Columnar Mucosa and Intestinal Metaplasia of the Esophagus
Fifty Years of Controversy

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Objective
To outline current concepts regarding etiology, diagnosis, and treatment of intestinal metaplasia of the esophagus and cardia.

Summary Background Data
Previously, endoscopic visualization of columnar mucosa extending a minimum of 3 cm into the esophagus was sufficient for the diagnosis of Barrett’s esophagus, but subsequently the importance of intestinal metaplasia and the premalignant nature of Barrett’s have been recognized. It is now apparent that shorter lengths of intestinal metaplasia are common, and share many features of traditional 3-cm Barrett’s esophagus.

Methods
Themes and concepts pertaining to intestinal metaplasia of the esophagus and cardia are developed based on a review of the literature published between 1950 and 1999.

Results
Cardiac mucosa is the precursor of intestinal metaplasia of the esophagus. Both develop as a consequence of gastro-esophageal reflux. Intestinal metaplasia, even a short length, is premalignant, and the presence of dysplasia indicates progression on the pathway to adenocarcinoma. Antireflux surgery, as opposed to medical therapy, may induce regression or halt progression of intestinal metaplasia. The presence of high-grade dysplasia is frequently associated with an unrecognized focus of adenocarcinoma. Vagal-sparing esophagectomy removes the diseased esophagus and is curative in patients with high-grade dysplasia. Invasion beyond the mucosa is associated with a high likelihood of lymph node metastases and requires lymphadenectomy.

Conclusions
Despite improved understanding of this disease, controversy about the definition and best treatment of Barrett’s esophagus continues, but new molecular insights, coupled with careful patient follow-up, should further enhance knowledge of this disease.

HISTORY
Stomach Versus Esophagus

Originally the term “Barrett’s esophagus” was used to describe an esophagus in which a portion of the normal squamous mucosa was replaced by columnar epithelium. Since the 1950s, when the term became popularized, much has been learned about this condition, and new concepts continue to emerge that force reevaluation of this disorder. In fact, the meaning of the term Barrett’s esophagus is perhaps more ambiguous now than ever before.

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when ulcers are found below the squamocolumnar junction, they represent gastric ulcers within “a pouch of stomach . . . drawn up by scar tissue into the mediastinum” or more likely represent “examples of a congenital short esophagus.”

In 1953, Allison and Johnstone demonstrated that the tubularized portion of the foregut declared by Dr. Barrett to be stomach had no peritoneal covering, normal esophageal musculature, and typical esophageal mucous glands. They concluded that “it appears better to refer to that congenital abnormality which from the outside looks like esophagus and from the inside looks like stomach as ‘esophagus lined with gastric mucous membrane.’” 3 Although they called the mucosa “gastric,” they recognized that oxyntic cells were not present.

In 1957, Dr. Barrett accepted the viewpoint that in some patients the columnar epithelium extended further proximally into the esophagus than could be accounted for by a hiatal hernia. Further, he concurred with Allison and Johnstone that the columnar mucosa, despite its “gastric” appearance, did not contain oxyntic cells and did not function like gastric mucosa. He agreed to the term “columnar-lined lower esophagus,” and subsequently his name became synonymous with the condition.

### Congenital Versus Acquired

In their 1953 report, Allison and Johnstone had noted that the presence of a columnar-lined esophagus was usually associated with a hiatal hernia, and that all of the patients had reflux esophagitis. Still, like Dr. Barrett, they considered it to be of congenital origin. Later Dr. Barrett, while still favoring a congenital etiology, conceded that “if the cardiac valve of a normal person were to become incompetent and if the lower esophagus were, as a result, to be bathed for a long time by digestive gastric juice, the squamous epithelium could be eaten away and totally replaced by columnar cells.” 2

In 1959, Moersch et al 4 reviewed the specimens from 36 patients who had undergone esophageal resections at the Mayo Clinic for esophagitis. They noted that “cells resembling young columnar cells were seen occasionally, and thus the question of inflammatory metaplasia had to be considered.” This was the first convincing evidence that the columnar epithelium of Barrett’s esophagus was acquired, and that it was caused by repetitive exposure of the distal esophagus to refluxed gastric juice. Subsequently several studies, including the 1970 landmark experimental report by Bremner et al, 5 confirmed the association between a columnar-lined esophagus and gastroesophageal reflux disease (GERD), and the congenital theory was discarded.

### Evolving Definition

#### The 3-cm Rule

In the late 1950s, the term Barrett’s esophagus was understood to mean a columnar-lined esophagus, and this rather vague definition persisted until the 1980s. Refinements in the definition came about as a result of two issues. The first was that as endoscopy became more common, it was recognized that many patients had hiatal hernias and esophagitis, and that it was difficult and error-prone for an endoscopist to determine precisely where the esophagus ended and the stomach began. In addition, Hayward in 1961 6 had written that the “normal” esophagus could have 1 to 2 cm of columnar mucosa at the distal end. Therefore, to avoid an overdiagnosis of Barrett’s resulting either from failure to recognize a tubularized portion of herniated stomach on endoscopy, or from failure to allow for the “normal” 2 cm of columnar mucosa in the distal esophagus, a 3-cm rule was introduced in the early 1980s. This rule stipulated that a diagnosis of Barrett’s esophagus required a minimum of 3 cm of columnar mucosa to be present above the perceived gastroesophageal junction. Although various authors used between 2 and 5 cm of columnar mucosa, some minimum length requirement was adopted by most physicians and persists in the minds of many people to this day.

#### Importance of Intestinal Metaplasia

The second issue that forced refinement in the definition of Barrett’s esophagus was the identification of a subset of patients with a columnar-lined esophagus who were at risk for developing adenocarcinoma. In 1951, Bosher and Taylor 7 described goblet cells indicative of intestinal metaplasia within a columnar-lined esophagus. In subsequent publications Allison, Barrett, and others noted that the columnar mucosa of Barrett’s esophagus, although “gastric” in appearance, was not normal gastric mucosa. 2,3 Despite these observations, most physicians paid no particular attention to the histology of the columnar lining within the esophagus. This changed in 1976 after a report by Paull et al 8 described the results of manometrically guided biopsies at multiple levels from 11 patients with a columnar-lined esophagus. Each patient was found to have one or a combination of three histologic types of columnar epithelium: a gastric fundic type composed of chief and parietal cells; a junctional type composed of mucous glands without parietal cells; and a specialized type with intestinal characteristics including villiform surface, mucous glands, Alcian blue-staining goblet cells, and no parietal or chief cells. In these 11 patients, Paull et al noted that the most prevalent type of columnar epithelium was the specialized type, and when present, the specialized mucosa was always found adjacent to the squamous epithelium in the most proximal portion of the columnar epithelium. If the specialized mucosa did not involve the entire columnar segment, then junctional mucosa was present below the specialized mucosa, and the gastric fundic type of epithelium was found most distal. The
importance of the specialized or intestinal type of epithelium within a columnar-lined esophagus was hinted at in this report, in which 1 of the 11 patients was noted to have marked dysplastic changes within an 8-cm segment of specialized columnar-type epithelium. Subsequently, Haggitt suggested and Skinner and then Reid confirmed that the intestinal type of columnar mucosa was premalignant, and further was the only type associated with malignant degeneration.9–11

**Traditional Definition of Barrett’s**

After these reports, the histology of the columnar-lined esophagus assumed great importance, and the definition of Barrett’s esophagus evolved again to require both 3 cm of columnar mucosa within the esophagus and intestinal metaplasia in histology. Consequently, a biopsy was now necessary to make a diagnosis of Barrett’s. Since the mid-1980s, most physicians have restricted the term Barrett’s esophagus to patients meeting these criteria; however, it remains important even now to scrutinize the definition of Barrett’s esophagus used when reviewing any paper written on the subject.

**Short-Segment Barrett’s and Intestinal Metaplasia of the Cardia**

Recently, with continued improvements in endoscopic equipment and the availability of potent acid-suppression medication capable of healing esophagitis, it has become evident that short tongues of columnar mucosa can be found extending up from a well-defined gastroesophageal junction. Further, biopsies from a normal-appearing gastroesophageal junction have been found to contain microscopic foci of intestinal metaplasia within cardiac mucosa, a condition referred to as intestinal metaplasia of the cardia. There is increasing evidence that, similar to traditional Barrett’s, these short lengths of intestinal metaplasia are associated with gastroesophageal reflux and may have malignant potential.12

**Current Definition**

The relation between intestinal metaplasia present only at the gastroesophageal junction, short-segment (<3 cm) Barrett’s, and traditional (≥3 cm) Barrett’s remains controversial. However, an acceptable current definition of Barrett’s is a change from the normal esophageal squamous mucosa to columnar mucosa of any length that is visible endoscopically and that on biopsy demonstrates intestinal metaplasia.15 Using this definition, intestinal metaplasia confined to the gastroesophageal junction would not be considered Barrett’s.

