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Barrett's Esophagus: Is the Goblet Half-Empty?

Stuart Jon Spechler, M.D.

Department of Medicine, VA North Texas Healthcare System, and the University of Texas, Southwestern Medical Center at Dallas, Texas

The condition we now call Barrett's esophagus bears little resemblance to the one described by Norman Barrett in 1950 when he contended that the columnar-lined viscus now identified as Barrett's esophagus was not esophagus at all, but rather a tubular segment of stomach that had been tethered within the chest by a congenitally short esophagus.¹ Over the next six decades, definitions of the disorder evolved as physicians acquired a better understanding of the nature of the columnar-lined esophagus and of how it predisposes to esophageal adenocarcinoma. Modern authorities generally agree that Barrett's esophagus involves replacement of the stratified squamous epithelium of the esophagus by a metaplastic columnar epithelium, but they disagree regarding the extent and type of columnar metaplasia required to make the diagnosis. Since few modern authorities would accept the definition originally proposed by Barrett himself, debates regarding diagnostic criteria for "Barrett's esophagus" necessarily involve contrived features. I have observed that these debates generally revolve around one issue: Does columnar epithelium in the esophagus predispose to cancer? If so, then it is a *bona fide* medical condition that warrants attention. If not, then it is an anatomic curiosity of little importance. Clinicians who ask the question, "Does my patient have Barrett's esophagus?" usually are not interested in arcane semantic arguments. Rather, they are asking, "Is my patient predisposed to develop esophageal adenocarcinoma?"

One of the most contentious recent issues in the debate on diagnostic criteria for Barrett's esophagus involves the importance of the lowly goblet cell, which normally resides in the intestines.² For years, it had been assumed that the sole function of the goblet cell was to secrete mucus. The recent observation that goblet cells also deliver luminal antigens to CD103+ dendritic cells in the small intestine suggests a role in maintaining immune tolerance to commensal bacteria and food.³ Irrespective of their function, goblet cells have unique morphological features that render them easily identifiable in biopsy specimens. When found in specimens from the esophagus or stomach, the goblet cell is a marker for intestinal metaplasia.

In 1976, Paull *et al.* reported a study of 11 patients with Barrett's esophagus who had esophageal biopsy specimens taken using manometric guidance.⁴ The patients were found to have up to three types of columnar epithelia lining their Barrett's esophagus: 1) intestinal metaplasia (also called specialized columnar epithelium or specialized intestinal metaplasia), which had mucus-secreting cells and prominent goblet cells, 2) junctional (also called

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Address correspondence to: Stuart Jon Spechler, M.D., Chief, Division of Gastroenterology (111B1), Dallas VA Medical Center, 4500 South Lancaster Road, Dallas, Texas 75216, Telephone 214-374-7799, Fax 214-857-1571, SJSpechler@AOL.com.

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cardiac) epithelium comprised exclusively of mucus-secreting cells and, 3) atrophic gastric fundic-type epithelium (also called oxyntocardiac) with mucus-secreting cells and some parietal and chief cells. Early reports on Barrett's adenocarcinoma that described the non-malignant columnar epithelium around the tumor almost invariably identified that epithelium as intestinal metaplasia with goblet cells.¹ By the 1980's, intestinal metaplasia was widely regarded as the most common type of Barrett's epithelium and the one associated with cancer development and, by the 1990s, the identification of goblet cells in the esophagus had become a *sine qua non* for the diagnosis of Barrett's esophagus. Most of what is known about cancer risk in Barrett's esophagus is based on studies that included patients with intestinal metaplasia either primarily or exclusively.

Cardiac epithelium, long assumed to be the normal lining of the gastric cardia, was largely ignored by esophagologists until 1997, when Chandrasoma and his colleagues suggested that cardiac epithelium was not normal, but rather a metaplastic lining acquired as a consequence of reflux esophagitis.⁵ They proposed that the normal squamo-columnar junction at the distal esophagus is one between squamous and oxyntic (acid-secreting) epithelia, not between squamous and cardiac epithelia. According to their hypothesis, reflux-damaged esophageal squamous epithelium is replaced first by oxyntocardiac and cardiac epithelia, which later evolve into intestinal metaplasia. In an interesting reversal of Norman Barrett's original contention that the columnar-lined esophagus was really the stomach, Chandrosoma's group argues that, if the rugal folds in what appears to be the proximal stomach (i.e. the gastric cardia) are lined by oxyntocardiac, cardiac or intestinal epithelia, then that organ is really the distal esophagus.⁶

