Dear Colleagues,

Over the past 12 years, a huge number of articles have been published in scientific journals, in which the pathogenetic diagnosis without scientific justification is replaced by manometric characteristics. Many of the manometric indicators are based on unproven or clearly false assumptions. Surprisingly, despite the presence of contradictions and a lot of questions, all the agreements take place at the meetings based on voting. There is no discussion in scientific journals. Physiological issues with the full support of the general line are demonstrated only by practical doctors as if someone destroyed the fundamental science. Dr. Mittal and I have started a scientific discussion and ask you to join us.

Yours faithfully

Michael Levin

Sumeet Mittal AZ-Phoenix <sumeet.mittal@commonspirit.org>
02.06.2021, Ср, 2:17

i respectfully disagree with a lot of what you have compiled
it all seems to be from a radiological perspective and anyone who has done an EGD knows that the SCJ/GEJ which is normally within the LES can move by a large amount
Additionally a lot of your summarizing is wrong and exposing incorrect understanding of physiology of the LES pressure zone
Skm

Dear Dr. Mittal,

It seems to me that your letter opens an opportunity for discussion based on scientific arguments.

For example, why do you think that X-ray examination is less scientific or less demonstrative than HRM? Second, the histological studies by Chandrasoma and DeMeester have shown that the generally accepted SCJ / GEJ boundaries are based on "two false dogmas that lead to two widespread fundamental errors. (1) This is the belief that the cardiac epithelium usually lines the proximal stomach, and (2) GEJ is determined by the proximal limit of wrinkle

folds ". Therefore, it is not correct to judge the movement of the LES based on the EGD.

I ask you to give a more detailed analysis of my resume.

Yours faithfully

Michael Levin

Sumeet Mittal AZ-Phoenix <sumeet.mittal@commonspirit.org>
02.06.2021, Ср, 20:39

I believe it will be hard for me to explain to you as you are jumbling several aspects along the spectrum of the disease to make a point.
I believe that Ba is the best study to look at esophageal motility - it is a lost art - so we record and look at all barium video esophagrams ourselves.

the LES moves up and down with swallowing - peristalsis -- sometimes more than others... HRM studies a particularly significant amount in subtypes of nutcracker patients, by Ba - sliding hernia in upright vs supine position and EGD -showing sliding hernia with varied degrees of distension.

Also our paper discusses 2 possible explanations for noticing a dual HPZ after peristalsis -- one being the LES-CD complex separates or potentially a very low pressure LES becomes 'visible' during the post relaxation hypercontractile state (but that is less likely)

I have read and strongly believe in the Dr D/Para concepts and infact currently authoring a paper on this aspect with them.

Skm

Dear Dr., Sumeet Mittal,

I must confess to you that I do not trust anyone. I only trust irrefutable scientific facts.

1. X-ray examination is a physiological demonstrative and reliable scientific method. My analysis of your article with co-authors showed that the LES does not move during swallowing. An example is also my analysis of the articles by Kwiatek et al (Figure 1) and Pandolfino et al (Figure 2).

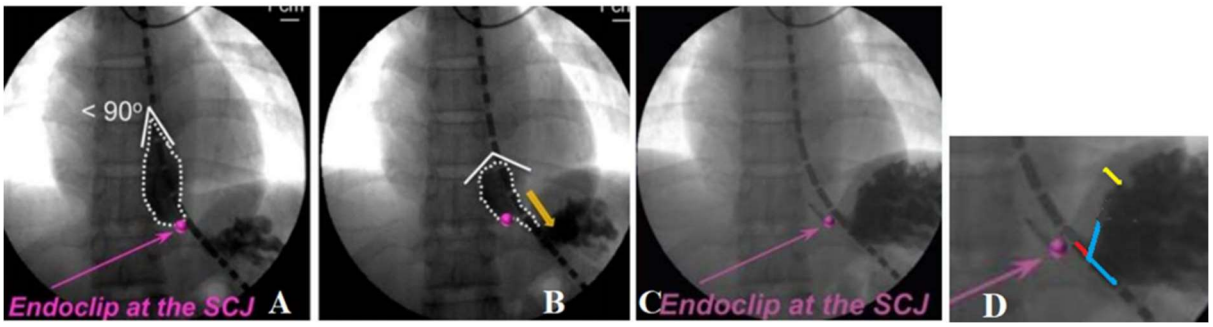

Figure 1. Radiographs from the article Kwiatek et al. [1], and scheme D to figure 1.C. In all the pictures endoclip is in the same place - to the left of the lower contour of the D-10. In Figure C, performed after numerous swallows, the pressure in the stomach increased, as evidenced by a large amount of barium in the stomach and the sharp decrease in the distance between the contour of the diaphragm and the stomach (the yellow line in the diagram). This led to the opening of the abdominal part of the LES (blue line), with the shortening of the distance between the endoclip and the stomach (the red line is the contracted part of the LES).

The endoclip was attached to the proximal end of the rough folds commonly thought to be the folds of the stomach. As shown by the histological studies of Chandrasoma and DeMeester, this opinion is erroneous [2]. X-ray studies confirm histological findings. In GERD, the inflammatory process in the esophagus leads to wall thickening and stiffness both in the esophagus and at the level of the LES, which is accompanied by the formation of folds. During endoscopy, the walls of the esophagus are stretched and the folds in the esophagus disappear, but they remain in the closed LES (Figure 2). Thus, the endoclip was attached not to the EGJ, but to the proximal end of the LES.

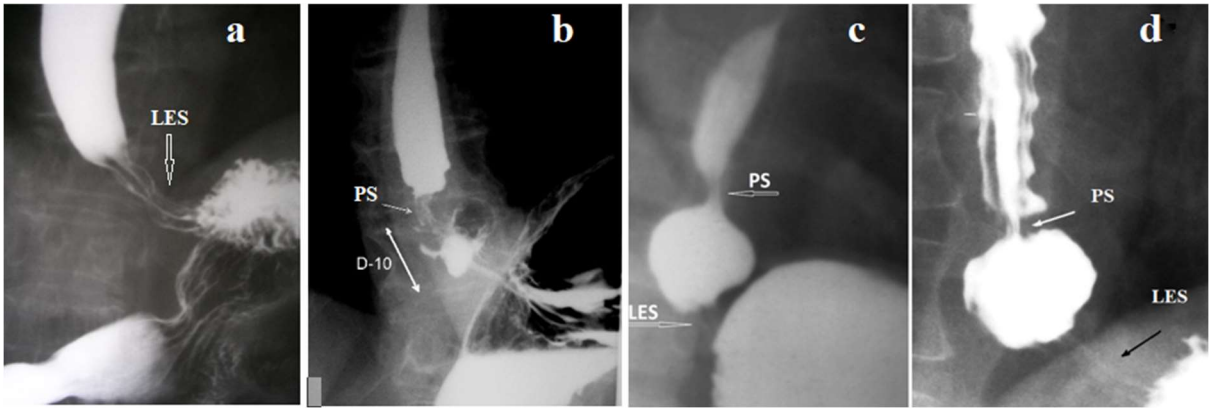

Figure 2. Radiographs of EGJ in patients with GERD. Each image shows longitudinal folds at the LES level (between the esophagus and stomach). Contraction of the proximal sphincter (PS), which blocks the lumen of the esophagus above the phrenic ampulla, provides high pressure in the ampulla, which injects the bolus into the stomach.

Thus, histological, and radiological studies show that the "rugal folds" above the stomach are at the level of the LES. Returning to Figure 1, we see that the clip, which is attached to the mucosa at the proximal end of the folds, is on the border with the ampulla. If we assume that the clip is attached to the EGJ, i.e., to the distal point of the LES, this means the proximal point of the LES located in the ampulla. The authors of this article came to such a paradoxical conclusion. X-ray images show how the peristalsis of the extended part of the esophagus (ampulla) approaches the upper point of the LES (clip), the position of which does not change. The ampoule is evidence of GERD. The LES opens without peristalsis. Combining them is impossible. This study provides further evidence of the fallacy of the notion that rugal folds refer to the stomach.

During swallowing, the distance between the clip and the stomach decreased due to the opening of the abdominal part of the LES, which proves the presence of GERD.

