GENERAL THORACIC SURGERY

THE EXTENT OF BARRETT'S ESOPHAGUS DEPENDS ON THE STATUS OF THE LOWER ESOPHAGEAL SPHINCTER AND THE DEGREE OF ESOPHAGEAL ACID EXPOSURE

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Objective: The purpose of this study was to assess whether the extent of intestinal metaplasia is related to the severity of the gastroesophageal reflux disease. **Methods:** A total of 556 consecutive patients with symptoms suggestive of foregut disease had upper gastrointestinal endoscopy with extensive biopsies from the gastroesophageal junction and the esophagus. All patients had esophageal motility and 24-hour pH monitoring. In 411 patients, cardiac-type mucosa was identified; in 147 patients, the cardiac-type mucosa showed intestinal metaplasia. They were divided into 3 groups based on the extent of intestinal metaplasia commonly seen clinically: long segments (>3 cm), short segments (<3 cm), and limited to the gastroesophageal junction. The duration of symptoms, the status of the lower esophageal sphincter, the degree of esophageal acid exposure, and the time to clear a reflux episode were assessed in each group. **Results:** The presence of intestinal metaplasia in cardiac-type mucosa was associated with the hallmarks of gastroesophageal reflux disease. The extent of intestinal metaplasia correlated strongly with the degree of esophageal acid exposure ($r = 0.711$; $P < .001$) and inversely with the lower esophageal sphincter pressure ($r = 0.351$; $P < .001$) and length ($r = 0.259$; $P = .002$). Patients with a long segment of intestinal metaplasia (>3 cm) had longer duration of symptoms (16 years) than those patients with a segment of intestinal metaplasia less than 3 cm (10 years; $P = .048$) or those patients with intestinal metaplasia limited to the gastroesophageal junction (10 years; $P = .01$). **Conclusion:** The extent of intestinal metaplasia, that is, Barrett's esophagus, is related to the status of the lower esophageal sphincter and the degree of esophageal acid exposure. (J Thorac Cardiovasc Surg 1999;117:572-80)

Barrett's esophagus is a complication of gastroesophageal reflux disease characterized by the presence of intestinal metaplasia in an esophagus lined by

cardiac-type mucosa; alternatively described as a columnar-lined esophagus with intestinal metaplasia or Barrett's mucosa. The clinical significance of this finding is that it confers a more than 50-fold risk of progression to esophageal adenocarcinoma. Beyond this, many of the details of the natural history of Barrett's esophagus remain an enigma. For example, it has been suggested that Barrett's esophagus develops quickly to its full extent, with little subsequent increase in length.¹ This suggestion was based on data from patients with only long segments of Barrett's mucosa within the tubular esophagus (ie, ≥ 3 cm). It is now accepted that intestinal metaplasia occurs in segments of cardiac-type mucosa that are less than 3 cm in length and that intestinal metaplasia can occur in small amounts of cardiac-

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type mucosa just below the squamous epithelium of an endoscopically normal-appearing gastroesophageal junction.²⁻⁴ These observations justify a reevaluation of the commonly held belief that Barrett's esophagus, once developed, does not progress.

We have recently shown that the presence of cardiac-type mucosa at the gastroesophageal junction is usually associated with an inflammatory infiltrate and is an early sign of gastroesophageal reflux disease.⁵ It has been further shown that, as the length of the cardiac-type mucosa increases, there is a progressive deterioration of the lower esophageal sphincter pressure and an increase in esophageal acid exposure.⁶⁻⁸ Recently, it has been recognized that segments of cardiac-type mucosa limited to the gastroesophageal junction can show intestinal metaplasia on biopsy.²⁻⁴ The histologic condition of these biopsy specimens is identical to biopsy specimens obtained from patients with Barrett's esophagus who have longer segments of intestinal cardiac-type mucosa. Because of the rather high frequency of this finding, its significance has been questioned.

