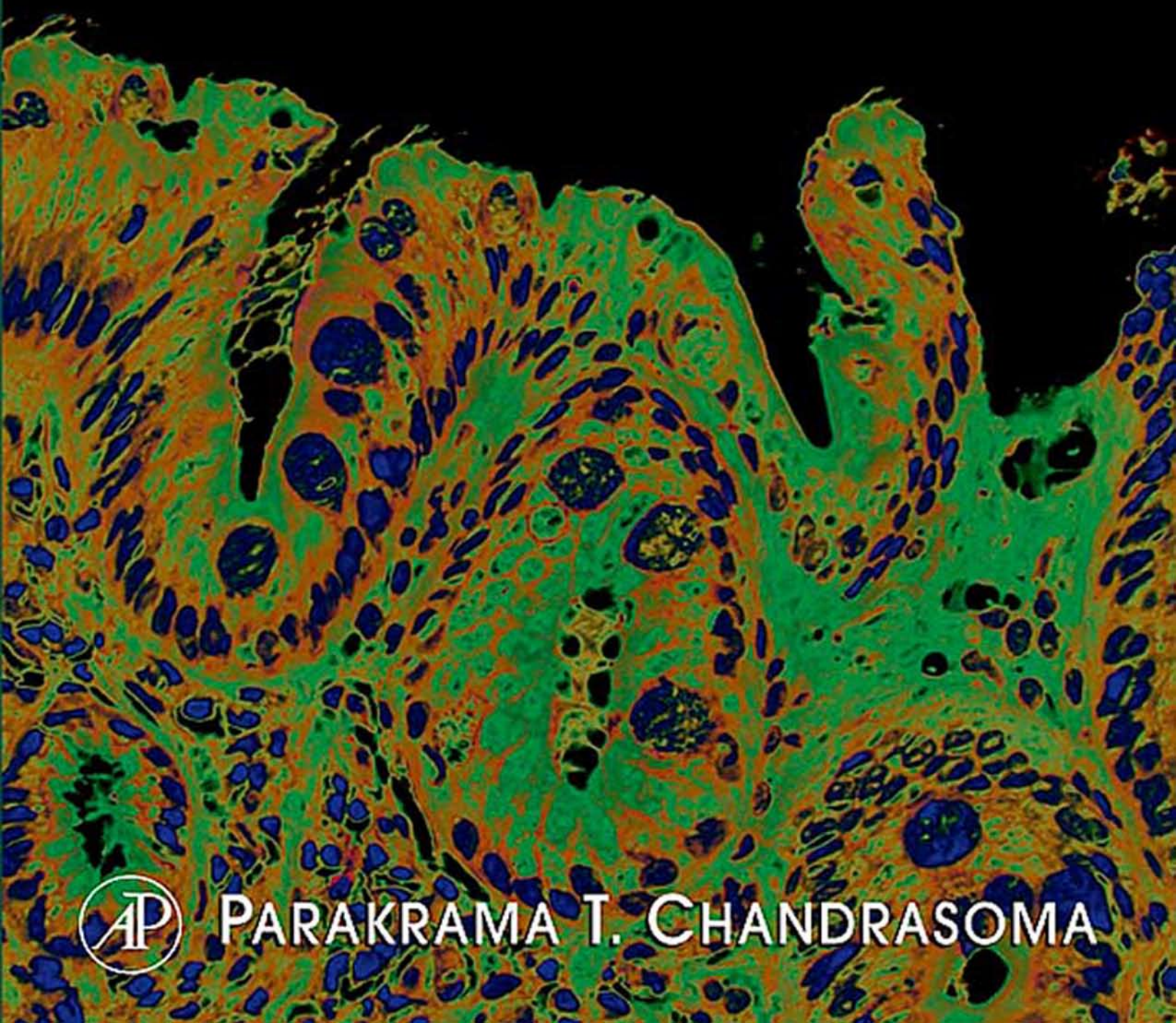
Diagnostic Atlas of Gastroesophageal Reflux Disease

A New Histology-Based Method



Parakrama T. Chandrasoma

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A New Histology-Based Method

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To my wife, Cherine.

THE BEST.

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About the Author

Dr. Parakrama Chandrasoma was born in Sri Lanka and received his medical education and initial pathology training at the University of Sri Lanka Medical School. He has postgraduate degrees in internal medicine, including an M.D. (Sri Lanka) and Membership of the Royal College of Physicians (UK). He immigrated to the United States in 1978. Upon completing his pathology residency, he assumed duties as Chief of Surgical Pathology at the Los Angeles County—University of Southern California Medical Center, a position he has held since. In 1991, after an initial interest in neuropathology, Dr. Chandrasoma joined Dr. Tom DeMeester's Foregut Surgery team as pathologist. This led to a productive study of gastroesophageal reflux disease spanning 16 years and resulting in the development of numerous original concepts relating to the pathogenesis of gastroesophageal reflux disease. Dr. Chandrasoma has written over 140 peer-reviewed papers and 6 pathology textbooks, including a general text on gastrointestinal pathology and a text on gastroesophageal reflux disease. He is a Professor of Pathology at the Keck School of Medicine at the University of Southern California. Dr. Chandrasoma is married with three children and lives in Pasadena, California.

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Other Publications by the Author

GERD: Reflux to Esophageal Adenocarcinoma (Parakrama T. Chandrasoma and Tom R. DeMeester, 447 pp., Elsevier Academic Press, 2006, ISBN: 978-0-12-369416-4)

Review from the *New England Journal of Medicine*

"Esophageal cancer is the seventh leading cause of all deaths from cancer worldwide, with an estimated 14,000 deaths from this cancer in the United States alone in 2006. Since the 1970s, esophageal adenocarcinoma has been the neoplasm with the fastest-growing incidence of any cancer in the Western world. This rising incidence implies a need for improvement in identifying those at risk for the disease and in both intervention and prevention. Regrettably, there is a lack of consensus among experts regarding the diagnosis and management of Barrett's esophagus. A book that is focused on this important subject has been long overdue.

This timely and authoritative book was written by two masters in the field whose experience spans two decades and includes supervision of studies involving more than 10,000 patients. The book is well written and demonstrates the advantages of having a limited number of authors and a narrow focus—namely, consistency of style and a cohesive philosophy. There is structural coherence, with a logical progression of the 17 chapters and minimal overlap between them. Early chapters provide overviews of gastroesophageal reflux disease (GERD) and Barrett's esophagus, followed by a review of embryological development of the upper gastrointestinal tract and of normal anatomy and histology. Subsequent chapters document the pathology of GERD at the cellular and anatomic level, with evolution through Barrett's metaplasia to adenocarcinoma. The book ends with suggestions for research strategies, discussions of the rationale for management of GERD and Barrett's esophagus, and strategies for preventing reflux-induced adenocarcinoma.

The book is compelling reading, made more so by its historical approach, as the authors trace the gradual evolution of medical thought in the field. A further strength is the literature review at the end of each chapter, where the authors summarize and offer their often strong opinions of landmark studies in the field.

The authors believe that the increasing incidence of esophageal cancer is at least partly a consequence of a failed medical approach to the precursor conditions of GERD and Barrett's esophagus. This problem, they write, stems from fundamentally flawed definitions of both conditions that underestimate their true prevalence, as do current practice guidelines stating that there is no need for biopsy of endoscopically normal gastroesophageal junctions. The authors argue that esophageal adenocarcinoma is preventable and that recognition of earlier stages in the reflux-to-adenocarcinoma sequence would

allow for interventions that might heavily influence its incidence. They also contend that the current therapeutic approach to GERD—acid-suppressive therapy—might be promoting the development of adenocarcinoma and that GERD should be managed with antireflux surgery.

The authors therefore propose several radical changes in the field, including new criteria for defining the gastroesophageal junction, GERD, and Barrett's esophagus, as well as a new classification system for adenocarcinoma of this region. They recommend a new biopsy protocol for patients with GERD who are undergoing endoscopy. They call for a radical overhaul in our current thinking and urge that GERD be viewed as a premalignant condition and treated with an appropriately aggressive approach.

[. . .] The authors are very opinionated, and many readers will not agree with their views, several of which are controversial. Although many of their ideas are indeed provocative and deviate from current consensus, we feel that the authors' vast experience gives their opinions importance—their perspective must be carefully considered. We therefore feel that this book is essential reading for anyone with an interest in esophageal disease, and particularly in GERD and esophageal adenocarcinoma.

—*New England Journal of Medicine,* 2007; 356: 1897–1898.

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CHAPTER 1

Reflux-Induced Cancer: An Epidemic We Need to Address Now

The medical establishment is generally thrown into disarray when new data emerge that change the fundamental basis by which diseases are defined. This is the present state in the diagnosis of gastroesophageal reflux disease and Barrett esophagus. Old ideas persist despite evidence to the contrary because standard textbooks, which are the source of information for many practitioners, change slowly. The ability to assimilate all the relevant evidence is limited by time and the fact that the data are spread out in the voluminous literature, and it is difficult to separate the chaff from the wheat.

Conferences and review articles are a little more helpful, but the ideas expressed therein tend to emphasize the controversial opinion of a given expert rather than provide clear practice guidelines. Experts have varying opinions based on the speed with which their minds adjust to change, adding to the sense of turmoil in the mind of the community physician. The loudest, most influential, and most-often heard voice is often the one that is believed. For gastroenterologists, when the change is based on histologic data that are difficult to comprehend because of their lack of training in this area, the confusion is even more profound. All this leads to great confusion and potential mismanagement of patients because the standard of care is not consistent among different physicians.

This atlas is designed to present practical diagnostic guidelines for the management of the patient with gastroesophageal reflux disease. It will incorporate the newest data to provide guidelines to the gastroenterologist, foregut surgeon, and pathologist about accurate diagnostic criteria for reflux, interpretation of endoscopic landmarks, protocol for biopsy, and interpretation of histology. It will progress logically through accurate histologic definitions, which are fundamental to understanding cellular abnormalities, the definition of normalcy, present diagnostic criteria, the meaning of histologic findings, to developing new definitions and diagnostic criteria for reflux disease that incorporate the new evidence. The atlas is basically a logical assimilation of new data into clinical practice.

For the changing concepts, definitions represent a moving target; in such cases, I will attempt to define both the present state of the art and what I believe is the logical end-point in the future. It is only by analysis of the evidence presented that individual gastroenterologist-surgeon-pathologist teams can determine what they want to believe and apply that to patient care. Whatever decision is made, the result will be better than the present confusion.

The ideas presented in this atlas have strong evidence to support them and essentially convert the opinion-based present management of gastroesophageal reflux disease to a method that is evidence-based. A more comprehensive presentation of the evidence has been previously published in a more thorough book format.[1] This atlas is meant to be largely a pictorial description that is designed to facilitate the practical application of the new information.

The methods suggested are based on the correct histologic interpretation of endoscopic biopsies with standard stains that are available in every hospital and laboratory in the world. There is little demand for new technology. There is, however, a demand for greater attention to detail that will increase the cost, but the hope is that it will lead to an understanding of the disease at a cellular level.

Epidemiology of Reflux-Induced Cancer

There is some urgency in the necessity to understand this disease. Reflux-induced adenocarcinoma of the esophagus is the most rapidly increasing cancer in the United States, Western Europe, and Australia (Figure 1–1). A recent study by Pohl and Welch[2] showed that esophageal adenocarcinoma incidence has increased more than sixfold between 1975 and 2000, from 3.8 to 23.3 cases per million (Figure 1–2). Adenocarcinoma of the esophagus, which was one-sixth as common as esophageal squamous carcinoma in 1975, overtook squamous carcinoma incidence in the mid-1990s (Figure 1–3).

This increase in esophageal adenocarcinoma has been paralleled by an increase in the incidence of adenocarcinoma of the "gastric cardia." The rising curve of adenocarcinoma in the two locations was similar between 1975 and 1990, but that of adenocarcinoma of the gastric cardia shows a recent flattening, whereas that of esophageal adenocarcinoma continues to increase (Figure 1–4). Despite this, the incidence curve for adenocarcinoma of the "gastric cardia" is much more similar to that of esophageal adenocarcinoma than noncardiac gastric adenocarcinoma, which has declined considerably during this same period in the United States[3] (Figure 1–5). The epidemiology suggests that adenocarcinomas of the esophagus and "gastric cardia" are different expressions of one disease.

In terms of actual numbers, however, cancers in these two sites are approximately equal, with esophageal adenocarcinoma recently overtaking adenocar-

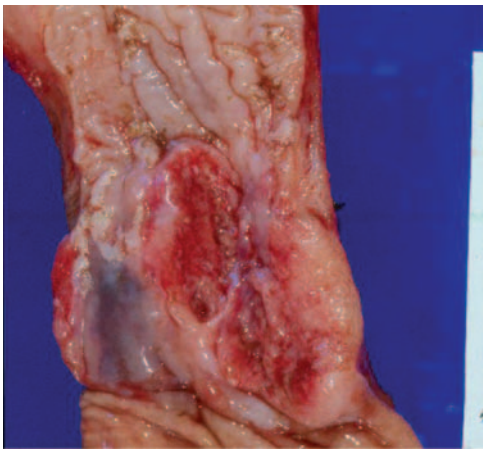


Figure 1–1 Distal esophageal adenocarcinoma. The tumor is an ulcerated mass that involves the distal third of the esophagus and extends to the proximal limit of rugal folds.

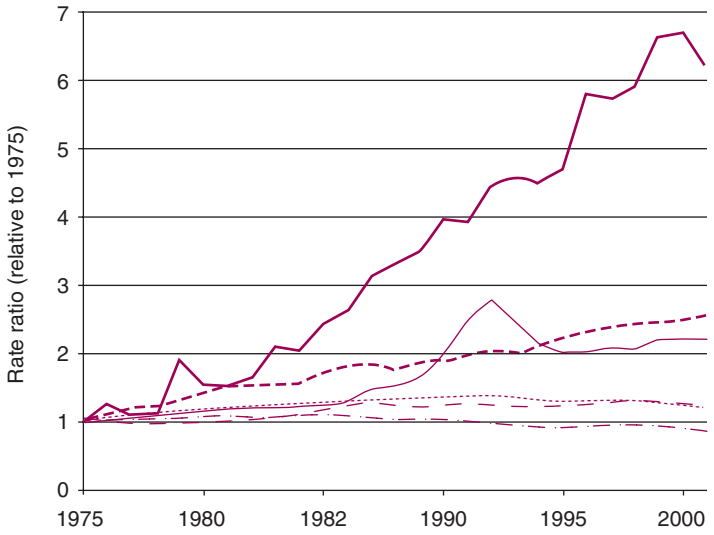


Figure 1–2 Relative change in incidence of esophageal adenocarcinoma and other malignancies from 1975 to 2000. Data from the National Cancer Institute's SEER program. *Thick red line,* esophageal adenocarcinoma; *dashed line,* breast cancer; *fine red line,* prostate cancer. Other cancers indicate melanoma, lung cancer, and colorectal cancer. (Reproduced with permission from Pohl H, Welch G: The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence, *J Natl Cancer Inst* 19:142–146, 2005.)

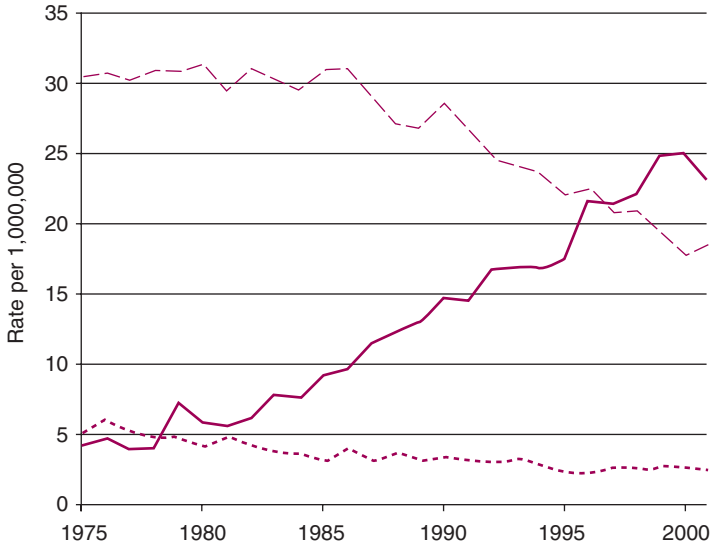


Figure 1–3 Changing incidence of esophageal adenocarcinoma *(solid line)* compared with esophageal squamous carcinoma *(dashed line)* from 1975 to 2000. The *dotted line* indicates cases that were "esophageal cancer, not otherwise specified." The absolute number of patients developing esophageal adenocarcinoma overtook squamous carcinoma around 1996. (Reproduced with permission from Pohl H, Welch G: The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence, *J Natl Cancer Inst* 19:142–146, 2005.)

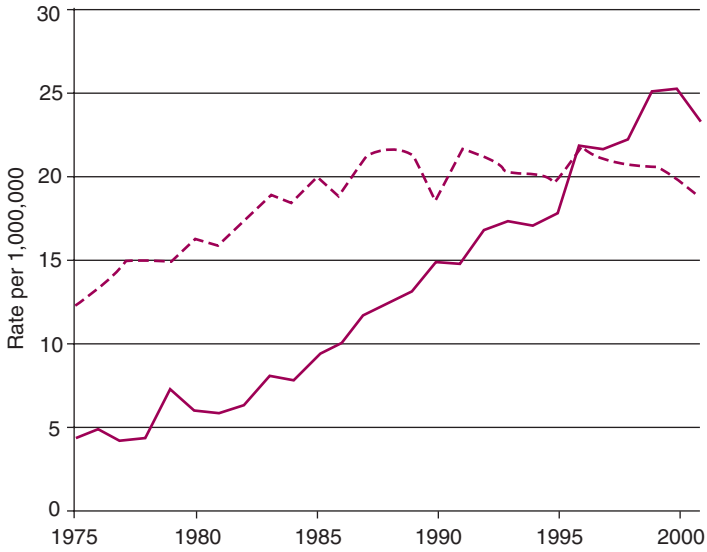


Figure 1–4 Trends in the incidence of adenocarcinoma of the esophagus *(solid line)* compared with adenocarcinoma of the gastric cardia (*dotted line*). The lines are parallel with a flattening of the increase for gastric cardia cancer in the last decade. (Reproduced with permission from Pohl H, Welch G: The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence, *J Natl Cancer Inst* 19:142–146, 2005.)

cinoma of the gastric cardia (see Figure 1–4). It is estimated that approximately 12,000 people in the United States develop adenocarcinoma of the esophagus each year, with a similar number developing adenocarcinoma of the gastric cardia.

Esophageal adenocarcinomas are induced by gastroesophageal reflux disease. Lagergren et al[4] showed a strong relationship between symptomatic reflux (defined as heartburn and/or regurgitation) and esophageal adenocarcinoma. The odds ratio for esophageal adenocarcinoma was 7.7 (95% confidence interval, 5.3 to 11.4) for patients with reflux symptoms compared to those without symptoms. The odds ratio increased progressively as the severity and duration of reflux symptoms increased, reaching 43.5 (95% confidence interval, 18.3 to 103.5) for patients with the most severe and longest-duration symptoms. The relationship between symptoms of reflux was also present for adenocarcinoma of the "gastic cardia," albeit at a lower level. Patients with symptoms of reflux had an odds ratio of 2.0 (95% confidence interval, 1.4 to 2.9) for adenocarcinoma of the "gastric cardia," increasing to 4.4 (95% confidence interval, 1.7 to 11.0) in those with the most severe and longest-duration symptoms.

From a practical standpoint, all adenocarcinomas of the esophagus are reflux-induced cancers occurring in the surface epithelium (Figure 1–6). There is no other known mechanism for adenocarcinoma in the esophagus except for rare tumors arising in esophageal glands. Reflux does not induce cancer in the squamous epithelium; Lagergren et al[4] showed that there was no relationship between symptomatic reflux and squamous carcinoma of the esophagus. The mechanism of carcinogenesis is believed to pass through columnar metaplasia, intestinal metaplasia in the columnar epithelium, and increasing degrees of dysplasia to adenocarcinoma (Figures 1–6 and 1–7).

If adenocarcinoma of the "gastric cardia" is a different expression of esophageal adenocarcinoma, it must also result from a similar pathogenesis.

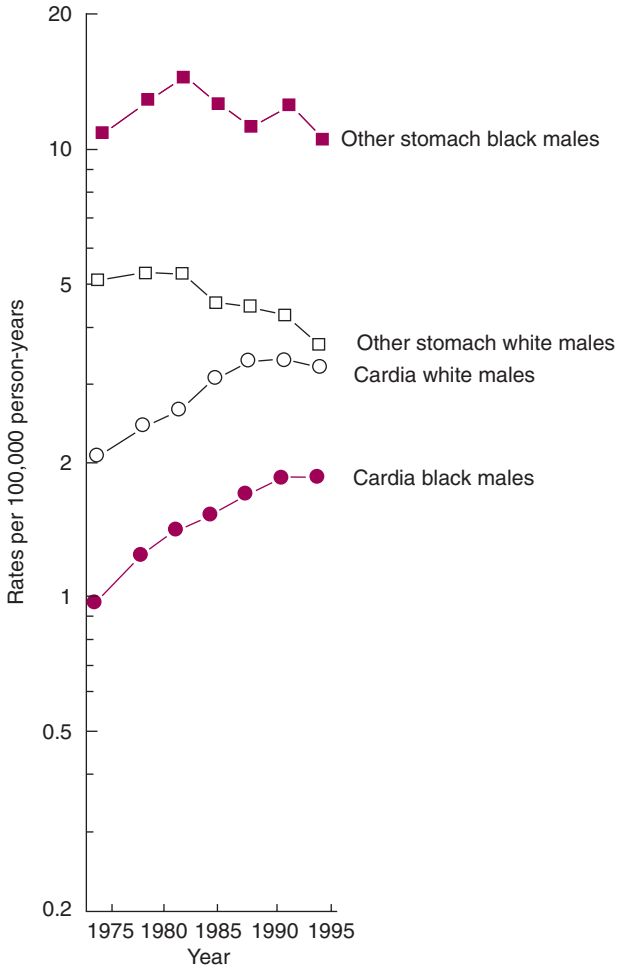


Figure 1–5 Trends in the incidence of adenocarcinoma of the stomach among males in the United States from 1975 to 1995. The incidence of cardia cancers, which are more common in white males than black males, has shown a sustained increase. This contrasts with adenocarcinoma of the distal stomach, which is more common in black males than white males and has shown a decline, particularly in white males. (Reproduced with permission from Devesa SS, Blot WJ, Fraumeni JF Jr.: Changing patterns in the incidence of esophageal and gastric carcinoma in the United States, *Cancer* 83:2049–2053, 1998.)

Although the medical community presently suspects this to be true, it is not an accepted fact.

At present, the medical community believes, somewhat oxymoronically, that adenocarcinoma of the "gastric cardia" is associated with gastroesophageal reflux disease. It should recognize that this is not possible; gastroesophageal reflux causes disease only in the esophagus, not in the stomach. I will show that the cause of this oxymoron is that what is presently designated as the "gastric cardia" is actually the reflux-damaged lower esophagus. I will also show that the vast majority of adenocarcinomas of the "gastric cardia" have a pathogenesis identical to esophageal adenocarcinoma and are reflux-induced.

Adenocarcinoma of the esophagus is largely a disease of affluent white males older than 40 years. Non-white Americans and women are at significantly lower risk. Although the racial distribution is similar for adeno-

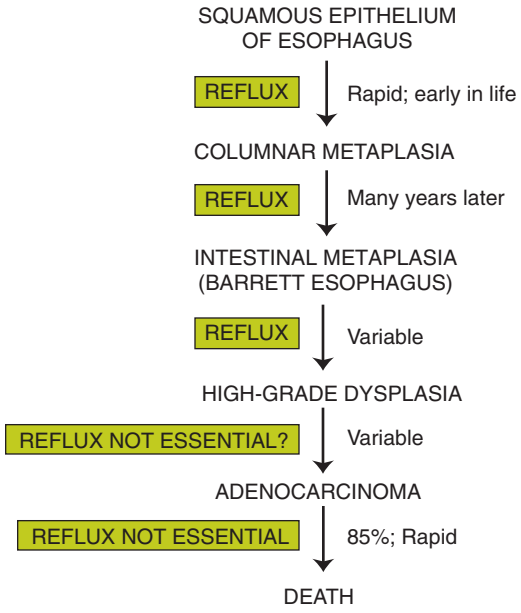


Figure 1–6 The sequence of changes by which gastroesophageal reflux results in adenocarcinoma of the esophagus. The first part of the sequence requires the interaction of the epithelium with molecules in the gastric refluxate. Once the genetic mutations of carcinoma have occurred, the progression to the phenotypic expression of cancer is independent of reflux.

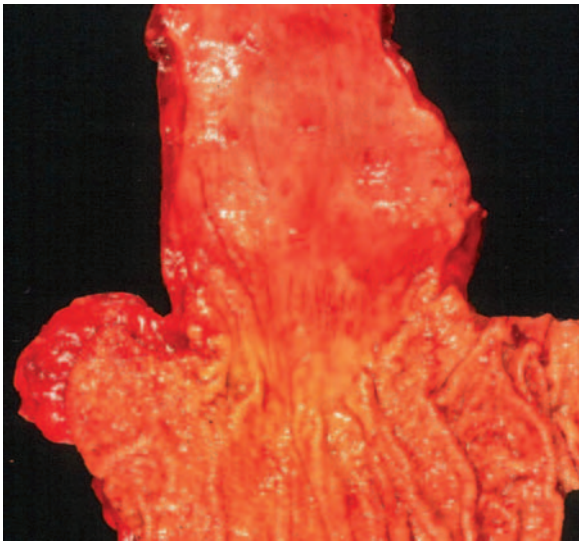


Figure 1–7 Columnar-lined esophagus, showing complete replacement of the distal tubular esophagus by columnar epithelium. The squamocolumnar junction is not seen; it is proximal to the top edge of the photograph.

carcinoma of the "gastric cardia," the sex difference decreases. Women are almost as likely to develop adenocarcinoma of the "gastric cardia" as men in the United States.

The Problem

The epidemiologic data just presented indicate that reflux-induced adenocarcinoma affected an estimated 16,000 patients in the United States in 2000. Exact numbers are not available for the past 5 years but can reasonably be expected to be higher. The overall mortality is in the 80% to 90% range for these patients; this means that between 18,000 and 20,000 Americans will die in 2007 from reflux-induced cancer. This amounts to 55 per day or 2.3 per

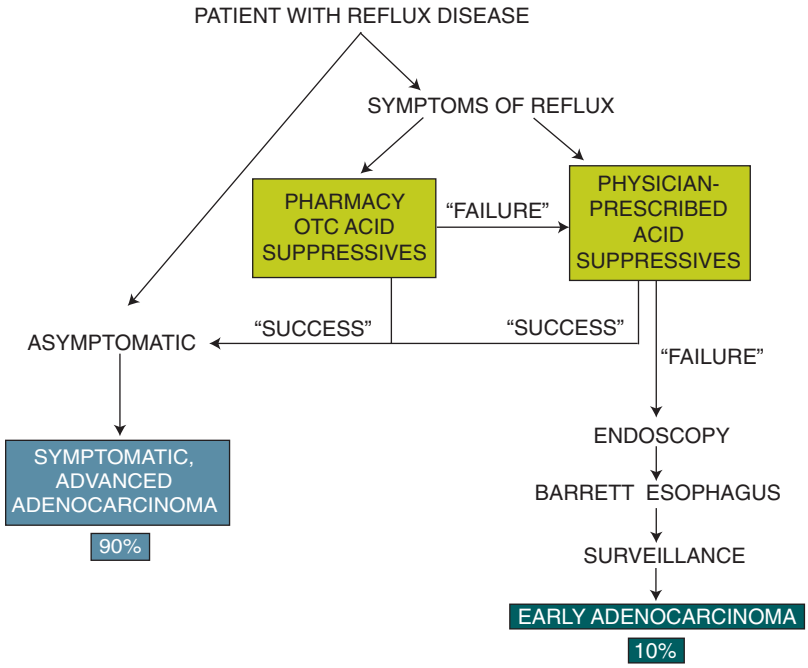


Figure 1–8 The cost of "successful" treatment of reflux disease for patients who are destined to develop adenocarcinoma is that they have their first endoscopy at the time they present with symptoms of advanced-stage cancer, with a near 90% mortality. "Failure" of treatment for reflux symptoms is better; it leads the patient earlier to endoscopy where Barrett esophagus is diagnosed, and they enter a surveillance protocol.

hour. We are in the midst of a raging epidemic that was declared as such by Rodger Haggitt in 1992.[5] The number of deaths from reflux-induced adenocarcinomas today is approximately one-half the number of deaths from breast cancer (approximately 40,000 per year) and one-third the numbers of deaths from colorectal cancer (approximately 55,000 per year)—and it continues to increase.

Despite this, the general population has little or no inkling that heartburn and reflux disease are harbingers of cancer. Although the risk is small, *every adenocarcinoma of the esophagus and most adenocarcinomas of the "gastric cardia" occur as a result of reflux disease.* There is no other pathogenesis for esophageal adenocarcinoma.

The intense direct marketing of highly lucrative acid-suppressive drugs by the pharmaceutical industry directs patients to seek a "cure" for their heartburn by going to the pharmacy where the most powerful proton pump inhibitors are available over the counter (Figures 1–8, 1–9, and 1–10). The use of these agents is highly effective in controlling the acid-induced symptoms of reflux disease. Many patients are prevented from seeking medical care and are extremely satisfied with the outcome of their visit to the pharmacy. Those in this group that inevitably go on to develop cancer are doomed.

The medical establishment is not much better educated than the general public. There is actually surprise and almost disbelief when primary care physicians and even gastroenterologists are presented with the evidence that approximately 20,000 Americans will die every year from reflux-induced adenocarcinoma. The number of physicians and gastroenterologists in the United States is so large that physicians believe this is a rare disease. Because of this perception, this disease is not taken seriously. When patients present to a physician with symptoms of reflux, most will treat these patients empirically

Figure 1–9 Over-the-counter acid-suppressive agents on display at a pharmacy. Proton pump inhibitors and H2-receptor blockers can be seen at eye level and are the most profitable.

Figure 1–10 Packages of proton pump inhibitors and H2-receptor blockers, exhorting sufferers of heartburn to self-medicate themselves to "cure."

with acid-suppressive drugs that they believe are miracle drugs that "cure" their patients (see Figure 1–8). With a prescription for a proton pump inhibitor and a smile from the physician, the patient is on his or her way to a so-called "successful outcome"—currently defined as the relief of symptoms. Endoscopy is not performed in the vast majority of these patients, and even if it is performed, the present practice guidelines result in failure of adequate assessment of these patients.

This previously described "cure" is dangerous for a patient with symptoms of reflux disease (see Figure 1–8). Although the outcome of rapid symptom relief is considered very successful for the millions of people who take acid-suppressive agents for reflux, those among this group that go on to develop adenocarcinoma are doomed to be the 85% of the 24,000 patients who will die from reflux-induced adenocarcinoma in 2007. Patients whose treatment is "unsuccessful" (in that the symptoms are not relieved) are likely to end up having endoscopy, receiving a diagnosis of Barrett esophagus, and being recognized as at risk for cancer (see Figure 1–8). The cancer is detected earlier in these patients, and their survival rates are better. Unfortunately, this group presently is less than 10% of patients. If we are to have an impact on the mortality from reflux-induced adenocarcinoma, we need to urgently find a method of changing this scenario.

Data show the medical profession is also guilty of the indiscriminate use of acid-suppressive drugs. In a study of pharmacy billing data for two insurers within a large eastern Massachusetts provider network,[6] 4684/168,727 (2%) of patients were prescribed chronic (more than 90 days) acid-suppressive drugs; 47% were taking H2-receptor antagonists, and 57% were taking proton pump inhibitors (4% were taking both). Diagnostic testing was uncommon in these patients, with only 19% on acid-suppressive drugs having undergone esophagogastroduodenoscopy within the previous 2 years.[6] Acid suppression is almost like a panacea for all symptoms in the abdomen.

If acid suppression is to be used as a panacea, there is an absolute requirement that these drugs are unequivocally safe. One only has to see the curve of the dramatic rise in the incidence of reflux-induced adenocarcinoma to ask the question whether acid-suppressive drug use has contributed to this increase. The rise in this incidence of cancer matches our effectiveness in controlling acid secretion by the stomach. H2-receptor antagonists came on the market in the 1960s, and proton pump inhibitors were introduced in the late 1980s. It is clear that these drugs greatly improved the acid-induced problems caused by reflux disease such as pain, erosions, severe ulceration, and complicated strictures. While this positive change occurred, the incidence of Barrett esophagus and reflux-induced adenocarcinoma dramatically increased. If we are to conclude that the "cure" of reflux symptoms, erosions, ulcers, and strictures resulted from acid suppression, surely we must ask the corollary question whether Barrett esophagus and reflux-induced cancer are promoted by acid suppression. All the available evidence suggests that this is true, although no randomized trial that has been performed has provided proof.

