secondly, the presence of depression in these patients is associated with daily suffering for many years.
   2. The law of the intestine (Bayliss and Starling) was formulated as follows: - "Excitation at any point of the gut excites contraction above, inhibition below"[38]. Cannon later proposed the term "myenteric reflex"[39][3]. This is the ABC of physiology, which excludes the connection of the myenteric reflex with either the spinal cord or the brain. When referring to I. Pavlov, the authors do not refer to conditioned and unconditioned reflexes but turn to a completely unrealistic scenario. "Even though the idea that the gut microbiome possibly manipulates host's behavior to its benefit might be intriguing, the ideas of evolved dependence or local manipulation are likely more realistic"[37].

E. X-ray picture of duodenitis which is called functional dyspepsia.

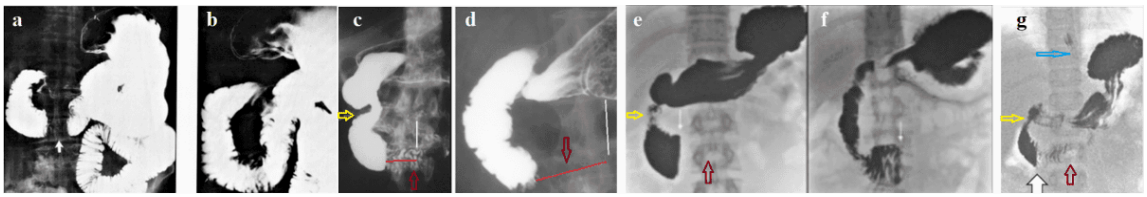

Figure 6. X-rays of patients with duodenitis. Sphincters are shown with arrows: Kapandji - yellow, Ochsner - brown, lower esophageal - blue. (a-b). Radiographs from the textbook. Signed: "Normal patient with transient proximal duodenal dilatation (a) Radiograph shows apparent obstruction third portion of the duodenum (arrow) suggesting the SMAS. (b) The view obtained slightly later shows the duodenal sweep to be entirely normal"[40]. (c) Radiograph from the article by Neri et al[41]. This radiograph is presented as SMAS, but neither the stomach nor the duodenum is dilated, the narrowing of the intestine begins to the right of the vertebra, i.e., away from the vessels. (d). A study with the addition of 3 grams of vitamin C to a barium suspension resulted in contraction of the Ochsner's sphincter. (e,f,g). From the article by Caterine et al, who believe that right-of-midline duodenal impression is a normal anatomical finding caused by the inferior vena cava (IVC) and should not be confused with superior mesenteric artery syndrome[42].

Eisenberg called the temporary contraction of the duodenum to the right of the spine normal, meaning that it excludes SMAS. However, it is a mistake to call the radiographic picture normal when examining a patient only based on excluding one of the possible diagnoses. Moreover, X-ray examination is not performed on healthy individuals. Caterine et al retrospectively evaluated 538 upper GI studies of children aged 6 years (1 month-17 years) with complaints of weight loss, reflux, and dysphagia. They wanted to determine whether the duodenum had vertical duodenal impression to the right of the vertebral midline. In 240 (44.6%) of 538 studies, a right-of-midline impression was found. The authors believe that radiologists should be aware of the normal variant of a right-of midline impression, on the D3 part of the duodenum, caused by the IVC[42]. Firstly, these authors examined patients with hypersecretion of hydrochloric acid. All radiographs show high tone of the Kapandzhi and Ochsner sphincters. Figure 6 g shows incomplete cleansing of the esophagus and an inflammatory process in the bulb. Meanwhile, it is known that since barium does not contain acid, it passes into the jejunum without delay. If it is delayed above the Ochsner sphincter, this indicates dyskinesia of the sphincter in response to damage to the wall by hydrochloric acid. Therefore, this radiographic picture, which does not correspond to SMAS, cannot be called normal. Moreover, it corresponds to duodenitis. Secondly, although the IVC is located behind the intestine, it does not exert

pressure on it. The opinion expressed by the authors and the opinion they refer to are not supported by evidence and contradict the topographic anatomy.

IV. Conclusion

Through trial and error, nature has created a system for mammals that can utilize food. Chemically aggressive gastric juice, which breaks down proteins and fats in food into small fragments, is dangerous for the walls of the digestive tract. To protect the body from the effects of hydrochloric acid and enzymes, nature has created an effective defense, described above. It works at the level of myenteric reflex, including intermuscular nerve plexuses, Cajal cells, in cooperation with enzymes and hormones. I have not found scientific evidence that the CNS is involved in this process. Some genetic features, such as lactose intolerance, as well as food allergies, overeating and obesity, destroy the defense against aggressive gastric juice, which causes damage to the mucosa, leads to an inflammatory reaction and changes the function of the intestine. My analysis suggests that changes in bowel function may result from organic damage, rather than being the primary cause. Hypersecretion of hydrochloric acid damages all parts of the digestive tract including the stomach, esophagus, duodenum, biliary system. Therefore, the clinical picture may include symptoms of all these organs in different combinations. During ontogenesis, when atrophic gastritis develops, the secretion of hydrochloric acid decreases sharply, but against the background of already existing sphincter dysfunction (lower esophageal, antral, pyloric, and all duodenal sphincters), bile is thrown into the stomach and esophagus, evacuation from the stomach is impaired (gastroparesis), evacuation from the duodenum is impaired (SMAS, duodenitis). The presence of depression in these patients is associated with daily suffering for many years. The inflammatory process in the upper digestive tract causes an increase in the tone of all parts of the digestive tract, including the colon and anal canal, which explains the occurrence of constipation in these patients[43]. There is reason to believe that all so-called functional gastrointestinal disorders (functional constipation without megacolon, irritable bowel syndrome, functional dyspepsia, postprandial distress syndrome, functional chest pain, functional heartburn, functional bloating[44]) are accompanied by an inflammatory process in the intestinal mucosa because of damage to the wall by hydrochloric acid, pepsin or bile. This hypothesis, which explains the etiology and pathogenesis of acquired pathology of the upper digestive tract, is presented for discussion.

Abbreviations

AMA – aorto-mesenteric angle; AS – antral sphincter; BMI – body mass index; CIC – chronic idiopathic constipation; DGBI – disorders of gut-brain interaction; EPS – epigastric pain syndrome; FD – functional dyspepsia; FGIDs – functional gastrointestinal disorders; GER – gastroesophageal reflux; GERD – gastroesophageal reflux disease; IBS-C – irritable bowel syndrome with constipation; IVC – inferior vena cava; PBS – postbulbar sphincter; PDS – postprandial distress syndrome; PPI – proton pump inhibitors; PS – pyloric sphincter; SMA – superior mesenteric artery; SMAS – superior mesenteric artery syndrome; SO – sphincter Oddi; SOD – sphincter Oddi dyskinesia.

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