

On the pathogenesis of gastroesophageal reflux disease. (Part 1).

Evidence-based medicine versus the Delphi method.

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Introduction The etiology of a disease is defined as its cause. Pathogenesis describes the development of the pathological process. In trauma, the etiological factor remains in the past. In infections, the etiological factor and pathogenesis coexist to the end. Most often, the etiological factor persists, periodically initiating pathogenesis.

Previous evidence-based research has shown that the etiologic factor in acid-related diseases is hypersecretion of gastric juice. A hypothesis has been proposed that explains the occurrence of hydrochloric acid hypersecretion by lactose intolerance [1]. Literary sources focus on gastroesophageal reflux disease (GERD), which is the tip of the iceberg because it is accompanied by more pronounced clinical symptoms since, unlike the stomach and duodenal bulb, the esophageal mucosa lacks protection from the damaging effects of gastric juice.

Currently, publications based on Delphi voting decisions predominate. The Delphi method seeks consensus among experts through multiple rounds of anonymous questionnaires and feedback. Its conclusions reflect collective professional judgment rather than direct empirical demonstration of a fact. Delphi doesn't create new facts. Two features are noteworthy. First, proponents of the Delphi method disregard scientific evidence that contradicts their ideas about the pathogenesis of GERD, without testing or refuting it in any way. Second, most of them declare a conflict of interest, as they receive financial support for advertising from manufacturers of equipment and medications. The following each consensus, literature reviews are published commenting on the new changes in recommendations based on the use of diagnostic equipment.

When determining the pathophysiology of GERD, voting participants evaluate the assumptions described in the literature and consider the pathogenesis of GERD to be complex and multifactorial. In this paper, I will present the results of evidence-based medicine, in which I will analyze the generally accepted statements from the typical literature reviews: "Currently, the pathogenesis of GERD is generally believed to be related to reduction in the pressure of the lower esophageal sphincter (LES), transient and excessive lower esophageal sphincter relaxation (TLESR), hiatal hernia, esophageal clearance dysfunction, acid pockets, esophageal hypersensitivity, and mucosal barrier damage" [2].

All review articles discuss factors that influence the development of GERD, and which have been described in studies of patients with GERD at different times.

I. Evidence-based medicine regarding the lower esophageal sphincter in healthy individuals and in GERD

Anatomy The length and width of the esophagus depend on the age. Bott et al showed that in healthy children the mean diameter at the cranial point of measurement was 6.75 mm at the lower weight (2.6 kg) and 14 mm at 74 kg. The average width of the esophagus in healthy adults is 15 mm with small individual fluctuations. The LES is a thickened continuation of the circular smooth muscle fibers. There is no clear anatomical transition from the esophagus to the LES in wall thickness, so the length of the LES cannot be measured either during surgery or anatomical examination. However, the LES has clear boundaries as a zone of constant pressure, which is always higher than the pressure in the stomach. The main problem with all studies in general and in determining the length of the LES in particular is the accurate selection of healthy individuals for the control group. According to pull-through manometry with catheter in control adults the length of the LES ranges from 34 ± 9 mm to 4.1 cm. The length of its intraabdominal part ranges from 21 mm to 23 mm. The LES length in adults is the same as in adolescents. I measured the length of the LES in different ages (Table 1) [3].

Table 2. Normal length LES in different age groups

	Length of lower esophageal sphincter (cm)					
Age	Up to year	1-3 years	4-7 years	8-10 years	11-15 years	21-65 years
Limits	0.7 - 1.0	1.2 - 1.5	1.5- 1.8	1.9 - 2.3	2.3 - 2.9	3.2 - 4.2
Mean $\pm$ SE	0.86 $\pm$ 0.03	1.40 $\pm$ 0.02	1.72 $\pm$ 0.07	2.10 $\pm$ 0.05	2.45 $\pm$ 0.11	3.60 $\pm$ 0.08

Physiology At rest, the esophagus is in a relaxed state with low internal pressure. When a bolus enters the esophagus, peristalsis moves it in accordance with the law of the intestine [4]. In the horizontal position, as the bolus approaches the LES, the peristaltic wave closes proximal to the bolus. At this point, a high-pressure zone is created between the closure zone and the LES, which leads to the opening of the LES, and the final peristaltic wave injects the bolus into the stomach. The high pressure of the final peristaltic wave exceeds the pressure in the stomach and prevents reflux into the esophagus. In the vertical position, the threshold pressure for opening the LES occurs under the hydrostatic pressure of the liquid food column. Although the

hydrostatic pressure decreases during esophageal emptying, the LES remains open until the esophagus is completely cleared. This suggests that opening of the LES, provoked by hydrostatic pressure, is a reflex act [3].