When I raise this issue at meetings attended by gastroenterologists, there is a vehement defense of acid-suppressive drugs. I am told that there is no proof that acid-suppressive drugs cause cancer. This, however, is not the proof that we should demand. I, who do not use acid-suppressive drugs, should not be asked to prove they promote cancer. *The responsibility lies with everyone who markets, permits the marketing of, and dispenses these drugs to prove that they do not promote cancer*. If such proof does not exist, then even a suggestion that they may promote cancer should cause concern.

There is more than a suggestion that acid-suppressive drugs promote reflux-induced cancer. A landmark epidemiologic study by Lagergren et al[4]

Figure 1–11 Statement regarding the increased risk of esophageal cancer among symptomatic reflux patients with a history of acid-suppressive medication use compared to those who have not taken these drugs. This is extracted from the influential article by Lagergren J, Bergstrom R, Lindgren A, Nyren O: Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma, *New Engl J Med* 340:825–831, 1999.

"WE COMPARED THE RISK OF ESOPHAGEAL ADENOCARCINOMA AMONG PERSONS WHO USED MEDICATION FOR SYMPTOMS OF REFLUX AT LEAST FIVE YEARS BEFORE THE INTERVIEW WITH THAT AMONG SYMPTOMATIC PERSONS WHO DID NOT USE SUCH MEDICATION. THE ODDS RATIO WAS 3.0 (95 PERCENT CONFIDENCE INTERVAL, 2.0 TO 4.6) WITHOUT ADJUSTMENT FOR THE SEVERITY OF SYMPTOMS AND 2.9 (95 PERCENT CONFIDENCE INTERVAL, 1.9 TO 4.6) WITH THIS ADJUSTMENT."

established the relationship between reflux disease, esophageal adenocarcinoma, and the use of acid-suppressive medications; the drug use was shown to increase the risk of adenocarcinoma (Figure 1–11). The odds ratio for adenocarcinoma was 3.0 (95% confidence interval, 2.0 to 4.6) for symptomatic patients using acid-suppressive medications compared to symptomatic patients not using such medications. When adjusted for severity of symptoms, the odds ratio remained high, at 2.9 (95% confidence interval, 1.9 to 4.6), suggesting that acid-suppressive medication was the primary association rather than the severity of symptoms. Despite the fact that this finding is from one of the most reliable and often quoted epidemiologic studies published in the most prestigious medical journal in the world, and despite the fact that there is no study in the literature that has contradicted this, the pharmaceutical industry and medical community have completely ignored this evidence.

It is clear that, at least in this instance, the medical community does not practice evidence-based medicine; it practices medicine based on the evidence that fits its needs. If I were a cynical person, I would suggest that the $13 billion of annual revenue from the sale of these acid-suppressive drugs was responsible rather than benign neglect and ignorance. I really do not know which of the two is worse.

The Reflux-to-Adenocarcinoma Sequence

For the past three decades, the medical community has largely treated reflux disease as if it were a disease that is completely explained by the acid component of the refluxed gastric contents. The drug industry's entire research focus has been to develop increasingly effective acid-suppressive drugs. When H2-receptor antagonists were produced in the 1960s, the belief was that they would make reflux disease a thing of the past. When this did not happen, the drug industry gave us proton pump inhibitors, which were substantially more effective in suppressing acid. This did not remove the reflux disease problem either. It seems as if the pharmaceutical companies and medical community believe that better acid suppression than that produced by proton pump inhibitors is the solution. However, the evidence suggests the reverse—better acid suppression has always resulted in an increase in reflux-induced cancer (Figure 1–12).

Reflux of gastric contents into the esophagus carries with it numerous molecules other than acid (see Figure 1–12). To treat this disease with the belief that acid is responsible for every molecular event is extremely naïve.

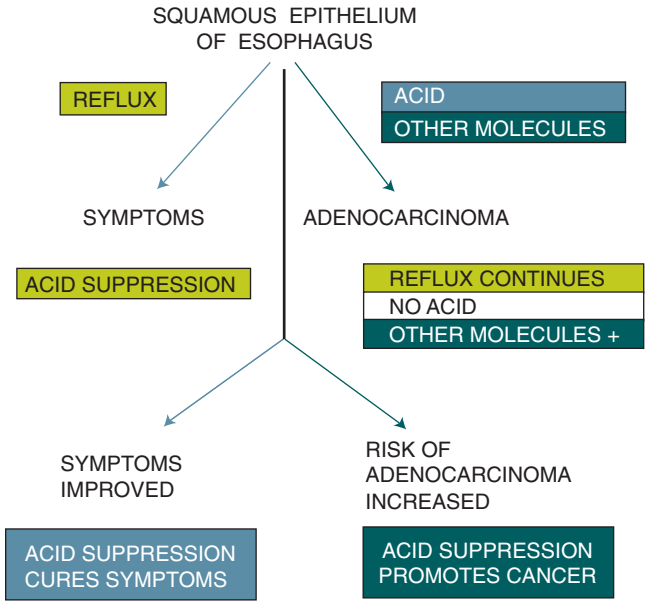


Figure 1–12 Outcomes in patients with reflux disease treated with acid-suppressive drugs. On the one hand, use of these drugs has dramatically decreased symptoms and cured erosive esophagitis. On the other hand, their use has been associated with a dramatic increase in adenocarcinoma. The obvious explanation is that refluxate molecules other than acid are responsible for the cancer.

Although acid is a highly injurious agent capable of damaging cells, it is highly unlikely that it is a direct carcinogenic agent. Carcinogenesis occurs when there is interaction between a cell receptor and a carcinogen, which causes a genetic transformation in the cell. Carcinogens are generally complex molecules that do not damage cells. They are not likely to be simple ions that cause cell damage. There is no evidence whatsoever that H+ ions are direct carcinogens.

The occurrence of adenocarcinoma in the esophageal epithelium passes through three sequential steps (Figure 1–13).

Step 1: Squamous Epithelial Damage with Columnar Metaplasia

Squamous epithelial damage begins at the most distal esophagus where the exposure to gastric refluxate is highest. I will show in Chapter 5 that H+ ions are largely responsible for setting the stage for columnar metaplasia of the esophagus. This first stage of reflux-induced columnar metaplasia occurs early in life and results in cardiac mucosa (i.e., non-intestinalized columnar-lined esophagus).

Increasing amounts of reflux cause progressively longer segments of columnar-lined esophagus (Figure 1–14). This is seen first as tongues of columnar epithelium extending into the squamous epithelium of the esophagus, causing the Z-line to become serrated (Figure 1–15). Later, with more severe damage, the columnar metaplasia involves the entire circumference of the distal esophagus, causing a cephalad migration of the Z-line (Figure 1–16).

It is expected that acid suppression will have an inhibitory effect on the conversion of squamous epithelium to cardiac mucosa (see Figure 1–13).

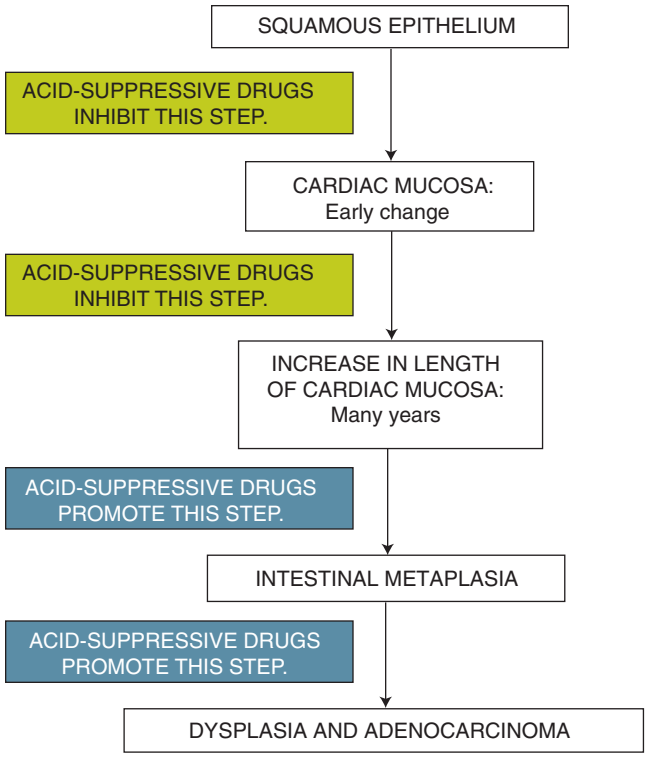


Figure 1–13 The three major steps whereby the squamous epithelium of the esophagus is converted to an adenocarcinoma by reflux. The first step, in which squamous epithelial damage results in cardiac mucosa, is acid dependent. The two later steps, the induction of intestinal metaplasia in cardiac mucosa (i.e., Barrett esophagus) and carcinogenesis, are caused by non-acid refluxate molecules that are promoted by removal of acid.

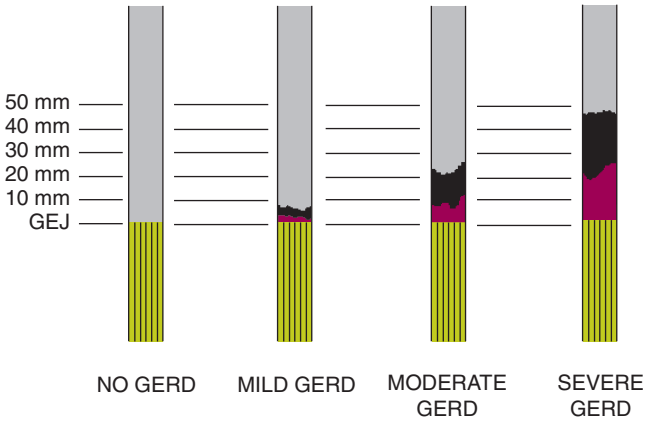


Figure 1–14 There is a direct correlation between the severity of reflux disease and the length of esophageal squamous epithelium that is transformed into columnar metaplastic epithelium. *GEJ,* Gastroesophageal junction; *GERD,* gastroesophageal reflux disease. *Black,* Cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa, with lines denoting rugal folds.

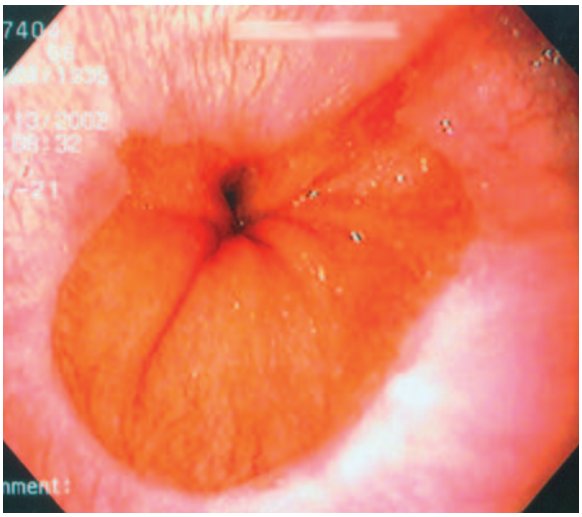


Figure 1–15 Endoscopic appearance of columnar–lined esophagus, seen as a non-salmon-colored area between the irrgular squamocolumnar junction and the proximal limit of rugal folds.

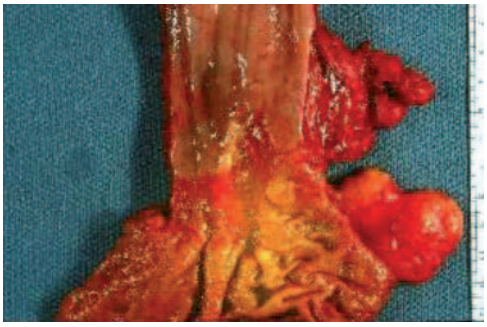


Figure 1–16 Short segment of columnar metaplasia in the distal esophagus. The visible columnar-lined segment extends from the serrated squamocolumnar junction proximally to the rugal folds distally. Note the presence of squamous islands in the columnar-lined segment.

Unfortunately, because cardiac metaplasia occurs very early in the reflux-to-adenocarcinoma sequence, it is very unlikely that acid suppression can be used early enough to prevent this step. When one compares the historical and present literature on the extent of columnar-lined esophagus, there is a suggestion that the prevalence of patients with very long segments of columnar-lined esophagus may actually be less today than 50 years ago. This would be the expected result of increasing effectiveness and use of acid-suppressive drugs.

Step 2: Intestinal Metaplasia of Cardiac Mucosa

This defines Barrett esophagus and is correctly believed to be a prerequisite change for the development of adenocarcinoma in the esophagus. Intestinal metaplastic epithelium in the esophagus is the only epithelial type in which the interaction between carcinogens in the gastric juice and the epithelium leads to cancer. Intestinal metaplasia does not occur in all individuals who have a columnar-lined esophagus. In patients who develop intestinal metaplasia, there is evidence of a long interval between columnar transformation

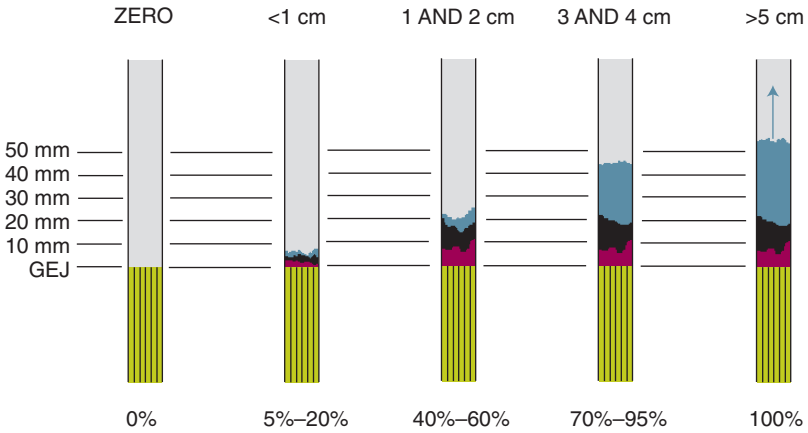


Figure 1–17 The prevalence of intestinal metaplasia increases as the length of columnar-lined esophagus increases. When the length is less than 1 cm, approximately 5% to 20% of patients have intestinal metaplasia, depending on the type of population studied. At 5-cm length of columnar-lined esophagus, intestinal metaplasia is almost invariably found. *GEJ,* Gastroesophageal junction. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa, with lines denoting rugal folds.

of the esophagus and the occurrence of intestinal metaplasia in cardiac mucosa (see Figure 1–6).

Unlike cardiac transformation of squamous epithelium, intestinal metaplasia occurs maximally at a point farthest away from the gastroesophageal junction. This is shown by two well-known facts: First, the prevalence of intestinal metaplasia tends to be highest in patients with the longest segments of columnar-lined esophagus[7] (Figure 1–17). At the present time, virtually 100% of patients who have a columnar-lined segment measuring 5 cm in length will have intestinal metaplasia. In comparison, approximately 15% of patients with less than 1 cm of columnar-lined esophagus demonstrate intestinal metaplasia. Second, in a patient who has columnar-lined esophagus with intestinal metaplasia, there is a constant zonation of columnar epithelial types[8,9] (see Figure 1–17). The intestinal metaplasia occurs most proximally adjacent to the squamocolumnar junction and extends downward for a variable distance. Non-intestinalized columnar epithelia line the distal region of the columnar-lined segment.

The occurrence of intestinal metaplasia is favored at points farthest from the gastroesophageal junction, which proves that this is not a direct, acid-induced change. The esophagus is normally pH neutral. When reflux occurs, a pH gradient is set up wherein the pH progressively increases from the gastroesophageal junction (where pH is gastric baseline and therefore the lowest) as one goes in a cephalad direction in the esophagus (Figure 1–18). This gradient is dependent on the volume of reflux; the higher the volume, the longer the pH gradient. The time exposure of the esophageal epithelium to refluxate is a measure of the number of reflux episodes, clearing of the esophagus, and volume of reflux. The probability of any acid-dependent event, such as cardiac metaplasia of squamous epithelium, is maximal in the most distal esophagus, which must be affected before the more proximal esophagus is affected (see Figure 1–14). The distribution of intestinal metaplasia is exactly the reverse of that expected from an acid-induced event (see Figure 1–17).

The fact that intestinal metaplasia occurs in 100% of people who have a columnar-lined esophagus of more than 5 cm must mean that the actual agent responsible for the transformation is ubiquitous in gastric juice. It is only that

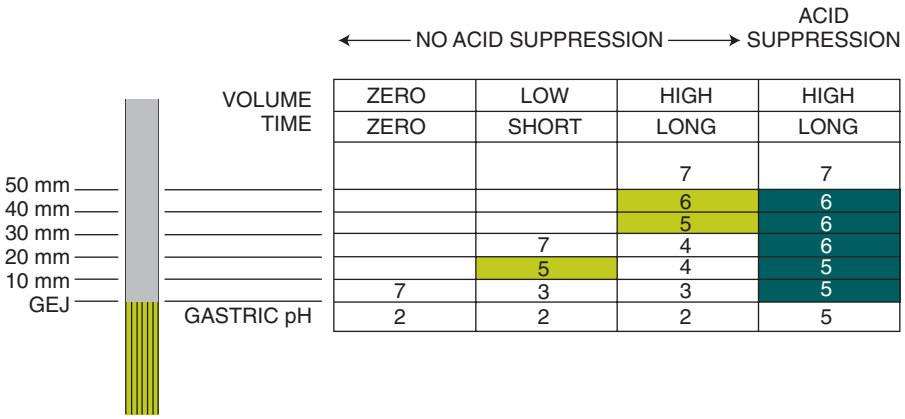


Figure 1–18 Differences in gastroesophageal pH gradient in three patients. The first column on the left shows a patient with no reflux; there is a sharp pH gradient at the gastroesophageal junction *(GEJ)*. The second and third columns show increasing volumes of reflux; the pH gradient widens with pH neutrality being reached increasingly more proximally in the esophagus. Note that the time exposure of the esophageal mucosa to refluxate is directly proportional to reflux volume. In the right column is the same patient in column three after acid-suppression therapy has increased gastric pH to 5; the esophagus is exposed to a much larger segment where the pH is 5–6 than before treatment.

a certain milieu is necessary for this ubiquitous molecule to induce intestinal metaplasia in cardiac mucosa.

In normal patients without any reflux, an effective lower esophageal sphincter causes this pH gradient to be sudden at the gastroesophageal junction, passing from the baseline gastric acidity to neutrality over a very short distance (see Figure 1–18). When reflux occurs, the gradient expands, and neutral pH is seen higher in the esophagus. As the volume of reflux increases, two things happen. The cells are exposed to refluxate for an increasing time and the more proximal regions of the esophagus are subjected to a pH that is less acidic than that in the more distal esophagus.

Intestinal metaplasia tends to occur in patients who have severe reflux disease compared with patients who do not have intestinal metaplasia. This suggests that a high volume of reflux is required to provide the necessary time exposure of the cell for intestinal metaplasia to occur. At this volume of reflux, the pH level is highest most proximally. Only patients who have cardiac mucosa at the critical proximal point in the esophagus will develop intestinal metaplasia.

This can be best explained by examining patients with mild reflux and severe reflux (Figure 1–19). The patient with mild (low-volume) reflux will have a short segment (<1 cm) of cardiac mucosa in the most distal esophagus. When reflux occurs, infrequently and in small volume, the time exposure is inadequate to cause intestinal metaplasia, even though there may be a point in the esophagus that has the correct pH at which the change is induced. The likelihood of intestinal metaplasia in this patient is low (15%). With a slightly higher reflux volume, the alkalinity needed to induce intestinal metaplasia is at a point above where cardiac metaplasia is present (see Figure 1–19).

In contrast, the patient with severe reflux will have a longer segment of columnar-lined esophagus (shown as 3 cm). The frequent, high-volume reflux will result in a long exposure of the cells to refluxate molecules. There is adequate time for the intestinal metaplasia to be produced in the cardiac mucosa. *The fact that intestinal metaplasia favors the proximal over the distal segment of columnar-lined esophagus must mean that intestinal metaplasia of cardiac mucosa is promoted by an alkaline environment in the esophagus.*

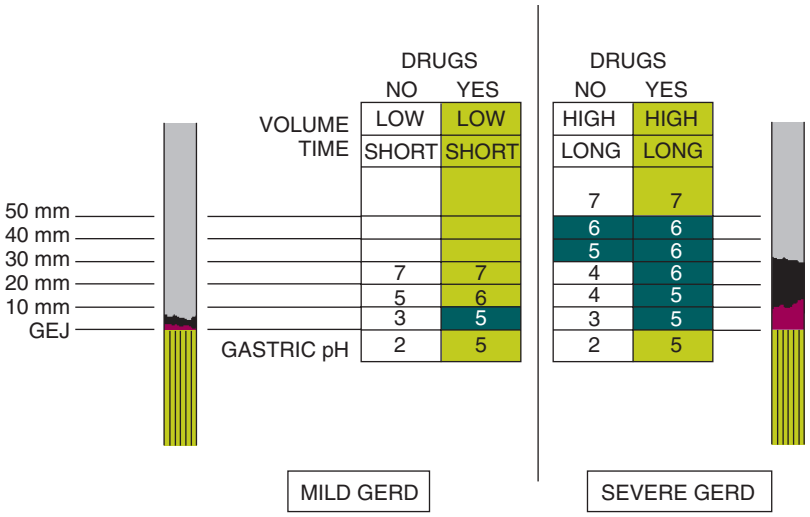
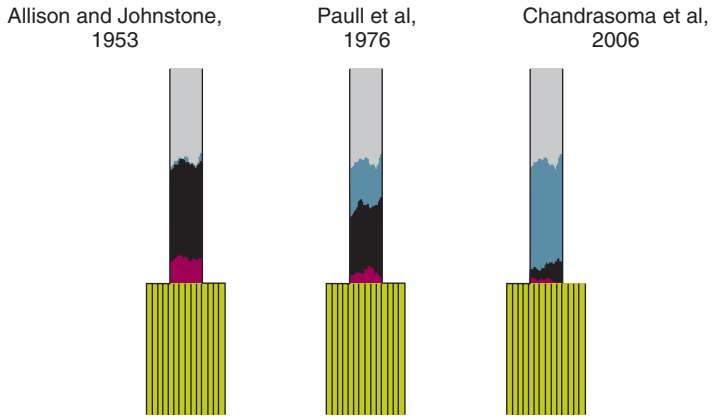


Figure 1–19 pH gradients in two patients with mild and severe reflux. The severity of reflux primarily determines squamous transformation to columnar epithelium and is greater in the patient with severe reflux, shown to occur with a pH less than 5 without acid suppression. If this patient is given acid-suppressive drugs to increase his gastric pH to 5, the pH milieu in the esophagus changes toward greater alkalinity, tending to promote intestinal metaplasia in the cardiac mucosa that is present. *GEJ,* Gastroesophageal junction; *GERD,* gastroesophageal reflux disease. *Black,* Cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa, with lines denoting rugal folds.

The use of acid-suppressive drugs results in an increased baseline gastric pH (the yellow boxes in Figure 1–19). In a patient with a columnar-lined esophagus, the pH gradient shifts with acid suppression such that the alkalinity of the more distal esophagus increases. In patients who did not have intestinal metaplasia before acid suppression, this shift would promote intestinal metaplasia (both patients shown in Figure 1–19). In patients who already had intestinal metaplasia limited to the proximal region of the columnar-lined esophagus, acid suppression would cause the intestinal metaplasia to involve increasingly distal regions of the columnar-lined segment (intestinal metaplasia is not shown in Figure 1–19).

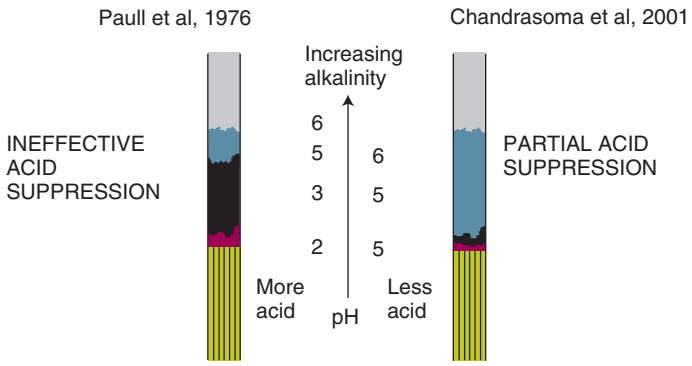
There is some historical data to support this. Comparison of the amount of intestinal metaplasia within the columnar-lined esophagus has shown an increase over the past five decades (Figure 1–20). In Allison and Johnstone's original description in 1953,[10] intestinal metaplasia was reported in only one patient among many patients with columnar-lined segments that reached the arch of the aorta. This should not be attributed to a failure of the pathologist to identify goblet cells; it is quite clear from studies that histology at that time was as good, if not better, than it is now. If goblet cells were present, they would have been reported. In 1976, Paull et al[8] from Harvard mapped the epithelia in patients with columnar-lined esophagus. It is clear that the extent of intestinal metaplasia in those patients is significantly less than reported by us in 2006.[11] Some patients in the report by Paull et al[8] did not have intestinal metaplasia in very long segments of columnar-lined esophagus, and rarely did the intestinal metaplasia reach the lower esophageal sphincter zone.

The most probable conclusion from these data is that as the effectiveness of acid suppression has increased over the past five decades, it has caused an increase in the prevalence of intestinal metaplasia in columnar-lined esophagus and has increased the amount of intestinal metaplasia within the columnar-lined esophagus (Figure 1–21). Intestinal metaplasia now occurs in the distal region of the esophagus much more than it did in the past. This is



FREQUENCY OF IM	VERY RARE	LESS COMMON	INVARIABLE
EXTENT OF IM	NOT REPORTED	LIMITED TO PROXIMAL	EXTENSIVE

Figure 1–20 Comparison of historic data relating to the amount of intestinal metaplasia *(IM)* present in long segments of columnar-lined esophagus. Evidence suggests that the amount of intestinal metaplasia has increased from the time columnar-lined esophagus was first reported by Allison and Johnstone in 1953, through 1976 as reported by Paull et al, to the present. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa, with lines denoting rugal folds.



Gastric baseline pH	2–3	4–6

Figure 1–21 The cause of the historical difference between the amount of intestinal metaplasia in a columnar-lined esophageal segment of similar length is most likely due to the change in the esophageal pH milieu induced by acid suppression. The increased effectiveness and use of acid-suppressive agents necessarily results in a shift of esophageal pH toward alkalinity. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa, with lines denoting rugal folds.

explained by the shift in the esophageal pH toward increasing alkalinity in the distal esophagus by acid-suppressive drugs (see Figures 1–18 and 1–19).

Step 3: Carcinogenesis in Intestinal Metaplasia

The final stage in the reflux-adenocarcinoma sequence is the production of mutations in the cells of the esophageal epithelium that is marked by the presence of intestinal metaplasia. If one assumes that this process results from the action of a luminal carcinogen, the culprit must be present in the gastric

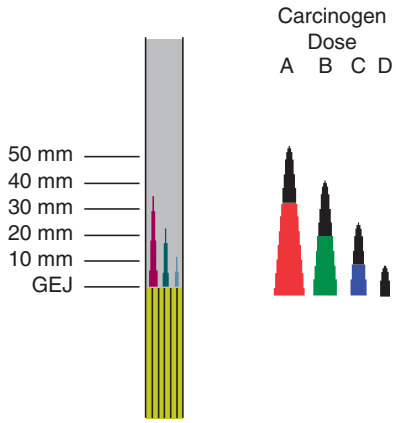


Figure 1–22 Different carcinogen doses in four patients, progressively decreasing from patient *A* to patient *D*. The effective carcinogen dose reaches a higher level in the esophagus in patient *A* than *B* and *C*. Patient *D* has such a low carcinogen dose in his refluxate that there is no effective carcinogenesis. *GEJ,* Gastroesophageal junction.

juice of patients who develop carcinoma. The fact that not everyone with Barrett esophagus develops carcinoma suggests that the carcinogen is not present in adequate dosages in all people. It is likely that the dose of carcinogen is the major factor that determines the likelihood of cancer. This is suggested by the observed patterns of adenocarcinoma. Some patients with very long segments of Barrett esophagus remain stable without dysplasia or cancer over decades of surveillance; these patients behave as if they had no carcinogens. In contrast, other patients develop cancer at a young age with very short segments of Barrett esophagus; these are likely to have high carcinogenicity.

Reflux-induced carcinogenesis requires three things:

1. The appropriate target cell in the esophagus; this is marked by the presence of intestinal metaplasia. Any part of the esophagus that is lined by non-intestinalized columnar epithelium or squamous epithelium is not susceptible to carcinogenesis.
2. Presence of carcinogen in the gastric juice. The nature of the carcinogen is unknown but is suspected to be derived from bile acid metabolism in the stomach in patients who have duodenogastric reflux.
3. Delivery of the carcinogen in adequate dosage to the target cell. The delivery of carcinogen is by reflux. If it assumed that this is a carcinogen that interacts directly with the target cell, the maximum dose of carcinogen is at the gastroesophageal junction and progressively declines in the more proximal esophagus. The actual level at which there is an effective carcinogen dosage in the esophagus will depend on the volume of reflux and amount of carcinogen in gastric juice (Figure 1–22). In any patient, however, the carcinogen dosage will be greatest at the most distal part of the esophagus.

This would mean that the likelihood of carcinogenesis in reflux disease will be promoted by any factor that causes the target cell (i.e., intestinal metaplasia) to move from the less carcinogenic proximal regions of the esophagus to the more carcinogenic distal region (Figure 1–23). In Step 2, I have shown how acid suppression can have this exact effect. There is now a strong theoretical reason for the epidemiologically demonstrated association between use of acid-suppressive drugs and esophageal adenocarcinoma.

The carcinogens responsible for reflux-induced carcinogenesis are suspected of being derived from bile acids that reach the stomach via duodenogastric reflux. There is a strong association between adenocarcinoma of the

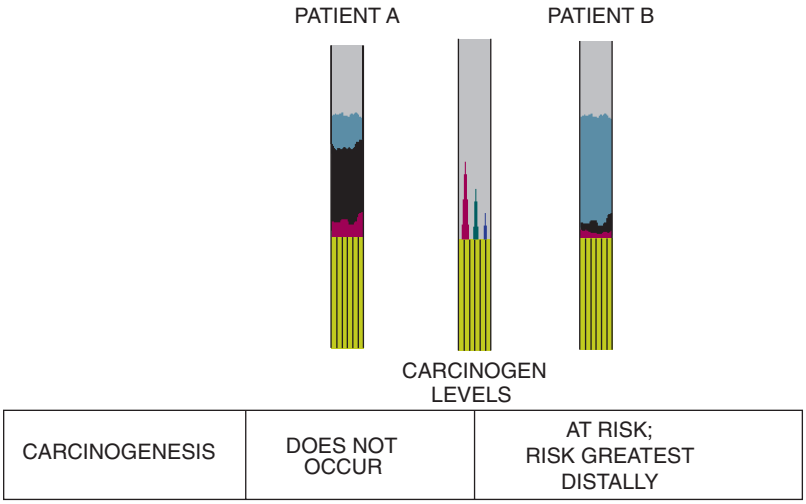


Figure 1–23 The relationship between the location of the target cell (only in intestinal metaplasia) and the effective carcinogen dose in the esophagus. If the area of intestinal metaplasia is limited to the proximal region of the columnar-lined esophagus, it does not receive an effective carcinogen dose; the patient will not develop cancer *(patient A).* If the intestinal metaplasia involves the distal region of the esophagus, the likelihood of progression to cancer increases because the carcinogen is delivered in adequate dose to the target cell *(patient B)*. *Blue*, Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa, with lines denoting rugal folds.

esophagus and the presence of duodenal contents in the esophagus as shown by a Bilitec probe in the esophagus.[12] The metabolism of bile acids in the stomach is highly pH-dependent. In normal patients, the gastric acidity (pH 1–3) causes the bile acids to precipitate and become inactive. In the pH range of 3–5, which is usual in most patients who are on acid-suppressive drug treatment, bile acid metabolism results in the production of soluble, un-ionized bile acid derivatives (Figure 1–24). These have been shown experimentally to enter esophageal epithelial cells and result in activation of genetic pathways that are associated with increased cellular proliferation.[13,14] Acid-suppressive drug therapy may therefore have an effect in promoting carcinogen formation in the stomach, thereby increasing the amount of the distal esophagus that becomes exposed to an effective carcinogen dosage at a given volume of gastroesophageal reflux.