**EPIDEMIOLOGY**

The prevalence of Barrett’s esophagus is unknown, but any estimate depends significantly on the definition one uses for Barrett’s. Using the traditional definition of at least 3 cm of columnar mucosa above the gastroesophageal junction, Barrett’s has been reported in 0.45% to 2.2% of all patients undergoing upper endoscopy and in up to 12% of patients undergoing endoscopy for symptoms of reflux.14 If all patients with a biopsy showing intestinal metaplasia, regardless of length, were included in the definition, then the incidence increases to 9% to 32% of unselected patients undergoing upper endoscopy.15 Based on an autopsy series, Cameron et al16 estimated the prevalence of traditional Barrett’s in the general population to be 376 cases per 100,000 population. Consequently, they suggested that for every known patient with Barrett’s, there might be 20 or more unrecognized ones in the general population. It is likely that the prevalence of any length of intestinal metaplasia within the esophagus is even greater.

**ETIOLOGY**

**Gastroesophageal Reflux**

Typically, patients with Barrett’s esophagus have the classic gastroesophageal reflux symptoms of heartburn and regurgitation, with or without dysphagia. Often these patients describe a longer duration of reflux symptoms than do patients with reflux disease without Barrett’s.17 Ambulatory pH monitoring demonstrates excessive acid reflux into the distal esophagus in nearly all patients with Barrett’s. The abnormal acid exposure is primarily due to a structurally defective lower esophageal sphincter (LES), with defects in length, pressure, or both demonstrated manometrically in more than 90% of patients with Barrett’s.18 In addition, patients with Barrett’s frequently have impaired esophageal motility with low contraction amplitudes and an increased frequency of abnormal waveforms in the distal esophagus compared with normal subjects.19,20 As a consequence, refluxed material is poorly cleared from the esophagus. The combination of frequent reflux episodes and poor clearance allows prolonged bathing of the distal esophagus in refluxed gastric juice, resulting in severe mucosal injury.

In addition to an increased amount and exposure time of refluxed gastric juice, the composition of the refluxed juice likely contributes to the pathogenesis of Barrett’s esophagus. The observations that gastric hypersecretion can be associated with Barrett’s and that Barrett’s has developed after total gastrectomy suggest that acid gastric juice is not the sole factor responsible for this disease.21 Recent reports are focusing on the importance of refluxed duodenal secretions in the development of intestinal metaplasia. Patients who reflux both gastric and duodenal juice have been found to have a higher prevalence of esophagitis and Barrett’s esophagus than do patients who reflux gastric juice alone.18 Analysis of the composition of reflux in 281 patients with GERD demonstrated that the patients with the greatest degree of mucosal injury were more likely to have both gastroduodenal and acid reflux as opposed to pure gastric reflux.
reflux (Table 1). In addition, patients with Barrett’s had a significantly higher prevalence and duration of abnormal esophageal bilirubin exposure, which is a tag for duodenal juice, compared with patients with only esophagitis. Among patients with Barrett’s, significantly greater esophageal bilirubin exposure has been demonstrated in those in whom dysplasia develops (Fig. 1).

Role of Bile

Evidence is accumulating that bile salts are the noxious component in refluxed duodenal juice, and that their ability to cause cellular injury is pH-dependent. For bile salts to enter mucosal cells and cause injury, they must be soluble and unionized. At pH 7, greater than 90% of bile salts are in solution and completely ionized. Acidification of bile to a pH of less than 2 produces irreversible precipitation. Thus, under normal physiologic gastric conditions, bile acids precipitate and are of minimal significance. However, in a more alkaline gastric environment, as can occur with the use of acid-suppression medication, bile salts are partially dissociated. At a critical pH between 3 and 5, a mixture of ionized salt and the lipophilic, unionized acid is present. Unionized bile salts can rapidly cross mucosal cell membranes. Once inside the alkaline environment of the cell, they are converted back into their ionized form. Consequently, they become trapped within the cell, accumulate, and ultimately become toxic to the mitochondria (Fig. 2).

Cellular Origin of Barrett’s

It is generally accepted that Barrett’s esophagus is an acquired condition that occurs as a consequence of gastroesophageal reflux. This implies that these patients at one time had normal squamous epithelium in their esophagus, and that this epithelium subsequently was replaced. Although most clinicians accept this concept, the sequence by which this occurs is controversial. Contained within the controversy are two issues: whether injured squamous mu-

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**Table 1. PREVALENCE OF INCREASED ESOPHAGEAL ACID EXPOSURE BY 24-HOUR pH MONITORING, INCREASED ESOPHAGEAL BILIRUBIN EXPOSURE BY BILITEC PROBE, AND STRUCTURALLY DEFECTIVE LES BY MOTILITY IN PATIENTS WITH INCREASING MUCOSAL INJURY SECONDARY TO GERD**

<table>
<thead>
<tr>
<th>Group</th>
<th>Prevalence of Increased Acid Exposure (%)</th>
<th>Prevalence of Increased Bilirubin Exposure (%)</th>
<th>Prevalence of Defective LES (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No mucosal injury</td>
<td>35.4</td>
<td>30.0</td>
<td>51.5</td>
</tr>
<tr>
<td>2. Esophagitis</td>
<td>80.0*</td>
<td>61.4*</td>
<td>85.7*</td>
</tr>
<tr>
<td>3. Short-segment Barrett’s</td>
<td>93.3*</td>
<td>73.3*</td>
<td>73.3*</td>
</tr>
<tr>
<td>4. Long-segment Barrett’s</td>
<td>96.9‡</td>
<td>84.4‡</td>
<td>93.8‡</td>
</tr>
</tbody>
</table>

GERD, gastroesophageal reflux disorder; LES, lower esophageal sphincter. Data from reference 22.

*P < .05 vs. group 1; ‡P < .05 vs. groups 1 and 2; †P < .05 vs. groups 1 and 3.

**Figure 1. Acid and bilirubin exposure times for patients with Barrett’s esophagus with and without complications.**

**Figure 2. Dissociation curve for bile acids demonstrating the critical pH range from 3 to 6 where bile acids exist in their soluble, unionized form and can penetrate cell membranes, accumulate within mucosal cells, and become toxic to the mitochondria.** At pH 2, bile acids irreversibly precipitate from solution, whereas at pH 7, bile acids exist in their noninjurious ionized form.
cosa is first replaced by or transformed into columnar mucosa, which then undergoes a second transformation into intestinalized columnar mucosa; and whether columnar epithelium and intestinalization gradually involve more of the esophagus, or whether Barrett’s rapidly develops to its full extent with little subsequent change. The answers to these questions are not known with certainty, but there is an ever-increasing body of data that provides insight about the process of esophageal columnization and intestinalization.

**Columnar-Lined Esophagus**

*Step 1: Transition Zone From Esophageal Squamous Mucosa to Gastric Columnar Epithelium*

When considering the effects of acid reflux on squamous esophageal epithelium, a logical place to examine is the esophagogastric junction. Amazingly, despite years of interest and investigation, even the normal anatomy of this area remains somewhat of an enigma. In 1961, Hayward\(^6\) published a visionary treatise on this area that, although fascinating to read, is unfortunately devoid of any supporting data. Careful review of the manuscript, however, suggests that his insight into this area was based on extensive dissection in probably many subjects. He began with a discussion of the meaning of the cardia—something equally relevant today. He defined the cardia anatomically as the lower portion of the esophagus between the insertion of the phrenoesophageal ligament and the gastroesophageal junction (Fig. 3). The squamocolumnar junction, he noted, was usually located just distal to the insertion of the phrenoesophageal ligament, and consequently a portion of the cardia was “normally” lined by a short segment of columnar epithelium extending from the gastroesophageal junction proximally to the squamocolumnar junction. He called this columnar mucosa junctional epithelium, and noted that it had the following characteristics:

- It was histologically distinct from normal gastric fundic and pyloric epithelium.
- It did not secrete acid or pepsin but was resistant to both.
- It was not congenital but acquired.
- It was mobile and varied in length, creeping progressively higher into the esophagus with continued gastroesophageal reflux.
- It was potentially reversible with correction of reflux.

Hayward clearly placed the anatomic cardia and the lining junctional mucosa within the lower esophagus. Unfortunately, there has been substantial confusion generated by the terminology used to describe this area. The confusion centers around the fact that anatomists have divided the stomach into five parts, with the area around the esophagogastric junction labeled as the cardiac portion of the stomach. Perhaps rather than focusing exclusively on the anatomical region, it would be best to combine the anatomic region with the histology at that location to distinguish reliably between distal esophagus and stomach. An important and unresolved issue is what is the “normal” mucosa at the esophagogastric junction. Recall that Hayward stated that “normally” the mucosa in this region was columnar, but distinct from gastric fundic mucosa, and was not congenital but acquired. Perhaps by “normal” he meant common, be-

![Figure 3. Hayward’s depiction of the gastroesophageal junction and region of the cardia. Line X-Y crosses the esophagogastric junction. Everything above the line is esophagus, and everything below is stomach. From A to C is esophagus lined by squamous epithelium. The phrenoesophageal ligament inserts at B. From B to D is the area of the esophagus called the cardia. It is partially lined by squamous epithelium (from B to C) and partially lined by cardiac mucosa (from C to D). Cardiac mucosa joins with fundic gastric mucosa at point E, whereas pure fundic mucosa is present at point F. (From Hayward J. The lower end of the esophagus. Thorax 1961; 16:36–41. Reproduced with permission from the BMJ Publishing Group.)](image-url)
Recent, Chandrasoma conducted a review of the gastroesophageal junction in a large number of autopsies in which there was no mention of GERD in the medical record. He determined that in most children and adults younger than 20 years of age, the squamous esophageal epithelium transitioned directly with oxyntic mucosa of the gastric fundus, with no interposed segment of cardiac (junctional-type) epithelium. Cardiac mucosa appeared in specimens from those older than 20 years, but its length was almost always less than 1 cm. From this he concluded that in the normal, nonrefluxing state, squamous esophageal epithelium changes abruptly to oxyntic mucosa of the gastric fundus. However, the presence of a small length of cardiac mucosa is common in adults.