In response to esophageal distension the pressure (tonus) of the LES decreases to pass the bolus to the stomach. During the fundus or body of the stomach is stretched the pressure (tonus) of the LES increases to prevent reflux of aggressive gastric contents into the esophagus. Shafik et al found that gastric balloon filling volume greater than 100-110 ml causes a reflex contraction of the upper and lower esophageal sphincters. This physiological feature formed the basis of the method I developed for diagnosing esophageal pathology using high pressure in the stomach [3] (**Figure 1**).

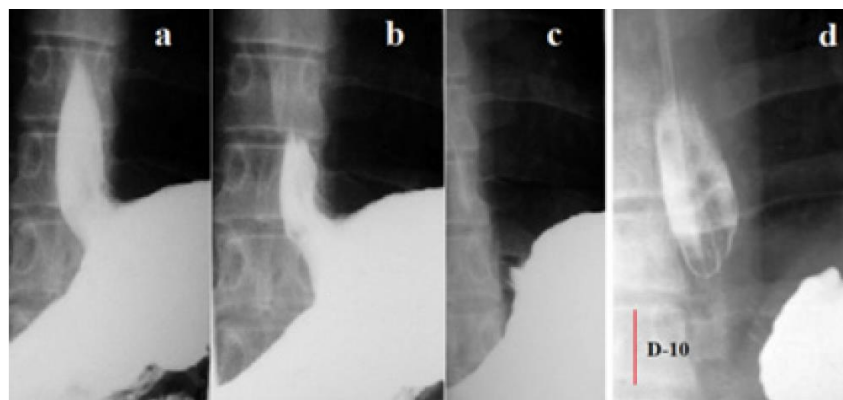


Figure 1. The passage of the bolus through the EGJ during abdominal compression in the horizontal position of patients. (**a, b, c**) In a patient without GERD symptoms, the peristaltic wave overcame the increased tone of the LES, because of which barium passed into the stomach without delay and the LES could not be detected. (**d**). In a patient with GERD, as evidenced by longitudinal folds in the esophagus and at the level of the LES, abdominal compression resulted in LES contraction. Its length can be measured as the distance without contrast medium between the esophagus and the stomach. Since the height of D-10 is approximately 2 cm, the true length of the LES can be calculated. It is 2.4 cm.

Mapping of the esophago-gastric junction (EGJ)

Abdominal compression during radiographic examination was used to estimate the length of the LES in patients whose gastrointestinal complaints had developed less than six months prior to presentation. I assumed that the LES length had not yet significantly shortened during this time. These results formed the basis for Table 1. I believe that the true dimensions are closer to the maximum limit, i.e., in adults, the LES length is approximately 4 cm. The LES length obtained by radiographic examination was the same as that obtained by manometric

measurement and the same as that obtained using the three-dimensional model of the EGJ from the article by Yassi et al [4]. This suggests that the obtained results are close to the true LES length.