The Future Without Change

The medical community has treated patients with reflux disease for the past five decades without understanding the mechanisms involved in producing the complex cellular changes that convert the squamous epithelium of the esophagus into an adenocarcinoma. They have been guilty of naïvely and incorrectly assuming that every manifestation of reflux disease, including Barrett esophagus and adenocarcinoma, results from the effect of acid. The single-minded and stubborn belief that acid suppression is the panacea to reflux disease has not changed, even as we have watched reflux-induced cancer rates explode. Although the pharmaceutical industry has increased its revenue to a staggering $13 billion per year, the number of people dying from reflux disease has increased from close to zero in the 1950s to approximately 20,000 Americans per year, and many more in other countries. This money has brought relief from heartburn for millions of people, but it has

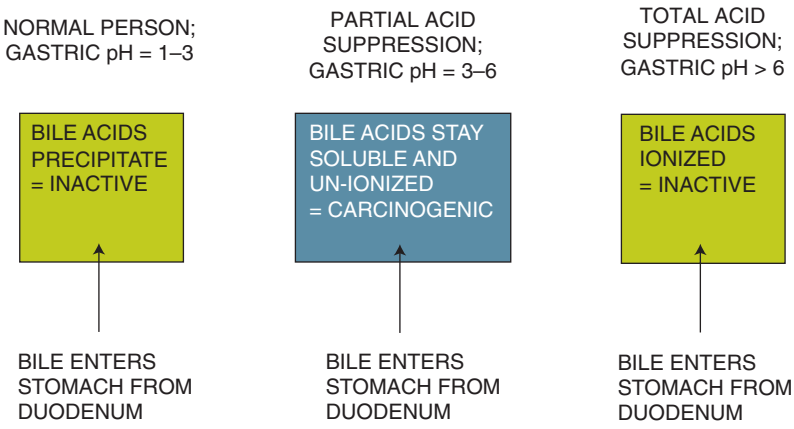


Figure 1–24 Influence of gastric pH on bile acids in patients who have duodenogastric reflux. The bile acids are inactive at highly acidic and neutral pH. In the intermediate pH range of 3 to 6, bile acids are converted into soluble, un-ionized metabolites that have been shown to be carcinogenic.

also brought death from reflux-induced and probably acid-suppressive drug–promoted cancer for many thousands. Surely, this is not an acceptable trade-off.

There is no reason to believe that the next three decades will be different than the last three if the present attitudes do not change dramatically and quickly. The expectation is for the pharmaceutical industry to produce the next and more effective acid-suppressive drug and for physicians to use this aggressively to treat patients with reflux disease in the hope that things will magically improve. The drug industry can be expected to persuade the government that more of these drugs should be sold over the counter to minimize health care costs. Direct marketing of these drugs to patients will cause them to treat themselves and avoid seeking medical care. The drugs will relieve their symptoms and improve their quality of life in the short term. Without public education, they will remain oblivious that they may harbor a disease that can produce cancer and death. As long as we define "cure" as the relief of symptoms, these drugs will be regarded as miracle drugs because of their efficacy. These people would be horrified if they knew that their acid-suppressive drugs are improving the painful but relatively harmless stage of their disease and potentially aggravating the silent, but ultimately fatal, stages of their disease. It is only when we define cure by the number of deaths or cancers that occur as a result of reflux that these drugs will be recognized as abject failures.

There should be no expectation that cancer incidence from esophageal adenocarcinoma will decline if we continue to do what we are doing now. We must work on the expectation that the rate of increase will continue. If we are wrong, there is no penalty. If we wait and expect it to level off, we may find ourselves in 2037 with another sixfold increase in incidence. Such an increase would mean that the annual incidence of reflux-induced cancer would be nearly 150,000 per year and the death rate (assuming no improvement in survival, which is probably not a good assumption) will be 120,000 per year. Cancer treatment will likely involve radical surgery and toxic chemotherapy, which is a high price to pay for survival. The optimistic viewpoint that a simple cancer cure will emerge in the next few decades is uncertain and unpredictable.

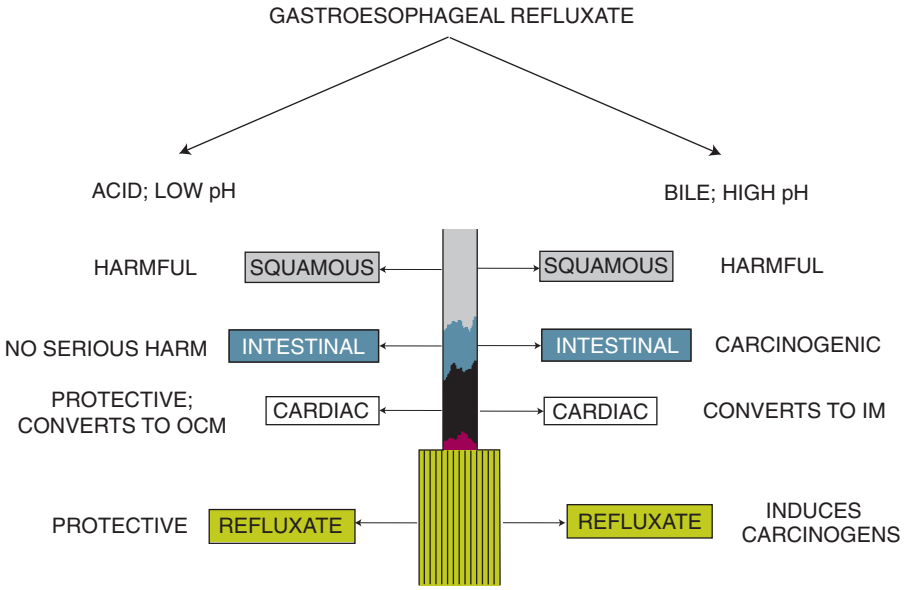


Figure 1–25 Elements in the refluxate have different effects on different components in the esophagus. Acid and a low pH damage squamous epithelium and induce cardiac metaplasia. However, they have a protective effect on cardiac mucosa, causing it to transform into oxyntocardiac mucosa *(OCM)*. Bile and an alkaline pH induce intestinal metaplasia *(IM)* in cardiac mucosa and promote carcinogenesis in intestinal metaplasia.

Colorectal carcinoma presently has an annual mortality of more than 50,000 patients per year in the United States, which is higher than that for both breast and prostate cancer. Reflux-induced adenocarcinoma has a significant mortality. There is a huge public awareness of and recommended and effective prevention methods for colorectal, breast, and prostate cancer. In contrast, there is little or no public awareness that symptomatic reflux (heartburn) is a significant risk factor for cancer. If not now, when do we place the emphasis of this disease on the cancer that is associated with it, rather than look at it as a patient comfort issue? We are treating a killer disease with a drug that is aimed only at controlling pain; this is like treating a brain tumor with aspirin to relieve the headache associated with it.

The failure of the medical community to understand this disease is a significant contributor to this problem. Patients who are induced by a pharmaceutical company to take an over-the-counter acid-suppressive drug or are prescribed a medication by their physician have no understanding about the potential effect of the drugs. The naïve belief is that everything gets better. The lack of understanding of the cellular elements that are being treated is profound; there is no appreciation of the fact that different elements in the refluxate may have different effects on different tissue types (Figure 1–25). The acid-suppressive drugs simply remove the acid from the refluxate. Reflux continues relatively at the same volume in these acid-suppressed patients. Every epithelial cell within the range of the refluxate is exposed to every molecule, except the acid. These epithelial cells include those in squamous epithelium, intestinalized columnar epithelium (Barrett esophagus), and non-intestinalized columnar epithelium (cardiac mucosa). The only epithelium on which the alkalinization of the refluxate by acid-suppressive drugs has a positive effect is squamous epithelium (see Figure 1–25). This positive effect removes the pain of heartburn, heals erosions, and prevents deep ulcers and strictures. However, alkalinization of the refluxate has a negative effect on cardiac mucosa, causing it to undergo intestinal metaplasia at an increasing

distal point in the esophagus. This, by bringing the target cell ever closer to the effective carcinogen dose in the distal esophagus, promotes cancer.

Good intentions are often thwarted by unintended consequences. This has happened throughout history. Asbestos and thalidomide are obvious examples. It is important to understand that acid-suppressive drugs are not carcinogenic to the normal esophagus. Animal testing or even human testing will not bring out any carcinogenic effect unless the drugs are tested over a long period in patients who have columnar-lined esophagus with and without intestinal metaplasia. This is the test we have used on patients with reflux over the past three decades. The fact that the test has not been controlled should not result in the failure to recognize the association between the use of acid suppression and reflux-induced cancer. The safest course is to assume the two are related; the present course is to assume that some other unknown factor must be responsible for the association.

Can Reflux-Induced Adenocarcinoma Be Prevented?

The present attitude toward reflux-induced cancer is one of defeatism and futility because it is believed that nothing can be done to prevent its occurrence and increasing incidence. This is not true. If nothing else, it is likely that if the use of acid-suppressive drugs is minimized, it will have a significant effect on reversing the trend and decreasing cancer risk.

Prevention of reflux-induced adenocarcinoma is theoretically simple. The disease is believed to result from the interaction between molecules delivered to the esophagus by reflux and the esophageal epithelium. This has to happen over a very long period of time and is associated with a sequence of epithelial change that I have described earlier in this chapter. These steps occur over many decades in a patient's life. Cancer results only when carcinogens in reflux produce multiple genetic mutations in intestinal metaplasia. Therefore, if we decrease gastroesophageal reflux adequately before these genetic mutations have occurred, there should be a theoretical certainty that reflux-induced cancer will be prevented.

Simple surgical methods are available to decrease gastroesophageal reflux (Figure 1–26). The most common is a Nissen fundoplication, which is now generally performed laparoscopically. The procedure is not easy, but it is within the range of most trained surgeons. Nissen fundoplication creates a new valve-like effect at the gastroesophageal junctional region that decreases reflux. Decreasing reflux means that the exposure of the esophageal epithelium to all refluxate molecules decreases. Decrease in acid exposure is more effective in relieving the painful symptoms and erosions than even the most successful acid suppressive drugs. Unlike acid-suppressive drugs, however, the operation has the theoretical potential to stop all other molecular reactions that cause progression of changes of the esophageal epithelium in the reflux-to-adenocarcinoma sequence (see Figure 1–26).

It is important to define a successful operation in terms of its ability to decrease cancer progression. A successful operation is not one that relieves symptoms and improves the quality of life. This can happen even with a relatively small decrease in the amount of reflux, because a slight reduction in acid exposure of the esophageal epithelium can relieve symptoms. A successful operation does not completely eradicate reflux. The new valve that can be created by current surgical techniques is never as effective as the lower esophageal sphincter, which prevents reflux completely without causing dysphagia because of its ability to maintain tone and relax completely at the appropriate moment of swallowing. If the new valve is designed to prevent

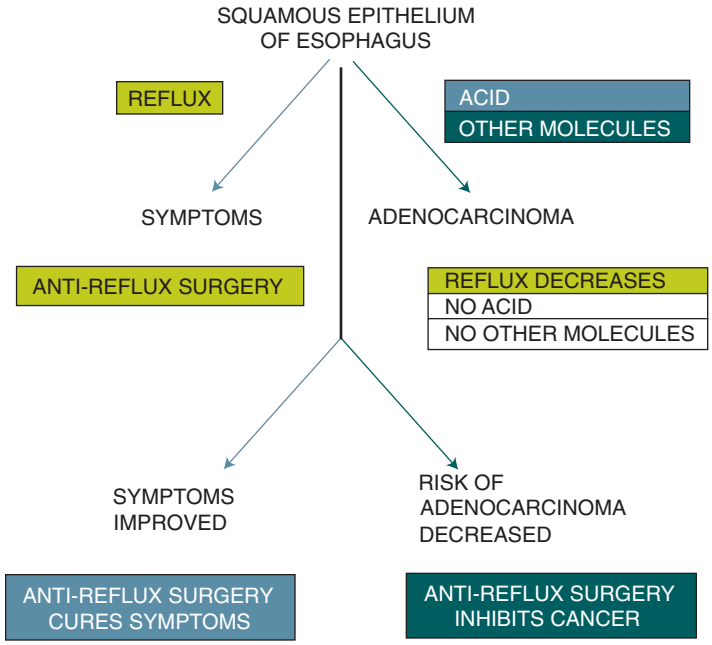


Figure 1–26 Outcomes in patients with reflux disease treated by anti-reflux surgery, which decreases reflux and prevents the target cells in the esophagus from being attacked by both acid and every other molecule in the refluxate. Anti-reflux surgery dramatically decreases symptoms and cures erosive esophagitis. It is also associated with a decrease in the incidence of adenocarcinoma. By decreasing all reflux, surgery removes all refluxate molecules that are responsible for the cancer.

reflux completely, it must also interfere with swallowing and cause dysphagia, because it has no ability to relax during swallowing. The operative technique therefore aims at creating a new valve that minimizes reflux without causing dysphagia. A successful anti-reflux operation decreases reflux sufficiently to normalize the 24-hour pH test, which is an accurate measurement of the amount of reflux. A failed operation is one that does not normalize the 24-hour pH test. An operation should not be called a failure if the patient continues to be symptomatic. Many symptoms unrelated to reflux occur after surgery; unless the symptoms are proven to be associated with an abnormal 24-hour pH test, the operation must not be declared unsuccessful. Many patients are placed too easily on acid-suppressive drug treatment based on symptoms without a 24-hour pH test. This is not appropriate. The aim of anti-reflux surgery is to minimize reflux so that progression of epithelial changes in the reflux-to-adenocarcinoma sequence can be prevented; the primary aim is not the control of symptoms. The presence of symptoms after surgery is a reason for concern that the anti-reflux operation has not met its primary objective; it should lead to a 24-hour pH test.

The literature strongly suggests that a successful anti-reflux operation is necessary to prevent progression in the reflux-to-adenocarcinoma sequence. It is much easier to find patients who have progressed to cancer after surgery that has failed to normalize the 24-hour pH study than patients who have had a successful anti-reflux operation. Normalization of the 24-hour pH test does not mean a cessation of reflux. A normal 24-hour pH test is defined as the detection of a pH less than 4 by a pH probe placed in the esophagus 5 cm above the upper limit of the lower esophageal sphincter for a period exceeding 4.5% of the 24-hour test (4.5% of a 24-hour period is 64 minutes, which means that patients with an anti-reflux operation defined as successful can

have a surprising amount of reflux). Even with anti-reflux surgery, the esophageal epithelium is not completely sequestered from harmful refluxate molecules. It is important for the surgical establishment to continue to improve this surgery to decrease reflux to the lowest possible level without causing dysphagia. It is only when surgery eradicates reflux completely that it will have a theoretical expectation of completely preventing reflux-induced adenocarcinoma. Until then, we are looking for a decrease in the incidence, not the complete removal of risk.

Anti-reflux surgery is likely to be more effective in preventing adenocarcinoma when the surgery is performed earlier than later in the reflux-to-adenocarcinoma sequence. At the present time, anti-reflux surgery is limited to the more complicated cases, such as patients with unsuccessful medical treatment and complex disease. These patients are likely to be at a more advanced stage in the cancer sequence. Some of these patients may have "prevalent cancers." These are defined as the presence of all the genetic mutations necessary for cancer in the cells; these are cancer cells that are in the lag phase before they express the cancer phenotypically. They cannot be identified without an understanding of the exact genetic changes involved. If such a patient undergoes anti-reflux surgery, the prevalent cancer will express itself after the surgery. This usually occurs within 1 to 2 years but can occur up to 5 years later. Even if only some of the genetic mutations for cancer are present in the cells, the fact that reflux is not completely prevented leaves the possibility of progression to cancer in advanced cases presently treated with anti-reflux surgery. Studies that compare cancer rates of patients treated by acid-suppressive drugs and anti-reflux surgery are therefore likely to have a bias toward a greater risk of cancer in the surgery group because they are treated at a more advanced stage in the reflux-to-adenocarcinoma sequence. Only randomized prospective trials will provide the necessary answers.

If anti-reflux surgery is as effective, or more effective, than acid-suppressive drug therapy in relieving symptoms, and if it also has a beneficial impact on the epithelial changes in the reflux-to-adenocarcinoma sequence, surgery is preferable for the treatment of symptomatic gastroesophageal reflux. This is a theoretical "no-brainer." If performed early enough in the sequence of change, the operation will prevent cancer more effectively than acid-suppressive drugs.

Is there any evidence to support this theoretical certainty that successful anti-reflux surgery will prevent the progression of epithelial changes in the reflux-to-adenocarcinoma sequence (Figure 1–27)? Let us consider the three steps in the pathogenesis.

Step 1: Squamous Epithelial Damage and Cardiac Metaplasia

This step occurs very quickly at the onset of reflux disease, often at a young age and often before symptoms occur. No patient will be considered for anti-reflux surgery during this stage.

Step 2: Intestinal Metaplasia of Cardiac Mucosa

Oberg et al[15] reported that patients with non-intestinalized columnar-lined esophagus more than 3-cm long had a lower incidence of developing intestinal metaplasia after anti-reflux surgery than if they were treated with acid-

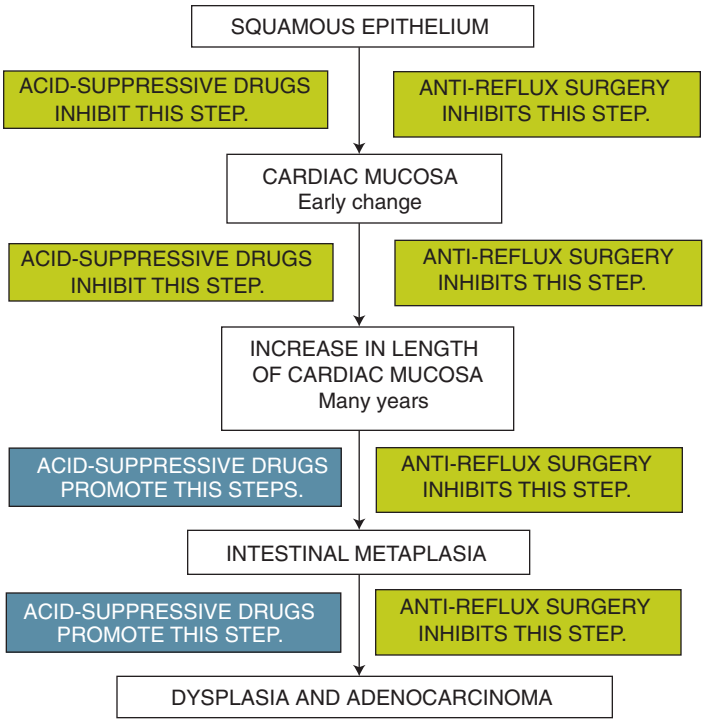


Figure 1–27 Comparison of acid-suppressive drug therapy and anti-reflux surgery in their impact on the three stages of the reflux-to-adenocarcinoma sequence. Unlike acid-suppressive drug therapy, which promotes the later steps, anti-reflux surgery inhibits all stages and prevents adenocarcinoma if performed early enough and if it is successful.

suppressive drugs. This provides evidence that anti-reflux surgery has a positive impact on this stage. All patients with cardiac mucosa in the esophagus prevented by the surgery from progressing to intestinal metaplasia will not be at risk for developing reflux-induced adenocarcinoma.

DeMeester et al[16] showed that anti-reflux surgery performed on patients with Barrett esophagus was associated with a reversal of intestinal metaplasia in a significant number of these patients. The reversal was most likely in patients with short-segment Barrett esophagus. Such a reversal would clearly be beneficial, removing the patient from the population at risk for developing adenocarcinoma.

Step 3: Carcinogenesis in Intestinal Metaplasia

The theoretical probability that anti-reflux surgery will decrease the progression of intestinal metaplasia to cancer has not been proven. Proof is a luxury that we do not have. The only method of proving this is to undertake a prospective randomized study. The duration of follow-up to give the study sufficient statistical proof will depend on the number of patients accrued. At the present rate of anti-reflux surgery, proof will be many years away. There is only one such study presently in progress.[17] The data, still without sufficient statistical evidence, show clearly that the incidence of high-grade dysplasia and adenocarcinoma is reduced after successful anti-reflux surgery defined by normalization of the 24-hour pH test.

Another method to suggest that anti-reflux surgery decreases cancer risk would be to demonstrate that adenocarcinomas occurred at a lower rate than

expected after surgery. This evidence supports the suggestion that anti-reflux surgery prevents adenocarcinoma. It is difficult to find a patient who has developed adenocarcinoma after a successful anti-reflux operation (success defined by normalization of the 24-hour pH test) 5 years after the procedure. Cancers are reported after successful anti-reflux surgery but tend to fit the expected profile of prevalent cancers. The maximal incidence is in the first 2 years after surgery and tails off by 5 years.

Hofstetter et al[18] reported the lack of progression to high-grade dysplasia and cancer in a group of patients with Barrett esophagus after 410 patient-years of follow-up. In this group, they also showed a reversal of low-grade dysplasia.

After considering these data, the logical conclusion is that anti-reflux surgery is superior to acid-suppressive therapy for treatment of reflux disease. It controls symptoms better and reverses and prevents progression of epithelial changes in the reflux-to-adenocarcinoma sequence. This is in stark contrast to acid-suppressive drug therapy, which promotes the epithelial changes that progress to cancer (see Figure 1–27).

Objections to Anti-Reflux Surgery

What then are the objections to anti-reflux surgery as the primary treatment of gastroesophageal reflux?

Cost

Anti-reflux surgery has a high initial cost. The procedure presently costs around $20,000 in the United States. This causes many health insurers not to approve the surgery for their members. This is irrational. If one assumes that the surgery is successful 85% of the time and that the alternative of lifelong, acid-suppressive drug use is avoided in these patients, the overall lifelong cost of treatment is actually less with anti-reflux surgery than drug treatment. The cost savings depend on the type of acid-suppressive drugs used, but in general, a successful surgery begins to provide a cost benefit after 4 to 5 years. Since the procedure is performed rarely, insurers will fail to recognize this because they will want to see a cost benefit within 2 years, which is the average duration of membership. An individual insurer is not willing to bear the high cost of the surgery for the benefit of a reduced cost for a future insurer. However, if anti-reflux surgery becomes more common, it is likely that insurers will approve the change because there will be an equal movement of patients treated by surgery among all the insurers, who will then collectively reap the long-term benefits of the reduced cost. Studies in countries with socialized systems of medicine such as Finland[19] and The Netherlands[20] show a decreased lifelong cost with surgery compared with acid-suppressive drug therapy. When one recognizes that insurers in the United States pay out many billions of dollars per year for acid-suppressive drug treatment of reflux disease, there is considerable room to maneuver. Ultimately, one cannot place a dollar value on the savings resulting from prevention of cancer in those presently doomed to develop this disease.

Public pressure will drive treatment. Insurers, including Medicare, will not be able to refuse public demand for a treatment that is shown to prevent cancer more effectively than the existing treatment. Just like public opinion drove the demand for mammography to prevent breast cancer, so it will drive the demand for anti-reflux surgery to prevent reflux-induced adenocarcinoma. The only question is when this will happen.

Surgical Mortality, Morbidity, and Failure

Even in its infancy, anti-reflux surgery is safe and has a very high success rate. Mortality is essentially zero, and complications occur in approximately 15% of patients who have an unsuccessful outcome. In most studies, the rate at which the 24-hour pH test is normalized after surgery is in the 85% to 95% range.[21] This represents the worst-case scenario. Anti-reflux surgery at present is limited to patients with the most severe reflux, patients who have complicated disease, and patients who fail medical treatment. When anti-reflux surgery is performed as the primary treatment for a patient with uncomplicated symptomatic reflux, when the experience with the procedure increases, and when technical innovations emerge, the morbidity and failure rate can be expected to decrease.

Despite all evidence to the contrary, a negative perception has been created regarding anti-reflux surgery. At best, it is suggested that it is often associated with failure and that many patients will still require acid-suppressive treatment. At worst, it has been suggested that there is an increased likelihood of death among patients who have had anti-reflux surgery.[22] Critical evaluation of this literature will reveal that these perceptions are false. Anti-reflux surgery is a highly effective treatment for reflux disease. In terms of safety, anti-reflux surgery has an excellent record that justifies its classification as a relatively minor operation that is performed laparoscopically with a very short recovery phase and hospital stay.

Not every patient will opt for anti-reflux surgery. There is a natural desire among people to avoid surgery. Surgery will ultimately be the choice of the patient. However, it is imperative that physicians provide patients with the correct information about the risks and benefits of avoiding treatment, acid-suppressive drug treatment, and anti-reflux surgery so that they may make an informed decision. At this time, the system is failing in this regard. We are minimizing the well-known risk of cancer in patients with reflux disease. If they are told the truth, the public reaction to acid-suppressive drugs and anti-reflux surgery is likely to change.

Feasibility

Anti-reflux surgery can be performed in almost any hospital in the world. The procedure is not difficult and can be learned quickly by a trained surgeon. It is most effectively performed laparoscopically and through the abdomen. Only very complicated cases require a thoracic procedure. The technological feasibility, although not presently available, can develop rapidly if demand increases. The immediate cost associated with the surgery is likely to result in a slow increase in demand unless something unexpected happens, such as sudden public recognition that acid-suppressive drugs promote cancer. If this occurs and results in a sudden withdrawal of acid-suppressive drugs from the market, anti-reflux surgery will become the only available method of treating patients with symptomatic reflux disease.

A Plea for an Aggressive Approach

Reflux-induced adenocarcinoma is a golden opportunity for cancer prevention. Instead of using a method that decreases the reflux (anti-reflux surgery), we have insisted on using acid-suppressive drugs, which do nothing to prevent the esophagus from being bombarded by every cancer-producing molecule in the refluxate. This course of action (or, more accurately, inaction) has resulted in a sixfold increase in the incidence of adenocarcinoma. We are

doing nothing in the middle of an epidemic. The price of our apathy is paid by the 22,000 to 24,000 Americans (and many more in Western Europe) who develop reflux-induced adenocarcinoma. We have watched these patients suffering with advanced local disease. They undergo radical esophagectomies, which are often followed by chemotherapy and radiation, with an overall expected death rate of 85%, often within 2 years—and we do nothing.

We may do worse than nothing by not recognizing the theoretical and practical evidence that suggests that acid-suppressive drugs may be promoting cancer and actually contributing to the causation of these cancers. We may be violating our basic motto: "Physician, do no harm."

We can do better. This is an eminently preventable disease. The following steps are a plea for a more aggressive approach aimed primarily at preventing cancer.

Aggressively Understand Reflux Disease at a Histologic Level

Partly because of the low level of understanding of the cellular events associated with gastroesophageal reflux, histology plays a very limited role in the diagnosis of reflux disease. Biopsies are considered of limited value in diagnosis of early reflux disease. Failure of biopsy results in a missed opportunity to understand the disease. The basis of the method described in this atlas is that all patients were biopsied according to a defined protocol, permitting histologic study of the earliest changes. I make a plea for an aggressive biopsy protocol for the study of patients with reflux disease.

Presently, biopsies are first indicated only when a columnar-lined esophagus is visualized endoscopically. The aim of biopsy is to diagnose Barrett esophagus, which is defined by the presence of intestinal metaplasia. If intestinal metaplasia is absent, the biopsy findings are considered irrelevant.

There is presently no histologic basis for the diagnosis of reflux disease; present histologic criteria are based on changes in squamous epithelium, whose sensitivity and specificity are so low as to make biopsy useless for diagnosis. Reflux disease is presently without any standardized definition. I will show that reflux carditis is a simple, reliable, and reproducible method of defining reflux disease at a cellular level. The ability to define reflux disease is fundamental to its understanding. I will also show that the present definition of Barrett esophagus is flawed and results in the failure to recognize the majority of patients who have Barrett esophagus.

The use of accurate histologic criteria in the diagnosis of all stages of reflux disease will make its study more reproducible and based on science. The use of histology is the basis of the new method I am proposing. Like many other diseases, the use of histologic criteria will bring order and clarity to the study of reflux disease and will replace the present confusion.

Aggressively Assess the Cancer Risk in a Given Patient

At the present time, we have no reliable method of defining the risk of adenocarcinoma. We know that the risk is associated with symptoms and increases with the severity of symptoms. However, we also know that adenocarcinoma can occur in asymptomatic patients.[4] We therefore have no method of reassuring anyone in the population that they are not at risk for developing adenocarcinoma.

I will describe a reproducible grading system that will permit recognition of risk and identify the approximately 60% of the population who are not at

any risk.[23] These patients have neither cardiac mucosa nor intestinal metaplasia. They can be safely treated with acid-suppressive drugs if they have symptoms. Patients with cardiac mucosa without intestinal metaplasia are not at imminent risk but can progress to develop intestinal metaplasia.

Patients with intestinal metaplasia (Barrett esophagus) are at imminent risk because they have an epithelium that is susceptible to carcinogenesis. The most advanced cases will be patients with dysplastic Barrett esophagus. These patients are at a risk whose immediacy increases with increasing grades of dysplasia. The presence of true dysplasia is the phenotypic expression of genetic mutations associated with cancer.

Aggressively Seek Patients at Highest Risk

The main failure of management of patients with reflux disease is the complete lack of interest to identify patients who are at risk for developing cancer. Although we know that patients who are symptomatic for reflux are at risk for cancer, we do nothing about it. We make the strongest acid-suppressive drugs available without prescription so that patients can "cure" themselves without seeking medical care. Those who seek care are prescribed acid-suppressive drugs on an empiric basis and "cured" of their reflux disease. Those among this "cured" group whose cellular changes are progressing to cancer will next seek medical care only when their cancer has become symptomatic. Approximately 90% of all reflux-induced cancers are found among these patients. The only saving grace for this management is that millions of patients not destined to develop cancer have been successfully treated with the least harm to them. In effect, the rationale of this treatment is that we sacrifice 22,000 to 24,000 Americans every year to adenocarcinoma and death so as not to trouble several million people. At what point, or incidences of cancers, does this not make sense? In 1975, when the number was 2500 per year, it probably was a reasonable course of action. In 2000, when the number was 16,000, we ignored it. Is it reasonable to ignore the 24,000 who will develop cancer in 2007? Do we wait until 2037 when the number may be 120,000?

The rationale for inaction is the attitude of futility and defeatism—there is no other alternative, because these deaths cannot be prevented, and if they cannot be prevented, we can do nothing. I believe this rationale has two fatal flaws:

1. The acid-suppressive drugs used to "cure" the millions of patients with symptomatic reflux are likely promoting cancer in some of them. This should not be acceptable.
2. It ignores the fact that a better method of treating reflux disease exists and that it very likely prevents the occurrence of cancer. An aggressive approach to this disease will cause a massive change in attitude to favor anti-reflux surgery over acid-suppressive drugs in the treatment of reflux disease.

If anti-reflux surgery becomes the primary treatment choice for reflux disease, a need will emerge to seek people in the population who are at greatest risk for cancer. This is defined at the cellular level by the presence of Barrett esophagus and increasing degrees of dysplasia. It is important to recognize two facts in this regard:

1. Although the highest probability of Barrett esophagus occurs in the most symptomatic patients, totally asymptomatic patients can also be at the highest risk. Thus any detection method that uses symptoms of reflux to

target the population at risk will have the highest yield but a significant failure rate.

2. There is no way to identify risk short of endoscopy and biopsy.

If we are to aggressively seek patients at risk, endoscopy and biopsy must be emphatically recommended. If we are interested in a high yield of patients at risk, we must target symptomatic patients. This is an excellent first population to target because it is composed of patients who will require lifelong treatment with acid-suppressive drugs with their cost and cancer-promoting danger. However, if we are interested in identifying everyone at risk, some kind of screening program is necessary. This is not likely to have a high yield and is an expensive proposition, because these patients do not presently need treatment. Because they are not being treated with acid-suppressive drugs, these patients are at least not having their cancers promoted by current treatment standards. Screening asymptomatic individuals for Barrett esophagus is not urgent or even likely to be feasible at this time. It will be considered in the future if reflux-induced cancer rates continue to increase. Demographic data that are associated with reflux-induced adenocarcinoma such as race (white), sex (male), age (more than 40 years), and socioeconomic level (more affluent) can increase yield but are unlikely to be used because of the relative low specificity.

