The cardia: esophageal or gastric? Critical reviewing the anatomy and histopathology of the esophagogastric junction

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INTRODUCTION

Gastroesophageal reflux disease (GERD) affects 20% to 30% of the population in Europe and North America (annual incidence: 0.5%)1-2. In addition to symptom induced impairment of the life quality and productivity, GERD alters the morphology of the esophagus3-5. Reflux mediates inflammation (esophagitis) and the development of columnar lined esophagus (CLE)6,7. With longer duration of the symptoms and increased length of CLE, 20% to 100% of patients with GERD develop non-dysplastic Barrett’s esophagus (8-12), which may progress to cancer (0.12% to 0.7% annual cancer risk)13-16.

Endoscopy aims to assess the morphologic consequences of reflux (esophagitis, strictures, rings, columnar lined esophagus)5,8. In order to accurately describe the extent of reflux induced changes the endoscopist should know where the esophagus ends and the stomach starts6. Unfortunately, inaccuracy exists regarding the accurate endoscopic, anatomical and histopathological definition of the esophagogastric junction (EGJ)6-9,10,17-19. As a consequence numerous terms and composita describe morphologic findings around the EGJ: cardia, junctional, gastric fundic, irregular z line, palisade vessels, gastric folds, rugal folds5,10. Most importantly, discrepancy exists regarding the accurate allocation of the cardia: esophageal7,9,10 vs. gastric6,17-19. Here we aim to summarize the concepts regarding the EGJ anatomy and histopathology. Furthermore we questioned in as much the concepts describing and defining the gastric cardia were based on valid anatomical and histopathological criteria.

METHODS

Our literature research used PUB MED, Scopus, and Google and incorporated the following search terms: "gastric cardia", "gastric cardia adenocarcinoma", "gastric AND cardia", "gastroesophageal reflux disease", "Bar-
rett’s esophagus", "columnar lined esophagus", "junctional epithelium", "cardiac mucosa", "oxyntocardiac mucosa", "intestinal metaplasia", "hiatal hernia", dilated distal esophagus", "squamo oxyntic gap", "esophagitis", "endoscopy", "fetal esophagus". We aimed to find valid anatomical and histopathological criteria for the definition of esophagus, cardia and stomach. Furthermore we analyzed in as much data obtained in anatomic, endoscopic and histopathological studies were based on valid definitions of the esophagus, cardia and stomach and allowed the conclusions drawn in the respective examinations. Hiatal hernia was considered, if endoscopically visible gastric type folds (rugal folds) were reported to commence > 2.0 cm above the level of the diaphragmatic impressions. The presence of endoscopically visible tongues, segments or islands above the level of the rise of the gastric type folds, i.e. rugal folds, described "endoscopically visible columnar lined esophagus (CLEv). Endoscopic and histopathological images were obtained and cataloged, as described previously22. Our analysis includes papers published between 1889 and 2012 and book chapters published since 1865.

RESULTS

We first examined early reports regarding the description of reflux related pathology of the esophagus and the cardia. At the end of the 19th century the term cardia was synonymously used to describe the functional sphincter mechanism within the distal 2 cm of the esophagus and the anatomy of the proximal portion of the stomach20,21. Consequently this definition started the confusion and inability to clearly define and allocate the cardia: esophageal vs. gastric20,21.

Prior to the introduction of endoscopy, radiology served to assess the morphologic irregularities of the esophagus20,21. Around the year 1900, esophageal ulcer became a leading topic of foregut pathology. Similarly to the stomach, esophageal ulcers developed as an inflammatory response in the setting of syphilis, tuberculosis, aneurysm, traction diverticula, foreign bodies, reflux (peptic ulcer) and cancer20,21. Surgery aimed to palliate dysphagia by transgastric dilatation, the placement of feeding tubes or the creation of a gastrostomy. Usually the patients died due to ulcer perforation into the aorta, mediastinum, lungs and pleura24. Thus in 1899 Alexander Fraenkel from Vienna described the presence of a columnar lining around an ulcer ex digestione, i.e. peptic ulcer20. The patient died due to an ulcer induced bleeding from an esophageal vein. At autopsy Fraenkel found, that in contrast to the stomach, the columnar lining of the esophagus contained lobulated glands, narrowly crowded goblet cell like formations of the epithelium and absence of oxyntic (papil)ar cells. At his time Fraenkel did not know, that, what he described, would have later been termed columnar lined esophagus (CLE) or Barrett’s esophagus22. Thus Fraenkel’s case can be considered as one of the very first descriptions of what we presently name Barrett’s esophagus22. The case described by Fraenkel was referenced in a paper by Wilder Tilestone from Harvard Medical School Boston, who visited the Pathological Institute in Vienna for the collection of esophagitis cases21.