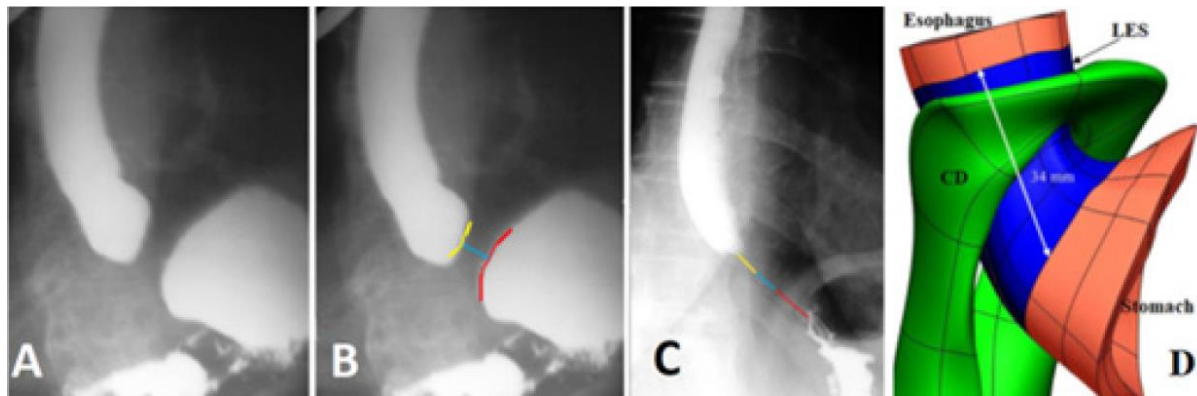


Figure 2. Radiograph (A) and scheme to it (B) of patient with GERD was done in a horizontal position with the abdominal compression. The sharp shortening of the LES because of the opening of the supra-diaphragmatic part of the LES (yellow) and inside the abdominal part of the LES (red) is determined. Only the diaphragm part (blue) of the sphincter is closed. (C). Radiograph of this patient in an upright position taken during abdominal compression. The LES contracted in response to the increased pressure in the stomach. It is visible as two longitudinal folds between the esophagus and stomach. Since the actual height of D-10 is ≈ 2 cm, the actual length of the LES is ≈ 3.4 cm. The LES parts: red - the abdominal segment, blue - inside the diaphragm, yellow - above the diaphragm. (D). Three-dimensional model of the EGJ from the article by Yassi et al [48]. The length of the LES is 3.4 cm (blue). Its abdominal part is ≈ 2 cm. About 1 cm is located at the level of the CD and 0.4 cm above the diaphragm.

As shown in the study by Shafik et al., “Anatomical and electrophysiologic evidence suggests that the loop muscle is an autonomous muscle that surrounds the lower esophagus and is not derived from the diaphragmatic crura. We call this muscle the 'striated gastroesophageal sphincter' or [5,6]. It has been shown that the CD relaxes with increasing esophageal pressure and contract with increasing gastric pressure synchronously with the LES. In another study by Shafik et al., electromyographic activity of the CD crura disappeared during prolonged straining after 15–18 seconds (mean 16.8 ± 1.2 s). The authors concluded that the CD consists of striated muscle fibers which are easily fatigable and cannot remain contracted for long periods [7]. These studies help explain the research of Mittal and Fisher, in which they showed that during swallowing, simultaneously with the opening of the LES, there is a “mechanical inhibition of the crural diaphragm” [8]. They confirmed the well-known fact that during

swallowing it is impossible to inhale, i.e., they determined the electrical activity of the diaphragm, and not the external esophageal sphincter.

Based on a literature review, the esophageal-gastric junction (EGJ) responsible for the antireflux function, is represented by the LES and the CD, which is correctly called the external esophageal sphincter (EES). The length of the LES in adults is approximately 3.4-4 cm. It consists of three parts: the intra-abdominal part, approximately 2.1-2.3 cm long, the intradiaphragmatic part, approximately 1 cm long, and the supradiaphragmatic part, 0.4-1.0 cm long. The EES loop surrounds the LES in the hiatal canal. The width of the EES encirclement is up to 1 cm. At rest, both sphincters are in a tonic state. During swallowing, the last peristaltic wave of the esophagus creates high pressure above the LES, which leads to relaxation of the LES and EES. After the bolus passes, the tone of both sphincters is restored and the EGJ closes. When the pressure in the body of the stomach increases, synchronous contraction of the LES and EES occurs. The LES can withstand high pressure for a long time, while the tone of the EES decreases within 30 seconds. The EES provides short-term support to the LES during periods of increased abdominal pressure, such as when rising from a seat, during defecation, etc.

Since high gastric pressure causes simultaneous contractions of the upper and lower esophageal sphincters, I developed an X-ray method for diagnosing esophageal diseases. The patient, in a horizontal position, drinks a barium suspension through a straw from a jar placed near their head. When they feel the barium run out (approximately 200 ml), they raise their outstretched legs. In the image taken at this time, the barium tightly fills the esophagus between the two contracted sphincters. На Figure 3 приведен анализ одного наблюдения.