The magnitude of the problem is daunting. It has been shown that 40% of the adult population in the United States has symptoms of reflux, and 5% to 15% have Barrett esophagus. This amounts to approximately 10 million to 15 million people in the United States who are at significant risk for reflux-induced cancer if "significant risk" is defined as the presence of Barrett esophagus.

Once a decision is made to actively seek patients at risk for cancer, it is critical to bring them to a point of medical care in which endoscopy and biopsy can be performed. There is no other way to identify high-risk patients. This will require public education that symptoms of reflux are a danger sign for cancer similar to a breast lump or rectal bleeding. Education can consist of requiring pharmaceutical companies to place labels on acid-suppressive drug packages that warn users that the symptoms being treated by the drug indicate a cancer risk and that the risk is not diminished if the symptoms disappear. The government should reconsider the availability of strong acid-suppressive drugs such as proton pump inhibitors and H2-receptor blockers and make them available by prescription only. These changes will result in an increased awareness and will convince at least the more concerned and severely symptomatic patients to consult a physician.

The primary care physicians who are the first contact for these patients must be taught that endoscopy is mandatory for all patients with symptoms of reflux. This must become a rule similar to mandating colonoscopy for patients with rectal bleeding. This will finally achieve the goal of bringing the symptomatic patient to a point where a decision can be made to perform endoscopy.

If endoscopy is performed under present practice guidelines, which mandates biopsy only when a columnar-lined esophagus is visualized at endoscopy, the yield is likely to be low. In Chapter 7, I will show that adoption of a suitable biopsy protocol will increase the yield of Barrett esophagus considerably. If a biopsy protocol is to succeed in the busy community setting, it must be simple and quick. I will show that a single four-quadrant biopsy at the squamocolumnar junction is adequate for most individuals. This biopsy protocol is designed to provide the following information based on the new information:

1. It will permit the diagnosis of reflux disease histologically.
2. It will permit assessment of the severity of reflux disease.
3. It will permit grading of patients according to their risk for cancer.

This information, based on well-defined, simple, and reproducible histologic criteria, is essential for correct recommendations and decisions.

There are two possible screening situations for patients who do not present with symptoms of reflux:

1. Patients who have an upper endoscopy for any reason. These patients represent a free screening opportunity. If the recommended biopsies are taken, the patient can receive information regarding the reflux-induced cellular changes that are present with minimal added effort and cost.
2. Patients who present for colonoscopic screening for colorectal cancer.[24] These patients are an affluent and educated group who are showing an interest in cancer prevention. A screening upper endoscopy with the recommended index biopsy can be added to the colonoscopy with minimal additional discomfort and cost with the same sedation. This is also the demographic group that is at highest risk for reflux-induced adenocarcinoma.

Although the information obtained by enlightened endoscopy and biopsy is useful to all people, it will be most valuable to patients who are sufficiently concerned about their cancer danger and who opt for anti-reflux surgery as a cancer-preventing method. Careful discussion before endoscopy can identify these patients with an understanding that anti-reflux surgery will be precipitated if pre-defined risk factors are found.

Aggressively Treat High-Risk Patients

When risk has been defined accurately by endoscopy and biopsy with the new proposed grading system, a decision can be made to aggressively treat patients at risk for cancer with anti-reflux surgery. A change from the present passivity to an aggressive approach will entail thinking along the following lines:

Barrett Esophagus with High-Grade Dysplasia

High-grade dysplasia is a term applied to the phenotypic expression of genetic changes of cancer except the mutation that gives the cells the capability of invasion. Without invasion, there can be no metastasis. The older term for high-grade dysplasia was "carcinoma in-situ." High-grade dysplasia may produce a visible lesion (e.g., plaque, nodule, or erosion) or be flat and not visible at endoscopy.

At present, there is controversy about whether these patients should be treated with a limited esophagectomy (vagal-sparing, transhiatal), some other form of ablation (endoscopic mucosal resection, radiofrequency ablation, or photodynamic therapy), or carefully followed with frequent endoscopy and multiple biopsies. There are two things to be considered in the management of high-grade dysplasia:

1. The presence of unsampled invasive carcinoma. If this is present, the patient will not be well served by any treatment short of esophagectomy or total ablation of the entire area of involvement. The presence of invasive

carcinoma is treated very poorly in many studies that advocate follow-up of patients with high-grade dysplasia. These patients develop cancer within 1 year of the original diagnosis and are discounted in these studies as "prevalent cancers."[25,26] This is not correct, because the decision to follow these patients delayed appropriate treatment for their prevalent cancer. This is a negative outcome that must be reported in such studies; instead, they simply drop out as irrelevant.

2. The imminence of invasive cancer. This is not known with any degree of certainty. However, most studies show a significant number of invasive cancers arising within 5 years of original diagnosis. The incidence of any invasive carcinoma transforms a patient who could have been treated effectively with a limited esophagectomy or endoscopic mucosal resection to a candidate for more radical surgery with a higher morbidity. Nonsurgical ablative methods are appropriate only in patients who cannot tolerate surgery; the lack of a specimen for examination precludes establishing whether there was invasion associated with the high-grade dysplasia.

There is no other place in the human body where a diagnosis of high-grade dysplasia is simply followed until cancer develops. This is akin to sitting on a barrel of dynamite waiting for it to explode before addressing the problem.

In our experience, high-grade dysplasia has an extremely high risk of prevalent invasive adenocarcinoma if there is a visible lesion at endoscopy or if the high-grade dysplasia is present in multiple biopsy levels. In many studies that recommend follow-up as treatment for high-grade dysplasia, these two criteria are taken as an indication for esophagectomy. Unifocal high-grade dysplasia without a visible lesion has a lower risk of prevalent invasive cancer and is the only type of high-grade dysplasia for which follow-up is even considered worthwhile. Follow-up involves frequent endoscopy with four-quadrant biopsies at 1- to 2-cm intervals; if there is no commitment to this intense follow-up on the part of the physician and patient, it should not be undertaken.

Barrett Esophagus with Low-Grade Dysplasia or Without Dysplasia

These conditions are currently diagnosed during any upper endoscopy, either during a workup for symptoms suggestive of reflux or incidentally. An abnormal columnar-lined esophagus is seen endoscopically and a biopsy is taken that shows intestinal metaplasia with or without low-grade dysplasia. Low-grade dysplasia may also be found during surveillance for previously diagnosed non-dysplastic Barrett esophagus.

The diagnosis of Barrett esophagus is a recognized premalignant lesion and is an indication for surveillance. The presence of low-grade dysplasia evokes a variable amount of added concern, often leading to an increase in the frequency of surveillance. A patient with low-grade dysplasia has a higher risk of progressing to high-grade dysplasia and cancer than a patient without dysplasia.

Except for the frequency of surveillance, patients with Barrett esophagus are treated in a similar manner regardless of whether they have low-grade dysplasia. They are usually given acid-suppressive therapy regardless of whether they are symptomatic. There is absolutely no justification for using acid-suppressive drugs in asymptomatic patients, because there is no evidence that they have a positive impact. On the contrary, they probably promote the progression in the reflux-to-adenocarcinoma sequence.

In a more aggressive treatment plan, the presence of Barrett esophagus, with or without low-grade dysplasia, will be an indication for immediate anti-reflux surgery. In both symptomatic and asymptomatic patients, the primary aim of the surgery is to prevent progression in the carcinoma sequence. The indication is greater in patients with low-grade dysplasia because their dysplasia is the phenotypic expression of neoplastic transformation. In these patients, the success of the anti-reflux surgery must be confirmed by demonstrating that the 24-hour pH test has been normalized.

In symptomatic patients, the operation will have a bonus in that it relieves symptoms more effectively than acid-suppressive therapy, obviating the need for drug therapy in the 85% to 95% of patients in whom symptoms are relieved. Although the initial cost of surgery is high, the overall lifelong cost for this treatment is less than lifelong drug treatment in the symptomatic patient. In all patients, the reduction in cancer risk justifies the cost by preventing cancer.

Reflux Disease Without Barrett Esophagus

Anti-reflux surgery is the optimal treatment of symptomatic reflux disease for patients who have cardiac mucosa in the biopsy. The alternative is the way they are presently treated, with long-term, acid-suppressive drugs, which probably increase the likelihood of development of intestinal metaplasia, representing a progression in the reflux-to-adenocarcinoma sequence. If anti-reflux surgery is an alternative to lifelong acid-suppressive therapy, there can be a total cost benefit with surgery. In patients without intestinal metaplasia, the primary aim of anti-reflux surgery is relief of symptoms, which is achieved at a higher frequency than the 85% success rate defined by normalization of the 24-hour pH test. The benefit of surgery over acid-suppressive drug therapy is greatest in younger patients because of the long duration of expected acid-suppressive treatment needed with the attendant increased opportunity for cancer promotion. It is also likely that younger patients have less reflux damage to their distal esophagus, increasing the likelihood that surgery will be easier and therefore more successful.

The number of people who have cardiac mucosa associated with symptomatic reflux is unknown because cardiac mucosa is not currently considered an indication of a pathologic state. It is likely that 35% to 50% of the adult population has cardiac mucosa and that this correlates with the 40% of the adult population in the United States who suffer from heartburn. However, the exact number of patients with cardiac mucosa whose heartburn is of sufficient severity to require long-term, acid-suppressive drug use is unknown. These are the patients for whom surgery is likely to provide the most benefit and cost-effectiveness.

Asymptomatic patients with cardiac mucosa in their biopsy require no treatment. These patients are demonstrating their natural response to their reflux. We are not harming them or promoting cellular changes that promote progression in the reflux-to-adenocarcinoma sequence. The only requirement is to ensure that they have not progressed to intestinal metaplasia by a follow-up endoscopy and biopsy at a much later time (e.g., in 5 years).

Patients who do not have either cardiac mucosa or intestinal metaplasia in their biopsy can be safely treated with acid-suppressive drugs if they are symptomatic. Acid-suppressive drug therapy stabilizes the squamous epithelium, preventing columnar metaplasia and therefore benefits these patients. In the absence of cardiac mucosa, alkalinization of the refluxate does not promote intestinal metaplasia. There can be increased carcinogen production

in the stomach from bile acid metabolism, but this is harmless without intestinal metaplasia.

Expectation of Change

I hope that these new ideas will produce change rapidly. However, I have no control over the speed of change. Truth and proof are in the eyes of the beholder. Although I am convinced of the truth of everything that I state and believe and I provide evidence that proves these new concepts, their acceptance depends on the interpretation of the evidence by others.

This is best exemplified by the following story. I was driving Rodger Haggitt, probably the best gastrointestinal pathologist who has ever lived, from his hotel in Pasadena to the Los Angeles County Hospital. He had graciously accepted my invitation to present a paper at our Grand Rounds. He had listened to a presentation of my new ideas relating to reflux at a conference in Brittany a few months earlier.

"Para," he said, while we drove to the hospital, "your new ideas regarding cardiac mucosa and reflux are interesting."

I smiled and replied, "Interesting? I presume that means you do not believe a word I am saying and think I am crazy."

He grinned and said, "Yes, that is true. But what annoys me is that I cannot find a way to prove you are wrong."

I had the last word. "Rodger," I said, "the reason for that is that I am right. Just remember that just as you are judging what I say, I am judging you for the speed with which you accept this truth."

Rodger Haggitt was a true scientist; he is the one person that I would have been able to convince because he had a mind that was as open as it was sharp. His tragic death a few months later was a disaster that set back gastrointestinal pathology many decades.

I have presented many papers and given many lectures on these new ideas. There has never been any open disagreement or dissent. The general trend of opinion has slowly moved toward the truth that is presented here. My hope is that this book will accelerate the understanding of this disease. Time is of the essence; as we struggle, we are failing the 55 Americans who die every day from reflux-induced adenocarcinoma. We owe those who are destined to develop cancer in the future a speedy transformation of the way we treat this disease so that we can prevent their outcome. We need to do something. We need to try. We need to do better—quickly.

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CHAPTER 2

The Present State of Diagnosis of Reflux Disease

Reflux disease currently lacks a standard definition; reflux is in the eye of the definer. There is complete agreement only when the patient develops adenocarcinoma of the esophagus. Between reflux and adenocarcinoma is a profusion of terms that results in confusion and lack of uniformity among different studies (Table 2–1).

The diagnosis of gastroesophageal reflux disease is made entirely by clinical criteria of definition (Table 2–2). These include symptomatic diagnosis, a therapeutic test that depends on the relief of symptoms when acid-suppressive drugs are used, confirmatory physiologic testing with 24-hour pH monitoring, multichannel impedance tests, and endoscopic diagnosis. Histology plays no significant role in the diagnosis of gastroesophageal reflux disease without a visible columnar-lined esophagus; most such patients are managed without histologic confirmation. The first absolute indication for biopsy is the presence of a columnar-lined esophagus, when biopsies are required for diagnosis of Barrett esophagus, dysplasia, and adenocarcinoma.

A careful examination of the available evidence shows that none of the present modalities permits a reliably reproducible definition of gastroesophageal reflux disease. The present confusion is the result of a lack of disease definition; one person's reflux is another person's control. The reality is that gastroesophageal reflux disease can exist in a patient who does not have any symptoms, has normal 24-hour pH and impedance tests, normal endoscopy, and a normal squamous epithelium if biopsies are taken from the squamous-lined esophagus. Such a patient may manifest for the first time with reflux-induced adenocarcinoma of the esophagus. There is no accepted method at present that can identify this patient, and no effort is made to identify patients who will ultimately develop cancer.

This is a problem that urgently requires a solution. Without a definition and an accurate method of diagnosis, many of the data in the literature are unintelligible and scientifically without merit. I will show that the correct understanding of the pathophysiology of the disease permits accurate definition of the disease at the cellular level.

Presently Used Diagnostic Criteria of Reflux Disease

Symptom-Based Diagnosis

The vast majority of patients with reflux disease are diagnosed on the basis of symptoms and treated with acid-suppressive drugs. When symptoms are

TABLE 2–1 The Profusion of Conflicting Clinical Definitions and Terms Presently Used in the Diagnosis of Patients with Reflux Disease and Barrett Esophagus

Diagnostic term	Definition
Reflux disease	Presence of symptoms classical for reflux (heartburn, regurgitation) at a frequency that varies among experts (one to three times per day to month for 1 to 6 months)
Atypical reflux disease	Reflux disease with atypical symptoms—"dyspepsia," abdominal pain, cough, chest pain, hoarseness, asthma, post-nasal drip, pulmonary fibrosis, sinus congestion
Asymptomatic reflux disease	Reflux disease without symptoms (manifesting as Barrett esophagus, adenocarcinoma)
Erosive reflux esophagitis	Endoscopic erosions in squamous epithelium in a patient with symptomatic reflux disease
Non-erosive reflux disease	Symptomatic reflux disease with normal endoscopy
Columnar-lined esophagus	Presence of endoscopically visible columnar metaplasia of the esophagus; ignored unless intestinal metaplasia is present in a biopsy (Barrett esophagus)
Barrett esophagus (common definition)	Presence of intestinal metaplasia in a biopsy taken from an endoscopically visible columnar-lined esophagus
Barrett esophagus (definition still used, although rarely)	Presence of a columnar-lined esophagus >3 cm in length regardless of presence of intestinal metaplasia

TABLE 2–2 Present Criteria for Diagnosis of Gastroesophageal Reflux Disease

Criterion	Definition	Problems
Classical symptoms (heartburn and regurgitation)	Undefined as to which symptom, frequency, and duration	1. Variable definition 2. Misses patients with atypical and no symptoms
Atypical symptoms	A multitude of upper abdominal, chest, ENT symptoms	Symptoms are not specific for reflux disease; associations weak at best
Endoscopy	Erosive esophagitis, grades 1–4	Misses non-erosive reflux disease (endoscopy normal)
Newer magnification endoscopic techniques	Not standardized; subtle criteria described in patients with non-erosive reflux disease (NERD)	1. Rarely used 2. Changes are non-specific
Reflux esophagitis on biopsy	Squamous epithelial changes	Accepted criteria have low sensitivity (50%) and specificity (90%)
Ambulatory 24-hour pH test	Abnormal = pH <4 for 4.5% of the 24-hour period; composite scores	Assesses the cause of reflux disease, not the disease
Multi-channel impedance test	Defined by abnormal reflux episode numbers and duration	Assesses the cause of reflux disease, not the disease
Barrett esophagus	Intestinal metaplasia in a biopsy taken from a visible columnar-lined esophagus	Misses reflux disease without Barrett esophagus
Columnar-lined esophagus without intestinal metaplasia	Ignored; histology shows cardiac mucosa (carditis) and oxyntocardiac mucosa	Everyone agrees that this is caused by reflux, but it is not used as a diagnostic criterion of reflux. Why?

classical (regurgitation plus heartburn) and occur frequently (once a week or more), the diagnosis is highly specific. Endoscopy with biopsy of the squamous epithelium does not improve the diagnostic accuracy in these patients. Endoscopy is negative in more than 50% (so-called *non-erosive reflux disease*); biopsy of squamous epithelium does not show features of reflux in approximately 50%; and although physiologic testing frequently confirms acid exposure and increased reflux, it only confirms an obvious diagnosis.

When reflux symptoms are less typical and less frequent and regurgitation is not present, their diagnostic specificity decreases. Many other symptoms can simulate non-typical pain of reflux disease. In addition, atypical symptoms of reflux are numerous and varied. Because of this lack of specificity, a diagnosis of "possible reflux disease" can be made in many patients with vague symptoms. The very high frequency of gastroesophageal reflux makes this

reasonable. There is presently no reliable test that can be used to accurately confirm or deny the diagnosis of "possible reflux disease."

For any patient who complains of any symptom that could potentially be caused by reflux (e.g., upper abdominal pain, non-cardiac chest pain, hoarseness, chronic cough), it is not uncommon for that patient to be prescribed acid-suppressive drugs on an empirical basis by family practitioners, internists, or gastroenterologists. If these patients' symptoms respond to a trial of acid-suppressive drugs, this is taken as a confirmation of the reflux diagnosis. Many clinicians would consider this a successful therapeutic test and good clinical practice.

In fact, the trend has been toward the elimination of the physician in this process. The pharmaceutical companies have convinced the U.S. government that the most powerful acid-suppressive drugs should be made available to the consumer as over-the-counter medications. The pharmaceutical companies, through intense direct advertising to the consumer, encourage patients to treat anything they consider as "acid reflux" with a Mylanta, Tums, Zantac, Pepcid, or Prilosec, which are available on the nearest supermarket shelf (see Figures 1–9 and 1–10). The proton pump inhibitors, Prilosec, and the H2-receptor antagonists, Tagamet, Pepcid, and Zantac, are becoming as familiar to the public as aspirin and acetominophen. The pharmaceutical companies also directly market the newer, prescription-only proton pump inhibitors such as Protonix and Nexium, encouraging patients to "ask your physician" about these drugs. They complete the loop by intensive advertising to primary care physicians and gastroenterologists, who prescribe these drugs almost by reflex whenever they are faced with a symptom that cannot be explained easily and may represent reflux. Acid-suppressive drugs generate an estimated $13 billion in revenue per year for the pharmaceutical industry.

In many scientific publications that study gastroesophageal reflux disease, there is no definition of reflux disease. Such papers that do not define reflux disease relate findings to the presence of "heartburn" or some other defined symptom complex. A good example is Hirota et al[1] from Walter Reed Medical Center, which studies the clinical associations of "specialized intestinal metaplasia . . . of the esophagus and esophagogastric junction." In their methods, they state: "Patients were asked if they had ever experienced heartburn symptoms before endoscopy; heartburn was characterized as either (1) burning sensation that moves from the stomach up into the chest and back down, (2) a burning sensation in the chest, (3) a pain in the upper part of the stomach/midchest, or (4) a pressure feeling in the chest." It is unlikely that this is everyone's definition of heartburn, but at least these authors define what they mean by heartburn. The authors show in their results table that 63% of patients with long-segment Barrett esophagus, 83% of patients with short-segment Barrett esophagus, and 59% of patients classified as "specialized intestinal metaplasia of the esophagogastric junction" reported *a history of heartburn symptoms* compared with 62% of reference patients without specialized intestinal metaplasia. Gastroesophageal reflux disease is not defined in any part of their paper; the relationship of specialized intestinal metaplasia to reflux disease is not explored. The reader is left to assume that the relationship to "a history of heartburn symptoms" is equivalent to a relationship to reflux disease; this is not true.

Authors of clinical studies commonly use the term *symptomatic reflux,* as in Lagergren et al,[2] who demonstrated that 60% of patients with adenocarcinoma of the esophagus had symptomatic reflux. However, "symptomatic reflux" is not gastroesophageal reflux disease. There is no argument that the 40% of patients with adenocarcinoma of the esophagus in Lagergren et al's study who did not have symptomatic reflux suffered from *asymptomatic* gas-

TABLE 2–3 Definition of Gastroesophageal Reflux Disease in Selected Papers

Reference and source	Definition
Spechler et al, 1997; Harvard[3]	Presence of heartburn equal to or greater than 1 day per week without mention of regurgitation
Goldblum et al, 1998; Cleveland Clinic[4]	Presence of heartburn and/or acid regurgitation at least twice per week for at least 6 months
Lagergren et al, 1999; Sweden[2]	Presence of heartburn and/or regurgitation once per week (5 years before diagnosis of adenocarcinoma)
Kahrilas et al, 2000; University of Chicago[5]	Presence of heartburn equal to or greater than three times per week controlled by acid suppression

troesophageal reflux disease, because there is no other pathway to esophageal adenocarcinoma other than gastroesophageal reflux disease (I am discounting extremely rare cases of adenocarcinoma reported as arising in the mucous glands of the esophagus). *Clinical studies mask the absence of a definition of reflux disease.*

Very few studies in the literature define gastroesophageal reflux disease with a specific quantity of reflux symptoms–usually heartburn and/or regurgitation (Table 2–3). There is no consistency in the definitions in these studies, making comparisons meaningless. Thus, a patient defined as having heartburn at a frequency of once per week will be in the reflux disease group at Harvard[3] and Sweden,[2] but in the control group at Cleveland Clinic[4] and the University of Chicago.[5] What madness is this?

In a screening study by Rex et al,[6] the prevalence of heartburn in the study population presenting for colonoscopy screening was 40.9%; this broke down to 25.1% who had heartburn less than once per week, 6.4% once per week, 6.5% several times per week, and 2.7% daily. One should recognize that adjusting the definition of reflux by the frequency of heartburn can dramatically affect results of any study.

The Gastroesophageal Reflux Disease Activity Index (GRACI) score[7] attempts to quantitate the severity of reflux symptoms. Patients are asked to maintain a diary of symptoms for 1 week; the GRACI score is calculated by assigning weighted numbers to a variety of symptoms (e.g., heartburn, regurgitation, coughing, wheezing), their severity, and duration. The GRACI score ranges from 74 (no symptoms) to 172 (worst symptoms) with mean scores for mild, moderate, and severe symptoms being 93, 110, and 125, respectively.

When one recognizes that severe complicated reflux disease such as long-segment Barrett esophagus occurred in 37% of patients without any heartburn,[1] and 40% of patients who develop adenocarcinoma of the esophagus have no symptoms,[2] it becomes clear that severity of reflux symptoms has little correlation with the severity of reflux disease at a cellular level. One can compare a finding with the severity of reflux symptoms using a GRACI score or other measures of severity and duration of symptoms of reflux, *but we cannot define gastroesophageal reflux disease by its symptoms as long as there are asymptomatic individuals who develop the most significant manifestations of the disease.*

Diagnosis by Physiologic Testing

The "gold standards" for diagnosis are the 24-hour pH study using a pH probe placed in the distal esophagus via a nasogastric tube or implanted Bravo capsule and multichannel impedance testing with an impedance probe in the distal esophagus. The 24-hour pH studies accurately test the exposure of the

esophagus to acid at the point of placement of the probes. Impedance studies detect reflux episodes accurately regardless of the pH of the refluxate; they are useful in assessing reflux in patients who take acid-suppressive drugs in whom alkalinization of gastric contents makes the 24-hour pH test useless as a detection method for reflux.

These two tests have three serious problems:

1. They are limited by the point of placement of the probe. In the 24-hour pH test, the probe is placed 5 cm proximal to the lower esophageal sphincter (approximately 9 cm above the gastroesophageal junction); in impedance studies, the probe is 3 cm above the sphincter (7 cm above the gastroesophageal junction). When one recognizes that the maximum effect of reflux disease is in the most distal esophagus, it is quite possible that significant reflux disease can occur without the reflux reaching the level of the probes in these two tests. I compare this to taking the temperature at the wrist to demonstrate the effect of dipping a finger into hot water.
2. The establishment of normal values is very difficult. An abnormal 24-hour pH test is not defined as the presence of acid exposure. This is not feasible, because some acid exposure is present in virtually all people. An abnormal 24-hour pH study requires a pH less than 4 in the esophagus for more than 4.5% of the 24-hour period (i.e, more than 64 minutes of the day). This normal value was established as that amount of acid exposure associated with the presence of reflux symptoms.[8] It should not be surprising then, that significant cellular changes can be present in the esophagus in patients with normal 24-hour pH studies.
3. Both these tests assess reflux and not the cellular manifestations of the disease. This is akin to diagnosing actinic keratosis by the amount of exposure of the skin to ultraviolet radiation.

In general, though, studies that relate findings to 24-hour pH test results are more objective and interpretable than studies that relate findings to symptoms. Despite their problems, these tests provide a measurement of pH or change in impedance across the study group that remains consistent among patients because the study methods are well standardized. Studies that relate findings to these objective tests do not have the major problem of patient variability and subjectivity that exist in studies that relate findings to symptoms. The statement that a given finding has a correlation with the findings of a 24-hour pH test is valuable because it establishes the relationship of that finding with the amount of gastroesophageal reflux within the parameters of test limitations that I have just described.

The correlation between a finding and an abnormal 24-hour pH test does not mean that the finding is associated etiologically with acid. Acid is simply a marker for gastroesophageal reflux. Any molecule that accompanies acid in the refluxate can be responsible for the correlation. Similarly, the Bilitec probe, which detects bilirubin, is a marker for the presence of duodenal contents in the refluxate.[9] Correlation of a finding with an abnormal Bilitec study does not mean that bilirubin is the cause of the finding; any component of duodenal contents could be the culprit.

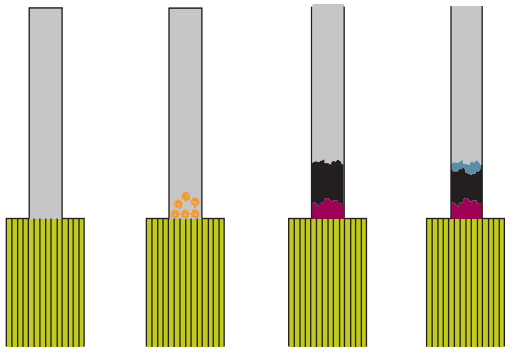
It should be noted that every gastroesophageal reflux disease study that I have participated in has used the correlation between the finding being evaluated and the result of the 24-hour pH test. For example, in one study, we established that the length of columnar-lined esophagus correlates with the severity of reflux[10] (Table 2–4). This study provides strong statistical evidence for a relationship between the amount of reflux (measured by the

24-hour pH study) and the length of columnar-lined esophagus, defined as the cumulative length of cardiac and oxyntocardiac mucosa, with and without intestinal metaplasia.

TABLE 2–4 Extracted Data from our Study[10] on the Significance of the Relationship of the Length of Columnar-Lined Esophagus to the Severity of Reflux as Measured by the 24-Hour pH Test*

Defining characteristics	Number of patients	Median	Range	IQR (Q_L, Q_U)
All patients	53	10.4	1.1–54.3	5.7, 20.5
CM+OCM >2 cm; IM+	15	30.6	3.6–54.3	16.1, 41.1
CM+OCM <2 cm; IM+	15	10.5	1.8–39.7	6.6, 20.5
CM+OCM <2 cm; IM–	23	6.1	1.1–18.2	4.2, 9.8

*This is a summary of pH data expressed as percentage of time pH is less than 4 in 53 patients (Normal = <4.5%).
CM, Cardiac mucosa; *OCM,* oxyntocardiac mucosa; *IM,* intestinal metaplasia.



Erosive esophagitis	No	Yes	No	No
Columnar-lined esophagus	No	No	Yes	Yes
Biopsy presently indicated	No	No	Yes	Yes
Intestinal metaplasia in CLE	N/A	N/A	No	Yes
Diagnosis	NERD	Erosive esophagitis	CLE	Barrett esophagus

Figure 2–1 Present classification of patients with classical symptoms of reflux disease. **A,** Patient with no endoscopic abnormality: no biopsies are recommended, and patient is diagnosed with non-erosive reflux disease *(NERD).* **B,** Patient with erosive esophagitis (*orange areas* are erosions in squamous epithelium); quantity of erosions used to grade severity of esophagitis. **C,** Patient with visible columnar-lined esophagus: biopsies are taken and do not show intestinal metaplasia. This patient has columnar-lined esophagus *(CLE)* but is not diagnosed as having reflux disease because cardiac mucosa *(black area)* and oxyntocardiac mucosa *(red area)* are not recognized at present as criteria for the diagnosis of reflux disease. **D,** Patient with intestinal metaplasia *(blue area)* in a biopsy taken from the visible columnar-lined esophagus; this patient has Barrett esophagus. *N/A,* Not applicable.

Endoscopic Diagnosis

Endoscopic diagnosis of gastroesophageal reflux disease is based on the presence of erosive esophagitis; this does not need histologic confirmation (Figure 2–1, patient B). The severity of reflux disease is graded endoscopically by changes in the squamous epithelium based on the extent of erosions (Los Angeles classification; Table 2–5; Figures 2–2, 2–3, and 2–4).

Patients with classical reflux symptoms are designated as having non-erosive reflux disease (NERD) if erosive esophagitis is not present (Figure 2–5;

TABLE 2–5 Los Angeles Classification for Grading Erosive Reflux Esophagitis	
Grade A	One or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds
Grade B	One or more mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds
Grade C	Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference
Grade D	Mucosal breaks that involve 75% or more of the esophageal circumference

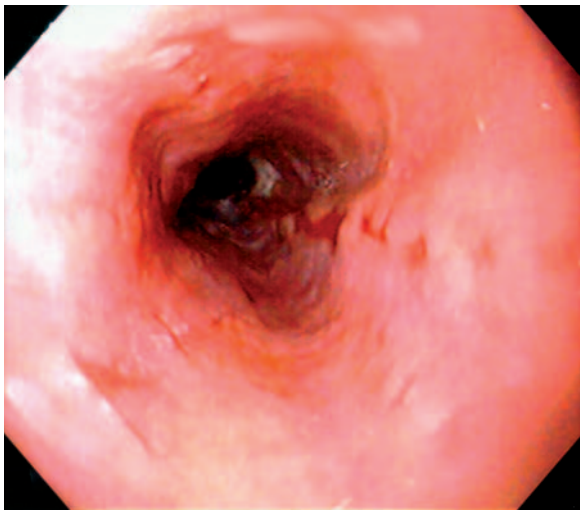


Figure 2–2 Endoscopy showing mild (Los Angeles grade 1) erosive esophagitis with erythema and a few small erosions in the squamous epithelium. (My thanks to Dr. Franz Martin Riegler of Vienna, Austria, for many of the excellent endoscopic images in this atlas.)

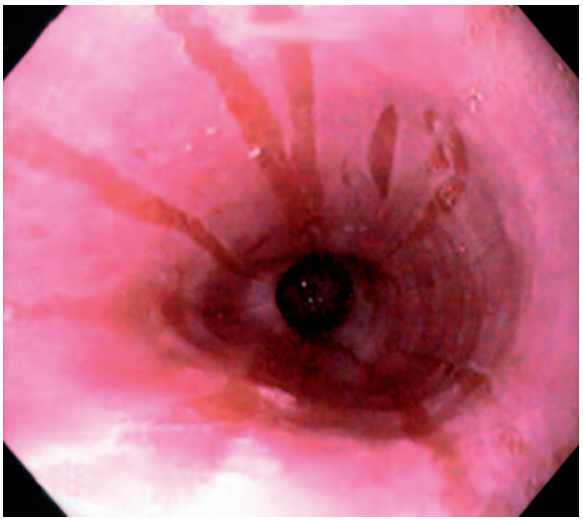


Figure 2–3 Endoscopy showing a greater degree of erosive esophagitis (Los Angeles grade 2) with confluent linear erosions.