Oxyntic mucosa, like that found in the stomach near the gastroesophageal junction, is not affected by acid. Consequently, it is logical to conclude that cardiac mucosa, if not present at birth, must develop from injured squamous epithelium. This likely involves a change in the direction of differentiation of the germinative squamous epithelial cells toward more acid-resistant columnar cells as a consequence of repetitive exposure to acidic gastroesophageal reflux. In keeping with the concept that cardiac mucosa represents transformed squamous mucosa, cardiac mucosa is the simplest type of columnar epithelium. It is characterized histologically by the presence of only columnar cells and mucous cells. There are no specialized cells such as parietal cells, chief cells, or goblet cells.

The hypothesis that cardiac mucosa develops as a consequence of acid-induced injury to esophageal squamous epithelium is supported by both animal and clinical evidence. Experimental evidence comes from a 1970 study by Bremner et al. in this study a series of dogs underwent stripping of the distal esophageal squamous mucosa with or without creation of a cardioplasty to destroy the function of the LES. They noted extensive squamous cell reepithelialization in the animals without gastroesophageal reflux, whereas squamous regeneration was absent or minimal in the animals with cardioplasty-induced acid reflux. In the animals with reflux, the esophagus was reepithelialized by a columnar epithelium that lacked submucosal glands and parietal cells—the equivalent of cardiac mucosa in humans. Evidence that columnar mucosa can replace normal esophageal squamous epithelium in humans comes from follow-up studies in patients who have undergone partial esophageogastricomy with an intrathoracic anastomosis of the esophagus to the fundus of the stomach. This arrangement leads to a near-constant bathing of the remaining esophagus in refluxed gastric juice, and over months to years columnar epithelium histologically identical to what was unquestionably the esophagus, and in what unquestionably had been squamous epithelium. In a report by Lindahl et al., the mean time to detection of cardiac mucosa above the anastomosis was 8.2 years (range 2.2–13.9 years).

Therefore, it is our opinion that in the truly normal or congenital state, squamous esophageal mucosa ends abruptly at the gastroesophageal junction and abuts the oxyntic mucosa of the stomach. However, in many or perhaps most older children and adults, chronic, low-level reflux occurs, and repetitive bathing of the squamous mucosa at the gastroesophageal junction with gastric juice induces the development of cardiac-type columnar mucosa. Recently, we reported that most of the patients being evaluated for symptoms of gastroesophageal reflux had cardiac mucosa juxtaposed between esophageal squamous and gastric fundic mucosa. Further, the cardiac epithelium almost always had histologic evidence of inflammation unrelated to either Helicobacter pylori infection or mucosal pathology elsewhere in the stomach. Instead, the presence of inflamed cardiac mucosa, or carditis, correlated closely with objective markers of GERD, including an incompetent LES, increased esophageal acid exposure on 24-hour pH monitoring, a hiatal hernia, and erosive esophagitis. We suggested that carditis may represent the earliest manifestation of reflux disease, and that with continued reflux there might be a creeping columnarization of the squamous epithelium within the LES, a progressive loss of sphincter competency, and ultimately explosion of the disease into the body of the esophagus.

Step 2: Extension of Columnar Mucosa Proximally Into the Distal Esophagus

Exposure of the squamous esophageal mucosa to gastric juice in persons without prior surgery is most likely to occur postprandially, when the stomach is distended and the distal esophageal sphincter is taken up by the enlarging fundus. Csendes et al. have demonstrated that with increasing severity of gastroesophageal reflux, the squamocolumnar junction progressively shifts or creeps proximally, resulting in a gradual increase in the length of cardiac-type columnar mucosa within the esophagus. In addition, studies using 24-hour pH monitoring have shown that as acid exposure increases, the length of columnar mucosa within the esophagus steadily and significantly increases as well (Fig. 4). The importance of this progressive increase in the length of cardiac-type columnar mucosa in the esophagus with increasing severity of GERD lies in the direct correlation between the length of cardiac mucosa and the likelihood of finding an area of intestinal metaplasia. We found that the prevalence of any intestinalization within cardiac mucosa increased from 12% when cardiac mucosa was limited to the gastroesophageal junction, to 50% with less than 3 cm, and nearly 100% with 3 cm or more of cardiac mucosa (Fig. 5). Spechler et al. reported similar findings. They noted that 36% of patients with a 1- to 2-cm columnar segment in the esophagus had intestinal metaplasia, and this increased to 93% of patients when the columnar segment was 3 cm in length or more.
Step 3: Intestinalization of Cardiac Mucosa

The primary importance of inflamed cardiac mucosa is that it seems to represent the only mucosal type that can progress to intestinal metaplasia.26 Intestinalization of the cardiac mucosa occurs when hypertrophic cardiac mucous cells develop acid rather than neutral mucin and, most importantly, goblet cells appear. Once intestinalized, the cardiac mucosa seems to have an increased ability to withstand damage by refluxed gastric juice, because there commonly is little or no inflammation present on biopsy. However, the development of intestinal metaplasia within cardiac mucosa is considered a detrimental or progressive change, because this mucosa is capable of further progression to epithelial dysplasia and adenocarcinoma. Available evidence would suggest that cardiac mucosa itself is benign, and that it is only with the development of intestinal metaplasia that the mucosa becomes premalignant.26

The specific cellular event that induces a change from cardiac mucosa to intestinalized cardiac mucosa is unknown. Current theories support a second insult, perhaps from noxious luminal contents. Data from our esophageal laboratory on patients with short lengths of columnar mucosa in the esophagus suggests that compared with patients without intestinal metaplasia, those with intestinal metaplasia tend to have a longer duration of symptoms (5 vs. 10 years) and a greater frequency of abnormal exposure to refluxed bilirubin, as determined by Bilitec probe (Medtronic Functional Diagnostics, Shoreview, MN) monitoring for 24 hours. The frequency of abnormal acid exposure by 24-hour pH monitoring was similar between groups (DeMeester TR, unpublished data).

It is also unclear whether the development of intestinal metaplasia represents a phenotypic change secondary to the induction of genes, or a mutational event within the columnar cells. Mendes de Almeida et al33 have demonstrated biochemically that both cardiac mucosa and intestinal metaplasia express sucrase-isomaltase and crypt cell antigen, two small intestine marker proteins; however, in that study only three patients with cardiac mucosa were evaluated. Recently, Griffel et al34 have shown that the murine antibody DAS-1, which stains specialized columnar mucosa, reacts positively with cardiac mucosa, and that on repeat biopsies histologic evidence of intestinalization later developed in six of the seven patients. If true, these findings would suggest that biochemically cardiac mucosa and intestinal metaplasia are similar, and that cardiac mucosa is the precursor of intestinalized columnar epithelium, or Barrett’s.

Fitzgerald et al35 have recently suggested that the dynamics of acid exposure may effect columnar cell proliferation and differentiation. Using cultured human Barrett’s biopsy specimens, they demonstrated that continuous exposure to acidic media at pH 3.5 resulted in increased villin expression (a marker for epithelial cell differentiation) and reduced cell proliferation. In contrast, villin expression was not detected when the culture medium was made more acidic (pH < 2.5). A dramatic increase in proliferation occurred when the Barrett’s tissue was exposed to a short (1-hour) pulse of acidic medium (pH 3.5) followed by a return to neutral pH. Consequently, alterations in luminal pH and the pattern of exposure may lead to altered growth properties and may contribute to the molecular and structural heterogeneity seen in the esophageal mucosa of patients with Barrett’s.

