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Inflammation and Specialized Intestinal Metaplasia of Cardiac Mucosa Is a Manifestation of Gastroesophageal Reflux Disease

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Objective
The purpose of the study was to test the hypothesis that cardiac mucosa, carditis, and specialized intestinal metaplasia at an endoscopically normal-appearing cardia are manifestations of gastroesophageal reflux disease.

Summary Background Data
In the absence of esophageal mucosal injury, the diagnosis of gastroesophageal reflux disease currently rests on 24-hour pH monitoring. Histologic examination of the esophagus is not useful. The recent identification of specialized intestinal metaplasia at the cardia, along with the observation that it occurs in inflamed cardiac mucosa, led the authors to focus on the type and condition of the mucosa at the gastroesophageal junction and its relation to gastroesophageal reflux disease.

Methods
Three hundred thirty-four consecutive patients with symptoms of foregut disease, no evidence of columnar-lined esophagus, and no history of gastric or esophageal surgery were evaluated by 1) endoscopic biopsies above, at, and below the gastroesophageal junction; 2) esophageal motility; and 3) 24-hour esophageal pH monitoring. The patients were divided into groups depending on the histologic presence of cardiac epithelium with and without inflammation or associated intestinal metaplasia. Markers of gastroesophageal reflux disease were compared between groups (*i.e.,* lower esophageal sphincter characteristics, esophageal acid exposure, the presence of endoscopic erosive esophagitis, and hiatal hernia).

Results
When cardiac epithelium was found, it was inflamed in 96% of the patients. The presence of cardiac epithelium and carditis was associated with deterioration of lower esophageal sphincter characteristics and increased esophageal acid exposure. Esophagitis occurred more commonly in patients with carditis whose sphincter, on manometry, was structurally

defective. Specialized intestinal metaplasia at the cardia was only seen in inflamed cardiac mucosa, and its prevalence increased both with increasing acid exposure and with the presence of esophagitis.

Conclusion

The findings of cardiac mucosa, carditis, and intestinal metaplasia in an endoscopically normal-appearing gastroesophageal junction are histologic indicators of gastroesophageal reflux disease. These findings may be among the earliest signs of gastroesophageal reflux and contribute to the authors understanding of the pathophysiology of the disease process.

Confidence in the diagnosis of gastroesophageal reflux disease is related to histologic evidence of inflammation or metaplasia, which is inflammatory infiltrate of the mucosa, or intestinal metaplasia in a columnar-lined esophagus. Clinical experience has shown that more than half the patients with symptoms of gastroesophageal reflux disease have no known histologic evidence of inflammatory change.[1,2] More subtle signs of injury in the squamous mucosa such as papillary elongation, basal zone hyperplasia, or balloon cells have proved to be unreliable.[3] Consequently, other markers of gastroesophageal reflux disease are necessary to make the diagnosis in its early or mild form. The most accurate and commonly used marker is increased esophageal acid exposure on 24-hour esophageal pH monitoring.[4] Despite the usefulness of 24-hour pH monitoring, the ability to identify histologic evidence of inflammation or metaplasia in the early stages of gastroesophageal reflux has remained, to the current time, a desired goal.

Recent observations have suggested that the mucosa of the gastroesophageal junction may be susceptible to the injurious effects of gastroesophageal reflux. Several laboratories over the past 4 years have reported a high incidence of intestinal metaplasia in the columnar epithelium commonly found on biopsy of the gastroesophageal junction in patients without endoscopic evidence of Barrett's metaplasia in the esophagus.[5–8] We noted in every instance that biopsy results of this columnar epithelium showed histologic evidence of inflammation. This gave rise to the concept of "carditis" and the possibility that cardiac mucosa may be metaplastic. From these observations, we have hypothesized that alterations in the type and condition of the transitional epithelium at the gastroesophageal junction may be the earliest histologic evidence of gastroesophageal reflux disease. The purpose of this study was to test this hypothesis in a large cohort of patients undergoing evaluation of chronic foregut symptoms.

PATIENTS AND METHODS

Study Population

Between July 1991 and November 1996, 334 consecutive patients with symptoms of foregut disease, no evidence of columnar-lined esophagus, and no history of gastric or esophageal surgery were evaluated in our department. This included 196 males and 138 females with a median age of 53 years (range, 13–89 years). All underwent upper endoscopy with biopsies, esophageal motility, and 24-hour esophageal pH monitoring. Esophageal acid exposure, lower esophageal sphincter (LES) characteristics, histology of the gastric antrum and cardia, and prevalence of a hiatal hernia were noted.