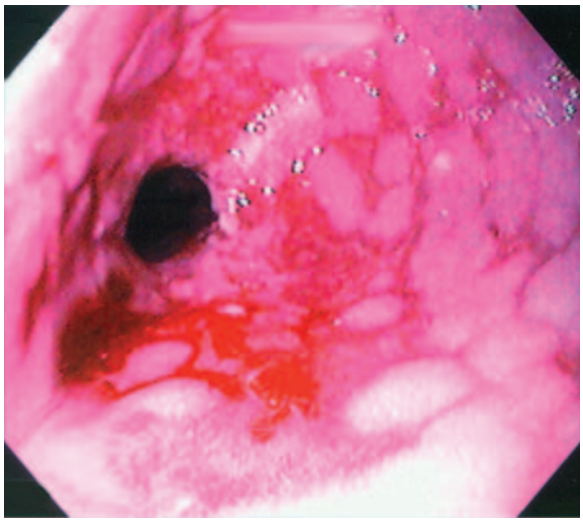


Figure 2–4 Higher grade (Los Angeles grades 3–4) of erosive esophagitis with large areas of confluent erosion and marked erythema.

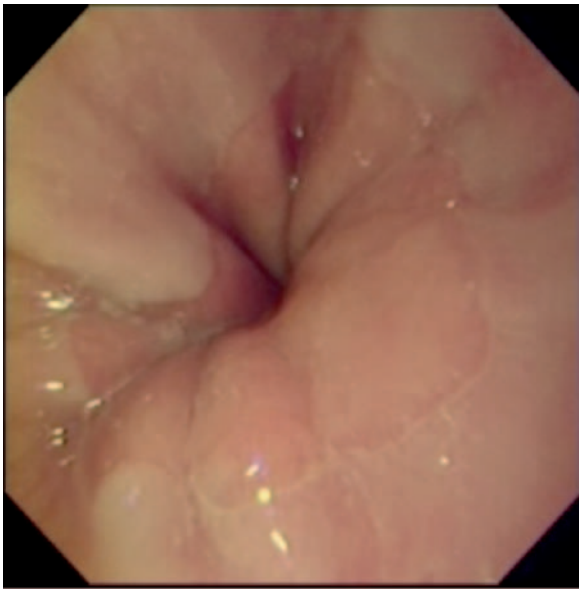


Figure 2–5 Normal endoscopic appearance of the gastroesophageal junction. The squamous epithelium shows no erosions or erythema. The squamocolumnar junction (Z-line) is horizontal and reaches the end of the tubular esophagus. The rugal folds reach the Z-line. There is no evidence of columnar-lined esophagus.

see Figure 2–1, patient A). Most patients who undergo endoscopy for symptoms suspected of being caused by reflux disease do not have biopsies. The histologic diagnosis of reflux esophagitis (defined presently by changes in the squamous epithelium) is so low in sensitivity and specificity that it has no practical diagnostic value.

The first definite indication for endoscopic biopsy in a patient with reflux disease arises when an abnormal columnar-lined esophagus is visualized at endoscopy. The presently accepted concept of normal endoscopic and gross appearance (Figures 2–5, 2–6, and 2–7) is that the entire tubular esophagus is lined by squamous epithelium, which ends as a horizontal line (the Z-line), which marks the distal limit of the esophagus. The rugal folds come all the way up to the Z-line. This coincident point where the squamous epithelium meets the rugated columnar epithelium is the present definition of the normal gastroesophageal junction.

An abnormal endoscopic and gross appearance is defined as the detection of a non-rugated flat columnar epithelium that is interposed between the proximal limit of the rugal folds (the endoscopic gastroesophageal junction) and the squamous epithelium. The length of this varies from "barely detectable" (based on the sensitivity of the examining eye) to very long (maximally extending to the proximal esophagus 25 cm above the gastroesophageal junction). At endoscopy, this is first seen as serration of the Z-line due to the upward extension of columnar epithelium into the esophagus as tongues of salmon-colored mucosa (Figures 2–8 and 2–9) or non-circumferential flat mucosa between the rugal folds and squamocolumnar junction (Figure 2–10). As the disease worsens, the Z-line migrates proximally, and a circumferential, flat, columnar-lined esophagus of increasing length is interposed between the

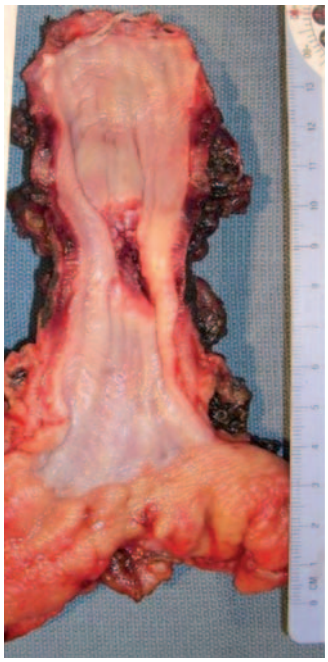


Figure 2–6 Resected esophagogastrectomy specimen showing the normal gross appearance that is equivalent to the normal endoscopic appearance. The squamocolumnar junction (Z-line) is horizontal and reaches the end of the tubular esophagus. The rugal folds are not very clear but reach the Z-line when they are present. There is no evidence of columnar-lined esophagus. Note the ulcerated lesion in the mid-esophagus, which was a squamous carcinoma.

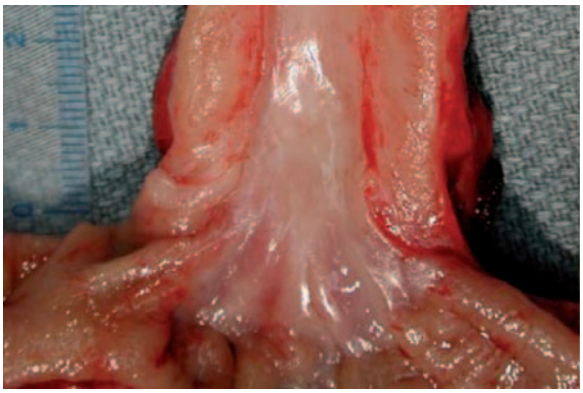


Figure 2–7 Resected esophagogastrectomy showing the end of the esophagus and proximal stomach. The squamous epithelium ends at the Z-line, which appears as a convex line with the base of the convexity at the end of the tubular esophagus. The rugal folds are better defined and reach the Z-line. Note the thickening of the wall of the esophagus; this patient had a lye-induced stricture of the esophagus.

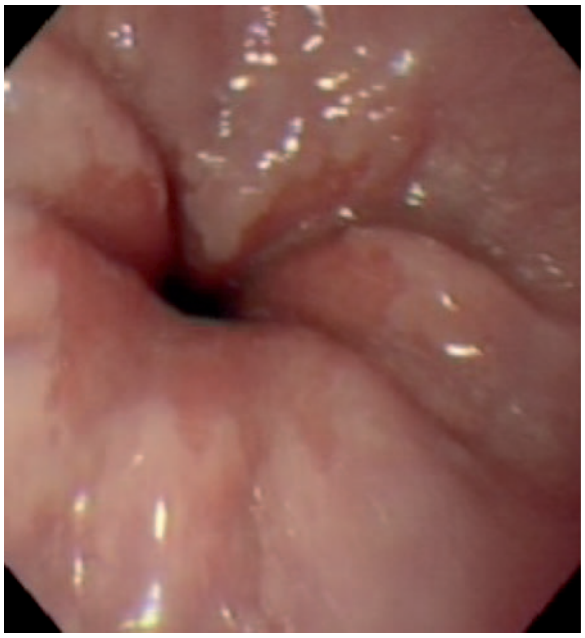


Figure 2–8 Early columnar-lined esophagus, showing serration of the squamocolumnar junction resulting from short tongues of pink columnar metaplastic epithelium extending up into the squamous epithelium.

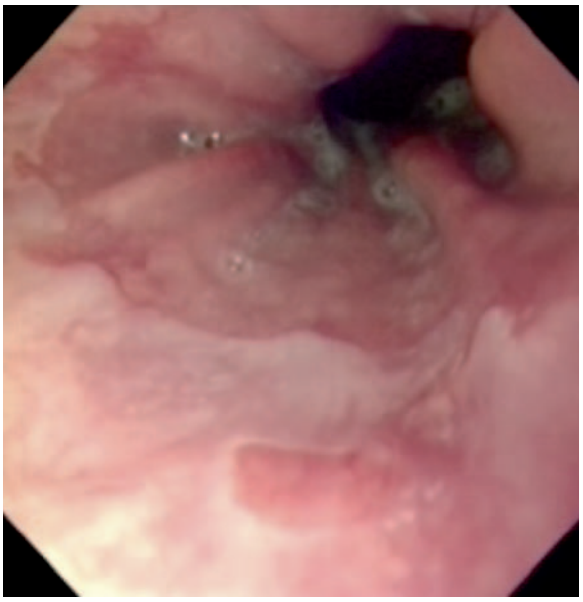


Figure 2–9 Columnar-lined esophagus, showing a tongue of columnar epithelium extending into the squamous epithelium above the junction. The rugal folds extend close to the Z-line but not in the entire circumference.

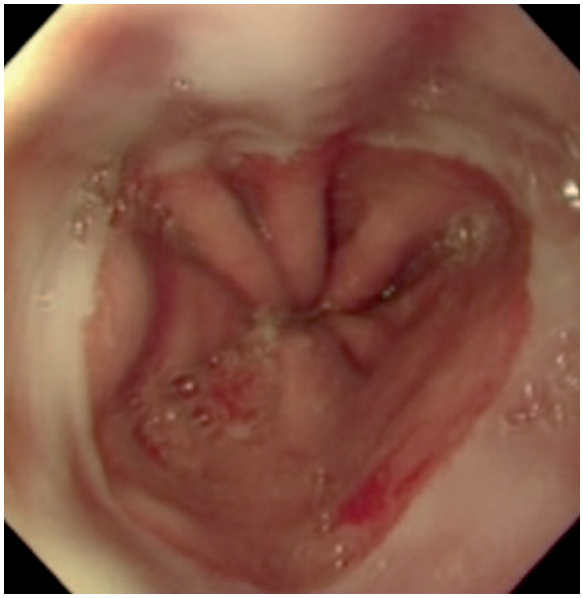


Figure 2–10 Columnar-lined esophagus. The Z-line appears horizontal, and in the upper half, the rugal folds reach the Z-line. In the lower half of the image, there is a flat, erythematous columnar epithelium that separates the proximal limit of the rugal folds from the Z-line, which, although horizontal, has been displaced proximally.

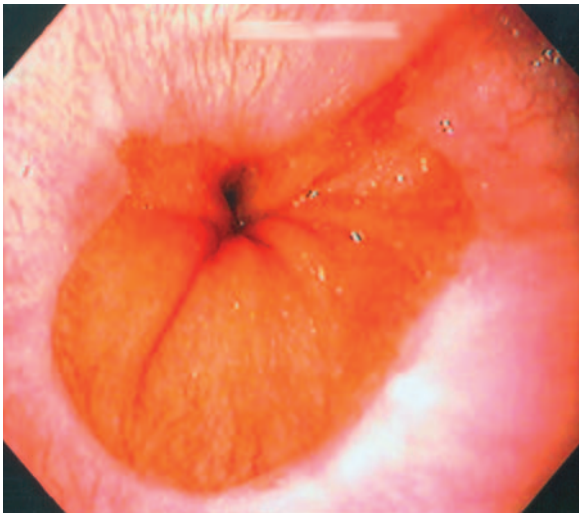


Figure 2–11 Circumferential columnar-lined esophagus of short length separating the proximal limit of rugal folds and the Z-line. Note the prominent linear vascular markings of the squamous epithelium in the upper part of the esophagus.

proximal limit of the rugal folds and the Z-line (Figures 2–11 to 2–16). The length of the columnar-lined segment can be measured at endoscopy and gross examination from the highest point of the Z-line to the proximal limit of the rugal folds. Columnar-lined esophagus is classified into short segment (see Figures 2–11 and 2–13) and long segment (see

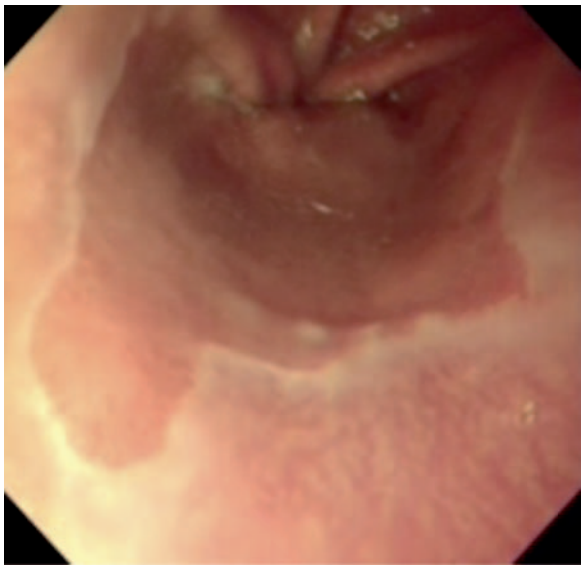


Figure 2–12 Columnar-lined esophagus, showing a circumferential flat columnar epithelium between the proximal limit of the rugal folds (seen in the deep part of the lumen) and the irregular Z-line. The Z-line shows a tongue of columnar epithelium extending proximally. Note that only part of the circumference of the Z-line is shown.

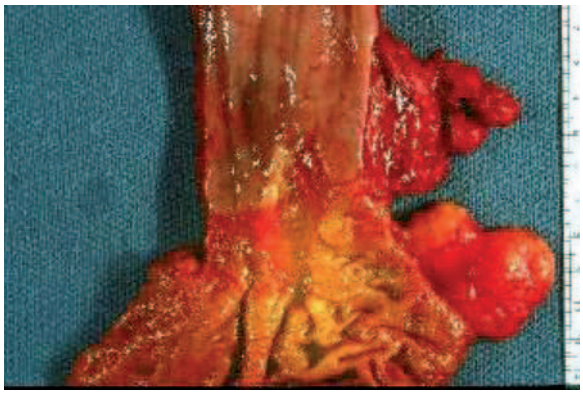


Figure 2–13 Gross appearance of columnar-lined esophagus, short segment, characterized by circumferential flat mucosa in the tubular esophagus between the proximal limit of the rugal folds and the squamous epithelium. The Z-line above the columnar-lined esophagus is serrated. Biopsies are necessary to determine whether this patient has intestinal metaplasia, which would lead to the diagnosis of Barrett esophagus.

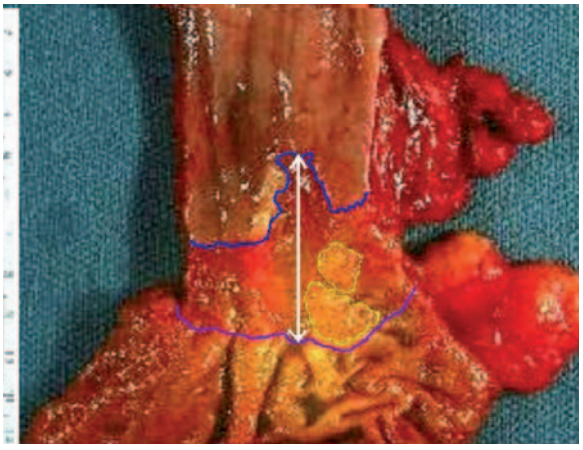


Figure 2–14 This is the image shown in Figure 2–13, with the serrated Z-line shown as a blue line; the proximal limit of the rugal folds is shown as a purple line. This is the gross extent of the columnar-lined esophagus, which measures slightly less than 2 cm from the highest point of the Z-line to the endoscopic gastroesophageal junction *(white arrows).* Two squamous islands are outlined in yellow.

Figures 2–15 and 2–16) when the measured length is less than or greater than 2 cm.

Although this idealized description of the normal and abnormal appearance is clear, there are many patients who do not have clearly definable landmarks. The demarcation of the Z-line is usually quite clear, although I do rarely receive biopsies taken from "an endoscopically visualized columnar segment" that shows squamous epithelium. The demarcation of the distal limit of the esophagus or the gastroesophageal junction can be quite difficult. In some patients, the proximal limit of the rugal folds is not in one horizontal line (see Figure 2–16). In others, the proximal limit of the rugal folds is clear, but the rugated epithelium has an appearance of erythema that is similar to

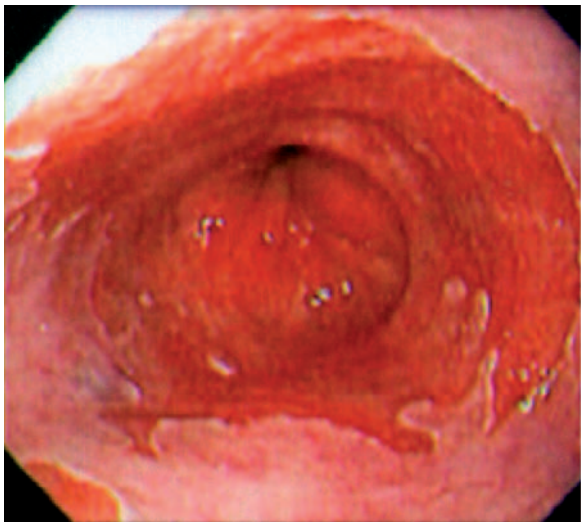


Figure 2–15 Endoscopic appearance of a long segment of columnar-lined esophagus showing the flat, erythematous columnar mucosa lining a large part of the tubular esophagus and the serrated Z-line proximally.

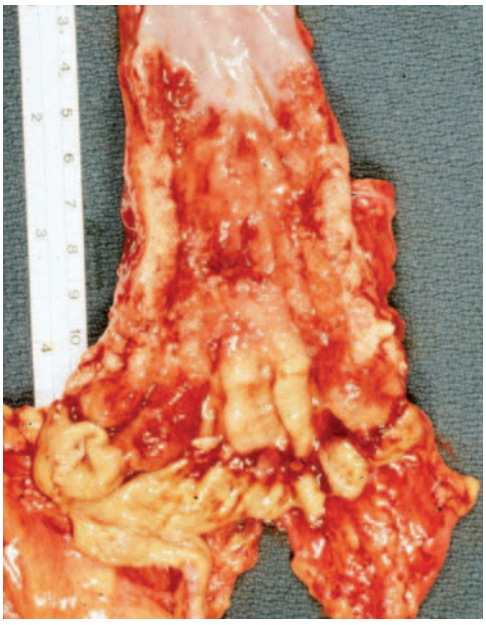


Figure 2–16 Columnar-lined esophagus, long segment, gross appearance. The squamocolumnar junction is irregular, and the distal esophagus is lined by a flat, markedly erythematous columnar epithelium. The rugal folds are an irregular line that is situated largely distal to the end of the tubular esophagus, although there is an island of possibly rugated mucosa at the end of the tubular esophagus. It is difficult to delineate the proximal limit of the rugal folds.

the flat columnar-lined esophagus (Figure 2–17). In other patients, the end of the tubular esophagus is separated from the proximal limit of the rugal folds (Figure 2–18). The term *hiatal hernia* is applied to any dilated segment distal to the end of the tubular esophagus. However, a true hiatal hernia consists of stomach and must therefore be lined by gastric mucosa. When the dilated segment distal to the end of the tubular esophagus is lined by flat mucosa and is clearly proximal to the proximal limit of rugal folds, a discrepancy arises (see Figure 2–18). The absence of any of these atypical presentations in the endoscopic literature suggests that these problems are conveniently ignored when encountered.

When an endoscopist suspects the presence of a columnar-lined esophagus, the only current objective is to establish the diagnosis of Barrett esophagus by taking biopsies from the abnormal columnar epithelium. The present American Gastroenterology Association (AGA) recommendation is to not perform biopsy on endoscopically normal patients, even when they are symptomatic.[11] When the amount of columnar lining is less than 1 cm, there is a significant interobserver variation among endoscopists as to whether an endoscopy is normal or shows minimal columnar-lined esophagus. As such, the sensitivity with which biopsies are taken at endoscopy will vary.

If the biopsies taken from an endoscopically visible columnar-lined esophagus show intestinal metaplasia (see Figure 2–1, patient D; Figure 2–19), a diagnosis of Barrett esophagus is made, and the patient is placed on surveillance to detect progression to dysplasia and adenocarcinoma. If the patient does not have intestinal metaplasia on the biopsy (see Figure 2–1, patient C), the fact that there was a columnar-lined esophagus is presently ignored. Every authority and all the evidence agree that this situation is caused by reflux, but no one (except me!) presently uses this as a diagnostic criterion for reflux

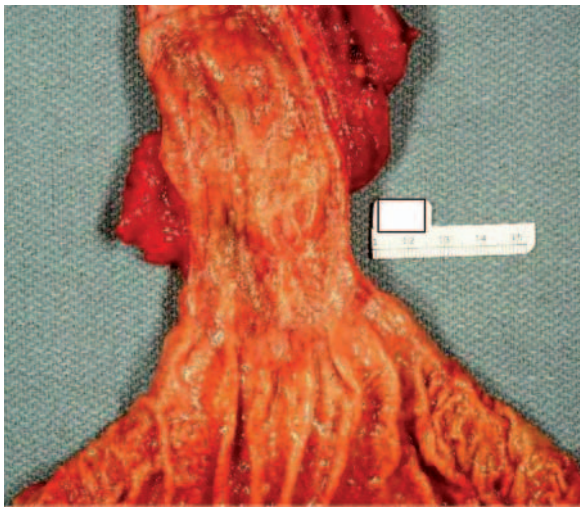


Figure 2–17 Long segment of columnar-lined epithelium. The proximal limit of rugal folds is well demarcated at the end of the tubular esophagus. However, the mucosal appearance above (columnar-lined esophagus) and below (gastric) the proximal limit of the rugal folds appears to be similarly erythematous and abnormal.

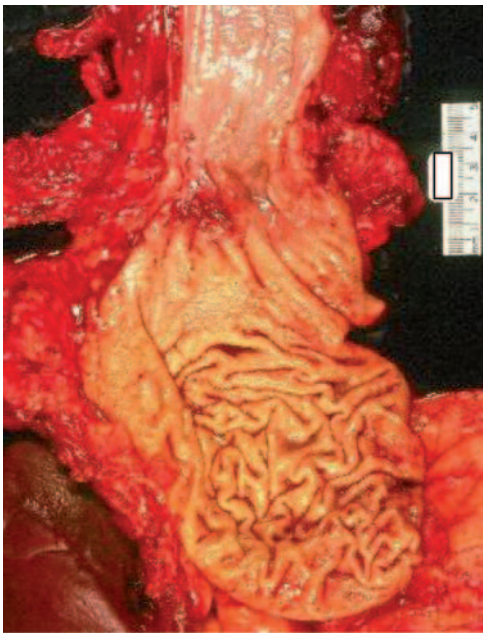


Figure 2–18 Markedly atypical appearance of the esophagus and proximal stomach. The end of the tubular esophagus is the Z-line; at this point is an ulcerated carcinoma. Below this is a dilated segment that is lined by flat mucosa that measures approximately 3 cm before the line of the proximal limit of the rugal folds is reached. What is this dilated segment? Is it a dilated esophagus because it is proximal to the rugal folds? Is it stomach (a hiatal hernia) because it is part of the saccular region distal to the end of the tubular esophagus? If the latter, why does it not have rugal folds?

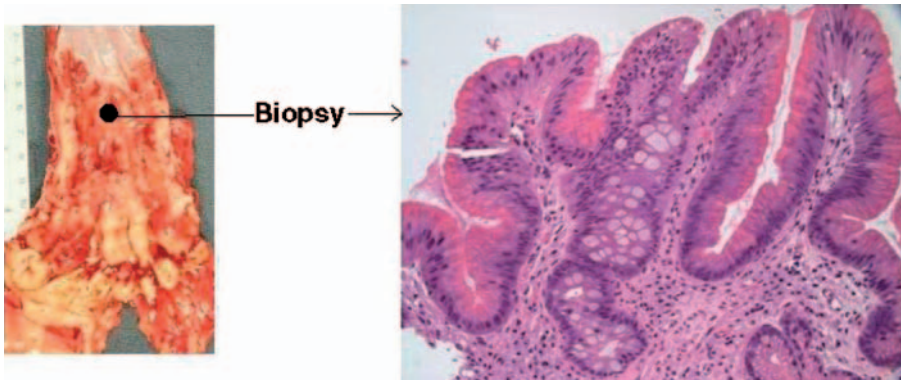


Figure 2–19 The diagnosis of Barrett esophagus can be made only when a biopsy from an endoscopically visualized segment of columnar-lined esophagus shows intestinal metaplasia.

disease. This is incomprehensible. People cite the controversy that exists about cardiac mucosa as their reason for not using this as a diagnostic criterion for reflux disease. *The controversy exists only for cardiac mucosa found distal to the endoscopic gastroesophageal junction; it does not exist when the cardiac mucosa is in the esophagus where it is universally agreed that it is a metaplastic reflux-induced epithelium.*

Endoscopic evaluation of reflux disease appears to recognize reflux esophagitis and columnar-lined esophagus as two distinct entities. Efforts at diagnosing reflux esophagitis are aimed at detecting abnormalities in the

squamous epithelium. In symptomatic patients with no abnormality at standard endoscopy (NERD), magnification endoscopy is used to detect subtle increases in vascular marking in the squamous epithelium, which increases diagnostic sensitivity. Histologic examination of biopsies taken from endoscopically normal squamous epithelium also increases diagnostic sensitivity, because it may show microscopic changes of reflux in some patients. Despite this, there remains a significant number of patients with classical reflux symptoms with no endoscopic or histologic abnormality in the squamous epithelium.

The focus of reflux disease diagnosis should not be aimed at finding changes in the squamous epithelium. Columnar metaplasia is by far the most specific and sensitive change that occurs in squamous epithelium. I will show that the key to accurately diagnosing reflux disease is the accurate detection of this columnar metaplasia, both by endoscopy and appropriate biopsies. When this is done, a diagnostic test emerges that has a 100% specificity and near 100% sensitivity for the diagnosis of reflux disease.

Histologic Diagnosis

The presently accepted histologic criteria of gastroesophageal reflux disease (Table 2–6) are limited to changes in the squamous epithelium. In many patients with proven reflux (classical symptoms, abnormal 24-hour pH test), the squamous epithelium is normal (Figures 2–20 and 2–21). In these patients, subtle changes such as dilated intercellular changes may be present on electron microscopy.[12] However, such changes are not specific for reflux and the expense of electron microscopy is not justified to make a diagnosis of reflux disease.

Reflux damage of the squamous epithelium results in an increased loss of cells at the surface, leading to a compensatory hyperplasia of the epithelium. This causes basal cell hyperplasia and papillary elongation in varying combinations with and without increased thickness of the epithelium (Figures 2–22 to 2–25). An increased number of proliferating cells are seen in the basal region, best seen in Ki67 stained sections (Figures 2–26 and 2–27). Acid induces damage in the squamous cells, resulting in separation of tight junctions and increased spaces between the cells ("dilated intercellular spaces").

TABLE 2–6 Presently Accepted Criteria for the Diagnosis of Gastroesophageal Reflux Disease*

Criterion	Specificity	Sensitivity
Basal cell hyperplasia exceeding 20% of epithelial thickness	Low; any cause of esophageal injury can cause increased proliferation	Low; approximately 50% of patients with proven abnormal reflux are negative
Papillary elongation exceeding 60% of epithelial thickness	Low; any cause of esophageal injury can cause increased proliferation	Low; approximately 50% of patients with proven abnormal reflux are negative
Erosion and ulceration	Low; many causes of esophageal injury other than reflux can cause erosion and ulceration	Low; approximately 70% of patients with proven abnormal reflux are negative (non-erosive reflux disease [NERD])
Intraepithelial eosinophils	Low; eosinophilia more common and marked in eosinophilic esophagitis	Intermediate
Intraepithelial neutrophils	Low; many causes of erosion and injury can cause neutrophil infiltration	Low
Dilated intercellular spaces (light microscopy)	Low; any cause of injury can cause separation of squamous cells	High (the most sensitive of the presently used criteria)
Dilated intercellular spaces (electron microscopy)	Low	Very high
Increased Ki67 expression	Low	Very high

*Excluding Barrett esophagus and adenocarcinoma, which can be correctly considered as diagnostic criteria for reflux disease at an advanced and complicated stage. All presently accepted criteria relate to changes in the squamous epithelium.

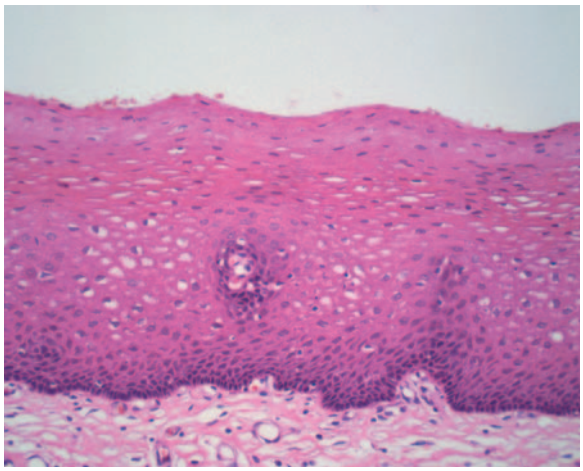


Figure 2–20 Normal esophageal epithelium, showing non-keratinizing stratified squamous epithelium. This is flat and thin with short papillary processes. The surface cells have flattened nuclei, and there is no stratum corneum or granular layer. The basal region is less than 20% of epithelial thickness.

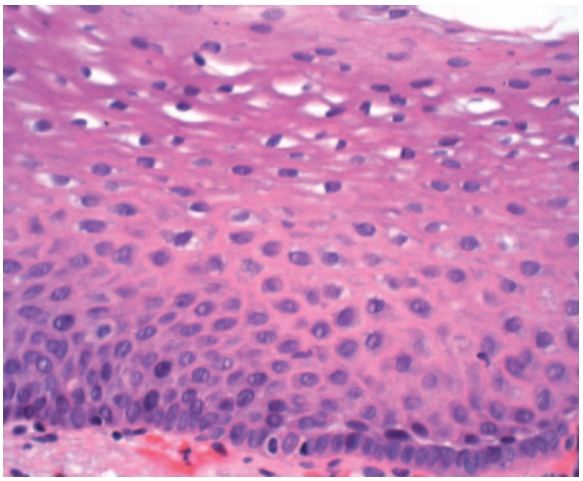


Figure 2–21 Normal squamous epithelium, higher power. The epithelium is flat, the basal region is less than 20% of epithelial thickness, and there are no spaces between the squamous epithelial cells visible at this magnification.

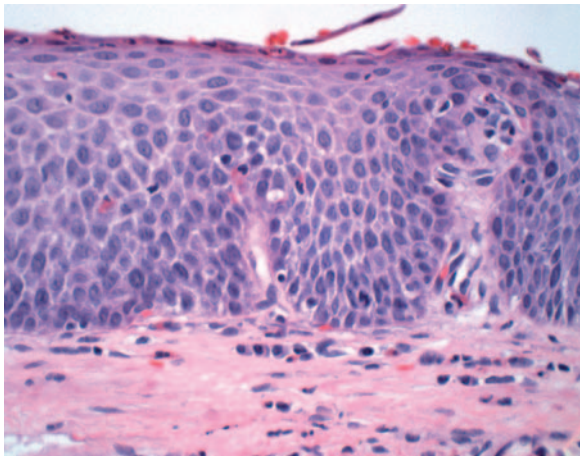


Figure 2–22 Changes of reflux esophagitis in an epithelium that is relatively normal in its thickness. The epithelium shows basal cell hyperplasia (greater than 20% of epithelial thickness), papillary elongation (greater than 60% of epithelial thickness), dilated intercellular spaces, and scattered intraepithelial eosinophils.

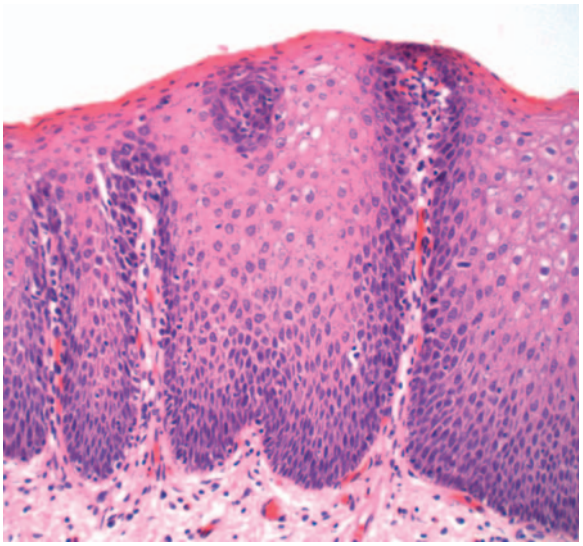


Figure 2–23 Squamous epithelium with marked thickening (acanthosis), basal cell hyperplasia, marked papillary elongation, and focal parakeratosis at the surface. There are no eosinophils in the epithelium. Dilated intercellular spaces are present but not pronounced. These changes are not as specific in the absence of eosinophils but still permit a diagnosis with the appropriate history. Similar changes occur in achalasia.