Intestinal Metaplasia of the Cardia

One unresolved issue is whether intestinal metaplasia limited to the region of the gastroesophageal junction develops in response to the same stimuli that produce traditional, or long-segment, Barrett’s esophagus. Recently, we reviewed 411 patients with cardiac mucosa either at the
gastroesophageal junction or extending up into the esophagus, and found that overall 35% of patients had intestinal metaplasia. When only the patients with intestinal metaplasia were compared, we noted that the length of intestinal metaplasia was inversely correlated with LES pressure and overall length and directly correlated with the percentage of time spent at less than pH 4 on 24-hour esophageal pH monitoring. Our interpretation of this data is that both intestinal metaplasia limited to the gastroesophageal junction (CIM) and Barrett’s are related through the common denominator of cardiac mucosa, and that CIM, Barrett’s, and cardiac mucosa are all linked to gastroesophageal reflux. Others, including Goldblum et al, have published their opinion that intestinal metaplasia of the gastroesophageal junction is related to H. pylori infection and intestinal metaplasia in the stomach. One problem is that they failed to distinguish clearly between gastric fundic and cardiac mucosa, as evidenced by the histologic finding of parietal cells on several “cardiac” biopsy specimens. Further, their study was flawed in that it lacked a reliable control group of patients, because 7% of the nonreflux “control” patients were found to have esophagitis on endoscopy. Certainly H. pylori infection and intestinalization of the stomach are present in some patients with intestinal metaplasia of the gastroesophageal junction. However, the intestinal metaplasia related to H. pylori infection in these patients is often diffuse throughout the stomach. Intestinal metaplasia limited to the gastroesophageal junction does not appear related to either H. pylori infection or intestinal metaplasia of the stomach. 

**Location of Intestinal Metaplasia Within a Columnar-Lined Esophagus**

Interestingly, as first described in the report by Paull et al, when intestinal metaplasia is found within cardiac mucosa, it is always present at the most proximal portion of the columnar mucosa at the squamocolumnar junction. Although intestinal metaplasia may involve the entire columnar segment, often an area of cardiac mucosa without intestinal metaplasia is found distally near the gastroesophageal junction. Morales et al and others have used this finding to suggest that CIM and Barrett’s are not related, or at least that CIM is not the precursor of Barrett’s. Instead, we propose that this observation supports the concept that intestinalization of cardiac mucosa and proliferation of Barrett’s occur as a consequence of the composition and pH of the refluxed juice and the pulsatile or continuous nature of the exposure. Extrapolating from the work of Fitzgerald et al, it is conceivable that because the proximal portion of the columnar segment is the area furthest away from the stomach, it is the area most likely to be exposed in a more continuous manner to a pH of 3.5 or greater due to the mixing of refluxed gastric juice and saliva. This would stimulate increased cellular differentiation and less proliferation, creating the opportunity for the development of intestinal metaplasia. If CIM and Barrett’s represent two unrelated conditions, each caused by different factors, then in some patients the two conditions should exist simultaneously—in other words, there should be some patients with intestinal metaplasia at both the proximal and distal ends of a segment of columnar epithelium, with cardiac mucosa in between. This does not occur. Rather, patients either have intestinal metaplasia throughout the entire length of the columnar epithelium, or it is confined to the proximal end of the columnar segment, and cardiac mucosa without goblet cells is found distally.

**Time Interval From Columnar to Intestinalized Columnar Mucosa**

There is increasing evidence, particularly from follow-up studies in children, that cardiac-type columnar mucosa develops within the esophagus initially, and with time intestinalization may occur. In a series of 11 children aged 1.1 to 13.3 years (average 5.9 years) with symptoms of gastroesophageal reflux and a columnar-lined esophagus, Cooper et al found that only 1 child had intestinal metaplasia on biopsy. In older children, Hassall et al and Hoeffel et al reported the presence of intestinal metaplasia within a columnar-lined esophagus, and in two patients (ages 11 and 16), adenocarcinoma was found within the Barrett’s. Qualman et al followed up 28 pediatric and 38 adult patients with a columnar-lined esophagus and noted that compared with the pediatric patients, the percentage of adult patients with goblet cells and intestinal metaplasia was significantly increased. The youngest patient with goblet cells in their report was a 5-year-old with intestinal metaplasia found only at the gastroesophageal junction. They also described one 10-year-old patient with a columnar-lined esophagus without intestinal metaplasia who was followed up with serial endoscopies and biopsies; at age 15, goblet cells developed in this patient.

Another source for information about the time interval from cardiac mucosa to intestinalized columnar epithelium are reports documenting follow-up on patients after esophagectomy with gastric pull-up reconstruction. In a review of 17 patients who had undergone partial esophagectomy with intrathoracic esophagogastrostomy, Hamilton and Yardley noted that columnar mucosa had developed above the esophagogastric anastomosis in 10 of the 17 patients. They noted that cardiac-type columnar mucosa without goblet cells could be found as soon as 2 months after surgery in an area that had previously been histologically shown to be squamous epithelium. In two patients, intestinal metaplasia was found within the cardiac mucosa at the squamous junction at 76 and 106 months after surgery.

These findings would suggest that cardiac mucosa is the precursor of intestinal metaplasia, and that the process of intestinalization occurs sequentially over a period of at least 5 years. In contrast to this stepwise extension theory is the common belief that Barrett’s develops rapidly and to its full
extent with little subsequent change. This concept is based largely on a study by Cameron et al in which 21 patients with 3 cm or more of intestinal metaplasia were followed up for a mean of 7.3 years. At the end of follow-up, the length of Barrett’s was not significantly different from what it had been initially, and the mean length of Barrett’s was similar in all age groups. However, we contend that patients with long segments of Barrett’s uniformly have profound defects in LES function, and further deterioration would not be expected. Consequently, the fact that the length of Barrett’s did not change in their study is not surprising. Important future studies documenting the natural history of short-segment Barrett’s and intestinal metaplasia limited to the cardia should help clarify this issue.

**METAPLASIA, DYSPLASIA, CARCINOMA SEQUENCE**

The development of intestinal metaplasia within cardiac mucosa heralds the onset of a mucosal change that ultimately may lead to the development of esophageal adenocarcinoma. Consequently, the term “benign Barrett’s” is an oxymoron. With continued inflammation and irritation of the metaplastic intestinal epithelium, some patients will progress through low-grade dysplasia, high-grade dysplasia, and subsequently invasive adenocarcinoma. It is unknown whether the movement toward cancer is due to mitogenesis secondary to chronic mucosal injury, or mutagenesis as a consequence of exposure to a mutagen. One theory is that bile salts in their unionized state act as mutagens, and studies are underway to investigate this possibility. In our laboratory, cell culture studies indicate that repetitive short exposure of cells to bile salts at a pH of 5 to 7 increases the mutation frequency without altering the growth curve of the cultured cells (DeMeester TR, unpublished data). If bile salts are demonstrated to contribute to the development of malignancy, then early intervention with an antireflux procedure should be encouraged. The precise risk of developing adenocarcinoma in patients with Barrett’s esophagus is unknown; however, it likely is 0.2% to 2.1% per year for a patient without dysplasia, which is an incidence 30 to 125 times that of the general population. A common estimate is that there will be one cancer found for each 100 patient-years of follow-up. This increased incidence of cancer is the rationale for enrolling all patients with Barrett’s esophagus in a surveillance program, and heightening the surveillance in patients with low-grade dysplasia.

Although intestinal metaplasia is itself a premalignant condition, the development of high-grade dysplasia is associated with a significantly increased risk for adenocarcinoma. Several reports have correlated the progression of dysplasia within Barrett’s with other cellular and genomic alterations, including mutations of the tumor suppressor gene p53, aneuploidy, and loss of the Y chromosome. Importantly, any focus of intestinal metaplasia is capable of undergoing dysplastic change and ultimately becoming an invasive adenocarcinoma. Cameron and Carpenter have demonstrated that areas of dysplasia and cancer within long segments of intestinal metaplasia are often small and patchy, and that microscopic areas of different grades of dysplasia are often dispersed throughout the Barrett’s. They suggested that dysplasia develops simultaneously in many areas and ultimately becomes confluent rather than spreading progressively outward from one site. In addition, they noted that cancers developed throughout the length of the intestinal metaplasia, including distally near the stomach. This is in contrast to prior reports indicating that the cancers always occur near the squamocolumnar junction at the proximal extent of the Barrett’s. This is likely a consequence of imprecision in the use of the term Barrett’s. As noted above, if intestinal metaplasia is present in a segment of columnar epithelium, it is always at the proximal end of the columnar segment. It may extend distally to involve most or all of the columnar segment, but it may be limited to the area near the squamocolumnar junction. Because available evidence suggests that adenocarcinoma occurs only within areas of intestinal metaplasia, it is likely that in these prior reports the intestinal metaplasia was limited to the proximal portion of the columnar-lined distal esophagus.

**DIAGNOSIS**

When performing an esophagogastroduodenoscopy, the endoscopist should carefully note the location of the gastroesophageal and squamocolumnar junctions as well as the crura. Barrett’s esophagus should be suspected when the gastroesophageal junction is located distal to the squamocolumnar junction, or when there are pink tongues of gastric-like mucosa extending up into the esophagus above an aligned gastroesophageal and squamocolumnar junction. Precise determination of the gastroesophageal junction can be difficult in these patients because frequently a hiatal hernia is present, and as a group patients with Barrett’s have a very low LES pressure. Identification of the proximal margin of the gastric folds with the stomach and esophagus deflated facilitates localization of the gastroesophageal junction.