A 53-year-old patient complains of depression, cough with sputum production, very frequent belching. Heartburn occurs very rarely – once a year. Symptoms occur during eating, after drinking, and during conversation. Taking PPI twice a day did not provide relief. Gastroscopy: mild antral gastritis. HRM: esophageal peristalsis is normal, LES length – 2.7 cm (normal 2.7–4.8), intraabdominal – 0, HH- 1.8 cm. Upper esophageal sphincter (pressure) – normal. Conclusion: the function of the LES is normal. The data are close to EGJ outflow obstruction. Ambulatory reflux monitoring (pH – impedance): mild increase in acid reflux (pH-4.9%). Conclusion: Suspected reflux disease is not severe.

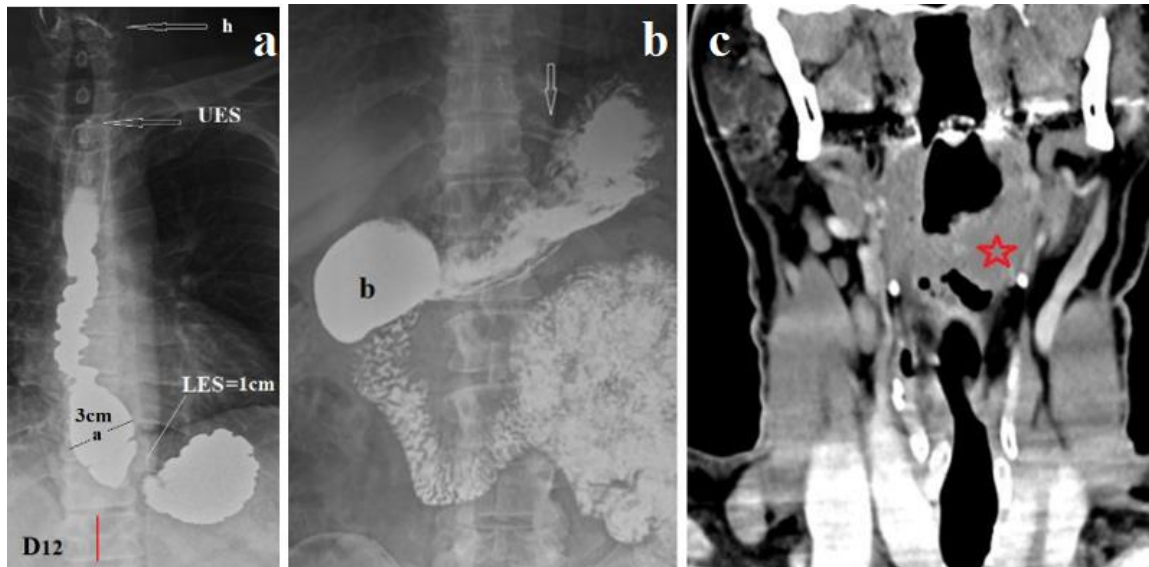


Figure 3. (a). In frontal radiography, the distance between the phrenic ampulla (a) and the stomach, which does not contain contrast, is the contracted LES. Its length is 1.0 cm, approximately 3 times shorter than normal. The ampulla width is 3.0 cm, which is 2 times wider than normal. The contours of the esophagus are tortuous and asymmetrical, indicating dyskinesia due to esophagitis. The upper arrow (h) indicates asymmetry of the left hypopharynx. (b). After 5 minutes, significant evacuation of barium from the stomach is detected. A barium collection [b] - duodenal bulb dyskinesia. The arrow shows thickened parallel folds in the LES, indicating inflammation. (c). On the section of the CT in the pharynx determine an asymmetric thickening (asterisk), suggesting an inflammatory process.

Conclusion: Extra-esophageal presentation of severe gastroesophageal reflux disease. Gastritis. Pharyngitis. Partial unilateral paralysis vocal cord, Cholesteatoma (LT), Eustachian tube dysfunction.

In all patients with EGJ radiography after abdominal compression for 30 seconds, a dilated camera, called a hiatal hernia (HH) located cranial to the contracted LES. This contraction zone could not be mediated by EES (CD), firstly because after 30 seconds of tension, EES (CD) relaxed, as striated muscle quickly fatigues. Secondly, the contraction length often far exceeded the 1 cm achieved by EES (CD). In all patients (more than 80) with the highest intragastric pressure, the phrenic ampulla was located above the contracted LES, regardless of its size. The LES was always at the same level relative to bony landmarks (D-10). Shortening of the LES occurred in patients with GERD due to opening of the intra-abdominal portion. The esophagus itself never shortened; it was the "esophagus + LES" complex that shortened. In the article by Kwiatek et al., a contrast clip attached to the mucosa did not change its position relative to the

thoracic vertebra during swallowing. A patient who was considered healthy was a patient with GERD. During swallowing, the LES shortened, bringing the clip closer to the stomach [9] (**Figure 4**).