Before the introduction of an effective anti-acid medication esophagitis was almost always associated with ulcer and stricture formation. In 1906 Tilestone published a fascinating series of 41 cases of peptic ulcers of the esophagus21. At his time peptic ulcers of the esophagus were observed in 6 out of 4496 autopsies, i.e. 0.13%. The age-dependent frequency peaked at 40-49 years and showed a male predominance. Tilestone observed that the ulcers predominantly developed at the right posterolateral wall of the distal esophagus with most proximal location at the level of the aortic arch. Peptic ulcer was hypothesized to develop as a consequence of the insufficiency of the cardia, which Tilestone suggested to result either from dysfunction of the cardiac sphincter or as a consequence of an ulcer arising at this location. Interestingly 100 years later studies reconfirmed the same demographics and predominant location of dysplastic lesions for CLE and Barrett’s esophagus11,12,23. Furthermore, the group around Peter Kahrilas and John Pandolfino from Chicago found an asymmetric 3D-pressure profile of the lower esophageal sphincter, which explained the impaired competency of the right (small gastric curvature) vs. the left portion of the anti reflux mechanism24. Going in line with these findings, acid exposure was significantly increased within the right portion of the circumference of the distal esophagus in GERD patients25.

Tilestone recognized two different types of cardiac relaxation. One form was considered as vagus nerve - regulated form of relaxation of the cardia during swallowing. The other type he described as rhythmical relaxations during the regurgitation of food in animals. Today this condition is termed “transient lower esophageal sphincter relaxation” and represents a major cause for postprandial reflux26-28.
Taken together, more than 100 years ago, Fraenkel and Tilestone understood that peptic ulcers of the esophagus developed as a consequence of the dysfunction of the cardiac sphincter and were associated with columnar metaplasia of the esophageal epithelium and adenocarcinoma. In these days the term "cardia" has been synonymously used to describe the lower esophageal sphincter and the proximal stomach.

In 1946, the thoracic surgeon P. R. Allison from Leeds published 3 cases of peptic ulcer of the esophagus and suggested that the condition resulted from the derangement of the mechanism of the cardia. This in turn was considered to favor the reflux of acid gastric juice into the esophagus. As a consequence esophagitis and peptic ulcer developed. Furthermore, Allison hypothesized, that the peptic ulcer of the esophagus was associated with an acquired or congenital hiatal hernia of the stomach, which causes shortening of the esophagus and contributed to the dysfunction of the cardia.

In 1950 Norman Barrett from London described a foregut condition, where he suggested the presence of a congenital short esophagus with an herniated intrathoracic stomach, which resided above the level of the diaphragm. However, in 1953, Allison and Johnstone provided evidence, that what had been taken for intrathoracic stomach by Barrett, in fact represented esophagus lined with a columnar epithelium, which they named "the oesophagus lined with gastric mucous membrane". They described a series of 7 cases of reflux induced esophagitis and ulcers (with one adenocarcinoma and one goblet cell containing CLE). Using valid anatomical criteria, the authors had no problem to define the level of the transition from the esophagus to the stomach, i.e. the peritoneal reflection. In addition they knew that the esophagus lacked a peritoneal coverage and contained submucosal glands, which are absent in the stomach. Thus, the organ above the peritoneal reflection was esophagus, that below the reflection was stomach. Furthermore, what has been taken for proximal gastric pouch by Barrett in 1950 was demonstrated to contain submucosal glands and lacked a peritoneal coverage and was thus proven to be esophagus. Most importantly Allison and Johnstone found that the transition from esophagus to stomach did not correlate with the squamocolumnar junction (SCJ), which resided far above the level of the peritoneal reflection. As a consequence they concluded, that the EGJ cannot be assessed from the mucosal, but from the outer side of the specimen. Using their valid anatomical criteria all mucosa above the level of the peritoneal reflection was considered esophageal. Based on this paper, Norman Barrett revised his opinion in 1957 and coined the term "The lower oesophagus lined by columnar epithelium". In addition Allison and Johnstone reconfirmed Fraenkel's observation, that in contrast to the straight tubular glands of the mucosa of the proximal stomach, CLE glands were lobulated. In contrast to Fraenkel, Allison and Johnstone found a mixture of mucus and parietal cells within the sub-foveolar region of the CLE glands. Thus, Allison and Johnstone correctly attributed the types of columnar epithelia to the esophagus and demonstrated the difference between CLE and the mucosa of the proximal stomach at the histopathological level. As a minor drawback, they used terms which suggested, that the epithelia were of gastric origin.