Because both erosive esophagitis and erythema of the esophagus may be confused visually with Barrett’s, confirmation of the diagnosis requires histologic identification of goblet cells within a columnar mucosa devoid of parietal cells. To maximize the likelihood of identifying intestinal metaplasia, multiple biopsy samples should be taken at the proximal extent of the columnar mucosa, just below the squamocolumnar junction, where intestinal metaplasia, if present, will always be found. If there is endoscopic suspicion of Barrett’s, the endoscopist should ascertain the length of involved esophagus and carefully examine the mucosa for any suspicious lesions. Biopsies of all mucosal abnormalities should be performed; in addition, once a diagnosis of Barrett’s is established, biopsies should be...
obtained at 1- to 2-cm intervals throughout the length of the metaplastic mucosa to evaluate for the presence of dysplasia.

Patients with intestinal metaplasia limited to the cardia do not have an endoscopically visible area of columnar epithelium within the esophagus. Thus, diagnosing CIM requires that biopsy samples be taken from a normal-appearing gastroesophageal junction. A combination of circumferential antegrade biopsies as well as biopsies taken with the esophagoscope retroflexed in the stomach will most reliably identify CIM. These biopsies, in our opinion, should be a standard part of the endoscopic evaluation of all patients suspected of having GERD.

**TREATMENT**

**Surveillance Endoscopy**

The rationale for endoscopic surveillance in patients with Barrett’s is straightforward: to detect progression of disease toward cancer, and to allow early intervention while cure is still likely. Predicated on this rationale is the concept that the surveillance will be frequent enough that rarely, if ever, does the disease progress beyond an early, curable stage during the surveillance interval, and that once disease progression is detected, an intervention is performed. Continued surveillance despite disease progression may help clarify the natural history of the disease but does little to benefit the patient. Controversy exists, however, about the point at which there has been sufficient progression to warrant intervention, and what intervention should be done.

Provenzale et al.\(^5\)\(^8\) used a Markov model of decision analysis to demonstrate that aggressive endoscopic surveillance combined with esophagectomy for high-grade dysplasia would markedly reduce the incidence of cancer in patients with Barrett’s esophagus and would increase both overall and quality-adjusted life expectancy. The predictions of the model have now been verified in several clinical series. We and others have reported that patients with adenocarcinoma detected within a surveillance program present at an earlier stage and have a significantly improved long-term survival after esophagectomy compared with patients who present de novo with symptoms.\(^3\)\(^5\),\(^5\)\(^6\)

The cost effectiveness of surveillance endoscopy for Barrett’s has recently been compared with mammography for the detection of breast cancer (Table 2).\(^5\)\(^7\) The cost per cancer detected and the cost per patient cured were similar, but the cost per life-year saved was dramatically lower for surveillance endoscopy in Barrett’s patients than mammography in women. This likely is because outside of a surveillance program, esophageal cancer often presents in an advanced stage, and the clinical course is rapidly fatal. In contrast, the lag time between mammographic and palpable detection of breast cancer is shorter, and the clinical course with breast cancer is often protracted.

The recommended frequency for endoscopic surveillance in patients with Barrett’s is based on available data about the likelihood and rapidity of progression. Important factors include the length of intestinal metaplasia and whether dysplasia is present. In longer segments of intestinal metaplasia, there is more mucosa at risk for progression, and patients with low-grade dysplasia have already moved a step closer to cancer. We advise our patients with any length of intestinal metaplasia within the esophagus to have yearly endoscopy, and we increase the frequency to every 3 to 6 months for patients with dysplasia. Sampliner and the Practice Parameters Committee of the American College of Gastroenterology\(^1\)\(^3\) have recently suggested that surveillance may be extended to every 2 to 3 years in Barrett’s patients lacking dysplasia on systematic biopsy at two endoscopies. For patients with low-grade dysplasia, they recommend that surveillance endoscopy be performed at 6-month intervals for the first year, and subsequently done yearly if there has been no change.

**Medical Therapy of Barrett’s**

There are three goals for treating patients with Barrett’s esophagus: stop reflux, promote or induce healing or regression of the metaplastic epithelium such that the risk mucosa (intestinal metaplasia) is eliminated, and halt progression to dysplasia and cancer. Most patients with Barrett’s are treated medically; however, adequate medical therapy is difficult because of the degree of impairment of the LES and the poor esophageal body motility frequently present in patients with Barrett’s. This is likely the reason why the least controlled symptom in patients with Barrett’s receiving medical treatment is regurgitation.\(^5\)\(^8\) Medical treatment options are limited to dietary and lifestyle modifications, promotility agents, and acid-suppression therapy. Recently, Sampliner and the Practice Parameters Committee of the American College of Gastroenterology\(^1\)\(^3\) stated that “the goal of therapy of Barrett’s esophagus should be the control of the symptoms of GERD” and that “symptom relief is an appropriate endpoint for the therapy of Barrett’s esophaga-

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**Table 2. COMPARISON OF COST OF SURVEILLANCE MAMMOGRAPHY FOR BREAST CANCER TO COST OF SURVEILLANCE ENDOSCOPY FOR PATIENTS WITH BARRETT’S ESOPHAGUS**

<table>
<thead>
<tr>
<th></th>
<th>Breast Cancer/ Mammography</th>
<th>Barrett’s Esophagus/ EGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per cancer detected</td>
<td>$54,513</td>
<td>$37,928</td>
</tr>
<tr>
<td>Cost per cure</td>
<td>$83,292</td>
<td>$83,340</td>
</tr>
<tr>
<td>Cost per life-year saved</td>
<td>$57,926</td>
<td>$4,151</td>
</tr>
</tbody>
</table>

EGD, esophagogastroduodenoscopy.

Data from reference 57.
Gastroesophageal reflux causes both Barrett’s and esophageal cancer. Symptoms are not part of the pathophysiology of the disease; rather, they are merely the variably expressed byproduct of reflux. Many patients with Barrett’s have few or no reflux symptoms, probably as a consequence of an altered sensitivity of the metaplastic epithelium to refluxed acid. Consequently, the eradication of symptoms, if present, cannot be equated with elimination of reflux. Katzka and Castell demonstrated that standard-dose omeprazole (20 mg/day) fails to suppress acid sufficiently to keep gastric pH neutral for a full 24 hours in patients with Barrett’s. Further, increasing the dose of omeprazole until all symptoms were alleviated was an unreliable measure of effective therapy, because 80% of patients studied with 24-hour pH monitoring still had abnormal distal esophageal acid exposure. Sampliner likewise found that high-dose proton pump inhibitor administration (lanisoprazole, 60 mg/day) failed to normalize the 24-hour pH test in more than one third of patients with Barrett’s tested while receiving therapy.

Consequently, for medical therapy to achieve the first of the three goals of treatment for patients with Barrett’s, prevention of reflux, the medical therapy will have to be aggressive and not guided by symptoms. Most patients require a minimum of twice-daily omeprazole. All patients should be tested while receiving acid-suppression therapy with 24-hour pH monitoring, and as suggested by Castell et al., the majority are likely to demonstrate night-time acid breakthrough and will need an evening dose of an H₂ receptor antagonist in addition to the twice-daily proton pump inhibitor. Lastly, given the concern about creating unionized, lipophilic bile salts, it may be that the endpoint of acid suppression in these patients needs to be a gastric pH of 7 rather than just a pH of more than 4. In the final analysis, incomplete therapy may prove to be worse than no therapy.

The second and third goals of therapy in patients with Barrett’s are to eliminate the risk mucosa (i.e., intestinal metaplasia) and to prevent progression to dysplasia and cancer. Medical therapy has not been shown to achieve either of these goals reliably. Several reports have concluded that medical therapy does not cause regression of intestinal metaplasia. This may be different in patients with short-segment Barrett’s. Weston et al. have described the loss of goblet cells from lengths of intestinal metaplasia less than 2 cm in 32% of patients treated medically for 1 to 3 years. In contrast, only 2 of 29 patients (7%) with lengths of intestinal metaplasia 3 cm or more had loss of goblet cells.

With respect to the efficacy of medical therapy in preventing progression of Barrett’s to dysplasia and cancer, there is speculation that prolonged and perhaps inadequate acid suppression may actually promote the development of Barrett’s and the complications of Barrett’s. Lagergren et al. recently reported that the risk of esophageal adenocarcinoma was increased nearly eightfold among persons in whom heartburn, regurgitation, or both occurred at least once a week compared with persons without these symptoms. Interestingly, they noted that the risk of esophageal adenocarcinoma was three times higher among patients who used medication for symptoms of reflux compared with those who did not use acid suppression medications. Others, including Ortiz et al. and Hameeteman et al., have also linked medical therapy for Barrett’s esophagus with progression to dysplasia and adenocarcinoma. In the study by Hameeteman et al. from the Netherlands, 50 patients with a columnar-lined esophagus were treated medically and followed up from 1.5 to 14 years (mean 5.2 years). Of these 50 patients, initially only 34 had intestinal metaplasia on biopsy of the columnar mucosa. At the completion of the study, 37 patients had intestinal metaplasia, indicating that Barrett’s developed in 3 patients during the 5-year study period. In addition, at the start of the study, six patients had low-grade dysplasia and one patient had high-grade dysplasia. By the end of the 5-year study period, 10 patients had low-grade dysplasia, 3 had high-grade dysplasia, and 5 had adenocarcinoma. Similarly, Sharma et al. followed 32 medically treated patients with short-segment Barrett’s (mean length 1.5 cm) for a mean of 36.9 months and found a 5.7% annual incidence of progression to dysplasia. During the 98 patient-years of follow-up in their series, high-grade dysplasia developed in two patients, and one of these patients progressed to cancer. Recall that the expected rate of cancer is 1 per 100 patient-years of follow-up. All patients in the study by Sharma et al. were treated with omeprazole, ranitidine, and/or promotility agents. They commented that most patients developed dysplasia while taking acid-suppression medication, and they concluded that medical treatment does not prevent the development of dysplasia.