Histologic Analysis

Multiple biopsy specimens were taken from the gastric antrum and the gastroesophageal junction. Biopsy was performed on the latter with the endoscope in the straight forward and retroflexed position (Fig. 1). A minimum of five biopsy specimens were obtained from the gastroesophageal junction and three from the gastric antrum. Biopsy specimens were fixed in 10% buffered formaldehyde solution and embedded in paraffin, sectioned, and mounted on slides using standard techniques. The type of epithelium was assessed after staining with hematoxylin and eosin. Fundic mucosa was identified by the presence of a pitted surface lined by mucus-secreting columnar cells and a deeper glandular layer, which contained pepsinogen producing chief and acid producing parietal cells (Fig. 2). Cardiac mucosa was differentiated from fundic mucosa based on the absence of chief and parietal cells in the underlying glands. Carditis was characterized by the presence of eosinophil or plasma cell infiltration of the lamina propria and hyperplasia of the mucous cells in the foveolar region (Fig. 3). Specialized intestinal metaplasia was defined by the presence of well-defined goblet cells on routine sections, confirmed in the

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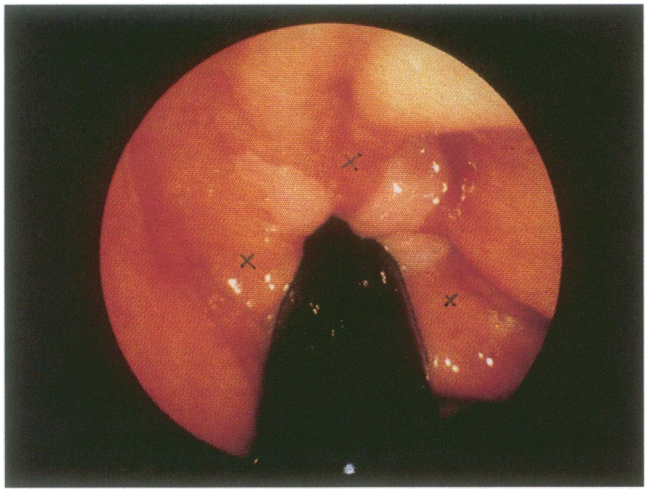