Conclusion. 1. The assumption that rugal folds are folds of the stomach has become an axiom as a result of repeated repetition but has no scientific basis. These folds are at the LES level. The superior point of the folds is in the proximal point of the LES.

2. X-ray and histological studies prove that the LES does not shift during swallowing. The shortening of the esophagus together with the LES is due to the opening of the abdominal part of the LES.

3. The picture of the esophageal ampulla and the shortening of the LES with or without swallowing are convincing symptoms of GERD. This means that the patient selection criteria for determining the HRM norm are flawed.

4. On what basis is a probe with multiple pressure transducers considered useful for the physiological study of the EGJ and diagnosis of diseases of the esophagus and EGJ?

The ball is now on your side. I look forward to your arguments. (5/03/2021)

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Dear Dr., Sumeet Mittal,

I still hope that we will continue to discuss important issues in the physiology of the esophagus and the EGL. I want to dwell on methodological errors. I am convinced that extremely strict selection criteria are required to determine the boundaries of the norm because if patients with GERD are included in the control group, the diagnosis of diseases is fraught with serious errors. For example, to establish the normal limit for prolonged pH-metry, it was necessary to select individuals without GERD in the control group. At that time, the most accurate method for diagnosing GERD was an endoscopic examination. It was considered that the examined persons did not have GERD, (1) If they have not, and have not been in the past the typical clinical symptoms of GERD (heartburn and regurgitation), and on endoscopic examination, there were no macroscopic signs of the esophagitis. However, …

First, it is now considered a fact that a significant number of patients with GERD, especially in the initial period of the disease, have no clinical symptoms.

Secondly, any symptom from the table below can be the symptoms of GERD.

Table of clinical symptoms and risk factors for the diagnosis of GERD.

Up to 2 years	**vomiting**	**poor weight**	**dysphagia**	**fussy infant**	**cough**	**putrid breath**	**wet pillow**	**anemia**
Over 2 years	**chest or abdominal pain**	**heartburn**	**sinusitis**	**dental erosion**	**pulmonary fibrosis**	**recurrent otitis**	**cough after eating**	**asthma**

Risk factors	Pre-maturity	Cow's milk intolerance	Acid hyper-secretion	Allergy	Family history		Obesity	Stress

Thirdly, it has been reliably established that it is impossible to exclude GERD without histological examination of the esophageal mucosa.

As a result of improper selection of individuals into the control group, it is considered normal if reflux of gastric contents with pH <4 is registered less than one hour per day. Allegedly "in patients with an undefined GERD diagnosis (acid exposure time between 4% and 6%), impedance allows measurement of other impedance variables to confirm or refuse GORD diagnosis" (consensus). The acid, which eats away at the iron, causes inflammation and ulcers in the stomach, which has anti-acid protection, cannot be safe for the esophagus. These fictitious boundaries are absurd because they contradict common sense have, but they had multiple consequences.

First. The gastroesophageal reflux (GER) diagnosis was changed to gastroesophageal reflux disease (GERD), which is reflux, which causes a painful condition. This contradicts numerous studies that show that the disease can occur without clinical manifestations at all and even more so without the so-called typical symptoms.

Secondly. As a result of natural selection in the human body, each tissue, and its function play an important role in normal functioning. I wonder what is the role in transient lower esophageal sphincter relaxations? Obviously, this role is damaging. This cannot be the norm. This is the result of a wrong selection of norms.

Thirdly. Previously, the presence of a hiatus hernia was thought to be evidence of GERD. How did it turn out that the HH can be without reflux? There, where pH-metry did not find GERD.

Fourth. How did the diagnosis of functional heartburn and reflux hypersensitivity come about? This is the result of a negative pH metry.

Unfortunately, the same errors apply to high-resolution manometry (HRM). This study is not physiological, since the probe itself is a foreign body that irritates the LES and causes it to contract. Secondly, the selection of persons to determine the norm was not accurate.

In the discussion of your article, based on a comparison of your study with the results of manometry with an open catheter and X-ray studies, I showed that the esophagus + LES complex is shortened during swallowing in patients with GERD

because of the shortening of the LES, while the length of the esophagus does not change.

Why do you deny the possibility of shortening the LES in patients with GERD?

Scientific discussion is a necessary method for determining the correctness of the results obtained. Anything that is determined to be the result of consensus has no scientific value.

I hope that you will provide evidence of the correctness of your position on the issues raised.

Yours faithfully

M.D. Levin (15/06/21)

Links to research studies are provided in my review. (https://4d90110e-2e9f-4032-b658
72b6d84114fd.filesusr.com/ugd/4d1c1d_2a4e2d59fb2b484c810c07b763904c64.pdf).

26.06.21

Dear Dr. Mittal,

You and your co-authors recently published an article “Botox injection into the lower esophageal sphincter induces hiatal paralysis and gastroesophageal reflux” [1]. I studied this work with great interest because, despite some shortcomings, the results obtained allow us to draw especially important conclusions.

1) **To EGJ physiology.** You subdivide the pressure produced by the lower esophageal sphincter (LES) and the crural diaphragm (CD) based on the article by Boyle et al [2]. They showed that the pressure at the level of the EGJ during expiration is due to the tone of the LES because during expiration CD is in a relaxed state. During inspiration, the diaphragm contracts, which is accompanied by a sharp increase in pressure in the EGJ. From which these authors and you, after them, assert that this pressure on inhalation "is generally due to the effect of crural diaphragm / hiatal contraction" [1]. Although the contraction of CD coincides with the rise in pressure in the EGJ, the causal relationship between them is questionable. It is known that the tone of the LES changes depending on the pressure in the stomach. An increase in pressure in the stomach causes a reflex increase in the tone of the LES [3,4,]. As shown by Shafik et al, "gastric distension after anesthesia does not affect the LES tone" [4]. This study proves the reflex

response of LES to increased pressure in the stomach and excludes the effect of CD. The LES is innervated by excitatory and inhibitory motor neurons and by descending esophageal inhibitory neurons [5]. An increase in pressure over the LES causes a decrease in the tone of the LES, and an increase in pressure in the stomach causes an increase in LES tone. This reaction follows the law of the gut. It has been proven that excitatory and inhibitory control of the LES and intragastric pressure are mediated by vagal efferent neurons locates in two distinct sites in the dorsal motor nucleus of the vagus [6]. In your study, performed with methodological violations, you "conclude that 1) there is an active contraction at the esophagogastric junction during periods of increased intra-abdominal pressure and 2) tonic contraction of the crural diaphragm is a mechanism for this LES pressure response" [7].

This conclusion contradicts the law of the gut and all other articles, both the ones given above [3,4,5,6] and all the others that cannot be listed. Research by Shafik et al showed that "The crural diaphragm has a resting tone that relaxes after esophageal distension and contracts after gastric distension". [8]. However, "The CD response disappeared when straining was sustained for more than 15–18 seconds (mean 16.8 ± 1.2) and was not evoked after frequent successive straining". "The disappearance of the crural response on prolonged straining and the non-response after frequent successive straining appear to be due to the fact that the CD consists of striated muscle fibers which are easily fatigable and cannot remain contracted for long periods" [9].

Thus, during an increase in pressure in the stomach, there is a simultaneous reflex contraction of LES and CD. The EGJ functions like the anal canal, with the internal anal sphincter (IAS) contracting continuously as the LES and the external anal sphincter (EAS) as the CD. Striated sphincters are contracted briefly to enhance the function of the smooth muscle sphincters. During coughing, there is a simultaneous contraction in IAS [10] and LES, as well as EAS [10] and CD.

It remained unclear what contribution LES makes to the antireflux function of EGJ during prolonged stimulation by numerous respiratory provocations, which will exclude the response of the CD. Your research has convincingly proven the correctness of the statement about the reflex nature of the LES contraction in response to the contraction of the diaphragm.

a) You have injected Botox into the LES. "Five injections of 20 units (1 mL) each were delivered 1–2 cm above the Z-line all around the circumference of the esophagus" [1].

b) «The HRMZ study conducted 2–4 wk after the ISIB revealed significant reduction in the end-expiratory EGJ pressure (LES pressure) from 23 (29) mmHg to 13 (16) mmHg, $P < 0.01$. There was also a dramatic reduction in the increase in EGJ pressure associated with tidal inspiration [39 (30) mmHg to 16 (19) mmHg, $P < 0.01$] and forced inspiration [111 (50) mmHg to 43 (22) mmHg, $P < 0.01$]» [1].