**Antireflux Surgery for Barrett’s**

Some of the problems and concerns associated with medical therapy for Barrett’s include issues about patient compliance, the safety of long-term high-dose acid-suppression therapy, and the prompt return of symptoms after drug withdrawal. In contrast, antireflux surgery restores LES function and abolishes reflux of gastric contents into the esophagus. Consequently, an antireflux operation ends the repetitive injury to both the metaplastic and normal esophageal mucosa. Randomized clinical studies have confirmed superior control of reflux after antireflux surgery compared with medical therapy, and antireflux surgery has been proven safe, effective, and durable. In addition, many patients are candidates for a minimally invasive laparoscopic approach associated with a short hospital stay and rapid recovery. We therefore favor the performance of an antireflux procedure in patients with Barrett’s.

There have been conflicting reports about whether intestinal metaplasia regresses after antireflux surgery. Brand et al., in 1980, described complete regression in 4 of 10 patients with Barrett’s who underwent fundoplication. Sub-
subsequently, most reports have demonstrated that although some regression of the length of Barrett’s is common, complete regression occurs only rarely. Review of the English language literature since 1977 documents follow-up on 340 patients after antireflux surgery. Complete regression occurred in only 13 patients; in 256 of the 340 patients (74%), the Barrett’s epithelium remained unchanged (Fig. 6). Thus, the available literature would suggest that regression of traditional Barrett’s cannot reliably be predicted or anticipated after antireflux surgery.

In contrast to the unreliable regression of traditional or 3-cm segments of Barrett’s, we recently demonstrated that 73% of patients with intestinal metaplasia at the gastro-esophageal junction had complete regression after antireflux surgery. By comparison, only 4% of patients with an endoscopically visible segment of Barrett’s had loss of intestinal metaplasia after an antireflux procedure. Many of these patients demonstrated the development of squamous islands or a shorter length of Barrett’s, but in our opinion regression should be considered only when there has been complete loss of the mucosa at risk for malignant degeneration. Recently, Low et al also reported complete regression of Barrett’s esophagus after antireflux surgery. In their report, loss of intestinal metaplasia occurred in 2 of 14 patients followed up for a mean of 25 months after surgery.

Perhaps of greater importance is the issue of progression of Barrett’s to dysplasia or cancer after surgical treatment of reflux disease. Compared with medical therapy, antireflux surgery is associated with a reduced incidence of dysplasia and adenocarcinoma. McCallum et al prospectively followed 181 patients with Barrett’s. Twenty-nine had antireflux surgery; the remaining 152 were treated medically. After a mean follow-up of 62 months in the surgical group and 49 months in the medical group, there was a significant difference in the incidence of dysplasia and adenocarcinoma. Dysplasia was found in 3.4% of the surgical group and 19.7% in the medical group. No patient in the surgically treated group developed adenocarcinoma of the esophagus, compared with two medically treated patients. They concluded that compared with medical therapy, an antireflux operation in patients with Barrett’s was significantly associated with the prevention of dysplasia and cancer. Similarly, Katz et al followed 102 patients with Barrett’s for a mean of 4.8 years. By 3 years, dysplasia had developed in approximately 8% of the medically treated patients. In contrast, patients treated by antireflux surgery had a significantly reduced risk of developing dysplasia (P = .03).

One factor complicating any analysis of progression of Barrett’s after antireflux surgery is that the cellular and genetic alterations leading to the development of dysplasia and adenocarcinoma may have already occurred before performance of the antireflux procedure. It has been estimated to take up to 6 years for adenocarcinoma to develop within Barrett’s with low-grade dysplasia, and thus some cancers, particularly those that present during the first few postoperative years, probably do not represent progression of disease after surgery. McDonald et al made this point in a study from the Mayo Clinic. They found invasive adenocarcinoma in two patients and carcinoma in situ in one patient during surveillance after antireflux surgery, but they noted that carcinoma did not develop in any patient after 39 months despite a median follow-up of 6.5 years and a maximum follow-up of 18.2 years.

Review of the English language literature since 1975 revealed 11 series and a total of 346 patients with Barrett’s followed after fundoplication. Patients were found to have esophageal adenocarcinoma after antireflux surgery in only 7 of the 11 reports. Apart from these series, four isolated reports were found describing adenocarcinoma developing in patients with Barrett’s after an antireflux operation. Although the length of follow-up was not always available, 11 of the 19 cancers (58%) developed within 3 years of fundoplication, and 15 (79%) developed within 5 years of fundoplication. The remaining four cancers developed from 5 to 10 years after fundoplication, but in each case the patient had recurrent reflux on the basis of symptoms or positive 24-hour pH monitoring (Fig. 7). Thus, a functioning fundoplication seems to provide protection from progression of Barrett’s to adenocarcinoma.

**Mucosal Ablation**

Theoretically, the ideal treatment for a patient with Barrett’s esophagus is one that will restore the normal squamous mucosa and eliminate the cancer risk associated with intestinal metaplasia. Currently, neither medical nor surgical therapy reliably offers this in patients with lengths of intestinal metaplasia of 3 cm or more. However, several experimental techniques for mucosal ablation show promise. Investigational techniques include the use of laser, photodynamic therapy (PDT), multipolar electrocoagulation, and the ultrasonic aspirator. In animal and limited clinical trials, some of these techniques have successfully
patients who underwent surgical resection, lymph node metastasis in Barrett’s the malignancy persisted, and in both this increased to 43% with the addition of Nd:YAG laser esophageal strictures developed in 34% of patients treated of stricture formation. In a review by Overholt et al, injury, and when applied circumferentially have a high rate techniques suffer from an imprecise control of the depth of the gastroesophageal junction.

cept in two patients with persistent intestinal metaplasia at patients. There was no residual metaplastic epithelium ex-

Figure 7. Review of the English language literature identified 11 series in which patients with Barrett’s were followed up after antireflux surgery. In 4 of the 11 series, adenocarcinoma developed in no patients during the follow-up period. A total of 346 patients were followed up and 12 cancers occurred. Seven additional cases of adenocarcinoma develop-
ing in Barrett’s esophagus after an antireflux procedure were found in other reports. Thus, a total of 19 adenocarcinomas that occurred after an antireflux procedure were found in the literature. Each case of cancer is plotted on the time line at the point where it occurred. Time is marked in 5-year segments, with 0 the time of the antireflux procedure. Note the maximum as well as the mean or median follow-up for each of the 11 series. Despite the long follow-up in these series, most cancers are clustered between 0 and 5 years after the antireflux procedure. These cancers probably occurred as a consequence of cellular and genetic alterations that took place before the fundoplication. For each of the cancers occurring after 5 years, there was evidence either by the recurrence of reflux symptoms or a positive 24-hour pH test that the fundoplication had failed.

produced ablation of the columnar mucosa and subsequent squamous reepithelialization.

Elimination of gastroesophageal reflux is critical to successful squamous reepithelialization after mucosal ablation of Barrett’s. Persistent or recurrent areas of intestinal metaplasia plague most series of mucosal ablation in patients taking proton pump inhibitors. In contrast, Salo et al recently reported successful ablation of Barrett’s using Nd:YAG laser after antireflux surgery. They followed up 11 patients for a mean of 26 months after the last laser treatment and noted complete squamous regeneration in all patients. There was no residual metaplastic epithelium except in two patients with persistent intestinal metaplasia at the gastroesophageal junction.

One problem with ablation for Barrett’s is that in most patients the intestinal metaplasia is circumferential, and often involves a large surface area. Many of the ablation techniques suffer from an imprecise control of the depth of injury, and when applied circumferentially have a high rate of stricture formation. In a review by Overholt et al esophageal strictures developed in 34% of patients treated with PDT. PDT eradicated Barrett’s in 8% of patients, but this increased to 43% with the addition of Nd:YAG laser ablation. In 23% of patients treated with PDT for adenocarcinoma in Barrett’s the malignancy persisted, and in both patients who underwent surgical resection, lymph node me-

tastases were found. Three patients died during treatment (3%). Biopsies showed no evidence of subsquamous glandular mucosa in 98% of patients; however, in 2% of patients areas of Barrett’s with high-grade dysplasia were found below squamous mucosa, and in one patient a subsquamous adenocarcinoma was found 6 months after PDT treatment.