The aim of this study was to determine whether intestinal metaplasia arising in cardiac-type mucosa, regardless of whether it is limited to the gastroesophageal junction or extending into the esophagus, is associated with the hallmarks of gastroesophageal reflux disease and, if so, whether the extent of intestinal metaplasia is dependent on the severity of the functional abnormality identified with this disease. If this were so, it would suggest that the formation of Barrett's esophagus is a progressive process. It starts with the intestinalization of endoscopically occult segments of cardiac-type mucosa arising at the gastroesophageal junction. With increasing severity of reflux disease, the intestinalized segment may extend into the esophagus within the region of the lower esophageal high-pressure zone and eventually, when the antireflux barrier is lost, further up into the tubular esophagus.

Patients and methods

Patient population. Between July 1991 and December 1997, 556 consecutive patients (336 male and 234 female; median age, 53.4 years; range, 18 to 89 years) were examined for symptoms suggestive of foregut disease. Symptoms consisted of heartburn, regurgitation, dysphagia, noncardiac chest pain, epigastric pain or those suggestive of aspiration such as recurrent pneumonia, wheezing, and persistent cough. Patients with named motility disorders and a history of previous gastric or esophageal operation were excluded. All patients underwent upper endoscopy with biopsy, standard esophageal manometry, and 24-hour esophageal pH monitoring.

Stationary motility. Standard stationary motility was per-

formed after an overnight fast. Lower esophageal resting pressure was measured at the respiratory inversion point, as previously described.⁹ The 3 criteria used to determine the structural integrity of the lower esophageal sphincter (resting pressure, overall length, and abdominal length) were calculated from the mean of 5 measurements. A structurally defective sphincter was defined by the presence of 1 or more of the following conditions: a resting pressure of less than 6 mm Hg, an overall sphincter length of less than 2 cm, or an abdominal length of less than 1 cm.

Ambulatory 24-hour esophageal pH monitoring. Esophageal pH monitoring was performed with a glass electrode (Ingold Inc, Urdorf, Switzerland) placed 5 cm above the upper border of the manometrically defined lower esophageal sphincter. Medications were discontinued 72 hours before testing, except for omeprazole, which was discontinued at least 2 weeks earlier. Esophageal pH was recorded on a portable digital data recorder and was analyzed as previously described.¹⁰ Patients with esophageal pH less than 4.0 for more than 4.4% of the monitored time were classified as having increased esophageal acid exposure.¹⁰

Endoscopy. All patients underwent upper gastrointestinal endoscopy with biopsy. The gastroesophageal junction was identified by the proximal extent of the gastric rugae. The squamocolumnar junction was identified by the change from pink-appearing glandular mucosa to the white pearly appearing squamous mucosa. All patients had 3 to 6 biopsy specimens obtained from the gastroesophageal junction. Patients with an irregular squamocolumnar junction that coincided with the gastroesophageal junction had 2 or more biopsy specimens obtained from the tongues of glandular mucosa extending into the esophagus. In patients whose squamocolumnar junction was separated from the gastroesophageal junction, biopsy specimens were obtained from 4 quadrants at 2-cm intervals throughout the length of the separation. The locations of the gastroesophageal junction, the squamocolumnar junction, and each biopsy specimen were recorded in centimeters from the incisor teeth.

Histologic evidence. All biopsy specimens underwent routine fixation and staining with hematoxylin and eosin and were analyzed for the type and the condition of the epithelium. Gastric fundic mucosa was characterized by glands that contained parietal and chief cells and was devoid of mucous cells, except those lining the surface and foveolar region. Cardiac-type or columnar mucosa was characterized by a columnar epithelium with glands composed entirely of mucous cells without any parietal or chief cells. Inflammation of cardiac-type mucosa was diagnosed by the presence of eosinophil or plasma cell infiltration of the lamina propria and hyperplasia of the mucous cells in the foveolar region. Specialized intestinal metaplasia was identified by the presence of well-defined goblet cells within columnar epithelium. The presence of goblet cells was confirmed by a positive staining with alcian blue at pH 2.5.