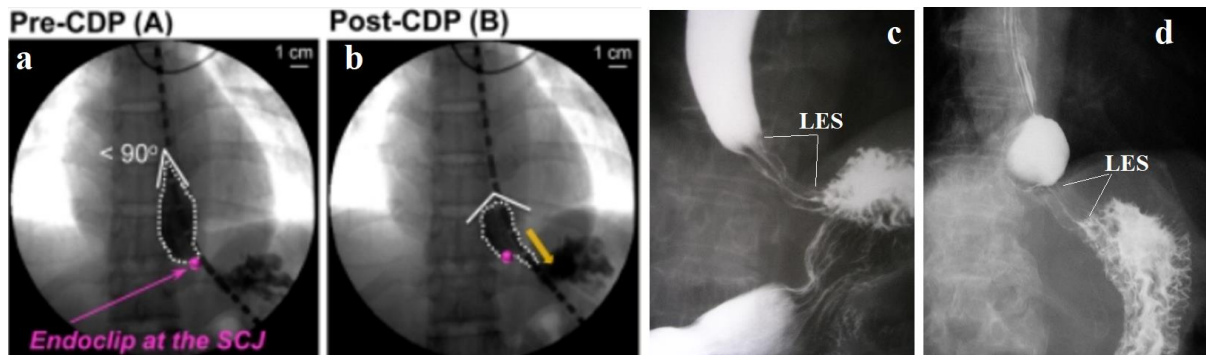


Figure 4. (a, b). From the article by Kwiatek et al [9]. The radiographs show that the clip did not change position during swallowing. In both pictures, it is located near the lower left corner of the D-9. **(c).** Short LES (2 cm) in the contraction stage with coarse (wide) folds, resulting from reflux esophagitis. **(d).** Contracted LES between the stomach and the phrenic ampulla. Above the ampulla, the folds in the esophagus are narrower. The width of the folds during inflammation depends on the wall thickness and tone. The wall of the LES is thicker, and the tone is significantly greater than that in the esophagus.

Why did the organizers of the Chicago Classification, who universally recommend pH monitoring for diagnosing GERD, select subjects based on the absence of GERD symptom as a control group for determining the normal limits for HRM [9]? It is not surprising that the normal limits for LES length differ by almost twofold. They attached a clip to the upper end of the broad folds of the stomach, assuming, that these folds of the stomach, and therefore the clip supposedly attachment site, correspond to the EGJ. As seen in radiographs (c, d), the EGJ is located between the stomach and the shortened but contracted LES. Its abdominal portion opened and filled with barium

In the case shown in Figure 3, antral gastritis and duodenal dyskinesia were diagnosed, indicating hydrochloric acid hypersecretion as an etiologic factor in the development of acid-related diseases. The length of the LES was significantly shortened due to the absence of the abdominal portion; therefore, LES function cannot be normal. The presence of HH is convincing evidence of GERD. The possibility of HH without GERD is an error caused by the low sensitivity of pH monitoring. Dilation of the distal esophagus, called the ampulla, is caused by the inflammatory process and the weakness of the last peristaltic wave. Therefore, the

ampoule is often unable to inject its entire contents into the stomach, leading to chyme retention in it (an acid pocket). "EGJ outflow obstruction" is, firstly, not a diagnosis, and secondly, as Figure 3b shows, most of the barium is in the intestine 5 minutes after ingestion, contradicting the assumption of possible gastric emptying obstruction. pH monitoring revealed a mild increase in acid reflux (pH 4.9%). This means that hydrochloric acid with a pH < 4 remained in the esophagus for 79 minutes over the course of 24 hours. The assumption that the reflux of aggressive gastric contents, which destroy food proteins but may be harmless to the proteins of the esophageal wall, defies common sense.