FIGURE 2.
HISTOPATHOLOGY OF A FULL THICKNESS SPECIMEN OF THE DISTAL ESOPHAGUS.
"gastric mucosa of fundal type" (later oxyntocardiac mucosa); "cardiac type of gastric mucosa" (which later became junctional and cardiac mucosa). However, at their time all seemed to be clear and well defined regarding GERD related esophageal anatomy. Again, the term "cardia" indicated the EGI and the anti-reflux mechanism within the lower end of the esophagus.

The confusion regarding CLE and the cardia increased with the search for an endoscopic definition of the EGI. What has been clearly demonstrated by Fraenkel in 1899, Tilestone in 1906, Allison and Johnstone in 1953 and Barrett in 1957 to be impossible was now to work: the assessment of the esophagogastric junction from the luminal aspect during endoscopy. In 1961, John Hayward from the Royal Melbourne Hospital, Australia, convinced the community, that in the foregut all the tube represented the esophagus, irrespective of its luminal coverage. In contrast to that, all pouch distal to the tube was considered as stomach. According to Hayward, the cardia represented the distal 2 cm of the esophagus including the segment of the lower esophageal sphincter and was covered by cardiac mucosa (=mucus cell only epithelium). Furthermore he suggested, that the cardiac mucosa normally extended into the proximal stomach over a distance of 2 cm. Hayward thought, that the oxyntic cell-free cardia protects the squamous lined esophagus from the acid producing proximal stomach and thus serves as a 4 cm long normal buffer zone (2 cm in the distal esophagus, 2 cm within the proximal stomach). Thus, in his mind, the cardia served to protect the squamous epithelium lined distal esophagus against reflux induced digestion. Therefore, what had been accurately defined by Allison and Johnstone in 1953 and by Barrett in 1957, based on valid anatomical and histopathological criteria, now again became a mystery.

In 1976, Paull et al. around Raj Goyal from Beth Israel Hospital, Harvard Medical School, Boston, characterized the histopathology of CLE using a morphologic and physiologic approach. Manometry was used to assess the level of the lower esophageal sphincter (LES) and to prove, that what was lined by cuboidal epithelium, in fact represented esophagus, i.e. demonstrated normal swallow induced esophageal contraction waves during manometry. Biopsies were obtained from the distal esophagus above and at the level of the lower esophageal sphincter, as assessed by manometry. Referring to Trier’s paper from 1970, Paull et al. listed 3 CLE types obtained during H&E staining of the biopsies: junctional (mucus cells only), gastric/fundic (mixture of mucus, chief and parietal cells) and specialized intestinal (goblet cells). Furthermore the authors demonstrated that the mucosal types distributed along a distinct zonation, with junctional and/or specialized intestinal mucosa in the proximal and gastric/fundic type mucosa in the distal portion of the CLE. Unfortunately, the term "junctional epithelium" suggested distal esophageal and proximal gastric location and nourished the insecurities regarding the allocation of the cardia.