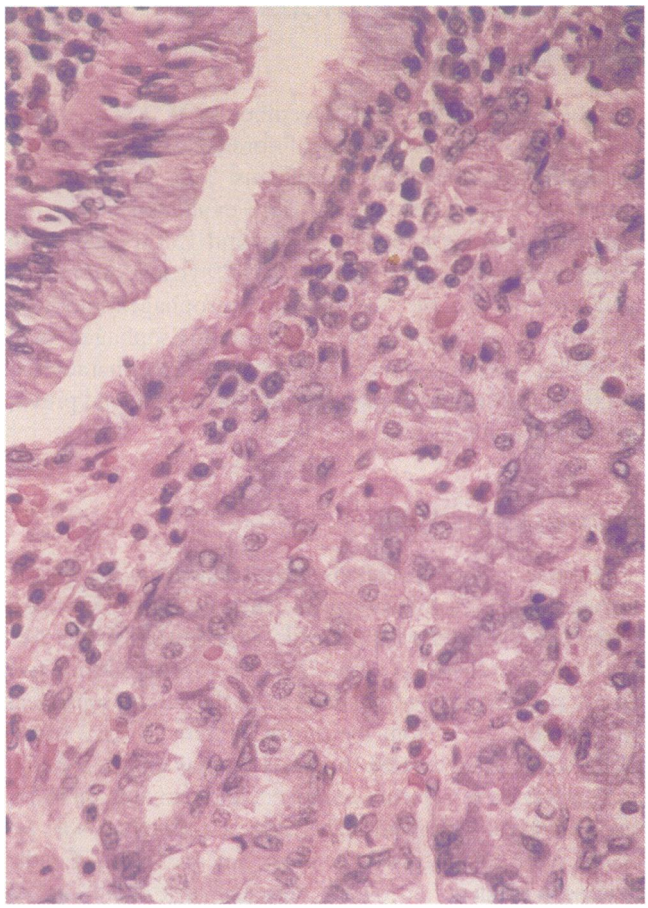

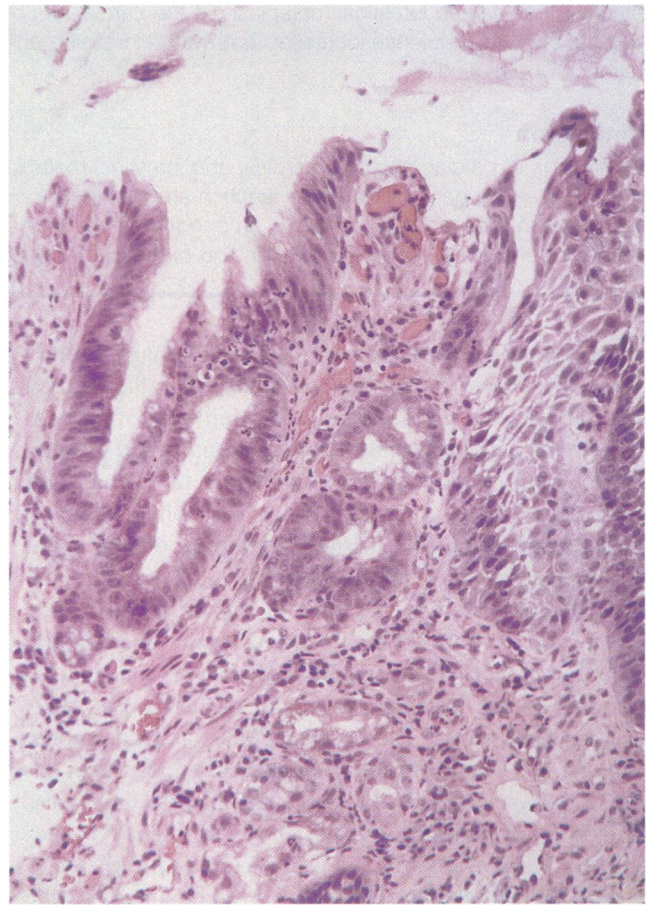

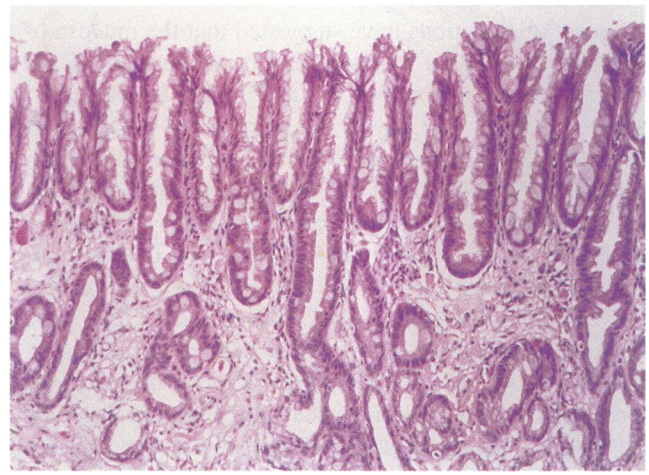

Figure 1. (top left) Retroflexed view of the prolapsed squamocolumnar junction. Multiple biopsy specimens were taken of the columnar mucosa immediately below the mucosal junction.

Figure 2. (bottom left) Normal fundic epithelium. The gastric glands are composed of parietal and chief cells. Mucous cells are limited to the lining of the foveolar pit (stain, hematoxylin–eosin).

Figure 3. (top right) Squamocolumnar junction. The glandular element is cardiac and shows active inflammation and foveolar hyperplasia (stain, hematoxylin–eosin).

Figure 4. (bottom right) Intestinal metaplasia characterized by villiform surface and the presence of numerous goblet cells in both surface epithelium and mucous glands (stain, hematoxylin–eosin).

less obvious cases by positive staining with Alcian blue at pH 2.5 (Fig. 4).

The presence of chronic gastritis, atrophic gastritis, and *Helicobacter pylori* infection was assessed in all biopsy specimens. The recognition of chronic gastritis was based on the infiltration of the gastric mucosa with increased numbers of lymphocytes and plasma cells and atrophic gastritis by atrophy of the gastric mucosa usually associated with intestinal metaplasia.

Endoscopic Definitions

The endoscopic gastroesophageal junction was defined by the squamocolumnar junction, which was always distinct and at the proximal extent of the gastric rugal folds. A hiatal hernia was diagnosed when, on endoscopy, the gastroesophageal junction was located 2 cm or more proximal to the crural impression. Esophagitis was identified by the presence of linear erosions or interlocking erosions giving the appearance of a cobblestone esophagus.

Stationary Manometry

Stationary motility was performed after an overnight fast using a single catheter assembly consisting of five polyethylene tubes bonded together with five lateral openings placed at 5-cm intervals from the distal end and oriented radially around the circumference. Using a pneumohydraulic low-compliance pump (Arndorfer Medical Specialties, Greendale, WI), the catheter was perfused with distilled water at a constant rate of 0.6 mL/minute. A stationary pullthrough of the LES and a manual analysis of the polygraph recordings were performed. Lower esophageal sphincter resting pressure was measured at the respiratory inversion point as described previously.[9] The resting pressure, overall length, and abdominal length were calculated from the mean of the five recordings. A structurally defective sphincter was defined either by a resting pressure of <6 mmHg, overall sphincter length of >2 cm, abdominal length of >1 cm, or any combination of these.