The most promising ablation technique uses the Cavitron Ultrasonic Surgical Aspirator (CUSA; Valley Lab, Boulder, CO) device to remove the mucosa without violating the muscularis mucosa. Animal studies have demonstrated that strictures are not produced if the muscularis mucosa is kept intact. In addition, the entire area of intestinal metaplasia can be eradicated at a single setting, and rather than destroying the mucosal cells, with this technique the aspirated cells are available for cytologic review. When combined with an antireflux procedure, this technique is likely to be the most reliable method to ablate Barrett’s and allow squamous regeneration. Refinements in the different techniques and careful clinical evaluation of the completeness of ablation, long-term complication rates, and impact on progression of Barrett’s to dysplasia and cancer with each of the techniques should be forthcoming in the near future.

Barrett’s With Low-Grade Dysplasia

Identification of low-grade dysplasia on biopsies from a patient with Barrett’s is of concern because it may represent progression of disease along a continuum that ends with adenocarcinoma of the esophagus. Patients who are found to have low-grade dysplasia on the basis of a random biopsy should undergo repeat endoscopy with systematic four-quadrant biopsies every 1 to 2 cm throughout the length of the Barrett’s segment to rule out high-grade dysplasia or cancer. In addition, any abnormal-appearing area within the columnar segment should be carefully biopsied. Because of the potential for confusion between inflammatory atypia and low-grade dysplasia, patients who have not been treated for reflux should receive a 3-month course of intensive acid-suppression therapy with 40 mg omeprazole twice a day. These patients should then undergo repeat endoscopy and biopsy. If low-grade dysplasia is again identified, these patients should undergo an antireflux operation followed by endoscopic surveillance. In our series of 60 patients with intestinal metaplasia of the esophagus or esophagogastric junction, we found that preoperative low-grade dysplasia was present in 10 patients. In 7 of the 10, the low-grade dysplasia reverted to Barrett’s without dysplasia after an antireflux procedure. Similarly, Low et al noted that 4 of their 14 patients had low-grade dysplasia, and in all 4 patients it regressed to Barrett’s without dysplasia after surgery. If the low-grade dysplasia persists after antireflux surgery, consideration should be given to mucosal ablation with the ultrasonic aspirator. Further, patients with low-grade dysplasia should be under frequent surveillance, because progression to high-grade dysplasia and cancer can occur quickly.
Barrett’s With High-Grade Dysplasia

Optimal treatment for patients with Barrett’s and high-grade dysplasia remains controversial. The major issues are:

1. What is the likelihood that adenocarcinoma will develop in a patient with high-grade dysplasia, and over what time interval does this typically occur?
2. What is our ability with current technology to detect a focus of adenocarcinoma within Barrett’s esophagus with high-grade dysplasia—and the corollary, how likely is it that no cancer is present if the endoscopy and biopsies show no cancer?
3. What are the treatment options for high-grade dysplasia, and what outcomes are associated with each?

Issue 1

Progression to adenocarcinoma was reported to occur in 26% of 58 patients with high-grade dysplasia followed for a median of 24 months by Levine et al from Seattle. How- ever, they excluded 12 patients found to have adenocarcinoma on an early rebiopsy after initially diagnosing only high-grade dysplasia. Inclusion of these patients would increase the frequency of progression to 39% in this group of patients followed up for 2 years. Similarly, Schnell et al reported progression to adenocarcinoma in 8 of 42 patients (19%) with high-grade dysplasia. The median length of follow-up was not specified; however, it was noted that five of the eight patients who progressed to carcinoma did so within 1 year. The literature would suggest that although the time required to progress from high-grade dysplasia to cancer is variable, most cancers develop within 3 years, and often the cancer is found within several months of initially finding high-grade dysplasia. Williamson et al reported that five patients with Barrett’s and high-grade dysplasia progressed to cancer at intervals of 2, 5, 6, and 8 months after developing high-grade dysplasia.

Issue 2

Currently, the only way to detect a focus of adenocarcinoma within Barrett’s esophagus is by histologic examination of a biopsy specimen, but differentiation between high-grade dysplasia and carcinoma is difficult and requires an experienced pathologist. Efforts are underway to identify markers that can indicate which patients with high-grade dysplasia are likely to progress rapidly to cancer. Examples of studied markers include DNA content abnormalities such as increased G2/tetraploid fractions, aneuploid cell populations, or both; mutations of the p53 tumor suppressor gene; c-erbB-2 oncogene overexpression; increased expression of epidermal growth factor receptor and transforming growth factor-alpha; decreased activity of glutathione S-transferase; p16 promoter hypermethylation; and increased expression of inducible nitric oxide synthase and cyclooxygenase-2. As yet, no clear correlation has been established that allows any of these to be clinically useful in assigning risk of progression to an individual patient.

The diagnosis of Barrett’s, dysplasia, and cancer continues to rely on histologic evaluation of biopsy specimens. Most endoscopic biopsies are obtained randomly from within Barrett’s in the sense that unless an ulcer or nodule is noted, the biopsies are taken from an area of Barrett’s that looks like any other area. It is important that the biopsies are taken circumferentially at close intervals, but the importance of using “jumbo” forceps and the number of biopsies that should be taken per linear 2 cm of esophagus continue to be debated. Given the typically large surface area of Barrett’s, as well as the irregular distribution of dysplastic changes, there is an inherent possibility of sampling error. Certainly taking multiple biopsy samples will reduce the error rate; however, the only way to eliminate the possibility of sampling error is to remove the entire mucosa. This fact is reinforced by data suggesting that up to 60% of patients who have an esophagectomy for high-grade dysplasia are found on careful pathologic examination of the surgical specimen to have an unidentified focus of carcinoma despite numerous preoperative biopsies that showed only high-grade dysplasia.

Endoscopic ultrasound has been used in patients with high-grade dysplasia in an effort to detect areas of cancer. However, current ultrasound probes, especially the balloon-tipped probes, cannot provide sufficient detail to evaluate the esophageal wall superficial to the muscularis propria. Cameron and Carpenter reported that endoscopic ultrasound identified only one of four early invasive cancers and gave one false-positive result in nine patients without cancer. In the future, it is hoped that new high-frequency ultrasound probes will be able to assess with accuracy cancers limited to the mucosa and submucosa. Recently, endoscopic fluorescence techniques have been used to try to identify areas of high-grade dysplasia or cancer within Barrett’s based on the different autofluorescence spectra of normal versus metaplastic versus dysplastic tissue. The utility of these techniques remains to be determined.

Issue 3

Treatment options for patients with Barrett’s and high-grade dysplasia include continued endoscopic follow-up, some form of mucosal ablation, or resection of the esophagus. The main issue to focus on during the next several years is the outcome associated with the various treatments for high-grade dysplasia. Important outcome measures include the recurrence rate for intestinal metaplasia, dysplasia, and cancer, treatment-related complication and death rates, and patients’ satisfaction with lifestyle and ability to eat. As more data about these issues become available, physicians and patients will have a better understanding of the pros and cons for each treatment option.

Currently one option is to repeat endoscopy and biopsy in patients with high-grade dysplasia until a definitive diagnosis of cancer is established. The obvious advantage of this type of approach is that the patient is spared the potential risks of surgery until cancer is identified. This is balanced
by the need for repeat endoscopies with multiple biopsies on a frequent basis, and the real possibility of a sampling error resulting in a missed focus of adenocarcinoma. An adenocarcinoma that is missed and allowed to invade into the submucosa has a 50% likelihood of associated lymph node metastases. Unfortunately, in these patients the opportunity for cure will have been compromised and the benefits of endoscopic surveillance potentially negated.

This concern is not theoretical. In the study by Hameeteman et al., five patients were found during surveillance to progress to adenocarcinoma, and three underwent resection. All three had cancers that invaded into the muscularis propria. These are relatively advanced tumors, and our data would suggest that 80% of tumors penetrating this depth into the wall of the esophagus will have lymph node metastases. Likewise, in the series by Williamson et al., five patients progressed from high-grade dysplasia to adenocarcinoma during endoscopic surveillance. All five patients underwent resection, and although four of the patients had stage 1 tumors, one patient was found to have a stage 3 tumor (T3 N1 M0). Thus, despite a policy of close endoscopic surveillance, invasive cancer developed in five patients and one had lymph node metastases. Perhaps this risk is warranted in older patients or those with multiple or severe medical comorbidities, but in young fit patients it is not justified.