In 1987, McClave et al. continued John Hayward’s conduct of reasoning. Their conclusions were drawn from observations made in 18 patients and 4 controls. The authors came up with the conclusion, that the proximal margin of the endoscopically visible gastric type folds (rugal folds) coincided with the anatomical EGI. Thus, without correlation with anatomical and histopathological criteria, McClave et al. convinced the community, that the rugal folds distal to the tubular esophagus were gastric. Consequently the mucosa lining the proximal portion of the rugal folds had to be gastric and invalid endoscopic criteria were applied to define esophageal and gastric pathologies. As a consequence the gastric cardia was convincingly introduced as a normal structure of the foregut interposed between the tubular esophagus and the body of the stomach. The gastric cardia was demonstrated to either be covered by a mucus cell only epithelium (i.e. carditis) and/or by a goblet cell containing mucosa, i.e. intestinal metaplasia of the gastric cardia. Based on these assumptions major efforts have been undertaken to examine what has been thought to represent the pathologies of the gastric cardia.
and how they related to other inflammatory foregut disorders (i.e. H. pylori gastritis, esophagitis). Furthermore, distortions of the geometry involving the proximal portion of the endoscopically visible gastric type folds were attributed to the stomach (hiatal hernia). Accordingly, CLE was considered to interpose between the SCJ and the level of the rise of the gastric (rugal) folds. With the Prague classification this view holds until today. Finally, the above confusion effectively infiltrated the management of foregut cancers. EGJ cancers were categorized as distal esophageal, cardiac and proximal gastric (AEG I-III), according to the location of the tumor center, i.e. above, at or below the level of the rise of the gastric type folds. Using the search terms "gastric AND cardia" and "gastric cardia adenocarcinoma" PUB MED lists 5502 reports from 1916-2012 and 1606 hits from 1959-2012, respectively. These numbers reflect how influential and dominant the "model anatomy" became for the academic science. Remains to be questioned in as much the misunderstanding of EGJ anatomy led to misclassification of EGJ tumors and affected the oncologic outcome data (survival for distal esophageal, gastric cardia adenocarcinoma?).

With the beginning of the 1990s cardiac mucosa was considered to be the normal lining of the gastric cardia and to constitute the coverage of the distal esophagus in patients with GERD. Thus, the same type of mucosa could be assessed at both sides of the EGJ. In the words of Parakrama Chandrasoma from Los Angeles, the anatomical EGJ was dislocated upwards above the level of the peritoneal reflection. Consequently the allocation of disease relied on the macroscopic definition of the biopsy location: tubular esophagus vs. gastric pouch. For example, goblet cells within biopsies obtained above or below the level of the rise of the gastric type folds defined intestinal metaplasia of the esophagus (Barrett’s esophagus) and intestinal metaplasia of the gastric cardia, respectively (Figure 1A-D). Interestingly nobody questioned, how inflammation could be restricted to a small proximal portion of the proximal stomach (cardia) without affecting the rest of the stomach? Here the medical community created a situation, where macroscopy suggested to be superior to histopathology, where endoscopy overruled microscopy. All that happened, because of the use of inaccurate invalid criteria for the definition of esophagus vs. stomach.

Going in line with Sir Charles Popper reasoning should prove and disprove, i.e. verification and falsification. It took until 1997, when Chandrasoma started to question the existence of the gastric cardia, the validity of the criteria of the endoscopic anatomy and to reevaluate the histopathology of CLE. The group around the esophageal surgeon Tom DeMeester provided standardized biopsies and resection specimens from patients with GERD, Barrett’s esophagus and esophageal carcinoma. Fusion of endoscopic and microscopical data using valid histopathological and anatomical criteria helped the twisted minds to develop a novel histopathology classification of CLE. The histopathological analysis of full thickness esophageal resection specimens revealed our novel understanding regarding the EGJ anatomy.

Chandrasoma simplified the classification by Paul et al. by the fact, that he omitted "noise", which complicated the diagnosis, i.e. chief cells, pancreatic metaplasia. His classification used well defined, valid criteria and...
listed the following mucosal CLE types:8,53 (Figure 2A-C): cardiac mucosa (CM): mucus cells only; oxyntocardiac mucosa (OCM): mixture of parietal cells and mucus cells within the subfoveal region of the glands; intestinal metaplasia (IM): mixture of goblet cells and mucus cells, this is Barrett’s esophagus without dysplasia (i.e. nondysplastic Barrett’s esophagus; NDBe). Assessment of the CLE types requires biopsies including the entire mucosal layer, otherwise the pathologist cannot assess the cells within the subfoveal region of the glands. While goblet cells distribute along the entire surface of the glands (superficial, foveolar region, subfoveal region of the glands), the differentiation between CM and OCM requires information on the cell types within the subfoveal region of the CLE glands: parietal cells, mucus cells. Therefore, the biopsy sampling depth is essential for an adequate histopathological diagnosis and should reach down to the level of the muscularis mucosae. Subsequent studies confirmed the practicability and reproducibility of the Chandrasoma classification for the diagnosis of CLE.39-62