Definition of study groups. The patients were divided into 3 groups on the basis of the extent of cardiac-type mucosa with intestinal metaplasia recently reported to be commonly

Fig 1. The prevalence of intestinal metaplasia occurring within cardiac-type mucosa of varying extents: limited to the gastroesophageal (GE) junction, involving short (<3 cm) and long (≥3 cm) segments of the esophageal body.

Table I. Demographic data in patients with varied lengths of cardiac-type mucosa with intestinal metaplasia

Demographic	Length of cardiac type of mucosa with intestinal metaplasia		
	Limited to the gastroesophageal junction	Involving <3 cm of the esophagus	Involving ≥3 cm of the esophagus
No. of patients	34	44	68
Male/female	22:12	29:15	53:15
Age (y)	53	52	54
Range	22-78	34-74	24-83
IQR	42-60	44-62	43-62
Duration of symptoms (y)	10	10†	16*
Range	1-30	1-48	1-48
IQR	4-14	5-17	9-20

IQR, Interquartile range; y, years.

* $P < .05$ vs all other groups.

† $P = .05$ vs limited to gastroesophageal junction.

seen in the endoscopy suite.⁴ Those patients with no endoscopically apparent cardiac-type mucosa above the gastroesophageal junction but in whom intestinal metaplasia in cardiac-type mucosa was found in biopsy specimens from just below the squamocolumnar junction were classified as having intestinal metaplasia limited to the gastroesophageal junction. Patients with intestinal metaplasia and a complete or partial separation of less than 3 cm between the gastroesophageal and squamocolumnar junction were classified as having short-segment intestinal metaplasia. Long-segment intestinal metaplasia was diagnosed when the separation

between the gastroesophageal and the squamocolumnar junction was 3 cm or more.

Statistics. Data are reported as medians and interquartile ranges unless otherwise stated. The χ^2 and Fisher's exact tests were used to compare proportions. Continuous data was compared in the 3 groups with the Kruskal-Wallis test. Comparisons between individual groups were performed with the Mann-Whitney U test.

Results

Overall, 411 of the 556 patients had cardiac-type mucosa on biopsy specimens of their esophagus or gastroesophageal junction. Of these, 147 patients (35%) had intestinal metaplasia. Fig 1 shows that the prevalence of intestinal metaplasia occurring within cardiac-type mucosa increased progressively in patients grouped according to the extent of the cardiac mucosa. Demographics of the 3 groups are shown in Table I. Patients with segments of intestinal cardiac-type mucosa 3 cm or greater had significantly longer duration of reflux symptoms than those patients with segments shorter than 3 cm or those patients in whom it was limited to the gastroesophageal junction.

Table II shows the hallmarks of gastroesophageal reflux disease in the 3 patient groups. There was a progressive reduction in the median lower esophageal sphincter pressure and abdominal length in the 3 patient groups. Further, when each patient was considered individually, there was an inverse correlation between the extent of intestinal cardiac-type mucosa and their lower esophageal sphincter pressure (Fig 2)

Table II. Functional characteristics of gastroesophageal reflux disease in patients with varied lengths of cardiac-type mucosa with intestinal metaplasia

Demographic	Length of cardiac type of mucosa with intestinal metaplasia		
	Limited to the gastroesophageal junction	Involving <3 cm of the esophagus	Involving ≥3 cm of the esophagus
Lower esophageal sphincter			
Resting pressure (mm Hg)	7.2 (5.5-13.3)	6.4 (3.6-10.2)	3.8 (2.0-6.2)*
Overall length (cm)	2.2 (1.8-3.0)	2.1 (1.4-3.5)	1.8 (1.2-2.6)†
Abdominal length (cm)	1.0 (0.4-1.4)	0.9 (0.2-1.6)	0.4 (0.2-1.0)*
Prevalence defective lower esophageal sphincter (%)	52.9	65.9	94.1*
Esophageal body			
Distal amplitude (mm Hg)	79 (53-117)	61 (36-79)†	51 (35-76)†
No. of reflux episodes >5 min	2 (1-4)	5 (2-7)†	7 (4-18)*
Duration of longest episode (min)	10.0 (5-21)	17.5 (12-25)†	28 (12-52)*
Esophageal acid exposure			
Time pH < 4.0 (%)	5.8 (3.9-8.2)	8.4 (6.1-14.0)*	16.5 (11.2-29.9)*
Prevalence abnormal exposure (%)	64.7	86.4†	92.6†
No. of reflux episodes	53 (19-91)	81 (57-139)†	197 (118-267)*

Values expressed as medians and IQR, except for prevalence data.