This is at first detectable at electron microscopy but later becomes visible in routine sections[13] (Figures 2–28 and 2–29). The separation of the squamous cells increases their permeability and permits entry of luminal molecules into the epithelium.[14] These cause damage and the release of a variety of chemokines,[15] which are chemoattractive to neutrophils and eosinophils (Figure 2–30). The presence of intraepithelial eosinophils, even in small numbers, is one of the more reliable indicators of reflux disease. More severe damage results in erosion and ulceration (Figure 2–31). Deep ulcers can be associated with fibrosis and produce strictures. Deep and perforating ulceration and

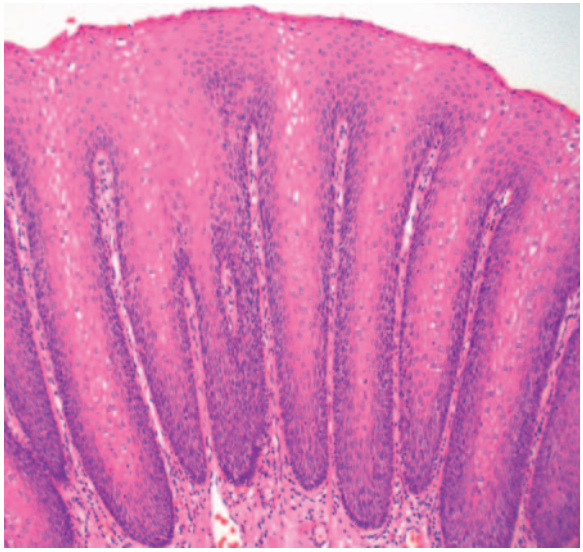


Figure 2–24 Markedly thickened (acanthotic) squamous epithelium with marked papillary elongation (but less basal cell hyperplasia than in Figure 2–23) and absence of eosinophils. The specificity of this change for reflux disease is even less. This patient indeed had clinical reflux disease.

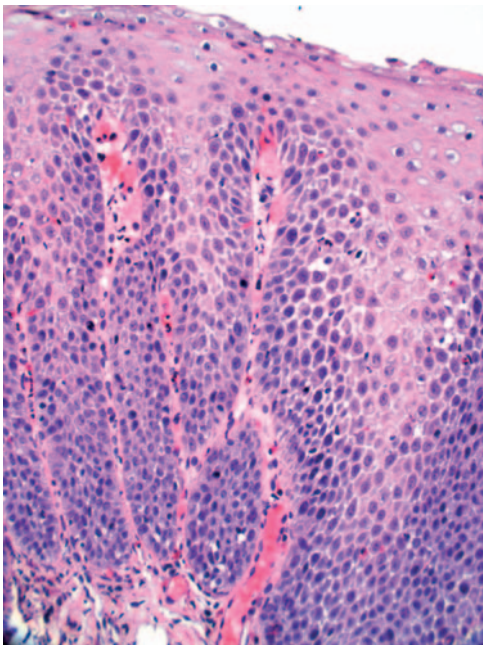


Figure 2–25 Typical features of reflux esophagitis in markedly thickened epithelium. There is basal cell hyperplasia, marked papillary elongation, dilated intercellular spaces, and intraepithelial eosinophils.

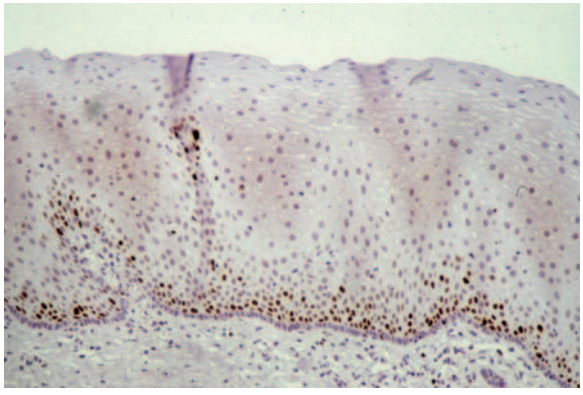


Figure 2–26 Normal esophageal squamous epithelium, stained by immunoperoxidase technique for Ki67, which is a marker of proliferation. The proliferating cells are limited to two to three layers above the basal layer.

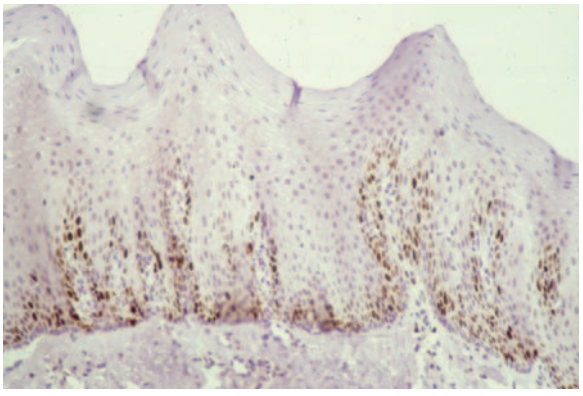


Figure 2–27 Squamous epithelium in a patient with symptomatic reflux. The histologic abnormality of reflux esophagitis is not well established. The Ki67 stain shows a slight but definite increase in the number of proliferating cells in the suprabasal region of the epithelium.

complicated strictures have become rare in reflux disease, largely because of the efficacy of acid-suppressive drug therapy.

These changes have such low sensitivity and specificity that they are essentially useless as a diagnostic test, either singly or in any combination.[16] Basal cell hyperplasia, papillary elongation, and epithelial thickening may occur in many esophageal diseases such as achalasia. Dilated intercellular spaces and intraepithelial eosinophils occur in eosinophilic (allergic) esophagitis, often to a degree more severe than in reflux disease (Figure 2–32). Neutrophils are associated with any infectious disease.

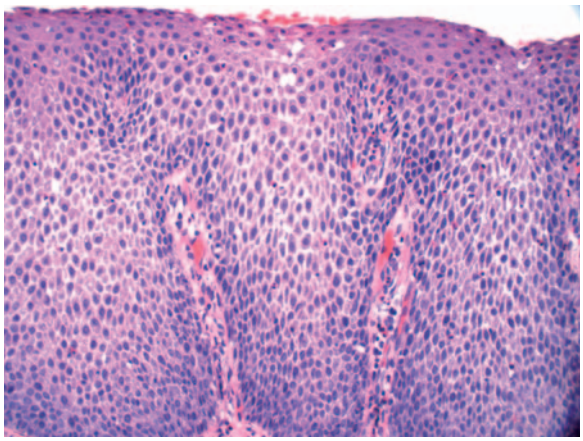


Figure 2–28 Squamous epithelium, showing dilated intercellular spaces indicated by separation of squamous cells.

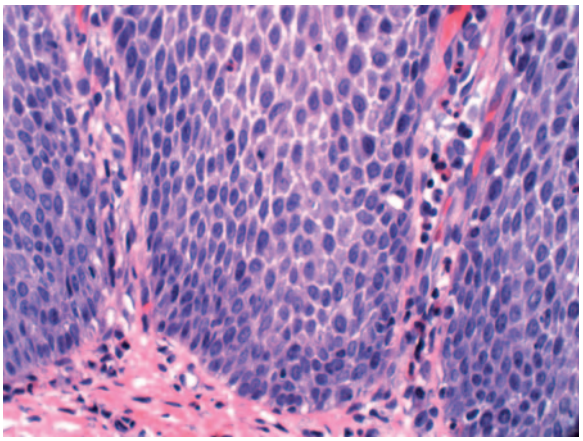


Figure 2–29 Higher power of squamous epithelium in reflux esophagitis, showing dilated intercellular spaces. The squamous cells are separated by clear linear spaces (equivalent to spongiosis). Intraepithelial eosinophils are also present.

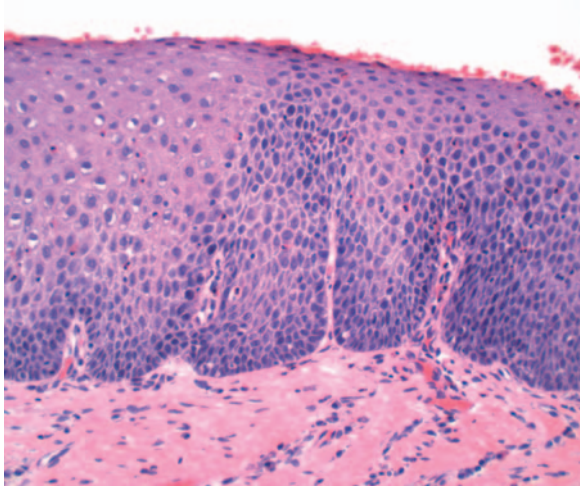


Figure 2–30 Reflux esophagitis, showing numerous intraepithelial eosinophils.

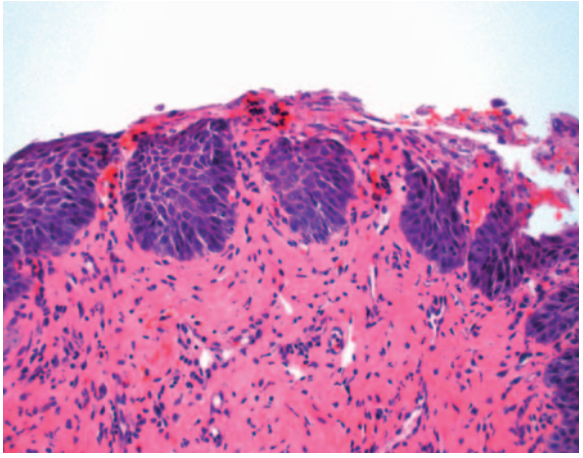


Figure 2–31 Acute erosion of the surface of squamous epithelium in erosive reflux esophagitis. The epithelium shows regenerative changes, which include basal cell hyperplasia.

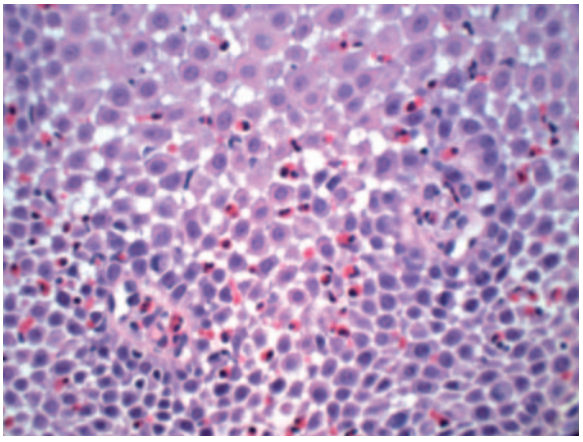


Figure 2–32 Esophageal squamous epithelium in a child with eosinophilic (allergic) esophagitis, showing marked (greater than 20/high power field) intraepithelial eosinophil infiltration. There are also markedly dilated intercellular spaces.

Erosion and ulceration, which are used as endoscopic criteria for the classification and grading of reflux esophagitis, are nonspecific. Erosion and ulceration occur in many esophageal diseases, including trauma, pill ulcers, pemphigus vulgaris, in neoplasms, herpes simplex, cytomegalovirus, esophagitis, and ulceration associated with human immunodeficiency virus (HIV) infection. It is only in the setting of classical reflux symptoms in an immunocompetent patient that erosions are fairly specific for reflux. When encountered by the pathologist in a biopsy, erosions are meaningless as a diagnostic criterion because the absence of an etiology within the biopsy does not mean that the patient has reflux disease. In fact, the assessment of the presence of reflux disease in a biopsy with erosion is impossible because erosions are almost always associated with regeneration and acute inflammation (see Figure 2–31). Regeneration associated with an erosion of any cause is often manifested histologically by squamous epithelial proliferation and basal cell hyperplasia, which are similar to the diagnostic criteria of reflux disease.

There is presently no requirement for histologic confirmation of a clinical diagnosis of gastroesophageal reflux disease. This is justified by the fact that there is no single feature or combination of findings that specifically either confirms or negates the diagnosis of reflux disease.

Columnar-Lined Esophagus: An Inexplicably Ignored Diagnostic Criterion for Reflux Disease

When Allison and Johnstone first described columnar-lined esophagus in 1953,[17] it was thought to represent a congenital abnormality in which heterotopic gastric mucosa lined the distal esophagus as a normal variant. Over the next 10 years, it became established that this was not correct. By 1961, it had been established that columnar-lined esophagus was an esophageal disease acquired as a result of damage caused in the squamous epithelium by gastroesophageal reflux. Hayward in 1961[18] described the process perfectly:

> When the normal sphincteric and valvular mechanism in the lower oesophagus and oesophago-gastric junction . . . fails, . . . reflux from the stomach occurs and acid and pepsin reach the squamous epithelium and begin to digest it. . . . In quiet periods some healing occurs, and in these periods the destroyed squamous epithelium may re-form, often with . . . junctional epithelium, usually not very healthy-looking. . . . Further reflux therefore attacks principally the squamous epithelium higher up. In the next remission it may be replaced by more junctional epithelium. . . . With repetition over a long period the metaplastic junctional epithelium may creep higher and higher. . . .

We have known for nearly five decades that columnar metaplasia of the esophagus is a manifestation of gastroesophageal reflux disease and is not caused by anything else. However, we do not use it for a diagnosis of reflux disease. Why? It is not like there is an accurate alternative cellular criterion for diagnosis of reflux disease; there is not.

Until the late 1970s, there was at least tacit acceptance that the presence of an endoscopically defined columnar-lined esophagus represented Barrett esophagus and was therefore a manifestation of reflux disease. During this period, the prevailing viewpoint was that the most distal part of this columnar-lined segment was "normal," and Barrett esophagus was diagnosed only when more than 2 or 3 cm of columnar lining was seen in the esophagus.

The recognition of short-segment Barrett esophagus in the 1990s changed that. We now believe that any visible columnar lining in the distal esophagus

above the endoscopic gastroesophageal junction (proximal limit of the rugal folds) is abnormal. We also know that it is caused by reflux disease. Why is this endoscopic abnormality not used as a diagnostic criterion for gastroesophageal reflux disease?

The only interest endoscopists have when an abnormal columnar-lined esophagus is present is to take biopsies to find intestinal metaplasia. They ignore the fact that the columnar-lined esophagus is diagnostic of gastroesophageal reflux disease regardless of whether it has intestinal metaplasia. When intestinal metaplasia is not present, the columnar-lined segment is lined by non-intestinalized metaplastic columnar epithelia of the esophagus; this is cardiac and oxyntocardiac mucosa. These are reflux-induced epithelia in the esophagus that were beautifully described by Paull et al in 1976.[19] The fact that they are not premalignant until intestinal metaplasia is present does not mean that they cannot be used as a criterion for the diagnosis of reflux disease.

When evaluating the present state of diagnosis of gastroesophageal reflux disease, the failure to use the presence of columnar epithelium in the endoscopically defined distal esophagus is totally inexplicable. To analyze this situation, let us look at what findings we can all agree about at the present time and see where that takes us.

Universally Accepted Endoscopic Conclusions

The following endoscopic conclusions can be regarded as valid and without controversy:

1. The entire esophagus is normally lined by squamous epithelium (see Figures 2–5, 2–6, and 2–7).
2. The presence of any columnar metaplastic epithelium in the esophagus is abnormal. Some may disagree with this statement, but it is important to understand that you cannot disagree with this if you accept the previous conclusion—that the entire esophagus is normally lined by squamous epithelium. I will suggest that if you believe that columnar-lined esophagus is normal, you are outdated by nearly two decades and need to change your viewpoint.
3. Columnar metaplasia of the esophagus is specifically caused by reflux. There is no disease other than gastroesophageal reflux disease that causes columnar metaplasia of the esophagus. Columnar epithelium in the distal esophagus does not represent congenital heterotopia of normal gastric mucosa. If you believe that heterotopic gastric mucosa occurs in the distal esophagus, you are outdated by four decades.
5. Columnar metaplasia of the esophagus results in a proximal displacement of the squamocolumnar junction. This occurs first as tongues of columnar epithelium extending up into the squamous epithelium (see Figures 2–8, 2–9, and 2–10); this is followed by circumferential columnar-lined esophagus (see Figures 2–11 to 2–18). The gap between the proximally displaced squamocolumnar junction and the gastroesophageal junction is the length of the columnar-lined esophagus (see Figure 2–14).
6. The length of columnar metaplasia (i.e., the amount of proximal displacement of the squamocolumnar junction) is proportional to the severity of reflux (Figure 2–33).
7. Columnar-lined esophagus is not Barrett esophagus. Barrett esophagus cannot be diagnosed at endoscopy; it *requires* the presence of intestinal metaplasia in a biopsy sample (Figure 2–34).

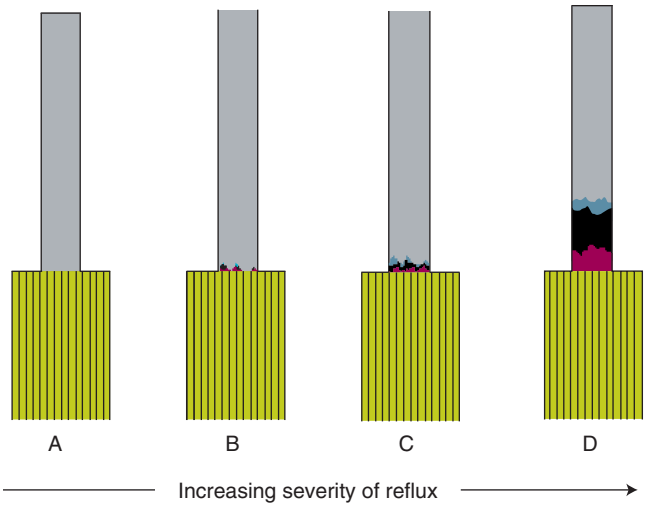


Figure 2–33 Stages of columnar-lined esophagus. **A,** Normal; the squamous epithelium *(gray area)* lines the entire tubular esophagus; the gastric rugal folds *(striped area)* reach all the way to the Z-line. **B,** Earliest visible columnar-lined esophagus where small tongues of columnar epithelium (*red, black,* and *blue areas*) extend upward into the esophagus, causing the Z-line to become serrated. **C,** Short segment of columnar-lined esophagus, seen as circumferential flat columnar epithelium in distal esophagus as well as serration of the proximally migrated Z-line. **D,** Long segment of columnar-lined esophagus. The length of columnar-lined esophagus is directly proportional to the severity of reflux disease. Note the consistent zonation of the three epithelial types; oxyntocardiac mucosa is found distally, and intestinal metaplasia proximally.

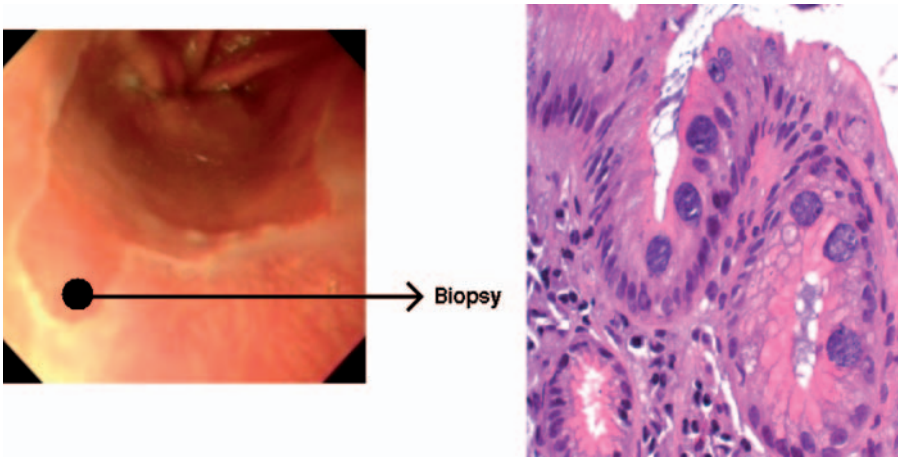


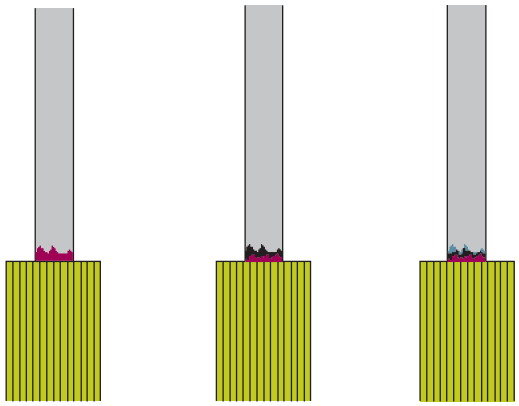
Figure 2–34 The current diagnosis of Barrett esophagus requires the presence of intestinal metaplasia in a biopsy taken from an endoscopically visualized segment of columnar-lined esophagus. Intestinal metaplasia is seen in the histologic image on the right as the presence of goblet cells in one foveolar complex within cardiac mucosa.

Universally Accepted Histologic Conclusions

The following histologic conclusions can be regarded as valid and without controversy:

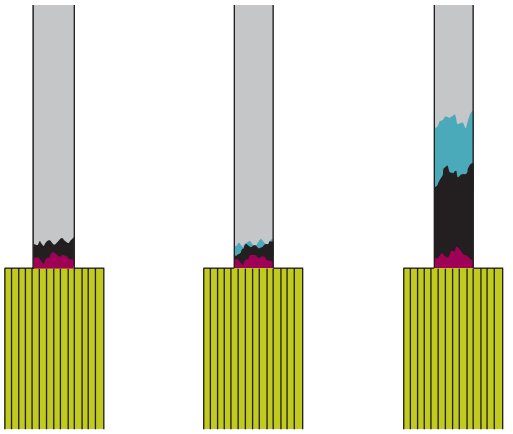
1. Metaplastic columnar epithelia of the esophagus include cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa (as defined by Paull et al, 1976 [with modification of terms to fit current usage].[10] In Chapter 3, I will define these epithelial types by precise and easily reproducible histologic criteria.

2. The finding of any metaplastic columnar epithelium in any part of the esophagus is abnormal and caused by gastroesophageal reflux disease. This is a highly specific finding that can only result from gastroesophageal reflux disease.
3. The length of columnar-lined esophagus is proportional to the severity of reflux disease (see Figure 2–33). At histology, the length of columnar-lined esophagus can be assessed only when measured biopsies are performed in a systematic manner within the columnar-lined segment.
4. A columnar-lined segment of esophagus contains one, two, or all three of the epithelial types defined in conclusion number 1. Patients with very short (less than 1 cm) segments may have only oxyntocardiac, a mixture of oxyntocardiac and cardiac, or all three epithelial types (Figure 2–35). When the columnar-lined segment reaches 1 cm, cardiac mucosa is almost always present in addition to oxyntocardiac mucosa (Figure 2–36). Intestinal metaplastic epithelium can be found in association with oxyntocardiac and cardiac mucosa in a columnar-lined segment of any length (see Figure 2–33), but its prevalence increases with increasing length of columnar-lined esophagus.[20] In patients with less than 1 cm of columnar-lined esophagus, intestinal metaplasia is present in 15%; with a 1- to 2-cm length, it is present in 50% to 70%; with a 3- to 4-cm length, it is present in 90%; and with a greater than 5-cm length, it is invariably present (Figures 2–36 and 2–37).
5. Intestinal metaplasia occurring in an endoscopically visible columnar-lined esophagus defines Barrett esophagus (see Figure 2–34). The criterion for definition is satisfied by the presence of a single definite goblet cell in cardiac mucosa. The extent of intestinal metaplasia within a columnar-lined



Oxyntocardiac	+	+	+
Cardiac	–	+	+
Intestinal	–	–	+
Diagnosis	See Chapter 4	GERD	Barrett esophagus

Figure 2–35 Diagrammatic representation of three patients with a visible columnar-lined esophagus measuring less than 1 cm. Patient *A* has only oxyntocardiac mucosa; this situation will be discussed in Chapter 4. Patient *B* has cardiac and oxyntocardiac mucosa, indicative of gastroesophageal reflux disease *(GERD)* (reflux carditis). Patient *C* has intestinal metaplasia in cardiac mucosa, indicative of Barrett esophagus. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa with lines denoting rugal folds.



	A	B	C
Length of CLE	1 cm	1 cm	>5 cm
Oxyntocardiac	+	+	+
Cardiac	+	+	+
Intestinal	–	+	+
Diagnosis	Moderate GERD	BE in moderate GERD	BE in severe GERD

Figure 2–36 Diagrammatic representation of three patients with columnar-lined esophagus *(CLE)*. Patient *A* has a 1-cm segment of columnar-lined esophagus with cardiac and oxyntocardiac mucosa. This is diagnostic of moderate reflux disease (reflux carditis). Patient *B* is similar but has intestinal metaplasia in cardiac mucosa. This is diagnostic of Barrett esophagus *(BE)* occurring in moderate reflux disease. Patient *C* has a greater than 5-cm columnar-lined esophagus with extensive intestinal metaplasia. This is Barrett esophagus-complicating severe reflux disease. *GERD,* Gastroesophageal reflux disease. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa with lines denoting rugal folds.

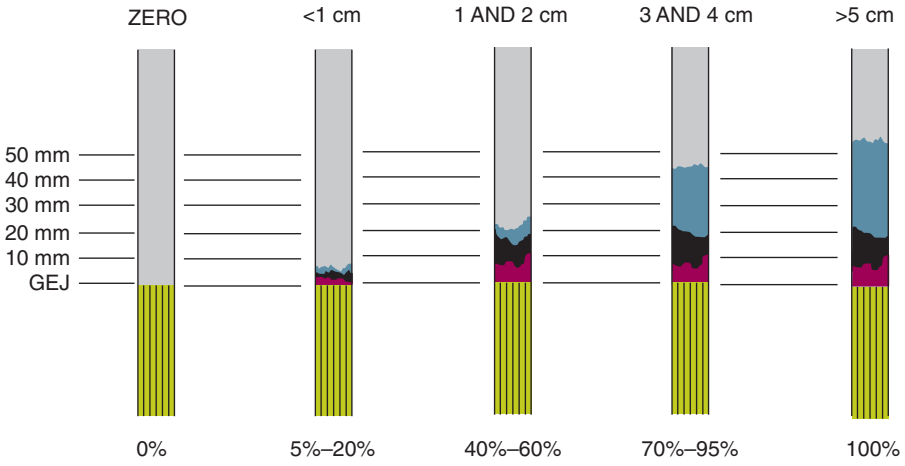


Figure 2–37 There is a direct relationship between the length of columnar-lined esophagus and prevalence of Barrett esophagus (intestinal metaplasia). Barrett esophagus does not exist when there is no columnar-lined esophagus, is present 5% to 20% of the time with lengths less than 1 cm, and is invariably present when the length of columnar-lined esophagus exceeds 5 cm. *GEJ,* Gastroesophageal junction. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa with lines denoting rugal folds.

segment is extremely variable and can be assessed only with standardized mapping biopsies of the columnar-lined segment (Figure 2–38).

6. In a columnar-lined segment of esophagus, the epithelial types tend to have a consistent zonation, regardless of the length of the segment (see Figures 2–33, 2–36, and 2–37).[19,21] Oxyntocardiac mucosa tends to be found in the most distal region, immediately proximal to the gastroesophageal junction. Intestinal metaplasia tends to be found in the most proximal region, immediately distal to the squamocolumnar junction. Cardiac mucosa is found throughout. The amount of these three epithelial types varies considerably among patients (see Figure 2–38).

Recommended Changes to Present Diagnostic Criteria by Accepted Data (Table 2–7)

It is incomprehensible, based on the universally accepted and undisputed evidence that columnar metaplasia of the esophagus is a manifestation of reflux disease, that the presence of an endoscopically visualized columnar-lined esophagus is not used to diagnose reflux disease. There is absolutely no reason not to accept the following recommendation[22]:

1. The visualization of a columnar-lined esophagus at endoscopy is diagnostic of gastroesophageal reflux disease (see Figures 2–8 to 2–12 and 2–15). The diagnosis of reflux disease by this criterion does not need biopsy confirmation because all histologic types of columnar-lined esophagus are diagnostic of reflux. This is the most specific endoscopic criterion for reflux disease. It is far superior to erosive esophagitis, which can occur in a variety of esophageal diseases such as pill ulceration, Herpes simplex infection,

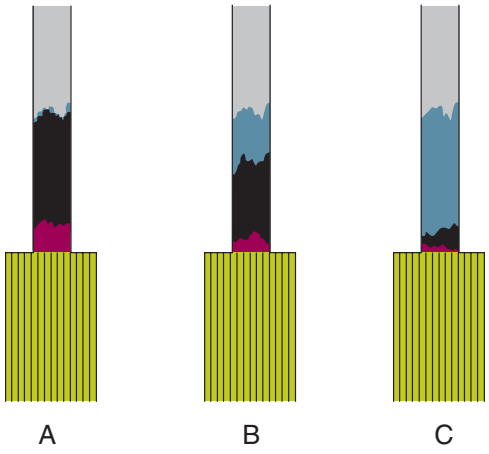


Figure 2–38 Diagrammatic representation of three patients with a columnar-lined segment of 6 cm. All three patients are shown to have intestinal metaplasia. By current definition, they would all be classified as having long-segment Barrett esophagus. However, the amount of intestinal metaplasia is very limited in Patient *A,* intermediate in Patient *B* and extensive in Patient *C. Blue,* intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa with lines denoting rugal folds.

TABLE 2–7 New Diagnostic Criteria to Assess Reflux Disease Based on Facts that Are Universally Accepted

Diagnostic criterion	Present status	Recommended change
Endoscopically visible CLE	Ignored unless IM is present on biopsy	Diagnostic of reflux disease
CLE >2 cm, negative for IM on biopsy	Ignored	Diagnostic of severe reflux disease (reflux carditis)
CLE <2 cm, negative for IM on biopsy	Ignored	Diagnostic of moderate reflux disease (reflux carditis)
IM present in a biopsy from visible CLE	Diagnostic of Barrett esophagus	Diagnostic of Barrett esophagus
IM present in a biopsy from visible CLE >2 cm	Long-segment Barrett esophagus	Barrett esophagus-complicating severe reflux disease
IM present in a biopsy from visible CLE <2 cm	Short-segment Barrett esophagus	Barrett esophagus-complicating moderate reflux disease

CLE, Columnar-lined esophagus; *IM,* intestinal metaplasia.

pemphigus vulgaris, HIV infection, and cytomegalovirus esophagitis, among others. To not use this criterion is an omission that is difficult to understand.

2. The length of columnar-lined esophagus measured at endoscopy as the distance between the proximal limit of rugal folds and the most proximal point of the squamocolumnar junction is proportional to the severity of reflux[23] (see Figure 2–33). This is the best indicator of the severity of reflux. Again, histology is irrelevant to this assessment. By this criterion, severe reflux disease can be defined as the presence of a visible segment of columnar-lined esophagus greater than 2 cm (see Figure 3–36) and moderate reflux disease as the presence of a visible segment of columnar-lined esophagus measuring less than 2 cm (see Figure 2–36). This criterion is more specific than the presently used criterion of severity of erosive esophagitis to assess severity of reflux disease (such as in the Los Angeles classification).
3. Biopsy is not necessary to establish the diagnosis of a visible columnar-lined esophagus; this is an endoscopic diagnosis. However, biopsy is necessary when reflux-induced columnar-lined esophagus is visualized at endoscopy to establish the diagnosis of Barrett esophagus, which requires the presence of intestinal metaplasia (see Figure 2–34).
4. Patients with intestinal metaplasia in the biopsy have Barrett esophagus (see Figure 2–34). This is the present standard of diagnosis of Barrett esophagus, which is defined as the presence of intestinal metaplasia in a biopsy taken from an endoscopically visualized columnar-lined esophagus.
5. The presence of cardiac mucosa (reflux carditis) without intestinal metaplasia in the esophagus is histologic proof of cellular pathology caused by reflux (Figure 2–39). This is the histologic equivalent of columnar-lined esophagus without intestinal metaplasia. ***Reflux carditis is the most specific and most sensitive diagnostic criterion of reflux disease.*** There is no rational basis to dispute this when inflamed cardiac mucosa is present in a biopsy taken from an endoscopically defined point above the gastroesophageal junction in the distal esophagus.
6. Long- and short-segment Barrett esophagus are misnomers. The presence of intestinal metaplasia in a long segment of columnar-lined esophagus is

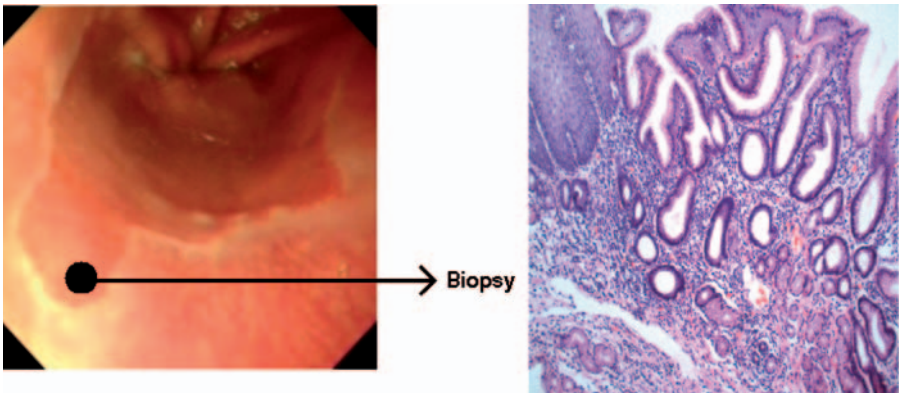


Figure 2–39 Biopsy at the squamocolumnar junction at the proximal limit of a visible columnar-lined esophagus. When this shows no intestinal metaplasia but shows cardiac mucosa, it represents reflux carditis, which is a highly specific diagnostic criterion for gastroesophageal reflux disease.