Biopsy and function test studies in GERD patients indicated that the presence of carditis (+IM) correlated with the severity of gastroesophageal reflux, as assessed by esophageal manometry and pH monitoring. An autopsy study indicated that more than 50% of individuals lacked carditis (CM) and that CM and OCM were not uniformly present at the entire circumference of the EGJ. Investigating EGJ resection specimens, Sarbia et al.64 found, that what has been taken for proximal stomach contained CLE with submucosal glands over a distance of 0.2 cm to 2.4 cm distal to the level of the rise of the gastric type folds. Furthermore, CM was not present at the entire circumference.

Next, Chandrasoma et al.58 fused the anatomy and the histopathology of full thickness EGJ resection specimens. Going in line with Allison and Johnstone31, absence of a peritoneal coverage, presence of submucosal glands defined esophageal location. The stomach lacks submucosal glands and contains a peritoneal coverage. In contrast to Allison and Johnstone31, who separated the esophagus from the stomach at the level of the peritoneal reflection, Chandrasoma et al.58 horizontally dissected the foregut specimen at the level of the rise of the gastric type folds, i.e. the EGJ according to the present endoscopic criteria (Figure 1A-D). All specimens contained submucosal glands at the level of the rise of the rugal (gastric type) folds. In addition, submucosal glands were present up to 2.0 cm distal to the level of the rise of the gastric type folds.58 Taken together, using valid criteria and methods for the accurate assessment of the anatomical location, the above studies showed that "cardia" is absent or not involving the entire circumference of the foregut in more than 50% of the cases.58-62 Furthermore, if present, the length of the "cardia" ranges from > 1 mm in children to more than 2 cm in adults.58-64 Finally, the presence and the length of the "cardia" correlates with the severity of gastroesophageal reflux.26,44,47,66

Fusion of esophageal manometry, pH monitoring and histopathology reveals our current understanding regarding the pathogenesis of the "cardia"24-28,67 (Figure 3A-E). Repeated gastric distensions (high volume meals, overeating, carbonated beverages) cause transient dilatations and relaxations of the lower esophageal sphincter (LES)27,28 (Figure 3A,B). Over time these repeated LES relaxations become permanent and the distal portion of the LES stays permanently open (Figure 3B-D).68 As a consequence the reflux alters the morphology of the squamous lined lower end of the esophagus: columnar lined esophagus (CLE) develops.7,8 Due to the lack of LES function, the distal esophagus dilates and forms gastric type folds covered with CLE (CM, OCM, IM)8,9,53. This is the dilated distal esophagus (DDE)10, which always develops at the cost of the competent LES and has been mistaken for gastric cardia by John Wayward33 and McClave et al.36 As the DDE extends above the level of the diaphragm it may be misinterpreted as gastric hernia (Figure 3C,D).44-56 However, biopsies obtained from this region reveal the presence of CLE and not oxyntic mucosa of the proximal stomach.59-62 (also see Fig. 3)

Normally the squamous lined esophagus fuses with the proximal stomach at the level of the peritoneal reflection, which resides below the level of the diaphragm (Figure 3A). Thus the mediastinum excavates below the diaphragm to surround the infra-diaphragmatic "abdominal" portion of the esophagus (Figure 3A). Initially the DDE involves the infra-diaphragmatic portion of the esophagus (Figure 3B). With time the DDE extends towards the upper level of the diaphragm (i.e. includes the intra-diaphragmatic portion of the esophagus) until the entire lower esophageal sphincter is taken up (Figure 3C,D). As the DDE reaches the level of the diaphragm it dilates the hiatus (Figure 3C,D). When the peritoneal reflection and the proximal stomach dislocate above the level of the diaphragm, the true hiatal hernia develops (Figure 3E). With greater DDE-length increases the likelihood of impaired competency of the lower esophageal sphincter and abnormal esophageal acid exposure, i.e. severity of GERD.32,42,44,56 Remains to be elucidated the consequences of the above findings for routine endoscopy in GERD patients?