**P* < .05 vs all other groups.

†*P* < .05 vs limited to the gastroesophageal junction.

and abdominal length (Fig 3). The extent of intestinal cardiac-type mucosa with intestinal metaplasia also increased as the number of defective components of the lower esophageal sphincter in each patient increased (Fig 4).

Also, the clearance function of the esophageal body decreased in the 3 patient groups (Table II). This was reflected by an increase in the median number of reflux episodes greater than 5 minutes in duration and the median duration of the longest reflux episodes. These markers of reduced clearance function were associated with significantly poorer esophageal contraction amplitudes in the patients with short (<3 cm) and long (≥3 cm) segments of intestinal cardiac-type mucosa compared with those with involvement limited to the gastroesophageal junction.

As would be expected from the loss of the lower esophageal sphincter function, the extent of intestinal cardiac-type mucosa was also related to the esophageal acid exposure (Table II). There was a progressive increase in the median acid exposure in the 3 patient groups as measured by the percentage of time the pH was less than 4 and the number of reflux episodes. When each patient was considered individually, there was a strong direct correlation between the length of cardiac mucosa with intestinal metaplasia and the percentage of time that their esophagus was exposed to pH less than 4 (Fig 5).

An important observation was that intestinal meta-

plasia was always found in the proximal portion of the cardiac-type mucosal segment, but its presence varied distally (ie, it was not found distally in 22 of 44 of the patients [50%] with a short [<3 cm] and 41 of 68 of the patients [60%] with a long segment [≥3 cm]).

Discussion

The results of the present study support the concept that the presence of intestinal metaplasia in cardiac-type mucosa, regardless of its extent, represents Barrett's esophagus, because these patients exhibit the hallmarks of gastroesophageal reflux disease, including decreased lower esophageal sphincter pressure and length and increased esophageal acid exposure.¹¹ The extent of the intestinal mucosa seemed to increase with progressive deterioration of the antireflux barrier. Compromised sphincter function may result from inflammatory changes in the muscularis propria caused by increased esophageal acid exposure.⁵ With time the lower esophageal sphincter deteriorates, allowing the esophageal body to be exposed to gastric juice. Cardiac-type mucosa with intestinal metaplasia can form in the tubular esophagus as a result of the increased exposure to gastric juice. The inflammation caused by this process results in the loss of esophageal body contractility classically seen in patients with long segments of Barrett's esophagus.¹² Intuitively, it appears logical that long segments of intestinal metaplasia are short before they become long. Fontollet and Monnier (Departments

Fig 2. The relationship between the extent of cardiac-type mucosa with intestinal metaplasia (*IM*) and resting pressure of the lower esophageal sphincter (*LES*) on standard esophageal manometry.

Fig 3. The relationship between the extent of cardiac-type mucosa with intestinal metaplasia (*IM*) and lower esophageal sphincter (*LES*) abdominal length on standard esophageal manometry.

of Pathology and Head and Neck Surgery, CHUV, University of Lausanne, Lausanne Switzerland. Personal communication; letter received September 18, 1998.) have observed 120 patients with Barrett's esophagus over a median of 60 months; in 29 patients, they measured a progression from 5.6 cm (3-15 cm) to 9.2 cm (5-20 cm). All of these patients had lengths of 3 cm or greater. To our knowledge, similar studies on lengths shorter than 3 cm have not been reported. It may be that it is endoscopically more difficult to measure increases in the length of shorter segments.