Conclusion. Since Botox was not injected into the CD, the decrease in pressure during inspiration compared to the pressure before injection confirms that this pressure is mainly is due to a tone decrease of the LES.

In the diagram, (Figure 1), you arbitrarily removed the walls between the LES and the CD to explain how Botox enters the CD. In fact, these structures are separate and there is no scientific basis to assert that the Botox injected into the LES somehow got into the CD or other surrounding organs. You cannot treat anatomy so arbitrarily. Therefore, we assume that Botox was injected into the esophageal wall and penetrated between the muscle fibers in the LES.

If we assume that there are vascular connections between the wall of the esophagus and the diaphragm, then they would prevent shortening of the esophagus and displacement of the LES cranially. These two ideas of yours are not compatible.

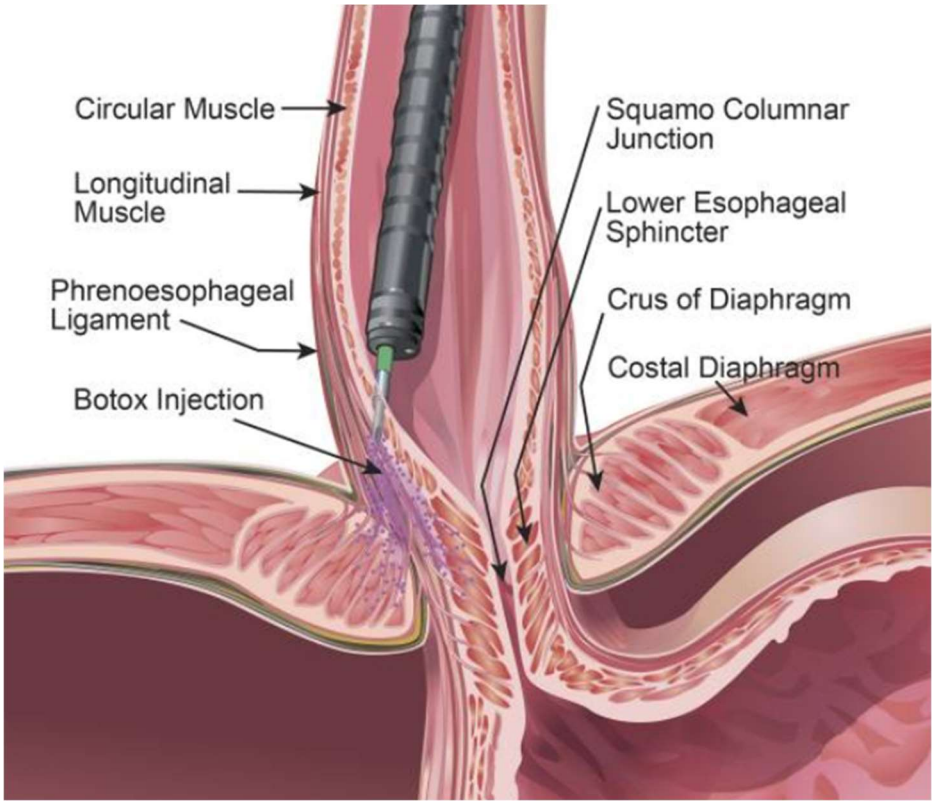

Figure 1. Schematic of the intrasphincteric injection of Botox into the distal esophagus and diffusion of Botox into the lower esophageal sphincter and hiatus. Scheme and signature to it from the article Kumar et al [1].

2). **Diagnosis.** "Studies were conducted in 14 patients (age range: 40–74 yrs.) who had undergone ISIB for the treatment of achalasia esophagus and other spastic esophageal motor disorders (nutcracker, jackhammer, diffuse esophageal spasm, outflow obstruction). All patients had bothersome dysphagia and chest pain as their major symptoms" [1]. To prescribe pathogenetic treatment, it is not enough to list the clinical and manometric symptoms. The diagnosis, which indicates the name of the disease, assumes known or hypothetical etiological, pathophysiological, pathogenetic features of the disease, as well as diagnostic methods and recognized pathogenetic methods of treatment, which either eliminate the disease or alleviate the patient's condition.

You claim that "Nine of the 14 subjects did not complain of GER symptoms before the Botox injection". I agree with you that there is no point in performing a pH-metry, endoscopy, and high-resolution manometry to diagnose GERD if there are clinical symptoms. However, bothersome dysphagia and noncardiac chest pain are known symptoms of GERD.

Thus, you did nothing to make a pathogenetic diagnosis and started treating the symptoms. You not only did not provide appropriate treatment to 14 patients with LES but, on the contrary, weakened the LES even more, practically eliminating its antireflux function. Medical science assumes symptomatic treatment only as temporary relief of the patient's serious condition during the diagnostic process. For example, prescribing antipyretics for hyperthermia or pain relievers for severe pain.

4) **Results.** "Nine of the 14 subjects did not complain of GER symptoms before the Botox injection. Seven of these 9 subjects developed GER symptoms at the 2–4 wk evaluation. They described regurgitation with deep breaths, bending over, and other physical activities. Some patients complained of new heartburn symptom; others who had heartburn and reflux before the ISIB complained that their symptoms increased after the ISIB. Of the 6 patients who were studied at both 2–4 wk and 6–12 mo after the ISIB, 3 patients developed reflux symptoms at 2–4 wk after the ISIB, which disappeared at 6–12 mo post-ISIB. The other 2 patients did not complain of reflux symptoms at any time during the study. One patient who had no reflux before the ISIB developed reflux at 2 wk, which was present even at the 8-mo study" [1].

Analysis of the article shows that such unreasonable "treatment" causes increased pain in the chest. Heartburn before Botox injection was in 5 out of 14; after 2-4 weeks in 12 out of 14. This means that pressing pain behind the breastbone has been replaced by more severe pain.

In summary, you declare:

1) "Our study shows that the ISIB, in addition to the LES, has a major effect on the crural diaphragm, the two major important components of the EGJ".

I believe this statement is false, as it is based on the manipulation of anatomical data. Scientific analysis of your article shows that when you inhale, the tone of the LES increases in response to an increase in pressure in the stomach. This does not exclude some influence of the contracted CD on the pressure in the EGJ but it is obvious that the tone of the LES predominates.

2) "Reduction in the LES pressure by Botox provides a good rationale for the beneficial effects of Botox for the relief of dysphagia".

The results of your experiment indicate a worsening of the patients' condition. In patients with GERD, the introduction of Botox into the LES is contraindicated.

There is no discussion in your article in the "discussion" section because you only link to articles that match your assumptions.

Dear Dr. Mittal. You submit that «Endoscopic intrasphincteric injection of Botox (ISIB) is used routinely for the treatment of achalasia esophagus and other spastic motor disorders». Most of the links on this topic point to your articles. Do you intend to continue the administration of Botox in patients with GERD and to promote this method, which is supported by grants?

Michael Levin

26.06.21

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Mittal, Ravinder <rmittal@health.ucsd.edu>
27.06.2021, Bc, 8:14
Dear Dr Levin: thanks so much for your interest in our paper and work. You have raised many important points. Will like to answer few that I can answer with objectivity

1) Contribution of crural diaphragm/hiatus to the EGJ pressure. I attach our recent paper in patients with hiatus hernia where one can record two high pressure zones, one related to the LES and other to the CD. Whether intra-abdominal pressure causes reflex contraction and relaxation of the LES is

questionable, to the best of my knowledge, which is based on my 38 years of focused research in this subject. I have done studies in animals and humans and my conclusions are based on my own observations, and not just reading of the literature.

2) Anatomy of the EGJ - Based on all published literature, best I can tell is that the LES and CD are anchored to each other by the upper and lower leaves of phrenoesophageal ligament. These 2 leaves penetrate into the muscularis propria of the esophagus, in between the bundles of circular and longitudinal muscles of the esophagus. Therefore, our schematic of the EGJ and how botox may travel from the site of injection into the CD is reasonable, I believe.