Ambulatory 24-Hour Esophageal pH Monitoring

Esophageal pH monitoring was performed using a glass electrode (Ingold Incorporated, Urdorf, Switzerland) placed 5 cm above the upper border of the manometrically defined LES. Medications were discontinued 48 hours before testing, except for omeprazole, which was discontinued at least 2 weeks earlier. The subjects were instructed to carry out their normal daily activities but to avoid strenuous exertion. They were asked to remain in the upright position during daytime and were given a diet sheet and recommendations of foods with a pH in the range of 5 to 7. A diary was kept of food and fluid intake, symptoms, and the time of the supine and upright positions.

Esophageal pH recording was stored on a portable digital data recorder (Digitrapper; Synectics Medical, Inc, Irving, TX) and downloaded to a personal computer for analysis. Esophageal acid exposure was analyzed using a computer program (Gastrosoft, Dallas, TX) to calculate the total percentage of time that was spent at pH below 4 during the total monitored period.

Table 1. HALLMARKS OF GASTROESOPHAGEAL REFLUX DISEASE IN PATIENTS WITH AND WITHOUT CARDIAC MUCOSA ON BIOPSIES OF THE GASTROESOPHAGEAL JUNCTION

	Findings on Multiple Biopsies of the Cardia		
	No Cardiac Epithelium (n = 88)	Cardiac Epithelium (n = 246)	p
% time pH < 4	1.1 ± 4.6	6.0 ± 7.4	<0.01
% hiatal hernia	25.0	55.1	<0.01
LES pressure (mmHg)	13.2 ± 12.8	8.0 ± 8.0	<0.01
LES abdominal length (mm)	1.6 ± 1.1	1.0 ± 1.2	<0.01
LES overall length (mm)	3.0 ± 1.2	2.2 ± 1.6	<0.01
% defective LES	27.2	62.3	<0.01
% esophagitis	11.2	33.2	<0.01

Values are medians ± interquartile range.
LES = lower esophageal sphincter.

Statistical Analysis

Fisher's exact test was used to compare proportions between individual groups. Comparisons of proportions between more than two groups were performed using the chi square test. The Kruskal–Wallis test was used to compare continuous data between more than two groups, and the Mann–Whitney *U* test was used to compare continuous data between individual groups. Values expressed as medians and interquartile ranges. A p value of < 0.05 was accepted to denote statistical significance.

RESULTS

Histologic examination of the biopsy specimens of the gastroesophageal junction showed cardiac epithelium in 246 (73.7%), and only fundic epithelium in 88 (26.3%) of the 334 patients. The presence of cardiac mucosa was strongly associated with the hallmarks of gastroesophageal reflux disease, including increased esophageal acid exposure, a hiatal hernia, a structurally defective LES, and erosive esophagitis (Table 1). A striking feature was

Table 2. HALLMARKS OF GERD IN PATIENTS WITH AND WITHOUT CARDITIS ON BIOPSIES OF THE GASTROEOSOPHAGEAL JUNCTION

	Findings on Multiple Biopsies of the Cardia		
	No Carditis (n = 9)	Carditis (n = 237)	p
% time pH < 4	3.1 ± 4.5	6.1 ± 7.2	0.14
LES pressure (mmHg)	10.6 ± 12.4	7.8 ± 8.2	0.03
LES abdominal length (cm)	1.4 ± 0.4	1.0 ± 1.2	0.10
LES overall length (cm)	3.3 ± 0.7	2.2 ± 1.6	0.02
% defective LES	11.1	63.7	<0.01

Values are medians ± interquartile range.
GERD = gastroesophageal reflux disease; LES = lower esophageal sphincter.

that, when present, cardiac mucosa had histologic evidence of inflammation in 96% of the patients. Table 2 compares patients with cardiac mucosa with and without inflammation. Carditis was associated with a shorter LES and a sphincter with lower pressure and, as a consequence, a marked increase in the prevalence of a structurally defective sphincter.

The differences in the features of gastroesophageal reflux disease in patients with carditis with and without erosive esophagitis are listed in Table 3. Patients who had esophagitis had greater esophageal acid exposure, a high prevalence hiatal hernia, deterioration in the LES pressure, overall length and abdominal length, and, as a consequence, a greater prevalence of structurally defective LESs. Table 4 shows that patients with carditis and a defective LES, but no esophagitis differed from those with esophagitis, in that those without esophagitis cleared their reflux episodes more rapidly by a more vigorously contracting esophageal body. This suggested that the structurally defective LES in patients with carditis but without esophagitis was compensated by a more active esophageal body pump.