In contrast to this stepwise hypothesis is the commonly accepted belief that Barrett's esophagus develops rapidly to its full extent with no subsequent change. This concept is based largely on the report of Cameron and Lomboy,¹ whose study consisted entirely of patients with an esophageal columnar lining of 3 cm or more. They observed 21 patients with Barrett's esophagus for a mean of 7.3 years. The average initial length of columnar epithelium was 8.29 cm, and the final length was 8.33 cm, not significantly different. Their strongest evidence that the extent of Barrett's esopha-

Fig 4. The relationship between the extent of cardiac-type mucosa with intestinal metaplasia (*IM*) and degree of lower esophageal sphincter (LES) competency. Values of each subject are plotted; the horizontal line denotes the mean of each group.

Fig 5. The relationship between the extent of cardiac-type mucosa with intestinal metaplasia (*IM*) and the percentage of time spent below pH 4.0 on 24-hour esophageal pH monitoring.

gus does not change significantly over time was that the mean length of columnar epithelium was similar in all age groups. These findings would be expected because patients with long segments of columnar lining uniformly have profound defects in the antireflux mechanisms that results in very high esophageal exposure to gastric contents.¹² Such patients represent a stage of disease in which further deterioration of the antireflux

mechanism or increases in esophageal exposure to gastric juice would not be expected to occur.

Rather than implicating the sudden occurrence and unchanging extent of Barrett's metaplasia, their findings can be explained by the normal gradient between the positive pressure in the stomach and the negative pressure in the thoracic esophagus. When the antireflux mechanism completely deteriorates, gastric juice flows

to the point of lowest esophageal pressure in the midthoracic esophagus.¹³ Under these conditions, intestinalized cardiac-type mucosa may develop to this point with no apparent subsequent change in length.

The most controversial issue is whether the intestinalized cardiac-type epithelium found at the gastroesophageal junction represents the Barrett's metaplasia seen in reflux disease.¹⁴ In part, this controversy exists because most authors base the diagnosis of intestinal metaplasia of the cardia on the location of the biopsies, that is, the anatomic gastric cardia, which infrequently harbors cardiac-type mucosa, rather than the type of underlying mucosa in which the intestinal metaplasia occurs.^{15,16} Further, intestinal metaplasia arising in fundic or antral mucosa has been associated with *Helicobacter pylori* infection, and it would seem reasonable that the same would hold true for the cardia.¹⁷⁻¹⁹ It has been shown, however, that intestinal metaplasia in cardiac-type mucosa is not associated with the presence of *H pylori* or other gastric pathology; rather, it is associated with gastroesophageal reflux disease.^{5,8} If intestinal metaplasia of cardiac-type mucosa in patients with an endoscopically normal-appearing distal esophagus is a manifestation of gastroesophageal reflux, then it follows that it most likely represents endoscopically inapparent segments of Barrett's metaplasia. Further, this observation is in keeping with the rapid and parallel increase of adenocarcinoma of the esophagus and the gastroesophageal junction, that is distinct from that of the stomach and is a known complication of Barrett's esophagus.^{20,21}

The observation that not all patients with cardiac-type mucosa experience the development of intestinal metaplasia suggests that the development of Barrett's esophagus is a 2-step process. In the first step, cardiac-type mucosa forms as a normal response of the squamous epithelium to acid exposure.^{5,22,23} Intestinal metaplasia develops in time under the proper luminal condition and stimulus as a second step. Indeed, in children in whom the esophagus is lined by columnar epithelium, intestinal metaplasia rarely occurs before the age of 5 years, and clinical studies have shown a time lag of 5 to 7 years for the development of intestinal metaplasia in adults.²⁴⁻²⁶ Patients with long segments of cardiac-type mucosa are more likely to show intestinal metaplasia, because based on the duration of symptoms the process has been going on for a longer time (Table I). In support of the 2-step hypothesis, Hamilton and Yardley²⁷ reported the development of Barrett's mucosa in the esophagus above the anastomosis in 3 patients after esophagogastrectomy. In 2 of these patients, they documented progression from

squamous epithelium to cardiac mucosa and subsequently intestinal metaplasia over 6.3 and 10 years.