3) We presented symptoms in the paper, but you well know that subjective symptoms often do no correlate with the objective physiological measures. Since what I found and reported in this paper, I always put my patients after botox injection on PPI therapy for at least for 4-6 weeks to prevent reflux.

Thanks again for your interest and best wishes!

Ravi Mittal

Dear prof. Mittal,

In the analysis of your article "Pathological Implications of Swallow-Associated Transient Lower Esophageal Sphincter Elevation", as well as during the discussion, I **proved** that during any provocation, the LES does not change its position, and the shortening of the esophagus+LES complex during swallowing is due to shortening the LES by relaxing its abdominal part. I want to draw your attention to the fact that LES shortening in GERD this is not mine, but the generally accepted point of view (**Figure 1**).

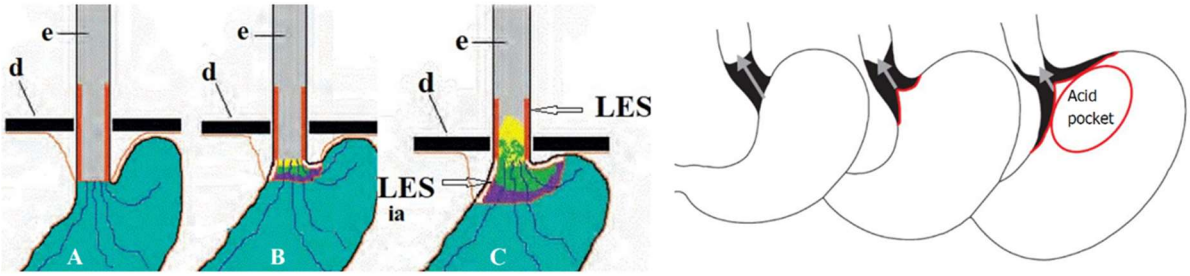

Figure 1. These diagrams, taken by me from various articles (not mine), show the generally accepted understanding of the pathogenesis of GERD. **A)** In a healthy individual, the entire LES is in a closed state. **B)** The initial form of GERD, when acid damages only the abdominal part of the LES and does not enter the esophagus. This stage is not available for pH-metry. **C)** The abdominal part of the LES is weakened and, during a provocation, does not withstand the pressure and opens. The acid enters the esophagus. Recurrent reflux is always

pathological, even though for a long time it can proceed without clinical symptoms.

Even though I gave pieces of evidence both manometric and radiological, you wrote: «i respectfully disagree with a lot of what you have compiled it all seems to be from a radiological perspective, and anyone who has done an EGD knows that the SCJ/GEJ which is normally within the LES can move by a large amount». Firstly, if the evidence is reliable (not refutable) by X-ray examination, then it is true. Second, what everyone knows is based on two false dogmas that result in two widely believed fundamental errors. 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 [1].To this conclusion of the histologists, I also brought X-ray evidence. Why are you ignoring scientific evidence and not presenting evidence that you are right? What is this discussion if you have not answered any of my questions?

Let us see if the name really reflects the accuracy of this method.

A) The Chicago Classification is periodically updated, where the discussion participants come up with some recommendations by voting. At the last meeting, "there was no agreement on the significance of the RIP, only that it could localize either above the LES or between the LES and CD in cases of hiatus hernia ..." [2]. How does this consensus relate to science? Are scientific problems solved by voting?

B) HRM cannot be a reliable method because the study is not physiological. The probe is a foreign body that irritates the walls of the esophagus and partially, to varying degrees, blocks the lumen of the LES. Secondly, the accuracy of any method is based on normal values. The absence of typical symptoms of GERD does not exclude the disease. It follows from this that this method has no norm limits for any indicator.

C) The HRM does not determine the width of the esophagus, including at the level of the ampulla; does not determine the length of the LES in the abdomen and above it; does not differentiate ampoule from LES. On what basis did you decide that the two pressure peaks correspond to the tone of LES and CD? All studies by Shafik et al represent a methodologically pure experiment. They showed that the striated muscle of the DM contracts with a sharp rise in gastric pressure only for 15-18 seconds (mean 16.8 ± 1.2) and was not evoked after frequent successive straining [3]. Why isn't this reflected in HRM research?

If you doubt that intra-abdominal pressure causes reflex contraction of the LES, which is basic knowledge of the physiology of the EGJ, then this once again proves that the manometric study you are practicing is not an accurate method. I have already cited links to this topic, in which impeccably conducted studies prove that an increase in pressure in the esophagus causes a decrease in the tone of the LES, and an increase in pressure in the stomach causes an increase in the tone of the LES. Over the years, I have done research on the competence of EGJ, drawing on Shafik's research. X-rays were taken while the patient was drinking barium 30 seconds after the onset of abdominal compression. By this time, the CD had already stopped contracted [4]. In patients with GERD, radiographs of EGJ showed a contracted LES, which usually does not contract in response to provocation (Figure 2). Moreover, the zone of contraction above the stomach, neither in length nor in localization, can be a zone of CD contraction.

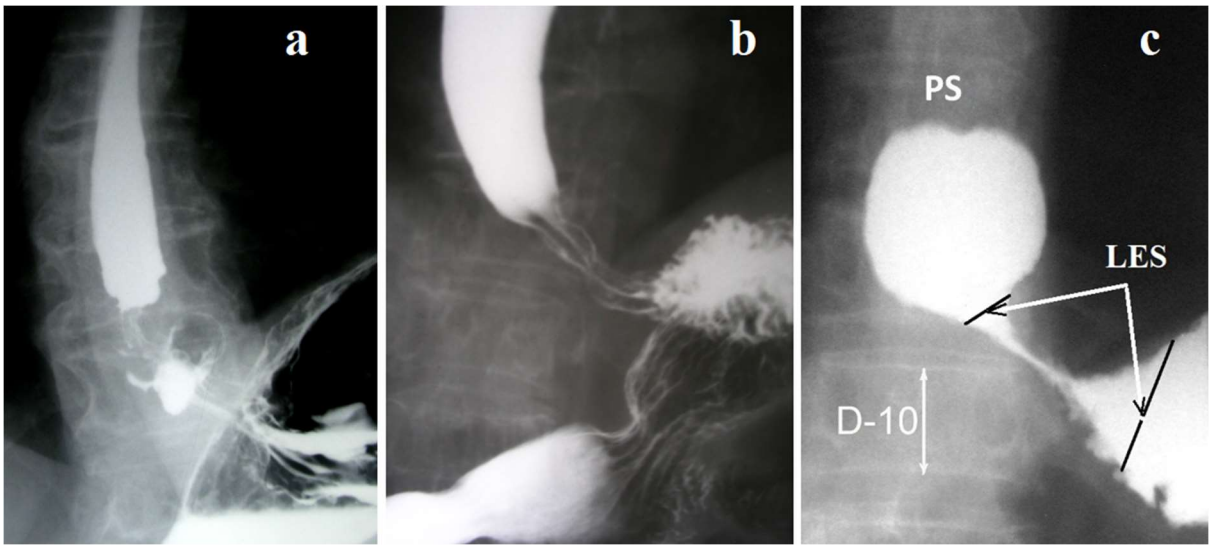

Figure 2. Radiographs of EGJ taken during barium swallowing, approximately 30 seconds after the onset of abdominal compression, when the CD contraction has ceased. (a) In the upright position, 2 zones of high pressure are visible: between the stomach and the incompletely emptied phrenic ampulla, a short LES is visible; a second high-pressure zone is visible between the esophagus and ampulla. None of these zones are related to CD. (b) A contracted LES with longitudinal folds like those of the stomach is visible between the esophagus and the stomach. How can you assume that this is not an LES, but a stomach? (c) On the radiograph, we see 3 high-pressure zones: the compression of the abdomen led to a contraction of the LES, which is located between the stomach and the ampulla. The LES is shortened due to the opening of the intra-abdominal part in the form of an angular deformation of the stomach, as well as the opening of the supraphrenic part of the LES. The contraction of the LES stopped the contraction of the ampulla. The ampulla must create high pressure for opening the LES and

its pressure must be greater than the gastric pressure. Since the height of D-10 is approximately 2 cm, the width of the ampulla is 3.7 cm, which, according to existing concepts, corresponds to a hiatus hernia. However, is it possible to imagine that the stomach penetrated through such a narrow channel? The third zone of high pressure is located above the ampoule, where the proximal sphincter (PS) has contracted, due to the contraction of which the ampoule can create high pressure. If it were not for this sphincter, then during the contraction of the ampoule, barium would penetrate the esophagus and the pressure in the ampoule would drop. Of these three high-pressure zones, there is no contraction zone of CD.