Table 5 shows that carditis was not associated with other noninfectious or infectious gastric pathology. There was no significant difference in the prevalence of gastric pathology or *Helicobacter pylori* infection in patients who

Table 3. HALLMARKS OF GERD IN PATIENTS WITH INFLAMMATION OF CARDIAC MUCOSA IN PRESENCE AND ABSENCE OF EROSIVE ESOPHAGITIS

	Carditis		
	No Esophagitis (n = 155)	Esophagitis (n = 82)	p
% time pH < 4	4.1 ± 6.5	9.2 ± 7.0	<0.01
% hiatal hernia	44.2	78.0	<0.01
LES pressure (mmHg)	10.0 ± 8.8	5.6 ± 5.0	<0.01
LES abdominal length (mm)	1.0 ± 1.2	0.6 ± 0.8	<0.01
LES overall length (mm)	2.4 ± 1.4	2.1 ± 1.6	0.06
% defective LES	54.2	81.7	<0.01
% intestinal metaplasia	8.3	19.5	0.02

Values are medians ± interquartile range.
GERD = gastroesophageal reflux disease; LES = lower esophageal sphincter.

Table 4. ESOPHAGEAL ACID EXPOSURE AND CLEARANCE CHARACTERISTICS IN PATIENTS WITH CARDITIS, DEFECTIVE LOWER ESOPHAGEAL SPHINCTERS IN THE PRESENCE AND ABSENCE OF EROSIVE ESOPHAGITIS

	Carditis Defective LES, No Esophagitis (n = 84)	Carditis Defective LES, Esophagitis (n = 67)	p
% time pH < 4	4.8 ± 6.1	9.2 ± 5.9	<0.01
Number of reflux episodes > 5 min	2.0 ± 2.5	4.0 ± 5.5	<0.01
Longest reflux episode (min)	12.0 ± 15.7	18.0 ± 15.0	0.06
Distal esophageal amplitude (mmHg)	86.0 ± 69.0	59.0 ± 32.0	0.03

Values are medians ± interquartile range.
LES = lower esophageal sphincter.

Table 5. GASTRIC PATHOLOGY AND HELICOBACTER INFECTION IN PATIENTS WITH AND WITHOUT CARDIAC MUCOSA AND CARDITIS

	No Cardiac Mucosa (%) (n = 88)	Cardiac Mucosa, No Carditis (%) (n = 9)	Cardiac Mucosa, Carditis (%) (n = 237)
Chronic gastritis	34.5	22.2	31.5
Atrophic gastritis	1.1	0.0	0.4
Gastric intestinal metaplasia	0.0	0.0	3.4
Helicobacter p. in antral mucosa	21.8*	11.1	10.9

* $p < 0.05$ *vs.* patients with carditis.

Table 6. GASTRIC PATHOLOGY AND HELICOBACTER INFECTION IN PATIENTS WITH AND WITHOUT INFLAMMATION IN FUNDIC EPITHELIUM ON RETROFLEXED BIOPSIES OF THE GASTROESOPHAGEAL JUNCTION

	Fundic Epithelium, No Inflammation (%) (n = 182)	Fundic Epithelium, Inflammation (%) (n = 98)	p
Normal antral mucosa	74.7	20.4	<0.01
Chronic gastritis	12.1	67.3	<0.01
Helicobacter p. in antral mucosa	2.2	36.7	<0.01

had carditis compared to those who did not. The only gastric area in which *H. pylori* was found commonly was in the antral biopsy specimens, and this occurred commonly more commonly in patients without cardiac mucosa. We also assessed *H. pylori* in biopsy specimens of the gastroesophageal junction. It was not commonly present in cardia biopsy specimens, and when it was seen, it was always seen in the antrum and had no association to the presence or absence of carditis. In contrast, when inflamed fundic mucosa was found at the gastroesophageal junction, it was strongly associated with both chronic gastritis and presence of *H. pylori* infection in both fundic and antral mucosa (Table 6).

Intestinal metaplasia in biopsy specimens of the gastroesophageal junction was seen in 29 (11.7%)of the 246 patients who had cardiac mucosa and always occurred in the presence of carditis. Table 7 shows that the presence of intestinal metaplasia also was strongly associated with the hallmarks of gastroesophageal reflux disease, including increased esophageal acid exposure, a hiatal hernia, a defective LES, and erosive esophagitis. In addition, there was a tendency for the features of gastroesophageal reflux disease (GERD) to be worse in patients with intestinal metaplasia compared to those without. Furthermore, the incidence of this metaplastic mucosa within the gastroesophageal junction increased with increasing esophageal acid exposure and the presence of esophagitis (Table 3). Intestinal metaplasia also was not associated with other noninfectious or infectious gastric pathology (Table 8).