**DISCUSSION**

The major finding of our analysis was, that much of the confusion around the gastric cardia originated from the use of invalid criteria to define the anatomy and the histopathology of the foregut.33,36 For a long time it has been assumed that the anatomical esophagogastric junction correlates with the level of the rise of the endoscopically visible gastric type folds (rugal folds).6,36

Our research demonstrated, that the presence of submucosal glands and the absence of a peritoneal coverage define the esophagus.7,31,58,64,69,70 (Figure 2A,B). In contrast, the stomach is defined by the presence of a peritoneal coverage and the absence of submucosal glands.31,58,64 Since these structures can not be assessed from the luminal (mucosal) aspect, endoscopy can not define
the anatomical esophagogastric junction. However, for clinical routine the level of the rise of the gastric type folds (rugal folds) may serve as a reproducible reference landmark (= level 0) during endoscopy to catalog the multi level biopsy sites (Figure 4). The histopathology defines esophageal (CLE) vs. gastric allocation (OM) of the biopsies. The biopsy level including the transition from CLE (IM, CM, OCM) to OM corresponds to the anatomical EGJ (Figure 3C). Future studies will elucidate the impact of this multi level biopsy sites (Figure 4). The histological EGJ represents the platform for the development of cancer ("cardia adenocarcinoma"), i.e. >5000 studies listed in PUB MED. The distance from the SCJ to the transition from CLE to OM defines the squamoxynitic gap (SOG). The length of the gap correlates with impaired LES function, increased reflux and cancer risk (Barrett’s esophagus, dysplasia). Future studies will have to elucidate in as much advanced microendoscopy guided optical biopsies contribute to define CLE, Barrett’s esophagus and OM at the cellular level and thus enable accurate assessment of the anatomical EGJ.

What has been mistaken for proximal stomach and hiatal hernia in fact represents the dilated distal esophagus (DDE) (Figure 1-4). Furthermore, DDE develops at the cost of the competency of the lower esophageal sphincter, which shortens and loosens its pressure (Figure 3). As a consequence reflux occurs. Recent studies indicate that the presence of a hiatal hernia is associated with increased acid exposure and the development of Barrett’s esophagus. Moreover it seems that the DDE enlarges the esophageal hiatus within the diaphragm. Conceptually the endoscopically visible pouch distal to the tubular esophagus, which is lined by a columnar epithelium, is arranged in the form of longitudinal rugal folds and localizes within the esophageal hiatus may represent DDE or proximally dislocated stomach (i.e. hiatal hernia). Thus, without histopathological information regarding the coverage of the pouch at the level of the diaphragm, endoscopy is not able to differentiate between DDE and hiatal hernia. When biopsies obtained from the level of the diaphragmatic impressions contain gastric oxyntic mucosa (OM), the condition represents an hiatal hernia (axial, paraesophageal). If the pouch at the level of the hiatus is covered by CLE (CM, OCM, IM) the condition should be termed "hiatus containing DDE" (Figure 3C). Future studies will elucidate the impact of microendoscopy for the differentiation between DDE and proximal stomach. Finally, insufflation of air during endoscopy distends and dislocates the SCJ and proximal limit of the pouch above the level of the diaphragmatic impressions and thus "produces" the endoscopic appearance of an hiatal hernia.

Discrepancy exists, if cardiac mucosa represents a congenital or an acquired condition, abnormality or disease. At the end of embryogenesis the fetal columnar ciliated epithelium of the esophagus is replaced by stratified squamous epithelium. This process exceeds the postnatal period until the first year after birth. It seems that the disappearance of the fetal epithelium within the distal segment of the esophagus is paralleled by the formation of a competent lower esophageal sphincter (LES). Studies suggesting that cardiac mucosa represents a congenital condition are suggested to have mistaken fetal for cardiac mucosa. Chandrasoma et al. and Glickman et al. demonstrated the absence of cardiac mucosa within the distal esophagus in 20% to 50% of newborns and children. In these cases the squamous lined esophagus (+submucosal glands) directly transitioned into the proximal stomach lined by oxyntic mucosa. With older age the likelihood increases that the cardiac mucosa was present and involved greater portions of the circumference of the distal esophagus. These findings indicated, that CM has been acquired after birth and represents a reflux induced anomaly and per se does not necessarily represent a disease requiring treatment. Association of cardiac mucosa with impairment of life quality due to GERD symptoms and/or an increased cancer risk (i.e. Barrett’s esophagus), defines disease and should be offered medical, endoscopic or surgical treatment.