You state that "LES and CD are anchored to each other by the upper and lower leaves of phrenoesophageal ligament. Therefore, your schematic of the EGJ and how Botox may travel from the site of injection into the CD is reasonable". If this were true, and the blood vessels from the LES penetrated into the CD, then this would prevent the LES from moving upward from the CP. But this is a misinterpretation of anatomy.

I asked, for what purpose have you injected Botox to patients with GERD who were having problems with a failed LES. Why you have excluded the LES from the antireflux function, thereby aggravating the condition of the patients.

Your answer surprised me. "Since what I found and reported in this paper, I always put my patients after Botox injection on PPI therapy for at least for 4-6 weeks to prevent reflux".

Answer at least one question. For what purpose did you inject Botox into the LES for patients with GERD and what results did you achieve?

Note that PPIs do not reduce reflux. In some cases, they reduce the release of hydrochloric acid. However, in patients with GERD after long-term use of large doses of PPI, these drugs not only do not alleviate the symptoms but, on the contrary, lead to hyperplasia of the secreting cells of the stomach, which secrete gastrin and thereby increase the secretion of hydrochloric acid [5].

Analysis of the article you submitted "Sliding Hiatus Hernia: A Two-Step Pressure Pump of Gastroesophageal Reflux" [6].

Sliding hiatus hernia is so-called because it is determined only in a horizontal position. It is assumed that the horizontal position facilitates the movement of the stomach above the diaphragm. In fact, in the vertical position, the hydrostatic pressure of the liquid barium suspension creates a threshold pressure above the LES. After opening the LES, barium enters the stomach. In the horizontal position, the bolus moves because of peristalsis, and normally the esophagus over

the LESs is no expansion. Dilation of the esophagus over the EGJ occurs only with GERD. The phrenic ampulla of the esophagus is the last peristaltic wave, the contraction force of which is weakened by expansion and inflammation. To create high pressure in the ampulla, it closed proximally by the so-called proximal sphincter (PS). Thus, the presence of a phrenic ampulla, regardless of its size, is evidence of GERD. Why is GERD not always diagnosed with the so-called HH? Because the pH-metry diagnoses only very severe forms of GERD, i.e., pH-metry is a completely meaningless research method.

As shown by X-ray and histological studies, the LES, firstly, does not move during swallowing but shortens if it is weakened. Second, rugal folds occur in GERD in the LES because of inflammation (irritation). Since there is no movement of the LES, then there is no movement of the stomach. During the compression of the abdomen and during swallowing, in addition to the LES tone, there is high pressure in the PS and in the phrenic ampulla. Your assumption that the second pressure peak is due to CD has no confirmation, especially since CD in response to a provocation is contracted for no more than 19 seconds.

You measured «pressures during forced inspiration for the stomach (2 cm below the CD, the CD, the middle of the HH, the LES, and the esophagus (5 cm above the LES)". On the pressure graphs, you have positioned the peaks of pressure from the stomach to the esophagus according to your notion of the pathophysiology of HH. In this sequence, the tone of the LES was determined by you cephalad to the NN. There are no specific characteristics of different cavities and sphincters on the pressure graphs. The article does not show pressure figures and the length of sphincters. Look at the numerous radiographs I have cited, none of which match your explanation (**Figure 3).**

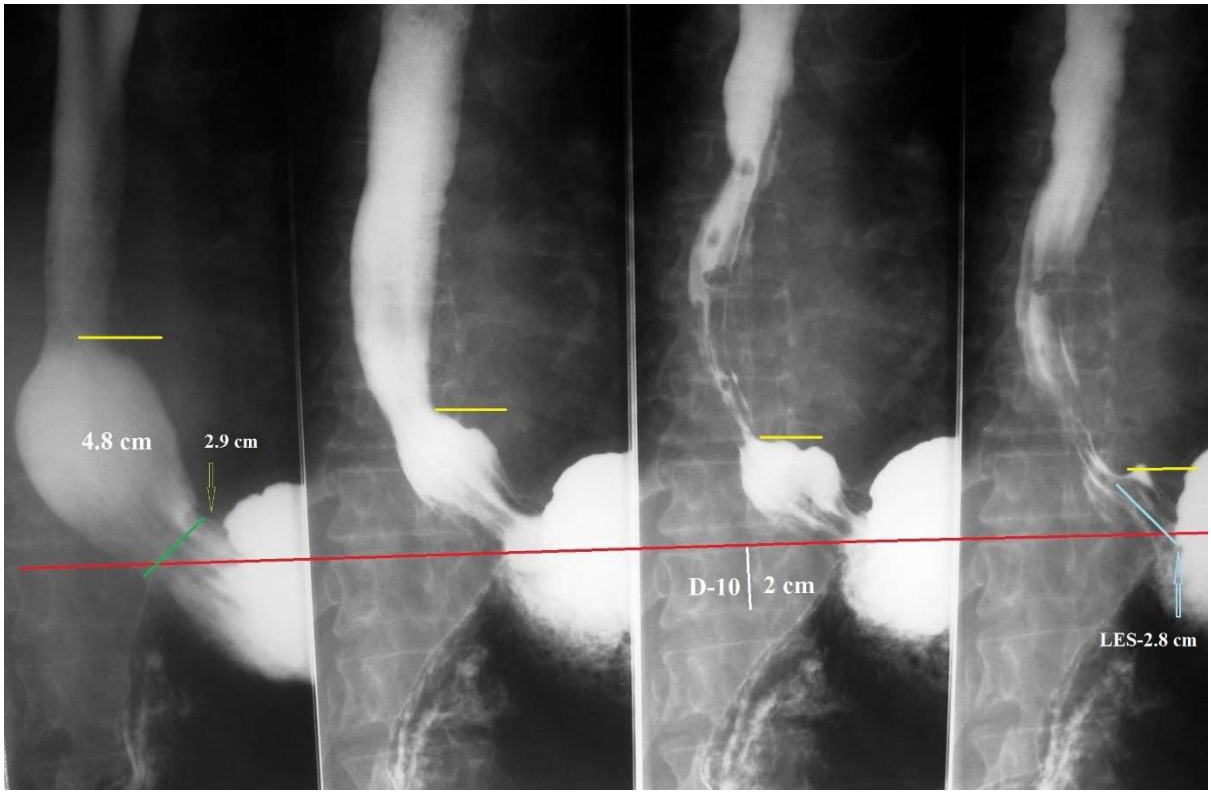

Figure 3. Sequential radiographs while drinking barium in a patient with GERD and esophagitis. At first, the ampoule with a diameter of 4.8 cm was filled. The diameter of the hiatus channel (green) is 2.9 cm. It is unlikely that the contraction of the CD can exert pressure on the EGJ with such a wide diameter of the hiatus channel. The size of the ampoule gradually decreases due to the approach of its upper edge to the stomach. This indicates peristalsis, which excludes HH since there can be no peristalsis in the fundus of the stomach because there are no Cajal cells in it. In the process of emptying the ampulla, the stomach is in the same place (the red line is drawn along the upper edges D-10). Longitudinal folds are defined along the entire length of the esophagus and at the level of the LES. The length of the LES is approximately 2.8 cm. After emptying the ampulla, no slip of the stomach into the chest is observed.

Figure 4 shows a study from your article [6].