DISCUSSION

Historically, it has been difficult to correlate physiologic measurements with anatomic landmarks at the gastroesophageal junction. Manometric studies indicate that there are three physiologically distinct areas in the junc-

Table 7. HALLMARKS OF REFLUX DISEASE IN PATIENTS WITH AND WITHOUT CARDIAC MUCOSA IN THE PRESENCE OR ABSENCE OF INTESTINAL METAPLASIA

	I No Cardiac Mucosa (n = 87)	II Cardiac Mucosa, No Intestinal Metaplasia (n = 218)	III Cardiac Mucosa, Intestinal Metaplasia (n = 29)
% time pH < 4	1.1 ± 4.6	5.8 ± 8.0*	6.7 ± 6.1*
% of hiatal hernia	25.3	52.8*	72.4†
LES pressure (mmHg)	13.2 ± 12.8	8.1 ± 8.2*	6.8 ± 8.8*
LES abdominal length (cm)	1.6 ± 1.1	1.0 ± 1.2*	0.8 ± 1.2*
LES overall length (cm)	3.0 ± 1.2	2.2 ± 1.7*	2.3 ± 1.7*
% defective LES	27.6	61.5*	69.0*
% esophagitis	10.3	30.3*	55.2†

LES = lower esophageal sphincter.
* $p < 0.05$ *vs.* group I.
† $p < 0.05$ *vs.* all groups.

tional zone: 1) the esophagus, which is above the LES, is at thoracic pressure and normally not exposed to gastric contents; 2) the LES zone, 2- to 5-cm long, is under a high resting pressure with the respiratory inversion point within it and normally not exposed to gastric contents; and 3) the stomach, which is below the LES, is at abdominal pressure and is normally exposed to gastric contents. The correlation of these physiologic regions to anatomy, endoscopy, and histology is not certain. For these reasons

Table 8. GASTRIC PATHOLOGY AND HELICOBACTER INFECTION IN PATIENTS WITH AND WITHOUT CARDIAC MUCOSA AND INTESTINAL METAPLASIA

	No Cardiac Mucosa (%) (n = 88)	Cardiac Mucosa, No Intestinal Metaplasia (%) (n = 218)	Cardiac Mucosa, Intestinal Metaplasia (%) (n = 29)
Chronic gastritis	34.5	31.2	21.1
Atrophic gastritis	1.1	0.7	0.0
Gastric intestinal metaplasia	0.0	2.0	6.9
Helicobacter p. in antrum	21.8*	10.1	17.2

* $p < 0.05$ *vs.* patients with cardiac mucosa with no intestinal metaplasia.

and others, we began to focus on mucosal changes at the gastroesophageal junction in patients with a distinct squamocolumnar junction at the proximal extent of the gastric rugal folds.

Our studies show that a transitional cardiac epithelium of the gastroesophageal junction is not always found. When present, it is associated with objective markers of gastroesophageal reflux disease, such as a decreased LES pressure, shorter sphincter length, and increased esophageal acid exposure. Further, cardiac mucosa has histologic evidence of inflammation in 96% of patients with symptoms suggestive of foregut disease. The high incidence of inflammation suggests that the columnar cells making up the cardiac epithelium are not resistant to gastric acid and other injurious components present in the refluxed juice. Neither is the inflammation related to the presence of *H. pylori* or gastric mucosal pathology elsewhere in the stomach. In contrast, when fundic epithelium was found on biopsy of a normal-appearing gastroesophageal junction, inflammation was uncommon (26%) and usually related to Helicobacter infection or distal gastric mucosal pathology. Further, inflammation of the cardiac mucosa or carditis is associated with structural failure of the sphincter, and when combined with defects in esophageal clearance, results in erosive esophagitis. The finding that the cardiac epithelium is almost always associated with inflammation and is linked causally to increased esophageal acid exposure suggests that squamous epithelium within the sphincter undergoes a metaplastic change to cardiac epithelium when exposed repeatedly to gastric juice.

The histology of this region has not been studied adequately in the past. Many assumptions were made without supporting data. Textbooks of histology traditionally have divided the epithelium of the stomach into three distinct zones based on the morphology and cellular content of the epithelial glands. The body and fundus of the stomach contain long, straight, simply branched tubules extending to abut the muscularis mucosa. They are lined by three types of cells: 1) mucous cells, which differ from mucous cells of the surface epithelium by their staining characteristics and flattened nuclei at the base of the cell; 2) zymogen or chief cells, which line the lower half of the gland and produce pepsinogen and other peptides; and 3) parietal or oxyntic cells containing eosinophilic granules and are responsible for hydrochloric acid production. The pyloric or antral region of the stomach is characterized by glands that are shorter, more tortuous, and less densely packed in comparison to the body and fundus. A single cell, similar or identical to the mucous cells of the fundic glands, lines them. Finally, the cardiac region is described as a narrow strip 0.5 to 3 cm in width at the gastroesophageal junction. It contains glands that are very short, coiled, and lined by mucous-secreting cells, devoid of oxyntic and chief cells.