Our historical journey regarding the cardiac commenced with Fraenkel and Tilestone and led us to Barrett’s, Allison and Johnstone. At their time cardia was synonymously used to name the region of the lower esophageal sphincter and the most proximal portion of the stomach. According to the anatomist Joseph Hyrtl the term “cardia” has been introduced by Homer to indicate the heart and the epigastric portion of the abdominal wall (i.e. adjacent to the heart). Later Galen transferred the term “cardia” to describe the inlet, i.e. the proximal portion of the stomach. However, irrespective of the linguistic historical background, Allison and Johnstone always used valid anatomical criteria to define esophageal vs. gastric location of a mucosa. They always knew if a columnar lined mucosa belonged to the esophagus (+submucosal glands) or the stomach (without those glands). In addition they pointed out that the distal end of the esophagus can not be assessed from the luminal side. Subsequent errors led to the invalid assumption that the level of the rise of the gastric type folds coincides with the anatomical EGJ. Consequently the level of the rugal (gastric type) folds was used as an endoscopic landmark to define the proximal stomach, i.e. the “cardia” (Figure 3C). At this point cardiac mucosa came into play and defined the normal mucosal coverage of the distal esophagus and the entrance of the stomach using valid, well defined anatomy, histopathology and physiology. Their paper stimulated Barrett to coin the concept of the
columnar lined esophagus (CLE). Thus our journey proves the important relevance of the concept introduced by the great philosopher, Sir Charles Popper: we should avoid the introduction of hypothetically criteria and definitions ("cardia", Siewert tumor classification). What has been mistaken for "cardia" in fact represents the dilated distal esophagus, which develops as a consequence of gastroesophageal reflux. "oxyntocardiac" mucosa should be used as a diagnostic histopathological criterion for gastroesophageal reflux. The level of the rise of the gastric type folds (rugal folds) serves as a landmark to catalog biopsy sites and endoscopic visible lesions, but should not be used to define the anatomical EGJ.

Second, symptomatic CLE without intestinal metaplasia, i.e. very low cancer risk, represents an abnormality without need for treatment (similar to asymptomatic arterial plaques). Presence of IM or CLE+/− IM and symptoms defines disease and should be offered treatment (medical, endoscopic, surgical). Annual cancer risk for CLE without IM and with IM has been reported to be 0.07% and 0.38%, respectively. Consequently surveillance in 5 years intervals can be recommended for those with asymptomatic CLE without IM, i.e. very low cancer risk. Conceptually, the management tailored based on the individual cancer risk profile and symptomatic CLE without and with IM should be tailored based on the individual cancer risk profile and impairment of the life quality due to GERD symptoms, and includes medical, endoscopic and surgical therapies. Taken together, we are at turn to make sure that our findings during diagnosis and therapy of inflammatory foregut disorders are based on methods using valid anatomical and histopathological criteria. Thus the Prague classification, which describes the morphology of the esophagus above the endoscopically visible rugal folds, should be improved by the inclusion of the DDE. Consequently the distal esophagus gets what it deserves: our valid attention. Referring to the Summa theologica by Thomas de Aquin (1225-1274), James Joyce’s Stephen the Hero abstracted a definition of beauty, which seems perfect to describe the requirements of a classification system for GERD related pathology: "Ad pulchritudinam tria requiruntur: integritas, consonantia, claritas."
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80. Chandrasoma PT. Fetal „cardiac mucosa” is not adult cardiac mucosa. Gut 2003; 52(12): 1798.