A second approach is to ablate the metaplastic mucosa, including areas of high-grade dysplasia. As discussed previously, techniques that have been used include PDT, electrocoagulation, laser, and argon beam coagulation. Long-term outcome after ablation by these techniques is not well defined, and none of these techniques remove a specimen or allow evaluation of the margins of resection. Consequently, an area of invasive cancer might not only go unrecognized, but might be inadequately treated as well. Ferguson and Nauheim reviewed three published series involving a total of 46 patients with high-grade dysplasia treated with PDT. During an average follow-up of less than 2 years, strictures requiring dilation developed in 46% of patients, 41% had residual Barrett’s, and 9% had residual high-grade dysplasia. In a series of 100 patients treated with PDT plus Nd:YAG laser reported by Overholt et al., residual Barrett’s was present in 57% of patients, and persistent or metastatic adenocarcinoma was found in 23% of patients with a pretreatment diagnosis of cancer. Dysplasia of any type persisted in 18% of patients, whereas high-grade dysplasia persisted in 10% of patients after treatment. Esophageal strictures requiring dilation developed in 34% of patients. These poor results suggest that PDT should not be considered first-line therapy for Barrett’s and high-grade dysplasia, but perhaps could be considered in patients who are poor candidates for esophagectomy.

A third treatment option, and one that we endorse, is esophageal resection. Esophagectomy represents the standard against which all other therapies must be compared for eradication of cancer. Ferguson and Nauheim reviewed the English literature from 1990 to 1996 and analyzed the outcome from 10 series totaling 110 patients who underwent esophagectomy for high-grade dysplasia. The death rate was 2.6%, and the overall 5-year survival rate was 82%. All patients were thought before surgery to have only high-grade dysplasia; however, cancer was found in 56 of the 110 patients (51%), and in 15 patients the tumors were stage IIa or higher.

We have recently reviewed our experience with high-grade dysplasia at the University of Southern California. Repeat biopsy in 23 patients referred for high-grade dysplasia demonstrated a focus of adenocarcinoma in 9 patients (39%). After esophagectomy, review of the specimen demonstrated an additional six cancers. Thus, of 23 patients referred for high-grade dysplasia, ultimately cancer was found in 15 (65%). Among 25 patients with adenocarcinoma in Barrett’s esophagus but no visible lesion, the tumor was limited to the lamina propria (intramucosal) in 22 (88%) but invaded into the submucosa in 3 patients (12%). Of the 25 patients with adenocarcinoma and no visible lesion, 10 underwent en bloc esophagectomy with systematic thoracic and abdominal lymphadenectomy. From these 10 patients, a total of 370 lymph nodes were removed and analyzed with both routine histology and immunohistochemical staining. Only a single node from one patient was positive for metastatic cancer. Consequently, we concluded that a routine lymph node dissection is unnecessary in patients with high-grade dysplasia or invasive cancer in the absence of an endoscopically visible lesion. However, given that in 12% of patients the cancer had invaded deeper than the mucosa, therapy directed purely at ablation of the mucosa is not adequate even in the absence of a visible lesion.

In contrast to the rarity of lymph node metastases in patients with cancer and no visible lesion, we found that 55% of patients with high-grade dysplasia and a biopsy showing cancer in the setting of a visible mucosal irregularity such as an ulcer or nodule had lymph node metastases. Further, in 75% of these patients the tumor had invaded into or beyond the submucosa. Therefore, the presence of an endoscopically visible abnormality and a biopsy of cancer mandates esophagectomy with lymphadenectomy. Obviously, when recommending esophagectomy, one must balance the potential risks against the benefits of curative resection in patients with high-grade dysplasia. This requires that the procedure be done at a center that is experienced with this type of surgery and has a low complication rate. In addition, it is important that the reconstruction in these patients functions well and does not predispose them to recurrence of Barrett’s. It is now recognized that patients with an intrathoracic anastomosis between their stomach and residual esophagus are prone to have continued reflux of gastric contents into the remaining esophagus. This has led to esophagitis and even the recurrence of Barrett’s. Because this is less likely to occur when the anastomosis is done in the neck, we believe that a cervical esophago gastric anastomosis should be performed routinely. Reconstruction
with the colon does not lead to this problem, and we believe that long-term function of a colon graft is superior to that of a gastric pull-up.

One technique we now use for high-grade dysplasia is a vagal-sparing esophagectomy with colon interposition. This procedure removes the esophagus by the minimally invasive technique of stripping and preserves the intact, innervated stomach. The diseased esophagus is replaced with an isoperistaltic left colon graft. The operation is very well tolerated, and our early experience suggests that these patients have excellent function of both their intact stomach and colonic graft. In addition, they demonstrate few of the side effects potentially associated with a traditional esophagectomy, such as early satiety, dumping syndrome, or diarrhea.

**SUMMARY**

Since its description in the 1950s the definition of Barrett’s esophagus has evolved from the macroscopic visualization of gastric-like mucosa in the esophagus to the histologic identification of goblet cells confirming the presence of intestinal metaplasia within a columnar-lined esophagus. The length of intestinal metaplasia necessary to be classified as Barrett’s and the relation between intestinal metaplasia of the esophagus and that limited to the cardia are being evaluated. Meanwhile, the definition of Barrett’s has once again become ambiguous. Perhaps the best solution for now is to use the term “Barrett’s esophagus” when there is an endoscopically visible area of columnar mucosa that on biopsy demonstrates intestinal metaplasia. The term “intestinal metaplasia of the cardia” (CIM) should be used when there is a normal-appearing gastroesophageal junction on endoscopy, but biopsies taken at the gastroesophageal junction demonstrate intestinal metaplasia within a columnar epithelium containing mucous cells but devoid of parietal cells.

There is evidence that cardiac mucosa is the common denominator for CIM and Barrett’s and a prerequisite for intestinal metaplasia. Further, it appears that although cardiac epithelium is benign, any segment of intestinal metaplasia can undergo dysplastic change and ultimately become a focus of adenocarcinoma. It is logical to expect the degree of risk for developing cancer to be proportional to the amount of intestinal metaplasia present; however, within a population, the low risk to any individual is balanced by the relative frequency of the process. Thus, given the large number of people in America with intestinal metaplasia of the cardia, even a small risk of progression to cancer will result in a large number of patients with adenocarcinoma of the cardia. This is exactly what is occurring today, with the incidence of adenocarcinoma of the cardia and esophagus currently rising faster than that of any other cancer in the United States.

The major risk factor for adenocarcinoma of the esophagus is intestinal metaplasia, and intestinal metaplasia occurs as a consequence of GERD. Patients with Barrett’s typically have severe GERD, with significant impairment of both LES function and esophageal body motility. Further, the composition of the refluxed gastric juice is different in patients with Barrett’s and complicated Barrett’s esophagus. Patients who reflux both gastric and duodenal juice have a higher prevalence of Barrett’s than do patients who reflux gastric juice alone, and among patients with Barrett’s a significantly greater esophageal bilirubin exposure has been demonstrated in those with dysplasia.

Reflux disease is difficult to control medically in patients with Barrett’s, and symptoms are unreliable as a guide. The most difficult symptom to control is regurgitation, and there is concern that regurgitation and continued reflux of pharmacologically altered gastric contents, particularly bile acids in their nonpolar form, may contribute to the development and progression of Barrett’s. Therefore, it is not surprising that both medical therapy and failed antireflux surgery are both associated with progression of Barrett’s to dysplasia and adenocarcinoma. In contrast, a functioning fundoplication appears to provide protection from progression of Barrett’s. Intestinal metaplasia extending 3 cm or more into the esophagus is unlikely to regress after antireflux surgery; however, intestinal metaplasia limited to the gastroesophageal junction is perhaps more dynamic. We found that CIM regresses in 73% of patients after fundoplication. In addition, we found that low-grade dysplasia regressed in 70% of patients after an antireflux procedure. Antireflux surgery is safe, effective, and durable and often can be performed using minimally invasive techniques.

Thus, antireflux surgery should be strongly considered in any patient with Barrett’s.

Patients with Barrett’s and high-grade dysplasia are at substantial risk for having a coexistent focus of adenocarcinoma, and even with multiple biopsies there is the possibility of sampling error. Further, adenocarcinoma can develop rapidly in the setting of high-grade dysplasia, and if the cancer is allowed to invade into the submucosa, 50% of these patients will have lymphatic metastases, and the purpose of surveillance will potentially have been negated. Patients with intramucosal adenocarcinoma are unlikely to have lymphatic metastases; however, current technology does not allow precise identification of the depth of wall penetration superficial to the muscularis propria. Consequently, therapy directed only at the mucosa is potentially inadequate and should not be considered appropriate treatment for cancer. Instead, esophagectomy represents the standard of care in these patients with a highly curable form of esophageal cancer.

Esophagectomy for adenocarcinoma of the esophagus should be tailored to the patient and the known extent of disease. For high-grade dysplasia and invasive tumors without an endoscopically visible lesion, a vagal-sparing technique with colon interposition provides an excellent functional outcome and removes the entire diseased organ. Patients with visible tumors are likely to have invasion deeper than the mucosa or lymph node metastases. There-
fore, those who are physiologically fit should undergo en bloc esophagectomy with thoracic and abdominal lymphadenectomy. In patients with extensive disease or those physiologically unfit, a palliative transhiatal resection or other nonsurgical palliative procedure may be appropriate.

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320 DeMeester and DeMeester

October 2000
DeMeester and DeMeester Ann. Surg.


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