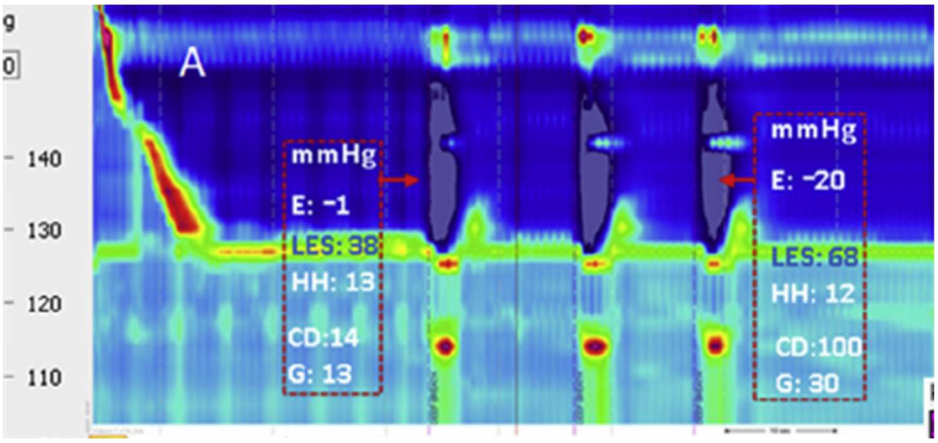

Figure 4. The two high-pressure zones (brown spots) do not have specific characteristics based on which anatomical affiliation could be accurately established. The length and extent of the upper zone are less than that of the lower one. Your designations for high-pressure zones correspond to the idea of shortening the esophagus and displacement of the LES into the chest. This leads to the misconception that CD plays a more important role than LES, which contradicts all previous studies of the physiology of the EGJ.

Considering that, in fact, the LES does not change its position, it is safe to say that the lower high-pressure zone is due to the contraction of the LES and CD. The shorter zone of lower pressure, located cranial to the ampulla, is the zone of contraction of the proximal sphincter (PS). **Figure 5** offers a diagram of the pathogenesis of GERD.

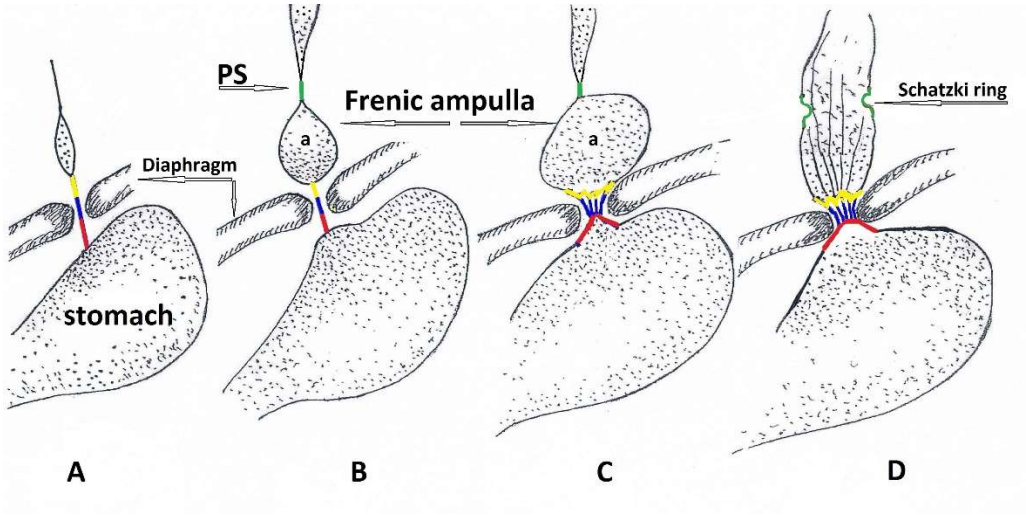

Figure 5. Scheme of progression the LES incompetence in GERD. **A).** The normal length of the three parts of the LES (red-intraabdominal, blue - diaphragmatic, yellow supradiaphragmatic). The ratio of the LES parts is approximate. **B).** Shortening of the intraabdominal part of the LES. Ampulla and PS (green) appeared. **C).** The ampulla increased in size. The shortening of the

LES due to the disclosure of both supradiaphragmatic and intraabdominal portions. Expansion of the hiatus combined with the appearance of folds at the level of the diaphragm. **D).** The shortening of the LES is independent of provocation. Only its diaphragmatic part is contracted. The hiatus channel is expanded so the diaphragm does not affect the contraction of the GEJ. In place of the PS, a fibrous tissue appeared (Shatsky's ring).

Dear Dr. Mittal. Our discussion turned out to be useful, at least for me. I invite you to review my evidence and share your opinion.

Yours faithfully

Michael Levin 1.07.21

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06.08.2021, Пт, 13:41
Esophageal Achalasia - 8-6-21.docx
2 МБ

Hi Dr Levin: please see my comments in red. I wish I had more time to respond to each of your comments, but I hope this helps. . I am very busy clinically and research wise. What you need is proper understanding of manometry and what it measures.

Late W.J Dodds, a radiologist from Milwaukee mastered both techniques and wrote some of the most beautiful work based on proper understanding of both techniques. You should read his papers. He understood strength and limitation of the two techniques, and I believe that you need to spend some time understanding of the manometry technique, its strength and limitation. Otherwise, the huge effort you are making in interpretation of the literature and your criticism of the literature is not accurate. Maybe you should spend some time in the manometry lab? I want to help you, but my time is limited! Also, keep in mind that not everything written in the literature, whether new or old literature is accurate. It helps to understand the methodology used in the papers, their strength and weakness, and make your own interpretation of the results.

Hope this helps and trust you will spend some time understanding manometry, does not matter old or new HRM

Ravi Mittal

Last Argument

Ricard Farré Marti <ricard.farre@kuleuven.be>

13.08.2021, Пт, 11:28

Dear Dr. Levin,
I am not sure if the email below was sent to Prof. Mittal or only to me by accident.
Anyway, I think that the tone of your email sent to him was far to be appropriate. Some researchers do not need to refer to reliable sources because they are reliable sources. I do not know if you know Prof. Mittal but he is one of the fathers of the oesophageal physiology, he published more than 120 publications only in the oesophageal field and more than 10 books. I think he deserves a bit more of respect.
Please, can you erase my email address from this discussion?
Many thanks in advance.
Have a nice day.
Regards,
Ricard
Ricard Farré i Marti, PhD

Conclusion

For more than 2 months we with Prof. Mittal exchanged messages, but to my chagrin, Prof. Mittal did not participate in the discussion. To all my questions and evidence, he did not give a single scientific argument, but only generally accepted dogmas.

For more than 40 years, doctors have unlearned to discuss scientific problems, because of which an attempt to prove the fallacy of established dogmas, without which science cannot develop, is perceived as an insult.

pH monitoring and HRM are designed with gross methodological flaws, because of which they have neither scientific nor clinical value. They are advertised in numerous articles that are the result of a collaboration between practitioners with no fundamental physiological training and diagnostic equipment manufacturers whose goal is to maximize sales. Then, the same authors get together and vote to get the approval for the recommendations.

This group of practitioners removed physiologists from the scientific field to prevent discussion and create an impression of universal support. Massive advertising of lies and the suppression of dissent is what is typical for dictatorial regimes. This is something that should not continue.

M.D. Levin, MD, PhD, DSc.

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Esophageal achalasia in the historical aspect.

Michael D. Levin

Comments on my work Prof. Mittal (in red).

My comments (in blue)

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. Your interpretation of manometry as to how LES relaxes is not correct. The LES relaxation is a neurologic event. It results from the swallow-induced activation of the inhibitory neurons of the myenteric plexus that releases nitric oxide which relaxes the myogenic basal tone of the LES. Hydrostatic pressure that you refer to cause opening of the LES. LES relaxation and opening are two distinct events. Manometry measures relaxation and radiology measures opening function of the LES. Late W.J. Dodds (radiologist) described these events beautifully in 1970'S.

In a more recent work by Schulze et al, with contributions from W.J. Dodds "They used esophageal manometry in normal opossum. At rest, separate and distinct high-pressure zones can be recorded at the level of the lower esophageal sphincter, diaphragmatic hiatus, aortic arch, and upper esophageal sphincter".