The observation that intestinal metaplasia consistently occurs in the proximal portion of the cardiac-type mucosal segment can be explained by the luminal pH exposure. The proximal portion of the cardiac-type mucosal segment is most likely to be exposed to the pH 3 to 5 because of dilution and neutralization of the refluxed gastric acid by saliva. Exposure of columnar epithelial cells to this pH range has been shown to encourage the phenotypic expression of intestinalization. In contrast, exposure to duodenal mucosa to an acid pH reduces the expression of intestinalization. This is in accordance with the observation that the small intestinal brush border is lost after exposure to acetic acid.²⁸ This would account for the observation that intestinal metaplasia is less commonly in the more distal portion of the Barrett's segment because this mucosa is more likely to be exposed to the acidic pH of refluxed gastric juice that has not been diluted or neutralized by saliva.

On the basis of our findings, we hypothesize that Barrett's esophagus spreads progressively in a stepwise fashion. Initially, intestinal metaplasia may develop in endoscopically indistinguishable segments of cardiac-type mucosa at the gastroesophageal junction. With weakening of the lower esophageal sphincter and continued acid exposure, intestinalized cardiac-type mucosa develops within the distal 3 cm of the esophagus. With time and the loss of the sphincter, the process is extended higher into the esophagus.

We conclude that the development of Barrett's esophagus is not a static but a dynamic phenomenon and that the extent of intestinal metaplasia is determined by the severity of the functional abnormalities identified with gastroesophageal reflux disease.

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Discussion

Dr Victor F. Trastek (Rochester, Minn). Adenocarcinoma of the esophagus is a deadly disease that is increasing in incidence and is related to Barrett's esophagus in almost all cases. The best way to improve survival in this dismal disease is to detect and treat it early. To do this, we must understand the pathophysiology of the entire process, the first portion of which is the development of the columnar-lined esophagus, or Barrett's esophagus.

Although this is most likely the result of acid and duodenal content reflux, it is unclear exactly how the Barrett's mucosa develops in a patient over time. Dr Öberg and his colleagues would suggest from their work that the columnar epithelium develops in a creeping fashion, progressing over time in the patient. This assumption is based on the fact that the longest length of columnar epithelium was found in the patients with the most severe gastroesophageal reflux disease, those who had had the worst functional parameters. Also lending support to this assumption was the fact that intestinal metaplasia was usually found at the most distal end of the Barrett's process.

I applaud Dr Öberg and his colleagues in lending more information to the pathophysiology and development of Barrett's esophagus, but I am not convinced that they have proved the progression theory. To truly prove progression, one must see increasing length sampled over time in a particular patient. This study shows differences in length at 1 point in time comparing 1 patient to another. The argument would have been much more compelling had the data points been sampled over a period of time that showed that the length of the Barrett's increased as the severity of the disease progressed.

It is still unclear from this study, by looking at just 1 point in time, whether the increased severity of disease caused the increased length. On the other hand, maybe the development of Barrett's esophagus in some way affects how the esophagus functions and therefore those patients have the most severe parameters of function. So, I do not think we know yet whether the cart comes before the horse or the other way around.

In your patient group, do you have any information sampling a single patient over a period of time in which you could show us that increasing severity of disease was linked

to increasing length of Barrett's disease? If progression is indeed the way this Barrett's mucosa develops, why do not all patients eventually end up with a total esophagus full of Barrett's mucosa?

Dr Öberg. Regarding the first question, none of the patients in this study were assessed more than once, so we have no longitudinal data. I completely agree with you that the best way of assessing this issue is to have longitudinal long-term studies of patients with short segments of Barrett's esophagus. However, this is very difficult to do because to study the natural history of Barrett's esophagus you need to leave the patients untreated, and I do not think we can do that.

You next asked why all patients do not progress to 8 cm of Barrett's esophagus. I believe that this does not happen because gastroesophageal reflux is a spectrum of diseases in which the severity varies. I think we can show, based on the data from this study, that the extent of Barrett's esophagus is determined by the severity of reflux disease. All patients do not experience the development of end-stage reflux disease and that is why not all patients experience the development of Barrett's esophagus to its full extent.

