CHAPTER 7

Barrett’s Metaplasia and Adenocarcinoma

Introduction and Definition

Although the phenomenon of a lower esophagus lined by columnar epithelium has been appreciated for over 30 years, only recently have the pathogenesis and significance of the change begun to emerge. Barrett and other earlier investigators considered the change to be a “congenital short esophagus” with a portion of gastric cardia and fundus being pulled up into the thorax. Subsequent clinical and experimental evidence has clearly shown the phenomenon to be an acquired metaplastic lesion with potential for neoplastic progression. As used currently, the term Barrett’s esophagus refers to a metaplastic change in which a variable segment of the normal squamous epithelium above the physiologic lower esophageal sphincter (LES) is replaced with a complex mixture of columnar epithelial types that include differentiation toward small bowel, gastric cardia, and gastric fundus.

Pathogenesis

A large body of clinical and experimental evidence supports the concept that Barrett’s metaplasia is caused by the reflux of acidic gastric or bile-containing small bowel contents into the distal esophagus. Reflux can cause ulceration of the normal squamous epithelium; in some cases subsequent epithelial regeneration is toward columnar epithelium.

Bremner et al. have established a model for Barrett’s metaplasia in the dog. Their studies have shown that ulceration of the squamous epithelium, persistent reflux, and acidity of the gastric contents are all important variables. They divided their experimental dogs into three different groups. The first group underwent excision of a portion of the squamous mucosa of the distal esophagus, but the underlying musculature and LES mechanism were left intact. Under these conditions, healing of the injured segment was always toward squamous epithelium. In the second group, the musculature of the lower esophageal sphincter was split, a hiatus hernia was created, and the mucosa of the lower esophagus was removed as in group 1. When healing occurred in this group, differentiation toward columnar and squamous epithelium was equal. In the third group, histamine stimulation was added to the surgical procedures performed in group 2 to induce hyperacidity. When healing occurred columnar epithelium was almost always found in the injured segment.

Reflux of acid gastric contents into regions of regeneration appears to be merely one mechanism leading to columnar metaplasia. Hamilton and Yardley, and Meyer et al. have shown that in patients with total gastrectomies reflux of bile containing small bowel contents into the distal esophagus also leads to Barrett’s metaplasia.

Clinical and anatomic observations strongly support the hypothesis that Barrett’s esophagus is an acquired rather than congenital condition. Numerous studies have shown a correlation between symptoms of reflux, the presence of hiatus hernia, and Barrett’s. In several studies of pa-
tients with reflux esophagitis, columnar transformation and retrograde progression have been documented.6,7,29 The risk of developing Barrett’s metaplasia has been estimated to be between 2 and 11% in those with reflux esophagitis.6,7,19,23,29 Most patients with columnar metaplasia complain of longstanding symptoms of reflux esophagitis, although not invariably.6--9,17,20,26,29 Patients with Barrett’s esophagus have been shown to have a significantly lower LESP and a greater number of reflux episodes lasting longer than 5 min than patients with only reflux esophagitis, and, of course, than normal controls.30 In addition, the extent of esophagus involved has been related to the degree of lowering of the LESP.31 Complaints commonly include dysphagia for solids, regurgitation of liquid, “heartburn,” and constant burning substernal pain.8

Paul et al.28 have provided manometric evidence that the involved segment is esophageal. The metaplastic zone produces a recording pattern similar to that of the esophagus. A high-pressure zone corresponding to the lower esophageal sphincter can be demonstrated distal to the metaplastic region. Peristaltic waves pass through the region as they would in the esophagus.

Johnston12 and others28 have pointed out that the segment has anatomic features of esophagus. The region derives its blood supply directly from the aorta in a segmental fashion, and is covered by adventitia rather than serosa. The musculature of the region is continuous with that of the esophagus, and does not splay out as does the muscularis propria of the gastric cardia. In addition, residual squamous islands and submucosal glands are a regular feature of the metaplastic segment.17,26

Although the pathogenesis of Barrett’s metaplasia is not clear, many authors think that the residual multipotent basal cells that are left behind following ulceration are directed along various lines of differentiation by luminal factors (trophic factors) such as small bowel or stomach contents that are not normally present.26,29 Such a hypothesis fits all the available facts, and explains the complex mosaic of epithelial types described in Barrett’s metaplasia. Such “trophic” factors are known to operate at other sites in the gastrointestinal tract such as the small bowel, where both bile salts and pancreatic secretion have marked effects on epithelial growth.35–38 Thus perhaps Barrett’s metaplasia is best considered to represent a situation in which the trophic messages that normally direct differentiation become mixed, yielding a complex variety of epithelial types and architectural forms.

Neoplasia in Barrett’s Metaplasia

In recent years, a large body of evidence has accumulated suggesting that Barrett’s represents the common neoplastic pathway for development of adenocarcinoma of the lower esophagus and gastric cardia.7,9,13–19,23,24,26,29,40–43 In various series, the risk of developing adenocarcinoma in patients with columnar metaplasia has been estimated to be from 0–10%.6,7,19,23,29

Numerous authors have noted a strong correlation between the presence of Barrett’s metaplasia and adenocarcinoma of the esophagus.6,7,9,17–19,24,29,41,42 The study by Haggitt et al.17 found evidence of Barrett’s metaplasia in the background of 86% of their cases of esophageal adenocarcinoma. These cases were strictly limited to those physically occurring in the esophagus, and not involving the gastric cardia. In one of the two instances in which Barrett’s was not found, the surrounding epithelium was so ulcerated as to preclude evaluation. In the other case, the tumor appeared to have its genesis in an esophageal submuco sal gland. Abnormal proliferative cell compartments similar to those seen in epithelial dysplasias at other sites have been demonstrated by several authors.41,42 The presence of epithelial dysplasia and carcinoma in situ has been reported frequently in Barrett’s metaplasia.7,16–19,26,29,43

In several studies including our own13,14,26 careful evaluation of adenocarcinomas occurring at the gastroesophageal junction has revealed that almost half contain small residual foci of Barrett’s metaplasia with varying degrees of dysplasia and carcinoma in situ. This fact has suggested that many adenocarcinomas of the lower esophagus and gastroesophageal junction share a common pathogenesis. In several other neoplastic systems fully de-