Barrett esophagus-complicating severe reflux disease (see Figure 2–36). The presence of intestinal metaplasia in a short segment of columnar-lined esophagus is Barrett esophagus-complicating moderate reflux disease (see Figure 2–36). Short- and long-segment Barrett esophagus can only be defined by quantitating the amount of intestinal metaplasia within a columnar-lined segment by histologic mapping (see Figure 2–38).

Applying these changes, which are based on non-controversial facts, will significantly improve the histologic diagnosis of reflux disease without any modification of present clinical practice. However, because the diagnosis is based on the present recommendation that biopsies be taken only in patients with an endoscopically visible columnar-lined esophagus, there is a significant underdiagnosis of reflux disease and Barrett esophagus. This is not a questionable statement. By the laws of physics, the resolution of the endoscope is limited. Changes of reflux disease must exist at a microscopic level before they become visible at endoscopy. The correct resolution of confusion in the diagnosis of gastroesophageal reflux disease will emerge only when we stop ignoring this microscopic phase of the disease. I will describe this in later chapters.

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CHAPTER 3

Histologic Definition and Diagnosis of Epithelial Types in the Esophagus and Stomach

The Importance of Histology in Understanding Disease

Virchow, in 1858, established the fundamental basis on which scientific medicine is practiced. In his now classic treatise, "Die Cellular Pathologie,"[1] he suggested that the understanding of disease must occur at the cellular level. Although future understanding will extend down to the molecular level, present technologic capability demands that gastroesophageal reflux disease be defined at the histologic level.

Unfortunately, present criteria for diagnosis of gastroesophageal reflux disease are not based in histology and have no established standard and universally accepted definitions. The result is chaos and confusion that ultimately results in suboptimal patient care and research. Histology only becomes useful in the diagnosis of reflux disease only at the stage of diagnosis of Barrett esophagus and beyond, where it becomes the mainstay of detecting intestinal metaplasia, dysplasia, and adenocarcinoma. One aim of this atlas is to change this situation. Once misconceptions and false dogmas are eradicated, histology can become a highly effective tool for the diagnosis of reflux disease from its earliest stage.

The first step in the systematic histologic study of a mucosal disease caused by luminal agents is to precisely define the various types of epithelia encountered. Defining these epithelia is the aim of this chapter. In later chapters, I will systematically seek to define the normal state, recognize it by histologic criteria, and then progress to demonstrate the sequential pathologic changes in the esophagus in reflux disease, from the earliest damage to esophageal squamous epithelium to the occurrence of reflux-induced adenocarcinoma. This will lead to accurate and easily reproducible histologic definitions of the normal state and all stages of reflux disease, replacing the present confusion with the necessary order for true scientific understanding. The standard equipment, used in every hospital in the world, is the glass slide, made from biopsies and stained by hematoxylin and eosin.

Embryologic Development

The Fetal Esophagus

The fetal esophagus (Table 3–1) is initially lined by a primitive stratified columnar epithelium.[2] This is replaced in the second trimester by a stratified

ciliated epithelium, which lines the entire esophagus. Beginning around week 22, this ciliated fetal epithelium is progressively replaced by the adult stratified squamous epithelium, which first appears in the mid-esophagus. Small areas of ciliated epithelium persist into late pregnancy and can be seen in autopsies of premature infants. They are rarely seen after full term. At full term, the entire esophagus is covered by stratified squamous epithelium, except for small areas at both ends, which are composed of a simple non-ciliated, tall columnar epithelium (Figures 3–1, 3–2, and 3–3). This columnar epithelium may persist into the early neonatal period but is ultimately replaced by adult-type stratified squamous epithelium within the first year of life. In adults, squamous epithelium normally lines the entire esophagus and stops sharply at the end of the esophagus (gastroesophageal junction).

Understanding the embryologic development of the esophagus is an important concept when one interprets studies of the fetal and neonatal

TABLE 3–1 Epithelial Differentiation in the Fetal Esophagus

Type	Description	Location	Gestational age
Fetal esophageal columnar type I	Stratified columnar epithelium; two to three layers; undifferentiated	Entire length	First trimester
Fetal esophageal columnar type II	Stratified ciliated epithelium	Entire length	Second and early third trimesters
Fetal esophageal columnar type III	Non-stratified tall or short columnar epithelium with short foveolar pit	Upper and lower ends	Third trimester; rarely after birth
Fetal esophageal columnar type IV	Intestinal type with goblet cells	Lower end—rare	Rare; transient
Superficial mucous glands (fetal and adult)	Initially associated with non-stratified columnar epithelium; later under squamous epithelium	Entire length; lamina propria of mucosa	Third trimester; persist into adult life
Squamous (fetal and adult)	Stratified squamous epithelium	Begins in middle third	22nd week to adult
Deep glands (adult)	Submucosal glands with gland ducts draining into surface	Entire length	Postnatal to adult life

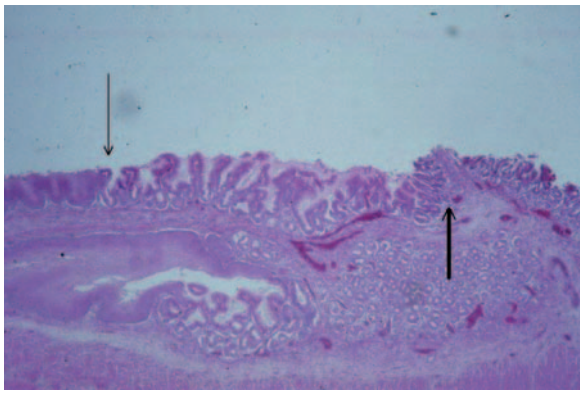

Figure 3–1 The junction between the esophagus and stomach in a premature infant born in the third trimester who survived only a few weeks. On the left is stratified squamous epithelium (*thin arrow* marks the distal limit of squamous epithelium). In the central region is undifferentiated late fetal columnar epithelium. Toward the right of the figure is mucosal glandular epithelium containing parietal cells, which can be identified below the surface layer (right of the *thick arrow*). The gastroesophageal junction is undefined at this point; it is somewhere within the undifferentiated fetal columnar epithelial zone. As development continues, this fetal columnar epithelium shrinks by differentiating into squamous epithelium on the esophageal side of the gastroesophageal junction.

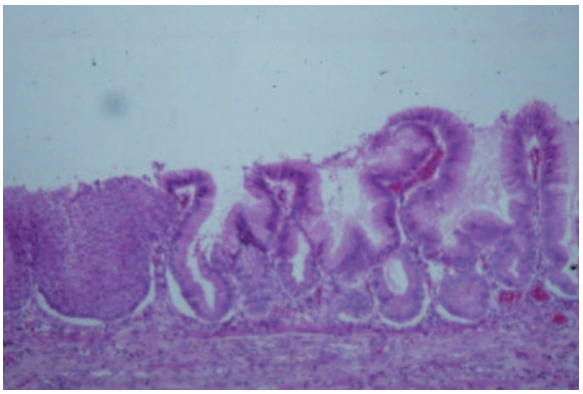

Figure 3–2 Junction between fetal stratified squamous epithelium and undifferentiated fetal columnar epithelium in the distal esophagus. The fetal columnar epithelium sits on the flat, developing muscularis mucosae and consists of a single layer of tall columnar cells, which are undulating in this collapsed state. No mucosal glands or parietal cells are seen.

esophagus. The correct interpretation of the finding of columnar lining at the distal end of the esophagus in late fetal and early neonatal life is that it is fetal epithelium. All studies show a progressive decrease in this fetal epithelium with increasing age, a feature that is typical of developing fetal structures. In the first year of life, this fetal epithelium disappears, to be replaced by stratified squamous epithelium. Three recent studies find this fetal columnar epithelium in late fetal life; two studies call this *cardiac mucosa* and conclude that cardiac mucosa is present as a normal structure in fetal life in all patients.[3,4] The third study calls this *transitional epithelium* and concludes that cardiac mucosa is not present in fetal life.[5] All three studies describe fetal columnar epithelium that is normally present in late fetal life.

The use of the term *cardiac mucosa* to describe fetal columnar epithelium must be discouraged. An epithelium composed entirely of mucous cells and devoid of parietal cells lines the entire esophagus at various stages of fetal life. This fits into the accepted definition of cardiac mucosa and means that the entire esophagus is lined by cardiac mucosa in early fetal life.

If the term *cardiac mucosa* is used for normal fetal columnar epithelium, as well as the cardiac mucosa found in adults, the distribution of cardiac mucosa shows a constant pattern until development is complete, usually in early postnatal life (Figure 3–4). At this point, fetal development of the esophageal epithelium is completed, and fetal columnar epithelium has been completely replaced by squamous epithelium. The occurrence of adult-type cardiac mucosa in the esophagus after this point is a pathological process resulting from metaplasia of the squamous epithelium induced by gastroesophageal reflux.

No one currently believes that cardiac mucosa is normally found in the esophagus in adult life. De Hertogh et al[3] clearly demonstrated that what they

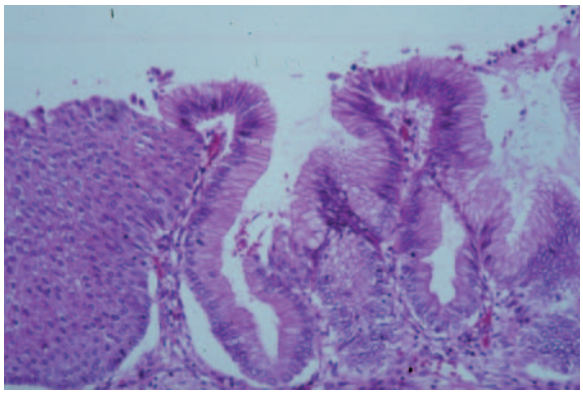

Figure 3–3 Undifferentiated fetal columnar epithelium distal to stratified squamous epithelium. The lamina propria is scanty with no inflammatory cells.

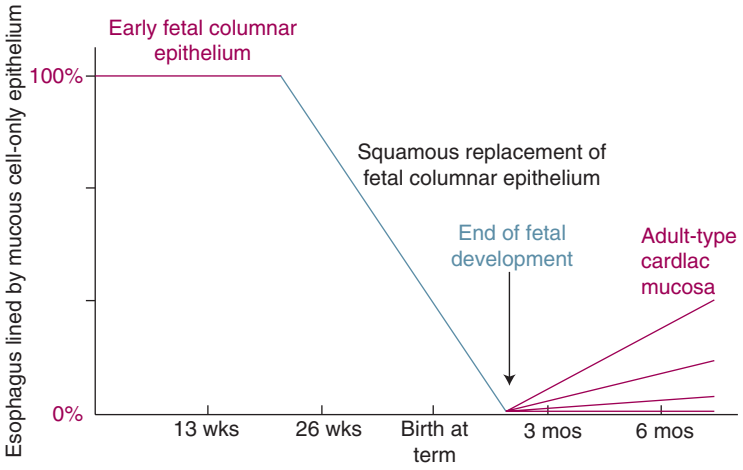

Figure 3–4 Distribution of columnar epithelium in the esophagus. Until 22 weeks of gestation, the entire esophagus is lined by a primitive columnar epithelium composed only of mucous cells, which in the second trimester becomes ciliated. Stratified squamous epithelium replaces the columnar epithelium, beginning at 22 weeks in the middle part of the esophagus and extending in both directions. This squamous replacement is complete somewhere in the third trimester to early postnatal life (in this figure, development is shown to be completed at 2 to 3 months). Normally, no columnar epithelium is present in the adult esophagus. Adult-type cardiac mucosa occurs in the esophagus as a pathologic metaplasia of the squamous epithelium induced by gastroesophageal reflux (i.e., columnar-lined esophagus), and its extent varies considerably among patients, depending on the amount of reflux.

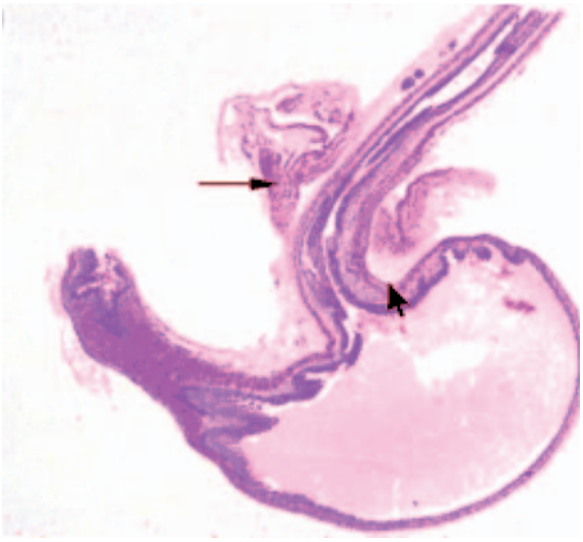

Figure 3–5 Autopsy specimen showing the esophagus and stomach with the diaphragm in place *(arrow).* The angle of His *(arrowhead)* marks the gastroesophageal junction. The area between the two is the abdominal esophagus. The data in the study showed that "cardiac mucosa" (in reality, fetal columnar epithelium identical in appearance to that shown in Figure 1–3) was found in the abdominal esophagus above the angle of His. (Reproduced with permission from De Hertogh G, Van Eyken P, Ectors N, et al: On the existence and location of cardiac mucosa: an autopsy study in embryos, fetuses, and infants, *Gut* 52:791–796, 2003.)

were calling *fetal cardiac mucosa* was present in the esophagus proximal to the gastroesophageal junction (the angle of His in their beautiful studies) (Figure 3–5).

Late fetal columnar epithelium in the esophagus is different from adult-type metaplastic cardiac mucosa in the following respects:

1. It is well organized, consisting of an undulating epithelium composed of a uniform population of tall columnar cells with apical mucin (see Figure 3–3) that has a horizontal muscularis mucosae beneath it.
2. It is completely devoid of inflammatory cells in the lamina propria.
3. It does not contain parietal cells; ciliated columnar cells are present in the second and third trimesters; and goblet cells may appear in fetal columnar epithelium in the second trimester as a transient event. This does not mean that Barrett esophagus can be a congenital phenomenon. The developing fetal epithelium is simply displaying its potential for differentiation.
4. Its length progressively decreases with increasing fetal age. Adult-type cardiac mucosa tends to increase in length with increasing age.

Two types of glands are encountered in the adult esophagus. Superficial glands are located in the lamina propria of the esophageal mucosa. They arise in fetal life as out-pouchings from fetal columnar epithelium.[2] When the fetal columnar epithelium is replaced by squamous epithelium, these glands remain and are seen in the adult esophagus. Deep glands are located in the submucosa. According to Johns,[2] they occur after fetal life and after the esophagus has been replaced by stratified squamous epithelium. They arise as out-pouchings of the squamous epithelium that traverse the mucosa and result in glands within the submucosa. The original out-pouchings remain as the ducts that drain these glands into the surface.

The Fetal Stomach

Normal human gastric mucosa is always columnar. In the 13th week of fetal life, the primitive stratified columnar epithelium invaginates into a foveolar pit and develops glands that contain parietal cells.[6,7] From this point, the gastric epithelium increases in thickness to become adult gastric mucosa. De Hertogh

et al[3] showed that parietal cells are present at the gastroesophageal junction (angle of His) in fetuses (see Figure 3–5), indicating that the entire stomach is lined by parietal cell-containing epithelium. There is normally no cardiac mucosa or fetal columnar epithelium devoid of parietal cells distal to the gastroesophageal junction after the 17th week of fetal development.

Histologic Definition of Epithelial Types in Postnatal Esophagus and Proximal Stomach

When defining the epithelia of this region, no attempt will be made to ascribe an esophageal or gastric location to the different epithelia. This is because the location of the gastroesophageal junction is controversial, and there is evidence that the present understanding of the location of the gastroesophageal junction is flawed. The anatomic area that is considered here extends from the beginning of the esophagus to the point at which gastric oxyntic mucosa in the body of the stomach transforms into pyloric antral mucosa. The true gastroesophageal junction is certainly included within this defined area.

In this chapter, I will concentrate on the definition and diagnosis of the various epithelial types. The exact placement of these epithelial types, their significance, and which epithelia are normal and abnormal will be discussed.

Stratified Squamous Epithelium

This is a flat epithelium with superficial keratinocytes and a proliferative basal region that is normally less than 20% of the epithelial thickness (Figure 3–6). The squamous epithelium is a dynamic epithelium in which surface epithelial cells are continuously lost during swallowing. The basal zone contains the progenitor stem cells of the esophagus, which continuously proliferate to replace lost surface cells. In the normal squamous epithelium, the proliferative zone of cells can be identified as two to three layers of suprabasal cells by Ki67 staining (see Figure 2-26). In the normal squamous epithelium, the time taken for a cell to move from the basal region and shed at the surface is 7 to 8 days.[8] During this process of migration to the surface of the epithelium, the squamous cell loses its mitotic capability, becomes keratinized, and flattens out at the surface.

The state of normalcy of the squamous epithelium is difficult to define. Gastroesophageal reflux is such a common occurrence in humans that it is difficult to be certain that any squamous epithelium examined has not been

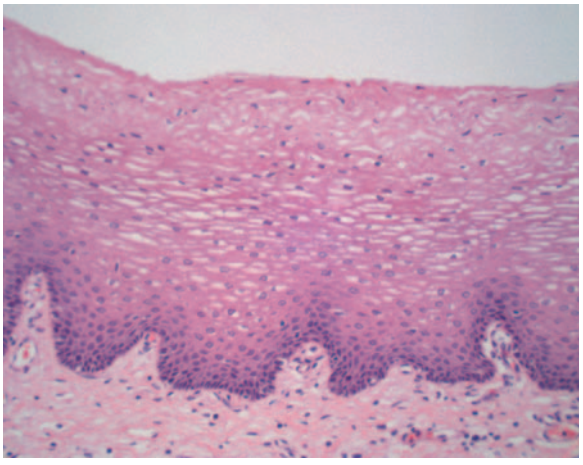

Figure 3–6 Normal stratified squamous epithelium lining the esophagus. This is non-keratinizing and flat with short (less than 60% of epithelial thickness) papillary extensions and a basal cell region that is one to three cells thick and less than 20% of the thickness of the epithelium.

exposed to gastric refluxate. It is likely that many very early and nonspecific changes caused by reflux fall within the present definition of "normal" squamous epithelium (see Figures 2-20, 2-21). This may include slight thickening of the epithelium because no limits have been established for "normal thickness." A few lymphocytes may appear in the epithelium without it being recognized as abnormal. The earliest recognized abnormalities described in Chapter 2 used for the diagnosis of reflux esophagitis are intercellular edema ("dilated intercellular spaces"), basal cell hyperplasia and elongation of papillae, and the presence of intraepithelial eosinophils. These have been established as abnormal and indicative of reflux because they have been associated with reflux disease diagnosed largely by the presence of reflux symptoms. Because symptoms are not a valid diagnostic criterion for reflux disease, the definition of these diagnostic criteria is also likely to be inaccurate. It is very likely that what we call "normal squamous epithelium" in fact has features of reflux damage that we do not recognize.

Normal stratified squamous epithelium is an excellent barrier that is impervious to luminal molecules (Figure 3–7). This barrier effect is the result of tight cell junctions that keep the keratinocytes closely apposed to one another. The squamous epithelium contains nerve endings that reach approximately halfway up the epithelium. These are sensitive to pain. These nerve endings are normally separated from luminal molecules by the superficial cells of the epithelium. The nerve endings may also play a role as afferents in the neuromuscular functions of the esophagus and the sphincter, but this is not well understood.

Mucous glands are found sporadically and are located both in the lamina propria (Figure 3–8) and submucosa (Figures 3–9, 3–10, and 3–11). They are easily seen in resection specimens (see Figures 3–9 and 3–10). Because of their location, they are rarely encountered in a biopsy specimen (see Figure 3–11). Glands, both mucosal and submucosal, tend to remain when the squamous epithelium of the esophagus undergoes columnar metaplasia. This is easy to detect in resection specimens (Figure 3–12) but more difficult in biopsies in which the glands tend to be more superficial and merge with the glands of the columnar metaplastic epithelium (Figures 3–13 and 3–14).

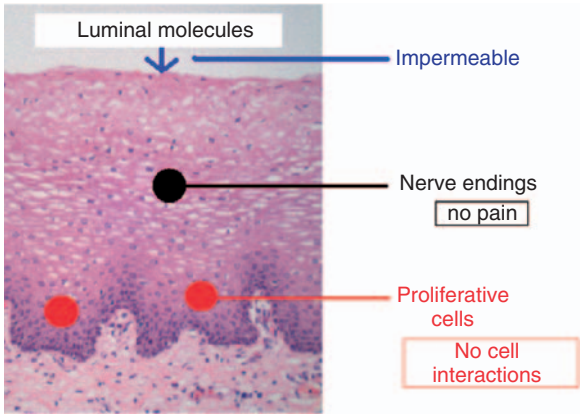

Figure 3–7 The normal squamous epithelium is impermeable to the entry of luminal molecules. Because of this, there is no interaction between luminal molecules and nerve endings in the mid-region of the epithelium or the proliferative cells that are restricted to the basal region.

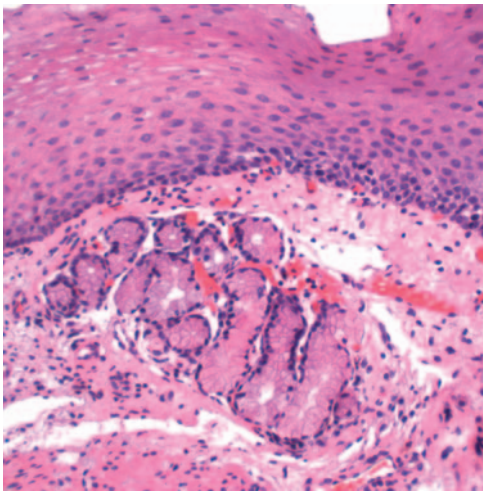

Figure 3–8 Esophageal biopsy showing a mucous gland in the lamina propria.

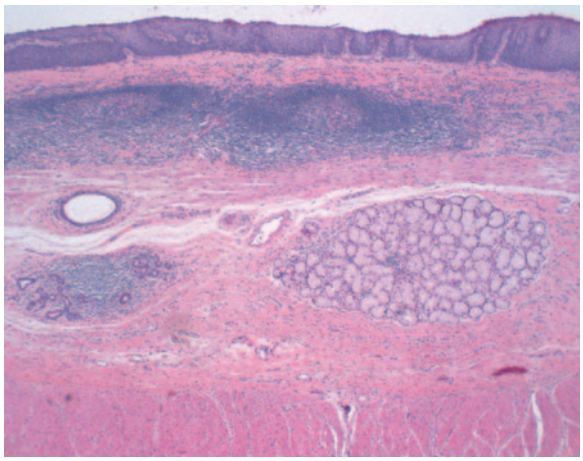

Figure 3–9 Esophagectomy specimen showing a deep mucous gland in the submucosa. The overlying mucosa is lined by squamous epithelium. The submucosal gland is located between the muscularis mucosae and the muscularis externa. Two glands are seen. The one on the left appears normal; the one on the right shows chronic inflammation, atrophy of acini, and dilatation of the duct. There are two lymphoid aggregates in the lamina propria above the inflamed gland. The significance of this is unknown.

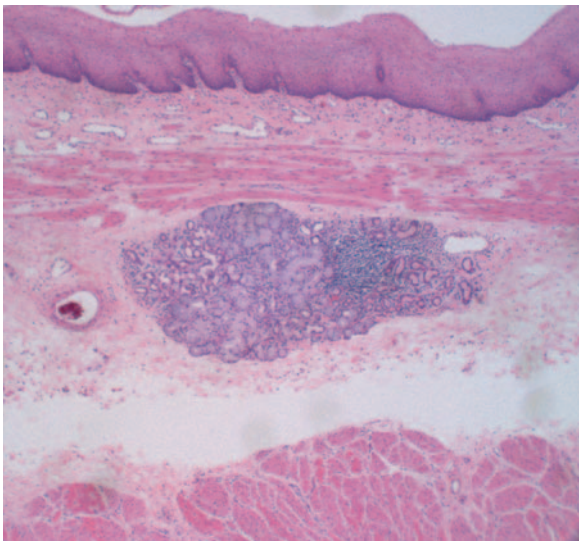

Figure 3–10 Higher magnification of deep esophageal gland located in the submucosa between the muscularis mucosae and muscularis externa. The gland shows focal chronic inflammation.

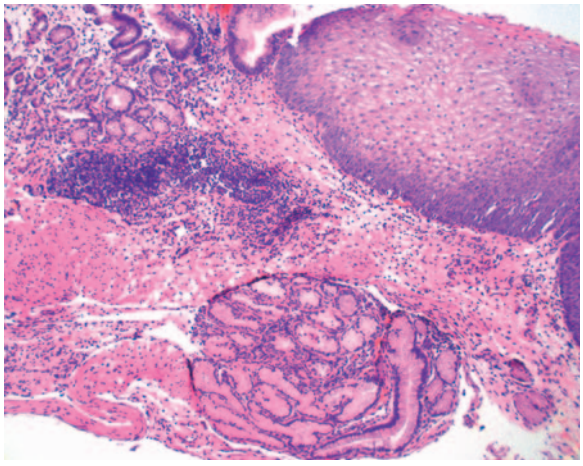

Figure 3–11 Esophageal submucosal gland at the squamocolumnar junction. Note the transition of squamous epithelium to oxyntocardiac mucosa. There is chronic inflammation in the lamina propria at the junction. The submucosal gland is immediately under the muscularis mucosae.

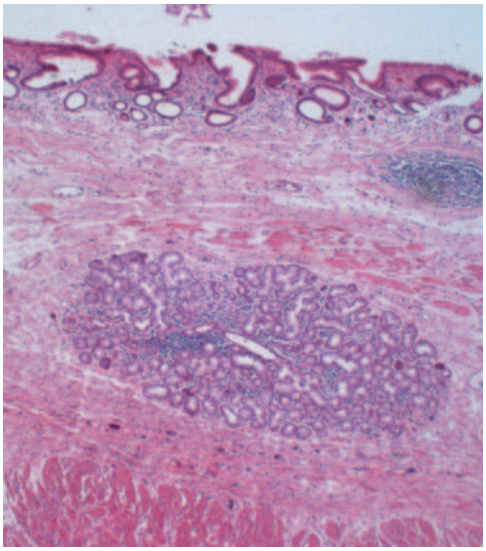

Figure 3–12 Submucosal mucous gland in the esophagus lined by metaplastic columnar epithelium of cardiac type. The presence of the gland confirms the esophageal location of this columnar lining.

These glands resemble minor salivary glands and drain to the surface via gland ducts that traverse the lamina propria and epithelium. The ducts of the submucosal glands can be identified within the lamina propria in mucosal biopsies and define the location of the biopsy as esophageal, whether the surface epithelium is squamous or metaplastic columnar types (Figures 3–15 to 3–20). The ducts are lined with a varying mixture of columnar and squamous cells (see Figures 3–15 to 3–18); rarely, ciliated cells (see Figure 3–19)

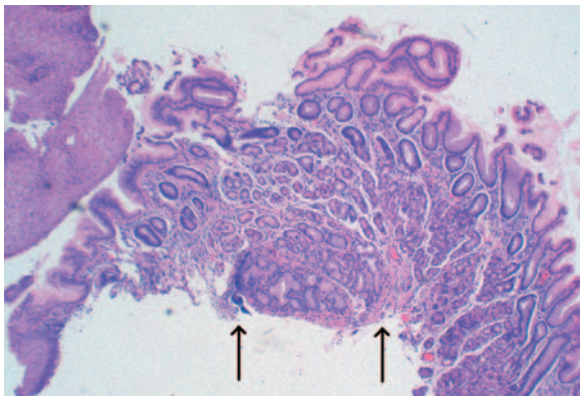

Figure 3–13 Superficial mucosal gland in the deep part of the metaplastic oxyntocardiac mucosa in the esophagus (between the two *arrows*). The gland can be recognized because of its lobulated appearance and its location deep to the glands of the epithelium, which contain parietal and mucous cells.

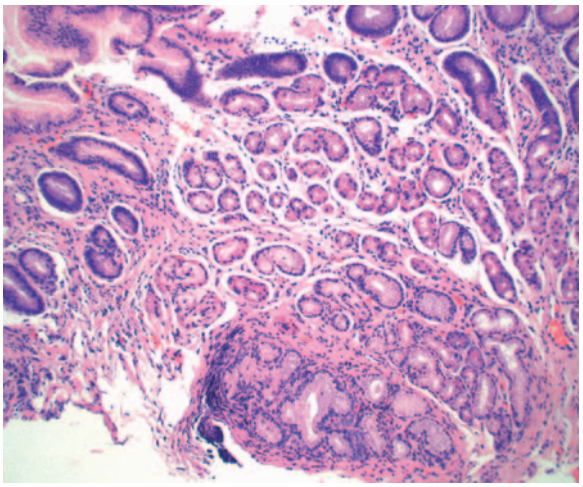

Figure 3–14 Higher magnification of Figure 3–13, showing a residual esophageal mucosal gland in oxyntocardiac mucosa.

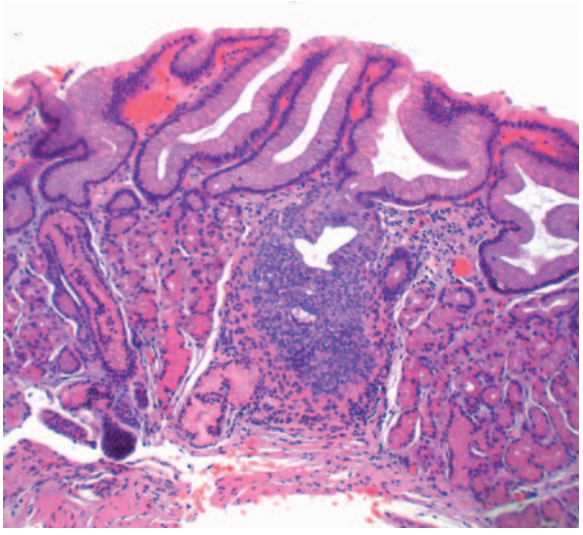

Figure 3–15 Gland duct in the lamina propria of metaplastic esophageal oxyntocardiac mucosa. The gland duct is lined by a mixture of columnar cells and basaloid squamous cells. It appears to open into the deep foveolar pit.

and columnar cells with basophilic cytoplasm that contain Alcian blue positive-acid mucin (see Figure 3–20) may be present.