Hayward[10] in an excellent article, but without supporting data, argues that the lower 1 to 2 cm of the esophagus is normally lined by a metaplastic mucus-secreting columnar epithelium that has the ability to resist acid-peptic digestion. He suggests that this mucosa is present to prevent squamous epithelial digestion at the junction, by providing a buffer between squamous epithelium and acid-pepsin producing fundic mucosa. This unsubstantiated report is the basis of the accepted fact that there normally is a zone of cardiac mucosa between the squamous epithelium and the gastric fundic mucosa. Despite the fact that Hayward's description places this cardiac mucosa in the lower esophagus, the cardiac mucosa has, over time and without any logical or scientific basis, come to be regarded as part of the stomach. The results of the current study provide data to indicate that cardiac mucosa is metaplastic and not normally present and question its existence as a normal finding.

Other evidence also suggests that the columnar epithelium making up the cardiac mucosa is metaplastic and derived from injury to squamous epithelium. First, the squamocolumnar junction has been shown to rise progressively higher in the sphincter and on into the tubular esophagus with increasing severity of gastroesophageal reflux. Csendes et al.[11] have shown that as the severity of gastroesophageal reflux disease progresses, the length of columnar lining above the anatomic gastroesophageal junction increases.[11] Second, patients who have their proximal stomach and distal esophagus resected, and the squamous-lined esophagus implanted into the fundus of the stomach, subsequently can have columnar mucosa develop in the esophagus above the suture line (personal observation JHP, TRD, 1994–1996). Third, studies of autopsy specimens of individuals younger than 20 years old indicate that the transition from esophagus to stomach occurs abruptly and is marked by the juxtaposition of squamous with fundic epithelium (unpublished data, P. Chandrasoma, 1997).

Recent studies have shown a high prevalence of specialized intestinal metaplasia at the gastroesophageal junction in patients without endoscopic evidence of columnar lining of the esophagus. In a previous study of patients undergoing evaluation for gastroesophageal reflux disease who had no endoscopic evidence of columnar-lined esophagus, we found a 9% incidence of unsuspected specialized intestinal metaplasia at the cardia.[4] Spechler and Goyal[6] have similarly reported that 9 of 142 patients (6%) undergoing routine upper endoscopy in a general endoscopic unit had specialized intestinal metaplasia below an endoscopically normal-appearing squamocolumnar junction. They concluded that this phenomenon was unrelated to gastroesophageal reflux dis-

ease, although data to support this conclusion were not given. Other studies now have confirmed this high prevalence of intestinal metaplasia at the cardia.[7,8,12] We have shown that intestinal metaplasia limited to the gastroesophageal junction universally occurs in the setting of inflamed cardiac mucosa. It is clearly metaplastic, because goblet cells are not normally found in either the esophagus or the stomach. Further, the finding of intestinal metaplasia at the cardia was not associated with its presence elsewhere in the stomach nor *H. pylori* infection. It was associated with the hallmarks of gastroesophageal reflux disease, including increased esophageal acid exposure, a short gastroesophageal sphincter with low pressure, and erosive esophagitis.

The incidence of adenocarcinoma of the esophagus and the esophagogastric junction is rising faster than any other tumor in the United States.[13,14] This increase in adenocarcinoma of the cardia has occurred in the setting of a dramatic decline in cancers of the antrum and body of the stomach.[15] Further, adenocarcinoma has been shown to occur in short segments (<3 cm) of visible columnar-lined esophagus containing specialized intestinal epithelium.[16,17] This suggests that patients with intestinal metaplasia confined to the cardia also are at risk of developing adenocarcinoma. The high prevalence of this finding compared to the prevalence of Barrett's esophagus may explain why the incidence of adenocarcinoma of the cardia is seven times the incidence of adenocarcinoma of the esophagus.[13]

The results of the current study suggest that cardiac mucosa, carditis, and intestinal metaplasia at the gastroesophageal junction is caused by injury of the squamous epithelium within the sphincter by gastric juice. The data fit our hypothesis that gastroesophageal reflux disease begins in the stomach.[18] Fundic distention occurs because of overeating and delayed gastric emptying secondary to the high-fat Western diet.[19] The distention causes the sphincter to be "taken up" by the expanding fundus, exposing the distal squamous epithelium of the sphincter to gastric juice. Repeated exposure causes inflammation of the squamous epithelium and columnar metaplasia and carditis. This may be the initial steps in the pathogenesis of gastroesophageal reflux disease and explain why early in the disease esophagitis commonly is limited to the very distal esophagus. The patient compensates by increased swallowing, allowing saliva to bathe the injured mucosa to alleviate the discomfort induced by exposure to gastric acid. Increased swallowing results in aerophagia, bloating, and repetitive belching. The distention induced by aerophagia adds to the repeated exposure of the squamous epithelium to gastric juice. Erosions of the terminal squamous epithelium exposed to gastric juice by this mechanism also may explain the reported problem of epigastric pain so often registered by patients with early disease. Healing of the erosions can lead to a fibrotic mucosal ring at the squamocolumnar junction and may explain the origin of the infamous and mysterious Schatzki's ring.[20]

Finally, the process of metaplasia to columnar epithelium extends the inflammatory process into the muscularis propria, resulting in the loss of sphincter function and increased esophageal acid exposure. This is very similar to the process that may occur in patients with Barrett's esophagus and the loss of esophageal contractility.[21] Over time, the process advances up the sphincter, resulting in the permanent loss of LES function and explosion of the disease into the esophagus. This accounts for the observation that severe esophageal mucosal injury is almost always associated with a structurally defective sphincter.[22] Antireflux surgery done early in this sequence may be the only means to prevent disease progression.