Dr Claude Deschamps (Rochester, Minn). Do you survey those patients who have limited Barrett's at the cardia differently than the patients who have more extensive Barrett's? For example, if your program does check on patients every year, do you survey those patients less often?

Second, when you perform cardiac procedures on these patients, do you charge as a cardiac surgeon?

Dr Öberg. In response to your first question, I do believe that these patients have an increased risk of the development of adenocarcinoma at the gastroesophageal junction. However, because intestinal metaplasia of the gastroesophageal junction is a frequent finding and the risk of the development of adenocarcinoma in these patients is unknown, we do not know whether they benefit from surveillance. Because we are interested in research and eager to know more about this disease, we offer these patients surveillance. I believe that until we know more about the effectiveness and benefits of surveillance, these patients should undergo surveillance only in controlled studies. The frequency with which this should be done is unknown.

To answer your second question, no, we do not charge for cardiac procedures.

Dr Andre C. H. Duranceau (Montreal, Quebec, Canada). If you find intestinal metaplasia in the proximal wall of the stomach, you call it intestinal metaplasia in the stomach. Why do you try to tag it on the esophagus when it is under the cardia?

Dr Öberg. This is a very important concept, and I am happy you asked this question because it is easy to get confused when you read the conflicting reports in the literature. Unlike most recent reports on this subject, the biopsy specimens in this study were obtained at the gastroesophageal

junction, just below the squamocolumnar junction, and not from the stomach. Many authors report on biopsy specimens obtained from the anatomic gastric cardia, which is part of the stomach, and find that the presence of intestinal metaplasia is associated with *H pylori* infection. We believe that this is not the way to study changes occurring in the transition between the esophagus and the stomach, because when you biopsy the anatomic gastric cardia you infrequently find cardiac-type mucosa, but you do find gastric fundic-type mucosa. We base our findings concerning carditis and intestinal metaplasia on the underlying mucosa rather than the location of the biopsy specimen. Inflammation and intestinal metaplasia in the gastric fundic mucosa is not likely related to reflux, because fundic mucosa is believed to be resistant to acid-peptic digestion but rather associated with *H pylori* infection. However, when found, cardiac-type mucosa is almost always inflamed, and as we have shown in previous articles it is associated with the presence of reflux.

Dr David W. Myers (Annapolis, Md). Did you collect information on the severity of the metaplasia, high versus low grade, as well as the extent? If you did collect it, did you find that it did correlate as well with the severity of gastroesophageal reflux just as the extent of the Barrett's correlated?

Dr Öberg. Within these 556 patients, there were 9 patients with low-grade dysplasia but no patients with high-grade dysplasia. Low-grade dysplasia occurred in all lengths of intestinal metaplasia, including those limited to the gastroesophageal junction. There was no difference in esophageal acid exposure between patients with and without dysplasia, but we have previously shown that there is an association with complicated Barrett's esophagus, including dysplasia, and the presence of duodenogastroesophageal reflux. However, this was not part of the present study.

Dr David J. Sugarbaker (Boston, Mass). You correlated rather nicely the amount of reflux with the extent of metaplasia. Do you have any data on long-term use of H_2 blockers or omeprazole (Prilosec) or other antacid therapy? Many patients these days are on long-term therapy, and I wonder if you could comment, from a demographic standpoint, about whether any of this has an effect on the development of metaplasia.

Dr Öberg. We know that almost all of these patients were treated with proton pump inhibitors and H_2 blockers; whether that treatment affected the formation of Barrett's esophagus is not known. However, we have shown that patients with Barrett's esophagus do have an increased prevalence of duodenogastroesophageal reflux. Treatment with proton pump inhibitors suppresses gastric acid secretion and results in elevated gastric pH, which may lead to bacterial overgrowth and deconjugation of the bile acids. These bile acids have been shown to be more harmful and may possibly affect the formation of Barrett's metaplasia. We are currently studying this, but to date, we have no definite data.