Figure legends

Figure 1: Antegrade (A-B) and retroflexed (C-D) endoscopic images of the esophagogastric junction (EGJ) in GERD patients. A: an irregular squamocolumnar junction with rugal folds starting at the level of the diaphragmatic impression (white asterisk). B: Endoscopically visible columnar lined esophagus above the level of the rise of the rugal folds (yellow arrows), which commence at the level of the diaphragmatic impression (white asterisk). C: The rugal folds (yellow arrows) arise above the level of the diaphragmatic impression (white asterisk). D: retroflexed vision towards the EGJ with the rise of the rugal folds and the SCJ (yellow arrow at right side = small curvature position) at the level of the diaphragmatic hiatus. Note the trumpet like opening which suggest dilated distal esophagus and incompetent lower esophageal sphincter. The histopathology of biopsies obtained from the rugal folds at the level of the diaphragmatic impression revealed CLE and not gastric oxyntic mucosa in A-E. Thus panels A-C image the proximal limit of the dilated distal esophagus (DDE) and correspond to the cartoons depicted in panels B-D of Figure 2. These findings
disprove the concept, that the level of the rise of the rugal folds coincides with the anatomical EGJ, as described in the text.

**Figure 2.** Histopathology of a full thickness specimen of the distal esophagus. (A): Horizontal section across the squamocolumnar junction (black bar in the inlet) reveals the transition from squamous epithelium (Squ) to cardiac mucosa (CM). Submucosal glands prove the esophageal origin of the columnar epithelium (CM). (B): Vertical section across the level of the rise of the rugal (gastric) type fold reveals presence of cardiac mucosa (CM) and oxyntocardiac mucosa (OCM). Submucosal glands prove the esophageal origin of the columnar epithelium (CM). Specimen in A and B has been obtained from a resection of a squamous cell cancer affecting the proximal third of the thoracic esophagus. (C): Goblet cell containing columnar lined esophagus (=non dysplastic Barrett’s esophagus) distal to the squamocolumnar junction (SCJ; red arrow). Specimen in C has been obtained from a resection of an adenocarcinoma of the distal esophagus. Arrow marks goblet cell. A-C: H&E stain, magnification: 50x.

**Figure 3:** Schematic drawing of the normal esophagogastric junction (EGJ) (A) and the dilated distal esophagus (DDE) reaching up to the infra- (B), intra- (C) and supra-diaphragmatic (D) portion of the lower end of the esophagus. (E): true hiatal hernia with proximal dislocation of the stomach and the peritoneal reflection (PR) above the level of the diaphragm.

A: normal situation. The squamous lined esophagus fuses with the proximal stomach (covered with peritoneum) at the level of the peritoneal reflection (PR). The lower mediastinum excavates into the abdomen below the level of the diaphragm (D) and surrounds the abdominal portion of the esophagus. LES: competent lower esophageal sphincter, as assessed by manometry.

B: dilated distal esophagus (DDE) comprising the infra-diaphragmatic portion of the esophagus. Note that the DDE develops at the cost of the competent lower esophageal sphincter (LES), which shortens.

C: dilated distal esophagus (DDE) extending towards the upper level of the diaphragm (i.e. comprising the infra- and infra-diaphragmatic portion of the esophagus), which develops at the cost of the shortening of the competent lower esophageal sphincter (LES).

D: dilated distal esophagus takes up the entire length of the lower esophageal sphincter, i.e. infra-, intra- and supra-diaphragmatic portion of the distal esophagus and increases the diameter of the diaphragmatic hiatus. Here LES function is absent.

E: dilated distal esophagus with dislocation of the proximal stomach above the level of the diaphragm, this is the true „hiatal hernia”. LES: lower esophageal sphincter.

Dilated distal esophagus, as depicted in panels B-D, has been recently mistaken for hiatal hernia, as described in the text.

**Figure 4:** Antegrade endoscopic view towards the esophagogastric junction shows multilevel biopsy locations for the assessment of the length and cellular composition of the dilated distal esophagus. The level of the rise of the rugal folds serves as reference landmark, i.e. level 0. „+” and „-“ indicate proximal and distal distances, respectively, from level 0 and are given in cm. Histopathology of these measured biopsies defines the anatomical allocation of the biopsy sites, esophageal vs. gastric, as described in the text. D: diaphragm.

**Figure 5:** Intraoperative laparoscopic image of the dilated distal esophagus (DDE) following dissection within the diaphragmatic hiatus (yellow arrows) during antireflux surgery. The white arrows indicate the peritoneal deflection, above which resides the dilated distal esophagus including the infra- and intra-diaphragmatic portion of the distal esophagus. The yellow dotted line marks the proximal limit of the dilated portion of the distal esophagus. The situation depicted in this image corresponds to the cartoon shown in Figure 2C.