It is concluded that cardiac mucosa, carditis, and intestinal metaplasia at the gastroesophageal junction are histologic indicators of gastroesophageal reflux disease. These findings may be among the earliest signs of gastroesophageal reflux and initiate the pathophysiology of the disease process.

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Discussion

DR. ALAN G. JOHNSON (Sheffield, England): This is an important paper with profound implications if it is true. The hypothesis is that all cardiac-type mucosa is abnormal and metaplastic, even at the junctional zone, and that it is very common. If this is also associated with intestinal metaplasia, which is premalignant, it may well go a long way toward explaining the increasing incidence of adenocarcinoma of the lower esophagus. My questions are threefold. How does this abnormal mucosa actually relate to the sphincter itself and to the respiratory reversal point? Is it in the abdominal part or the esophageal part? Because if this is in the lower part, would a fundoplication, for example, make any difference to this very minimal reflux? My second question is whether there was dysplasia in this intestinal metaplasia, because this is the important predictor of premalignant change.

Third, did you correlate the changes and, in particular, the intestinal metaplasia with alkaline or, as we prefer to call it, duodenal juice reflux? This may be important in the change to an intestinal-type mucosa.

DR. THOMAS P. J. HENNESSY (Dublin, Ireland): I am pleased to have the opportunity to comment on this paper, and I would like to congratulate the authors, Dr. Peters and Dr. DeMeester and the rest of the group, on what I think is a very important paper that contributes further to our knowledge of the pathophysiology of gastroesophageal reflux disease. It may also account for the development of adenocarcinomas around the cardia in the absence of any apparent Barrett's metaplasia.

In our experience for a long period looking at Barrett's esophagus, we have found that the most potent combination to provoke metaplasia and also dysplasia is bile and acids. I wonder whether the authors have looked at the possibility of bile reflux in this situation, because, as Professor Johnson has already remarked, the acid reflux here is minimal. I also wondered whether there was any alteration in motility of the esophageal body, as well as whether there were motor disorders in the sphincter.

The other thing that surprised me about this paper is the very high frequency of hiatal hernia. I noticed that in those patients who were relatively normal with no reflux changes, no inflammatory changes, and no cardiac mucosa, even they had a 25% incidence of hiatal hernia. So I wonder how relevant these hernias are.

Finally, I would like to inquire, do the authors think it is possible to reverse the process or have they tried to do so? One wonders what would be the response to intensive medical treatment at this stage of the condition.

DR. JOHN HUNTER (Atlanta, Georgia): This is a tremendous amount of exciting and provocative material. As I try to understand the story that lies beneath all this data, what I understand is that early gastroesophageal reflux is manifested by the development of columnar metaplasia in the region of the lower esophageal sphincter. That is to say, in a patient without Barrett's esophagus, our assumption that the stomach starts below the squamocolumnar junction is wrong. The cardiac glands belong to the esophagus. They are a result of acid injury to the squamous esophagus, they are usually inflamed when they exist, and their presence predicts gastroesophageal reflux disease.

If we are to believe this story, and I think we should, I have about a million questions. But I will try to ask just a few.

If the presence of intestinal-type epithelium represents healing of erosive disease in severe reflux and esophageal erosions are not seen in early disease, how does the cardiac metaplasia occur in patients with carditis? Is carditis, which is so uniformly found in patients with cardiac glands, really an epiphenomenon? If you took biopsies of their lower esophagus, do these patients have microscopic inflammatory changes above the squamocolumnar junction grade 1 injury in the Savory-Miller classification? As these studies progress, there are several other issues that need to be addressed. One is, how specific are these findings? Do the normal controls, patients without foregut symptoms or patients undergoing endoscopy for endoscopic retrograde cholangiopancreatography (ERCP), have any of these findings? What about omeprazole? We know it causes histologic changes to the stomach. Does it influence any of the histology of these cardiac glands? Lastly, in the methods section it was suggested that these biopsies were obtained sometimes by retroflex—some of the biopsies were obtained retroflex and some antiflex. Was there any difference in the biopsy findings when the scope was retroflexed or straight on?

DR. THOMAS R. GADACZ (Augusta, Georgia): Were any of the changes you describe with gastroesophageal reflux disease