The mapping of high-pressure zones was false. Firstly, because no one except them detected an increase in pressure at the level of the aortic arch. Secondly, it is known that the LES is partially located in the stomach, as well as at the level of the diaphragmatic opening. Thus, either the normal opossum esophagus is not an exact analogue of the human esophagus, or the determination of the location of the pressure zones was not correct.

Secondly, they claim that "peristalsis is not bolus-dependent and occurs with 98% of swallows", which is contrary to the law of the gut. So far, no scientific evidence has been published that would question the correctness of the law of the gut. Thus, not "Pressures generated by peristalsis", but peristalsis generated by pressure, which creates a bolus, which is in accordance with gut law. (Schulze K, Dodds WJ, Christensen J, Wood JD. Esophageal manometry in the opossum. Am J Physiol. 1977 Sep;233(3):E152-9. doi: 10.1152/ajpendo.1977.233.3.E152.)

It follows that the quality of works involving Dodds cannot justify their use as scientifically proven information, including the unsubstantiated claim that "LES relaxation and opening are two distinct events".

The concepts of "relaxed" and "open" are different. But we are discussing the function of the LES. During the evacuation of the barium column during X-ray examination in a vertical position, the LES opens under the influence of threshold pressure above the LES, when the level of the barium column reaches the 4th thoracic vertebrae. At the time when time, когда the barium enters the stomach, the barium level decreases, i.e., the pressure over the LES progressively decreases, but the LES remains open until all the barium has entered the stomach. Therefore, the assertion of some authors that the relaxed LES opens as a result of mechanically pushing the bolus is not true. The anatomical features of the EGJ show that relaxation and opening of the LES occur simultaneously. The muscle bundles of this of the inner muscle coat split up 10.2 mm +/- 3.0 SD above the oblique gastroesophageal ring (fixed specimen) and for a length of 25 mm +/- 8 SD formed short transverse muscle clasps on the lesser curve side. Those muscle bundles on the greater curve side formed long oblique gastric fiber loops. (Liebermann-Meffert D, Allgöwer M, Schmid P, Blum AL. Muscular equivalent of the lower esophageal sphincter. Gastroenterology. 1979 Jan;76(1):31-8.). Muscle fibers shorten during contraction. Above the LES, obliquely oriented muscle fibers are attached to the esophagus, while below the LES they are widely scattered and attached to both the lesser and greater curvature of the stomach. During contraction, they circularly stretch the wall of the LES, opening a channel inside it. It follows from this that the opening of the LES is an active reflex contraction of some muscle fibers of the LES.

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. I think this is where there is a problem – your diagnosis of achalasia is based on the radiological appearance which does not measure the LES relaxation, instead it measures the LES opening function. Generally, first the LES relaxes and then it opens. In many cases LES does not relax on manometry but it may open due to the hydrostatic pressure of the bolus. So, in these cases manometry diagnoses achalasia but barium swallow does not.

I think that practitioners who, with the help of engineers who have no idea about the physiology of the digestive system, began to introduce HRM into practice, have no idea of the value of a reliable scientific fact. As a result of many methodological errors, as well as the acceptance of false hypotheses, they transferred manometric indicators to the status of a diagnosis. So, instead of a rare diagnosis of esophageal achalasia, this diagnosis began to be made to a huge number of patients with GERD. So, for example, with true achalasia, heartburn is not described and cannot be. And all unthinkable hypotheses in this regard do not make sense.

Boeckxstaens gave a clear differential diagnosis of these two diseases: "Achalasia is characterized by reduction or even absence of the inhibitory innervation to the LOS, leading to impaired LOS relaxation with dysphagia and stasis of food in the oesophagus. On the contrary, GORD results from failure of the antireflux barrier, with increased exposure of the oesophagus to gastric acid". (Boeckxstaens GE. The lower oesophageal sphincter. Neurogastroenterol Motil. 2005 Jun;17 Suppl 1:13-21. doi: 10.1111/j.1365-2982.2005.00661.x.).

If the LES opens and freely passes barium, then this is not achalasia.

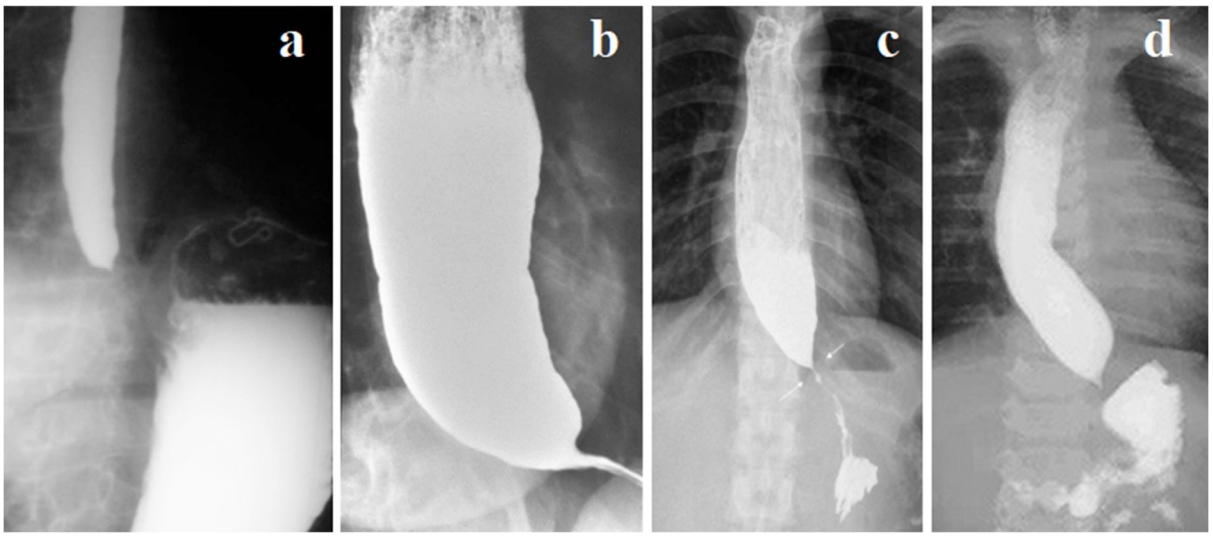

Figure 1. Radiographs with 'bird's beak' symptom. **(a)** Radiograph of an elderly patient with GERD in an upright position. Narrow esophagus with not even contours. A conical entrance to the LES that like a 'bird's beak'. The LES is in a contracted state. **(b)** The classic 'bird's beak' symptom. Unfortunately, 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. Bayless-Starling described two phases of peristalsis. First inhibition or relaxation and second excitation or contraction. Swallow induces peristalsis in the esophagus but not in the stomach. Whether all sphincters work in accordance with Bayless-Starling principle may not be true.

The law of the intestine by Bayliss and Starling - "Excitation at any point of the gut excites contraction above, inhibition below". Nothing can be added to what has been proven by great scientists. This is not a consensus where you can invent whatever you want. Cannon later proposed the term "myenteric reflex" for the phenomenon because it is due to the activity of the intramural nervous system, and not "results from the swallow-induced activation of the inhibitory neurons of the myenteric plexus that releases nitric oxide which relaxes the myogenic basal tone of the LES".

This law is valid not only for anatomical but also functional (acquired) sphincters of the digestive tract, as well as for sphincters of the urinary system, i.e., any peristaltic systems, as eloquently proved in numerous studies by prof. Shafik. 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]. This has not been confirmed by other studies. Generally, loss of peristalsis and degeneration of myenteric plexus is limited to the esophagus. For example gastric emptying in patients with achalasia is normal.

This text is talking about the true achalasia of the cardia, and not invented achalasia, which is GERD. Indeed, in GERD, the myenteric plexus is usually intact. However, evacuation from the stomach is very often delayed because GERD is accompanied by gastritis and/or gastric ulcer, as well as duodenitis because of hypersecretion of hydrochloric acid.

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]. There are lots of data to prove that

while pentagastrin does increase the LES pressure but these effects are not physiological, rather they are pharmacologic.