Based on histologic studies, Chandrasoma and DeMeester call to abandon two widespread fundamental errors: (1) that cardiac epithelium typically lines the proximal part of the stomach; (2) that the esophagogastric junction (EGJ) is defined by the proximal border of mucosal folds. They showed that normally (a) the esophageal squamous epithelium transitions at the EGJ to gastric oxyntic epithelium with no intervening cardiac epithelium; (b) cardiac metaplasia of the squamous epithelium due to exposure to gastric juice results in cephalad movement of the squamo-columnar junction. This creates the squamo-oxyntic gap and the dilated distal esophagus, which is distal to the endoscopic EGJ. The length of the squamooxyntic gap in the dilated distal esophagus is consistent with the shortening of the abdominal segment of the lower esophageal sphincter (LES); (c) in the early stages, the gap is <5 mm, and the LES retains its functionality. Reflux is rare, and patients are asymptomatic; (d) the length of the squamooxyntic gap increases proportionally to the degree of shortening of the lower esophageal sphincter, which becomes increasingly incompetent. At a gap length of 5-15 mm, reflux is sufficient to cause symptoms, but in most patients, symptoms are controlled, and endoscopy shows no abnormalities. The gap is located entirely within the dilated distal esophagus, which, according to existing criteria, is mistaken for the proximal stomach. (e) The end stage of GERD occurs when the squamooxyntic gap exceeds 15 mm. These patients experience severe reflux, with increasingly uncontrollable symptoms and columnar esophageal mucosa, both of which are irreversible. Understanding the pathophysiology of GERD will enable diagnosis of the disease in its earliest and most reversible stages.

Histological studies by Chandrasoma and DeMeester, published in several articles, fully agreed with the manometric and radiographic data. They demonstrated that the disease begins with the penetration of aggressive gastric juice into the abdominal portion of the LES. At this stage, it has not yet penetrated the esophagus. Consequently, acid cannot be detected in the esophagus at this early stage by the pH monitoring. Gastric juice enters the esophagus in the advanced

stages of the disease. Thus, it was proven that the idea of physiological reflux arose to justify pH monitoring, which does not identify GERD as a disease in its early stages. Damage to gastric juice leads to shortening of the LES due to its opening, as well as to dilation of the esophagus above the LES, which is called the phrenic ampulla. The rejection of the false assumption that wide folds above the stomach indicate gastric elevation and shortening of the esophagus demonstrates that what is commonly called a hiatal hernia is in fact the phrenic ampulla. This means, as it was previously believed, that HH is not the cause of GERD, but it's a reliable symptom.

These studies have sunk into oblivion. Why were they ignored despite no one refuting their validity? Why isn't this simple, accurate, and inexpensive method used in practice? In 2017, I sent Chandrasoma my article on GERD pathogenesis. I think his answer explains a lot.

Re: GERD- Article

PC

Parakrama Chandrasoma <ptchandr@usc.edu>

ОТВЕТИТЬ |

ЧТ 01.06, 20:44

01.06.2017 23:33.

Dear Dr. Levin

It is nice to see research in other specialties come to similar conclusions regarding the pathogenesis of GERD in its early stages before trans-sphincteric reflux occurs. I believe the identification of a "pre-GERD" stage of degradation of the abdominal segment of the LES will prove to be critical in the future management of GERD which must shift its objective from symptom control to prevention of cancer.

Your study shows a real time anatomic abnormality during swallowing that I never see as a person involved in looking at biopsies from this region and examining resected specimens. Ultimately, if we develop the correct understanding of the pathogenesis of this early or pre-GERD damage to the LES, all specialties must converge such that everyone with all different perspectives (endoscopy, clinical, pathology, radiology, anatomy, physiology) can explain the pathogenesis on the basis of this correct perspective. Right now, the situation is chaotic. Even though I cannot understand every element in your paper (never having seen radiology images), I get the feeling that we are saying the same thing in different ways.

Congratulations in having the open and innovative mind that you have.

My new book on GERD will be published in September. It has a major expansion of concepts that I have tried to present over the past 25 years.

Please continue your important work. It is very unusual to find a radiologist who thinks about GERD. I hope we can meet some day.

With best regards from Pasadena, California.

Para Chandrasoma

I am sending the first part of my analysis on the pathophysiology of GERD so that physicians without access to evidence-based medicine can be prepared to read the next part.

I strive to present scientific data conscientiously, but I understand that I cannot avoid errors or subjective judgment. Therefore, I would be grateful if I could stimulate discussion. You can write to me anonymously or instruct me not to disclose your data when citing your arguments.

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<http://www.anorectalmalformations.com>

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