There are a number of lines of evidence to support the notion that cardiac epithelium is the precursor of intestinal metaplasia and that, despite its lack of goblet cells, cardiac epithelium might have intestinal features and a malignant predisposition. In patients who have esophagectomy with esophagogastrostomy, which often results in reflux esophagitis and columnar metaplasia in the remnant esophagus, cardiac metaplasia appears to develop before intestinal metaplasia.⁷ Metaplastic, non-goblet columnar epithelium (cardiac/oxyntocardiac) in the esophagus has been shown to express molecular markers of intestinal differentiation such as villin and CDX2, and to exhibit DNA content abnormalities similar to those of intestinal metaplasia with goblet cells.^{8,9} A recent study of 141 patients who had endoscopic mucosal resections of small esophageal adenocarcinomas found that 71% had cardiac epithelium, not intestinal metaplasia, adjacent to the cancer.¹⁰ Finally, in a retrospective study of 712 patients in one hospital who had endoscopic biopsy specimens taken from the distal esophagus, no significant difference in the rate of esophageal adenocarcinoma development was observed between patients with and without goblet cells in their esophageal columnar epithelium (4.5% vs. 3.6% rate of cancer development, respectively) during a median follow-up interval of 12 years.¹¹

In 2005, the British Society of Gastroenterology defined Barrett's esophagus as one "in which any portion of the normal squamous lining has been replaced by a metaplastic columnar epithelium which is visible macroscopically".¹² This definition includes patients with metaplastic, non-goblet columnar epithelium in the esophagus. However, this definition was not proposed primarily because of concern regarding the malignant potential of the non-goblet epithelia, but rather because British pathologists believed that "intestinal metaplasia can always be identified in endoscopically-visible columnar metaplasia providing a sufficient number of biopsies are taken over an adequate time scale."

In a study published in this issue of *Clinical Gastroenterology and Hepatology*, Westerhoff and her colleagues at the University of Chicago explored potential consequences of adopting the British policy of dropping goblet cells as a diagnostic criterion for Barrett's esophagus.¹³

The investigators searched their hospital's database to identify 690 patients who had esophageal biopsy specimens taken for suspicion of Barrett's esophagus. 53 of those patients had only squamous epithelium found in the specimens and, among the 637 patients with columnar epithelium, 258 had goblet cells and 379 did not. 118 of the 379 patients without goblet cells had follow-up endoscopic examinations and, during a mean period of 5.8 years, goblet cells were eventually identified in only 12%. No patient without goblet cells developed dysplasia or cancer. The investigators concluded that dropping the diagnostic requirement for goblet cells would have increased the frequency of diagnosis of Barrett's esophagus by 147%, and would have included many patients who appear to have little risk for cancer development.

What can clinicians conclude from all this sound and fury regarding goblet cells and Barrett's esophagus? First, non-goblet columnar epithelium in the esophagus can be a metaplastic lining acquired as a result of chronic reflux esophagitis in some, if not all cases. Despite the lack of goblet cells, this epithelium has intestinal-type molecular features and appears to be the precursor of goblet cell metaplasia. Although the highly differentiated goblet cell itself seems an unlikely candidate for the cell of origin of esophageal adenocarcinoma, the goblet cell is a marker for malignant predisposition in the esophagus. The argument that intestinal metaplasia will always be identified in esophageal columnar metaplasia if enough biopsies are taken over an adequate period of time might be true, but this argument is speculative. In support of Westerhoff's findings, Pereira and Chaves also recently described a number of patients with non-goblet columnar epithelium for whom multiple esophageal biopsy procedures have failed to demonstrate goblet cells.¹⁴ It is not possible to exclude biopsy sampling error in such cases, but to insist that something is there when it cannot be demonstrated is religion, not science. Westerhoff *et al.* have shown that the inclusion of patients with non-goblet columnar epithelium under the rubric of "Barrett's esophagus" would more than double the number of patients with that disorder, which would substantially increase treatment costs. Although I am uncomfortable with the concept that financial considerations should influence the diagnostic criteria for a disease, the financial consequences of dropping the requirement for goblet cells as a diagnostic criterion would be substantial if patients with cardiac epithelium were entered into surveillance and treatment programs for Barrett's esophagus.

In a recent medical position statement from the American Gastroenterological Association, the authors made a distinction between the conceptual definition of Barrett's esophagus and its diagnostic criteria.¹⁵ They defined Barrett's esophagus conceptually as "the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus." The authors also wrote that, "Presently, intestinal metaplasia [with goblet cells] is required for the diagnosis of Barrett's esophagus because intestinal metaplasia is the only type of esophageal columnar epithelium that clearly predisposes to malignancy." That statement remains valid. Although there are contradictory data, most evidence suggests that non-goblet columnar cell epithelium in the esophagus is not strongly predisposed to malignancy. Now, Westerhoff *et al.* have demonstrated some potentially serious consequences of dropping the diagnostic criterion of goblet cells. Well designed, future studies are needed to resolve the issue but, for now, it does not seem advisable to put down the goblet.

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