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).**

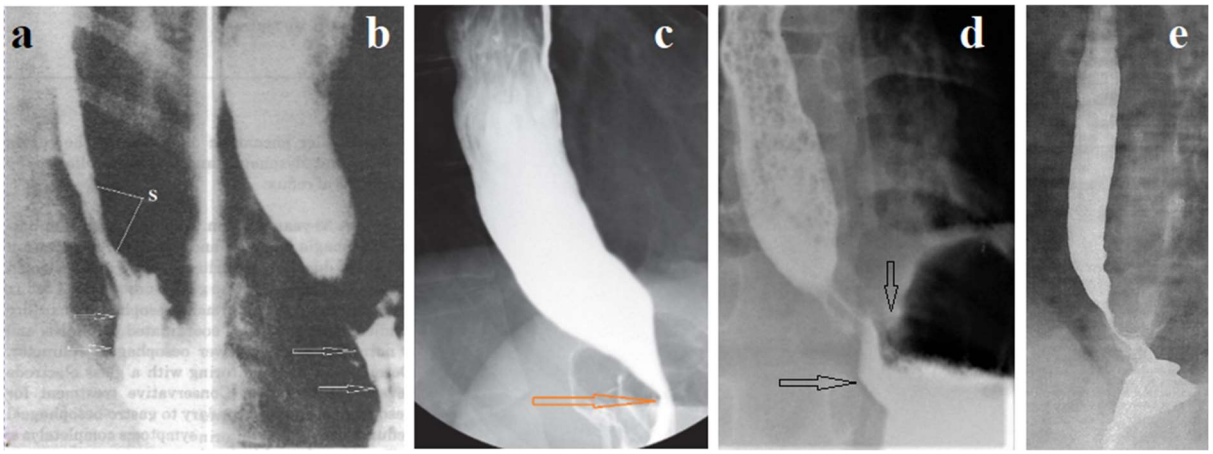

Figure 2. (a) In a patient with a gaping LES, i.e., with chalasia of the cardia (arrows), a sharp narrowing of the esophagus is visible, especially above the ampulla (s). **(b)** After 10 years, the lumen of this zone was sharply reduced, which led to the expansion of the proximal part of the esophagus. 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]. The thickening of the wall in esophagitis is different from the one in achalasia. In reflux esophagitis it is due to inflammation and fibrosis and generally in the mucosa. On the other hand, the thickening is due to muscle hypertrophy which is because of the increase in work overload of the esophageal muscle. They are contracting against resistance (non relaxing LES). The narrow segment of esophagus or LES in reflux disease is because of fibrosis and stricture formation. On the other hand, it is non-relaxing LES in achalasia esophagus.

With progressive GERD, there is a significant expansion of the esophagus. In such cases, the esophagus must work harder to create a threshold pressure for the LES to open. This leads to hypertrophy of the muscle layer.

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).** The LES moves 2-3cm into the chest during swallowing. The phrenic ampulla one sees on the barium swallow is part of the stomach in the chest. The diaphragm is located below the phrenic ampulla. The structures you label as PS and LES are not correct. PS is indeed the LES and what you label as LES is the hiatus of the diaphragm.

I provided proof and Dr. Mittal, once again cited his beliefs.

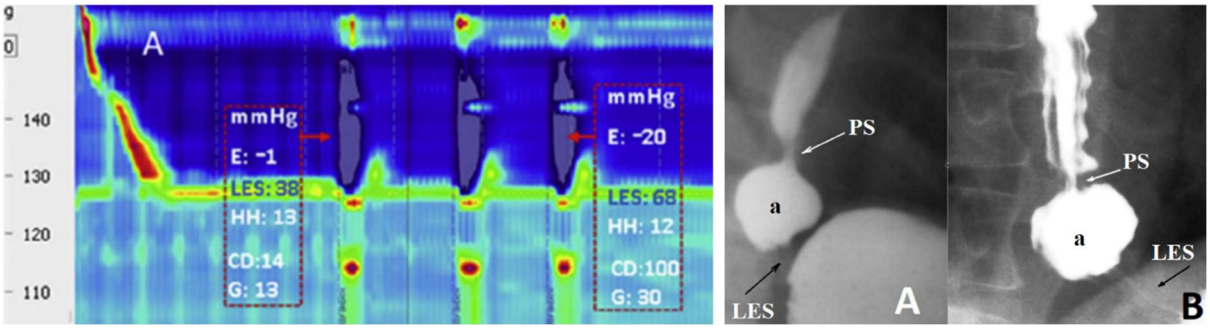

Figure 4. Manometric graph from the article of Mittal et al [25]. The two high-pressure zones (brown spots) do not have specific characteristics based on which anatomical affiliation could be accurately established. The length and extent of the upper zone are less than that of the lower one. A hiatus 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).

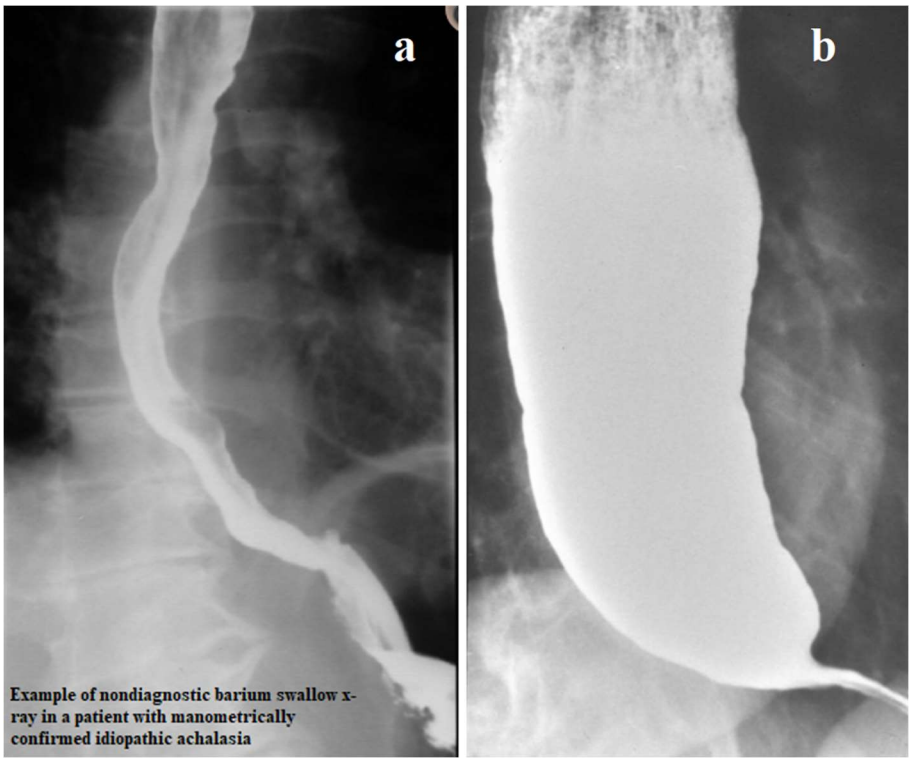

Figure 5. (a). From an article by El-Takli et al signed by the authors [25]. This X-ray does not show any of the signs of EA: the esophagus is not dilated, the LES is not contracted, evacuation to the stomach is not disturbed, and there is a large gas bubble in the stomach. In contrast, the esophagus 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. Manometry whether done by modern sensors or older water perfused system is just a tool to measure pressure. Display of the pressure using color plots has certain advantages. For e.g. it negates the motion induced artifacts in the LES pressure recording, and then there are other advantages. However, there are limitation as well. So reader of the paper has to know the strength and limitation of each technique and the question that is being asked.

Esophageal achalasia, jackhammer, diffuse esophageal spasm, and outflow obstruction are manometric characteristics, not diagnoses. As a result of the introduction of scientifically unfounded pseudo-diagnoses into medical practice, in patients with GERD, instead of preventing reflux, the authors of various "consensuses" and the Chicago Classification perform a dissection of the LES or inject Botox, thereby provoking the progression of the disease, which leads to the need for fundoplication. Prescribing PPI is not a treatment for a disease, but an attempt to control the symptoms. In some patients with GERD, long-term use of large doses of PPI causes a sharp (more than 5-fold) increase in gastrin secretion,

which causes hypersecretion of hydrochloric acid. For the treatment of GERD, it is necessary to completely stop taking products containing the provocateur of hydrochloric acid hypersecretion - lactose.

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