Because submucosal glands are distributed sporadically in the esophagus and vary in number among individuals, only the positive finding of a gland or gland duct can categorize the location of the biopsy as esophageal. The absence of gland ducts means nothing; specifically, it does not exclude the location as esophageal. We reported the finding of gland ducts in 64 (13.6%) of 471 biopsies that showed cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa.[9]

Pathologic changes occur in esophageal squamous epithelium due to diseases other than gastroesophageal reflux disease. These include infections (*Candida*, cytomegalovirus, herpes simplex, herpes varicella-zoster, human immunodeficiency virus), trauma, chemical injury (lye, pills), immunologic diseases (pemphigus vulgaris, scleroderma), and neoplasms (squamous

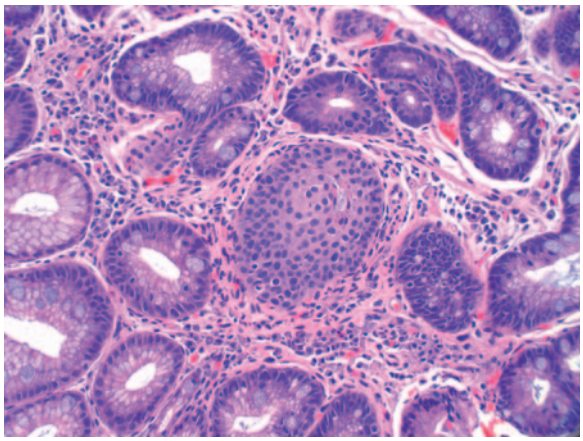

Figure 3–16 Gland duct in the metaplastic esophageal intestinal metaplastic epithelium. The gland duct consists of a small, slit-like, mucin-filled lumen lined by flat cuboidal epithelium, which is surrounded by basaloid squamous epithelium.

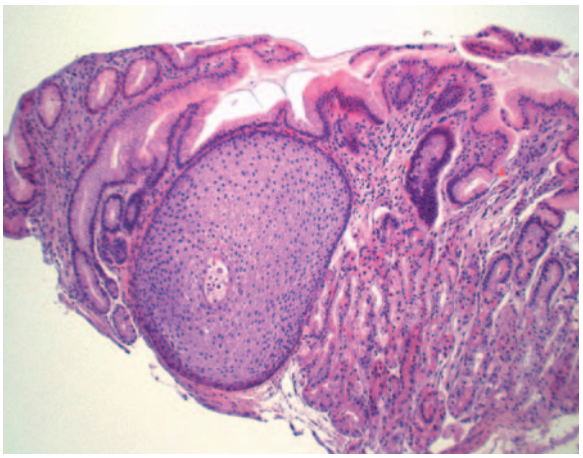

Figure 3–17 Large, predominantly squamous-lined duct in the lamina propria of metaplastic oxyntocardiac mucosa of the esophagus.

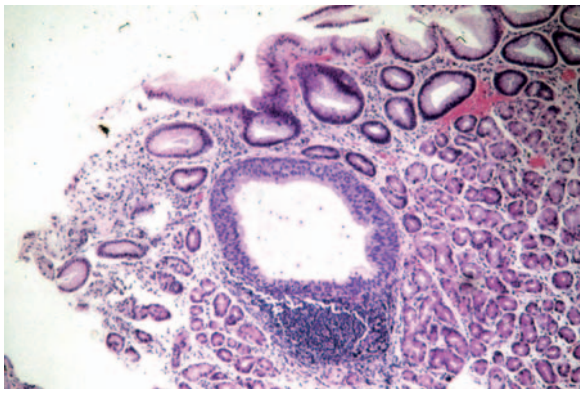

Figure 3–18 Gland duct in metaplastic esophageal oxyntocardiac mucosa. The duct is dilated and lined by a mixed glandular and basaloid squamous epithelium.

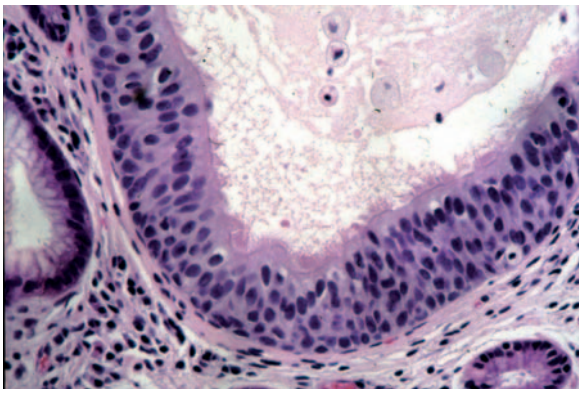

Figure 3–19 Higher magnification of the lining of the duct shown in Figure 3–18, showing ciliated columnar epithelium.

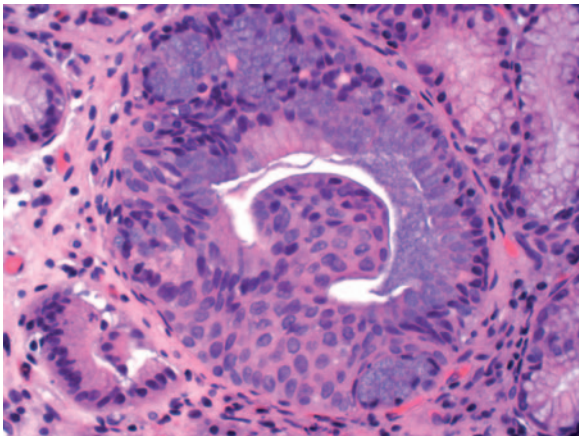

Figure 3–20 Gland duct in cardiac mucosa. The lower half is lined by squamous epithelium. The upper half of the duct is lined by columnar epithelium with prominent basophilic mucin in the cytoplasm ("columnar blue cells"). These cells can mimic goblet cells, and care is necessary not to diagnose them as intestinal metaplasia.

papilloma, carcinoma). These entities must be reported when they are encountered.

Columnar Epithelia

Basic Structure

Columnar epithelia in this region have three basic components—the surface epithelium, foveolar region, and glands[10] (Figure 3–21). Surface and foveolar pit cells are normally mucous cells; the cells comprising the glands are varied and can include mucous cells, parietal cells, chief cells, Paneth cells, and serous (pancreatic) cells. Neuroendocrine cells are scattered throughout columnar epithelia.

Columnar epithelial cells are continuously shed at the surface. These surface cells are replenished by proliferation of the progenitor stem cells. The stem cells in all columnar epithelia are located in the deepest part of the foveolar pit (Figures 3–21, 3–22, and 3–23). Ki67 stain shows proliferative cells normally limited to the deep foveolar region (Figure 3–24). The only exception to this is in a flat epithelium without a foveolar region; in this instance, the stem cells are in this flat layer of cells (see Figure 3–23).

Division of stem cells in the deep foveolar region in columnar epithelia of this region is associated with two lines of differentiation[8] (see Figure 3–22):

1. More than 95% of the products of stem cell division move upward in the foveolar pit. As they do this, they lose their mitotic capacity and differentiate into surface mucous cells with apical mucin. This line of differentiation is associated with a short life span of the cells.
2. In columnar epithelia that have glands, the stem cell products that are destined to differentiate into glandular cells move downward from the foveolar pit. These glandular cells lose their mitotic capacity and either remain as mucous cells or differentiate into parietal cells. Glandular cells

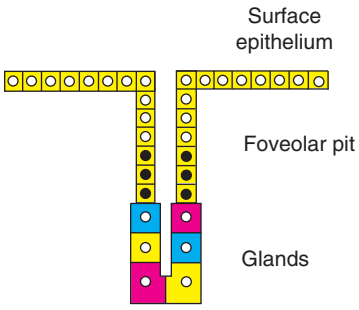

Figure 3–21 Diagrammatic representation of the basic structure of glandular epithelium in the esophagus and stomach. The surface and foveolar pit are lined with mucous cells. The proliferative zone is in the deep foveolar region (shown by black nuclei). The gland consists of long-lived stable cells of a variety of types; shown here are parietal cells *(pink),* chief cells *(blue),* and mucous cells *(yellow)*.

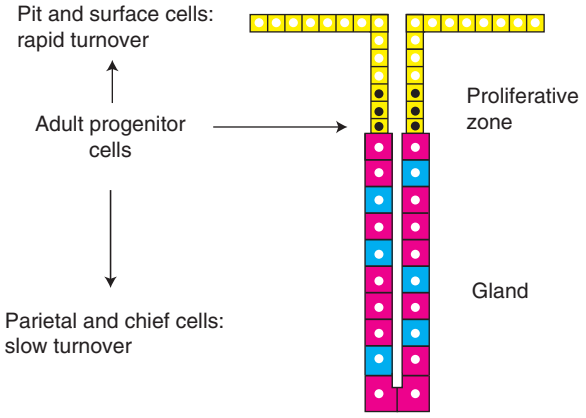

Figure 3–22 Diagram showing the cell kinetics of normal gastric oxyntic mucosa. The proliferative stem cells in the deep foveolar region divide and move toward the surface or downward into the gland. Those that move upward pass along the foveolar region to become the differentiated mucous cells of the surface and have a short life span. Those that move into the gland differentiate into parietal and chief cells and have a long life span.

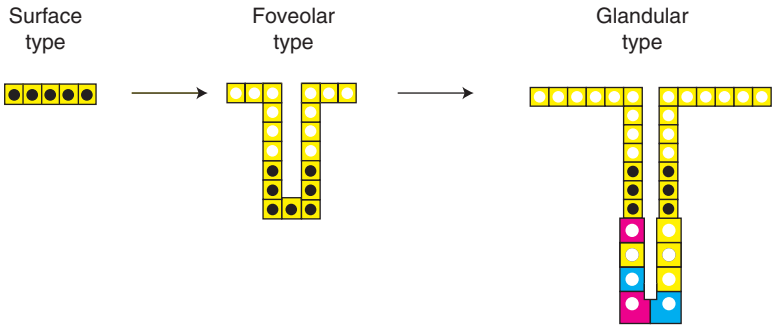

Figure 3–23 Three basic epithelial types in columnar-lined esophagus. The columnar epithelia evolve from the simplest, where it consists of a single layer of mucous cells, to the formation of a foveolar pit and then a gland. Only the gland contains parietal cells.

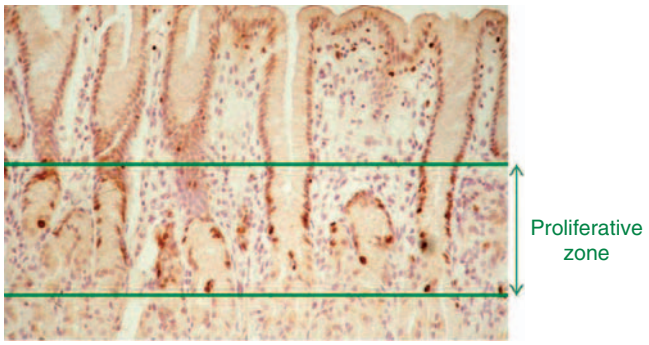

Figure 3–24 Immunoperoxidase stain for Ki67 in normal gastric oxyntic mucosa, showing positive staining in cells of the proliferative region, which is normally limited to the deep foveolar region (between the two horizontal green lines).

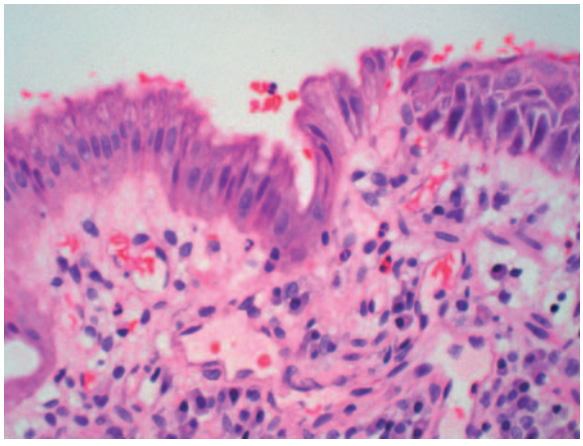

Figure 3–25 A section of the squamocolumnar junction showing transition from the thin squamous epithelium (on the right) to a single flat layer of columnar epithelial cells of mucous type. This is the "surface-only" type of cardiac mucosa.

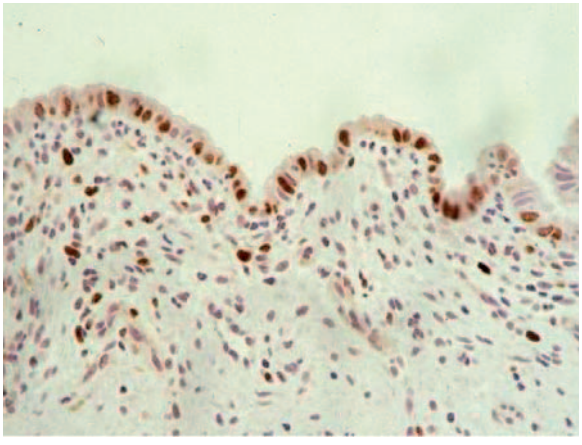

Figure 3–26 Immunoperoxidase stain for Ki67 on "surface-only" type cardiac mucosa, showing strong positive staining of the proliferative stem cell pool.

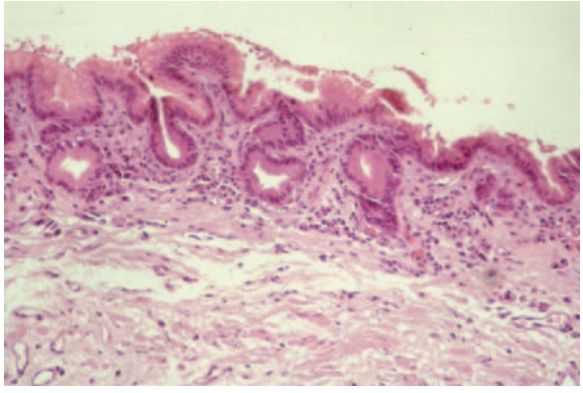

Figure 3–27 Early invagination of the surface columnar cells into a rudimentary foveolar pit. The cells are still entirely undifferentiated mucous cells. This is the "surface plus foveolar type" of cardiac mucosa.

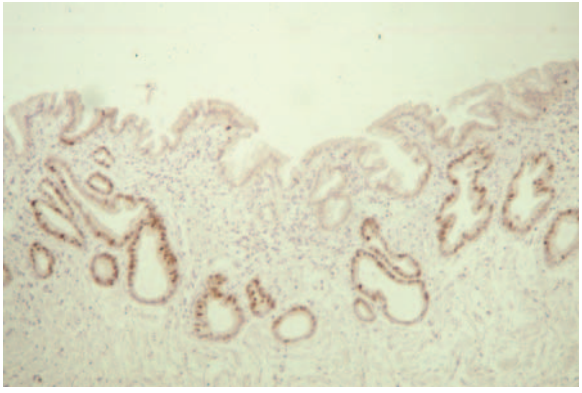

Figure 3–28 Immunoperoxidase stain for Ki67 on the "surface plus foveolar type" of cardiac mucosa, showing positivity limited to the deep foveolar region with the surface region being negative. This indicates that the proliferative stem cell pool has moved down into the deepest part of the foveolar pit.

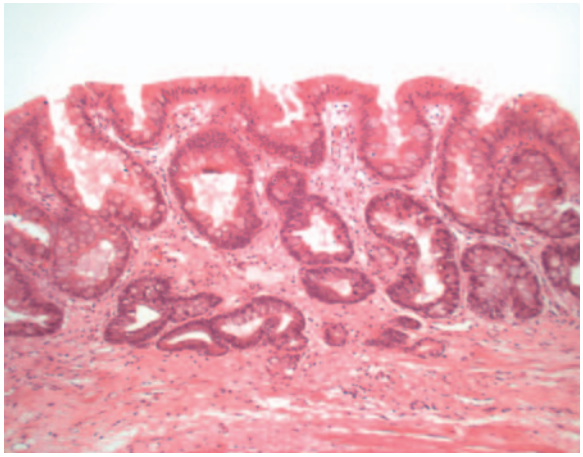

Figure 3–29 Well developed "surface plus foveolar type" epithelium showing tortuosity of the deep part of the foveolar pit. In this section, it is difficult to determine whether the deep part of the epithelium contains glands. The epithelium is a mixture of mucous and goblet cells, indicating cardiac mucosa with extensive intestinal metaplasia.

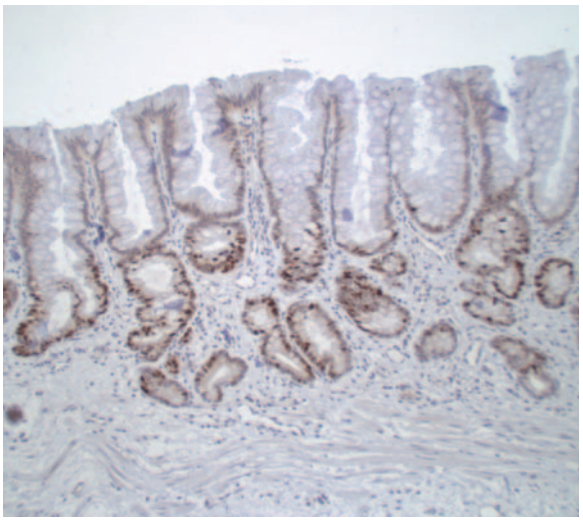

Figure 3–30 Immunoperoxidase stain on "surface plus foveolar type" of cardiac mucosa with intestinal metaplasia. This shows Ki67 positivity extending to the deepest part of the foveolar pit. There are no Ki67-negative glands deep to the foveolar region.

may also differentiate into chief cells, Paneth cells, serous (pancreatic) cells, or neuroendocrine cells. Glandular cells can be recognized by the fact that they are non-mitotic (i.e., Ki67-negative) and are located deep to the proliferative Ki67-positive cell zone in the deep foveolar region (see Figures 3–21 to 3–24). Glandular cells are stable and have a long life span that ranges from 1 to 6 months. They undergo programmed cell death and are replaced by new glandular cells from the stem cells. Ki67 staining is valuable in understanding the dynamics of glandular epithelial types in this region.

Columnar epithelia can be divided into three types (see Figure 3–23), based on which of the three components are present:

1. "Flat surface type," composed of a single layer of columnar mucous cells without a foveolar pit (Figure 3–25). This is usually seen in healing erosions and represents a regenerative epithelium. Intense Ki67 positivity in the flat surface layer is usually seen (Figure 3–26).
2. An epithelium composed of a surface layer, which has invaginated into a foveolar pit of varying length (Figure 3–27). In this "surface plus foveolar-type" columnar epithelium, the Ki67-positive proliferative zone and stem cells are located in the deepest part of the foveolar pit. The superficial foveolar region and surface are composed of Ki67-negative, terminally differentiated mucous cells (Figure 3–28). The flat surface type and surface plus foveolar epithelial types are normally composed of mucous cells only (see Figures 3–25 and 3–27) or a mixture of mucous cells and goblet cells (Figures 3–29 and 3–30).
3. An epithelium that contains a gland below the foveolar pit—"surface plus foveolar plus glandular-type." Specialized cells such as parietal and chief cells are found only in glands (Figure 3–31). The cells in the gland are long-lived, are not mitotically active, and are therefore negative for Ki67 (Figure 3–32).

In the pathological state of intestinal metaplasia, goblet cells occur in this region (see Figure 3–29). It can be difficult to differentiate a tortuous foveolar pit from a gland at the base of the mucosa on routine stains (see Figure 3–29). In such cases, Ki67 staining clearly demarcates the proliferative Ki67-positive foveolar pit from the Ki67-negative gland. If there is a Ki67-negative glandular structure below the proliferative zone, the epithelium is glandular in type (see Figure 3–32). If the Ki67-positive cells reach the base of the epithelium, the epithelium is a foveolar type of epithelium (see Figure 3–30).

In evaluating and classifying columnar epithelia, the basic structural unit that is considered is a single foveolar gland complex. The type of epithelium is determined by criteria applied to each unit. Thus, it is possible to categorize each biopsy or section into its exact composition (Figures 3–33 and 3–34). For example, in Figure 3–33, approximately 50% of the biopsy is composed of oxyntocardiac mucosa, and 50% is composed of cardiac mucosa. In Figure 3–34, approximately 50% is composed of intestinal and cardiac mucosa. An infinite mixture of the three epithelial types can be defined quantitatively. Such complexity of classification is not necessary in clinical reporting but is valuable in research if quantitation of the different epithelial types is necessary.

Cell Types

All columnar epithelia in this region have an identical surface layer and foveolar pit composed entirely of mucous cells (Figure 3–35). The surface mucous cells have the typical picket-fence appearance with basal nuclei, straight and parallel lateral cell borders that are very distinct, and a homogeneous eosinophilic cytoplasm without a brush border. The foveolar pit is lined by similar cells. The surface and foveolar mucous cells are often different in appearance than the mucous cells in the glands, which tend to be more rounded with flattened basal nuclei and vacuolated cytoplasm (Figure 3–36). This normal appearance of the surface and foveolar pit may be altered by the presence of multi-layered epithelium (Figures 3–37 and 3–38) and goblet cells (in intestinal metaplasia) (Figure 3–39).

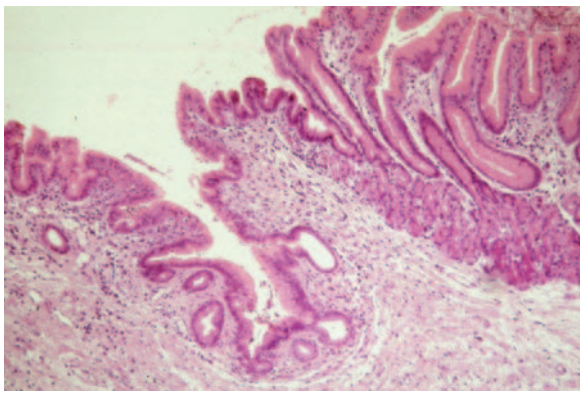

Figure 3–31 Evolution of the "surface plus foveolar type" of cardiac mucosa (on the right) to a glandular mucosa on the left. The glands are seen as lobulated structures composed of mucous cells and parietal cells deep to the foveolar region. This glandular mucosa in the right half of the picture is oxyntocardiac mucosa.

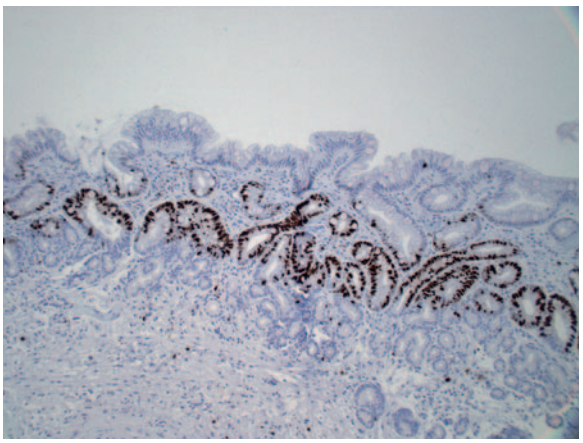

Figure 3–32 Immunoperoxidase stain on glandular-type mucosa showing the presence of Ki67-negative glands under the Ki67-positive proliferative stem cell zone in the deep foveolar region. The glands consist of mucous cells only without parietal cells. The surface and foveolar region are composed of a mixture of mucous and goblet cells, indicative of cardiac mucosa with intestinal metaplasia.

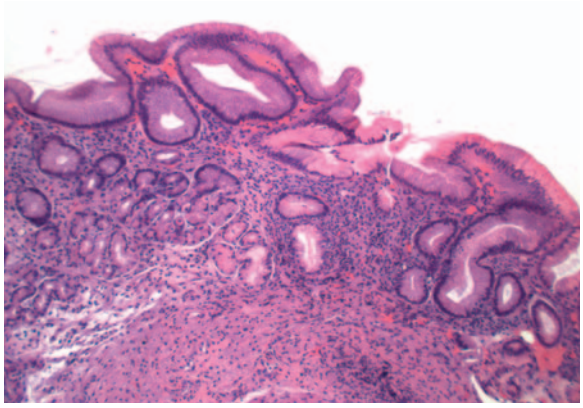

Figure 3–33 Biopsy from columnar metaplastic epithelium of the esophagus. The right half of the field shows cardiac mucosa consisting entirely of mucous cells. The left half of the field shows oxyntocardiac mucosa, with glands containing a mixture of mucous and parietal cells.

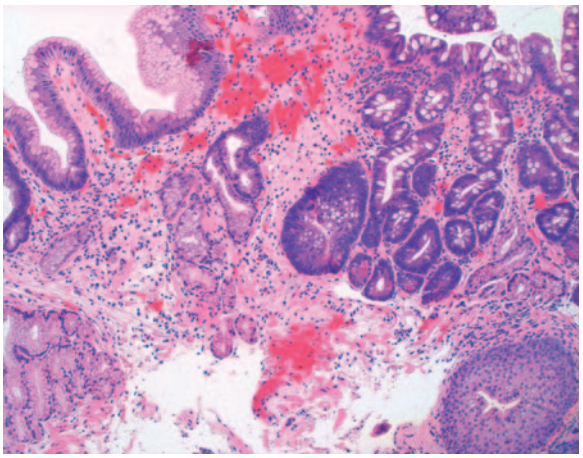

Figure 3–34 Biopsy from columnar metaplastic epithelium of the esophagus. The right half of the field shows cardiac mucosa with extensive intestinal metaplasia, including the presence of Paneth cells. The left half of the field is composed of cardiac mucosa with mucous cells only. Note the presence of a gland duct in the lamina propria, which characterizes the location of this biopsy as esophageal.

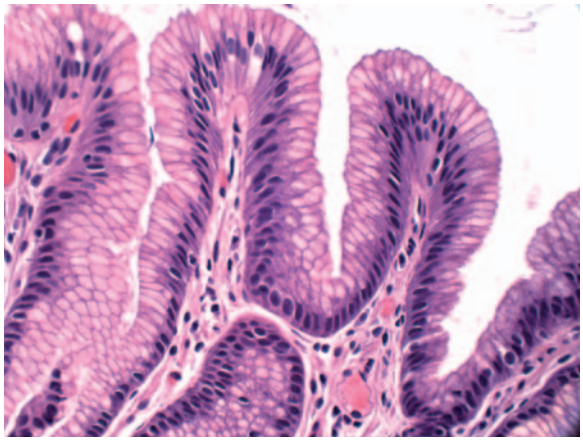

Figure 3–35 Mucous cells lining the surface and foveolar region. Although they appear identical morphologically, the deep foveolar region cells are the Ki67-positive proliferative stem cells, and the superficial cells are non-mitotic, terminally differentiated Ki67-negative cells.

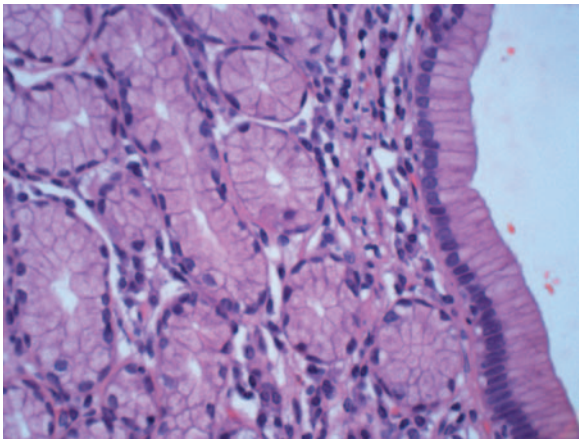

Figure 3–36 Mucous cells in the glandular element in cardiac mucosa are different in appearance than the foveolar cells. They are more rounded and have more flattened nuclei and foamy cytoplasm.

The presence or absence of parietal (i.e., oxyntic) (Figure 3–40) and mucous cells (Figure 3–41) in the glands and the presence of goblet cells (Figure 3–42) are used to define the different columnar epithelial types in this region (see Table 3–2). Parietal cells are large cells with a round contour and have eosinophilic cytoplasm (see Figure 3–40). Mucous cells that populate the glands have an appearance that is different than the mucous cells in the foveolar region. They are round and have more rounded nuclei and vacuolated cytoplasm that does not have the picket-fence appearance of the foveolar and surface cells (see Figure 3–41). The progenitor stem cells in the deep part of the foveolar pit are morphologically identical to mucous cells. There are

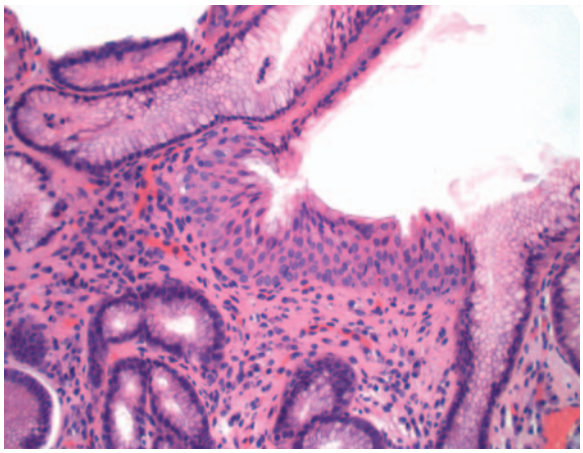

Figure 3–37 Multi-layered surface epithelium in cardiac mucosa, consisting of surface columnar cells with basaloid reserve cells under the columnar layer.

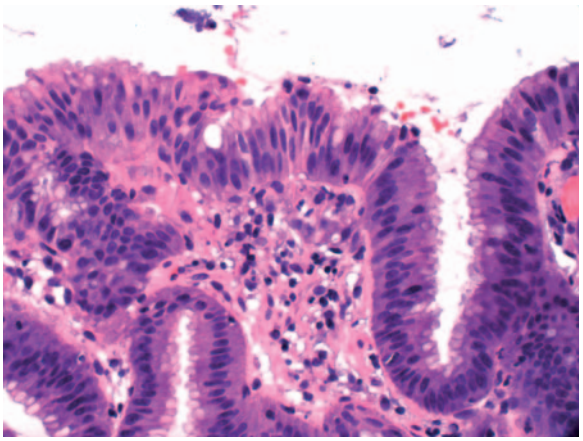

Figure 3–38 Multi-layered surface epithelium in cardiac mucosa, showing stratified columnar epithelial cells.

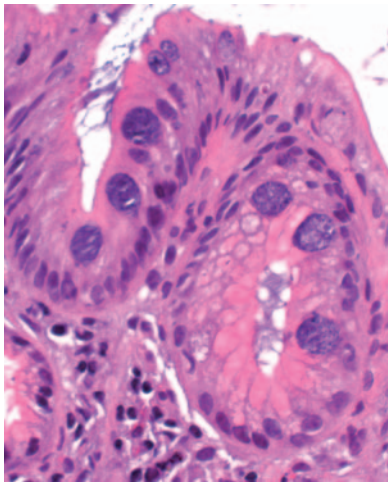

Figure 3–39 Goblet cells in cardiac mucosa, indicative of intestinal metaplasia. Goblet cells are large and round with a large cytoplasmic vacuole, which is filled with mucin. The vacuole distends the lateral cell borders. The cells may have a brush border (top left) or may be associated with the apical mucin typical of cardiac mucous cells (right). In this instance, the mucin stains deeply basophilic with hematoxylin. The mixture of cardiac-type cells with goblet cells is typical of "incomplete intestinal metaplasia." The presence of a brush border and Paneth cells indicates "complete intestinal metaplasia."

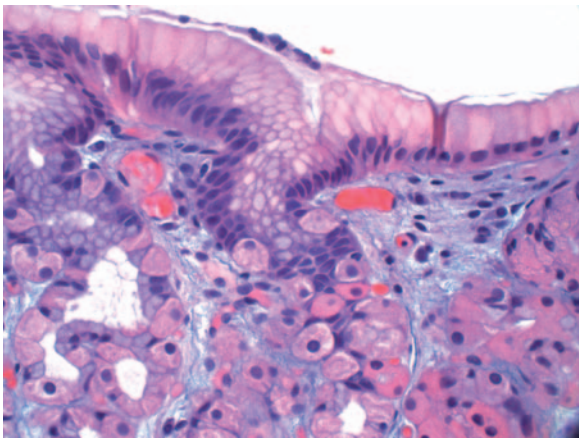

Figure 3–40 Gastric oxyntic mucosa, consisting of a surface epithelium and short foveolar pit, from which arise as glands containing parietal cells. These are large, round cells with small, round, central nuclei and abundant eosinophilic cytoplasm. They are the dominant cells in the gland. In the deep foveolar region of the gland complex on the left are scattered mucous cells in the isthmus of the gland. These have a somewhat basophilic cytoplasm. These cells are the mucous neck cells. Many of them show pre-zymogenic granules on electron microscopy and represent precursors of chief cells.

also mucous cells in the region of the gland immediately below the foveolar pit that contains mucous cells. These are known as *mucous neck cells* and frequently have basophilic cytoplasm (see Figure 3–40). They are frequently pre-zymogenic and are precursors of chief cells as shown by the presence of zymogenic granules on electron microscopy.[8]

Goblet cells have a single, round cytoplasmic vacuole that displaces the nucleus toward the base and distends the lateral cell border (see Figures 3–39 and 3–42). Goblet cells contain acid mucin. In hematoxylin-stained and

eosin-stained sections, goblet cells frequently have a basophilic granular content (see Figure 3–39). However, with some preparations, the vacuole can be empty and clear (see Figure 3–42).

The glands can contain numerous cell types apart from parietal and mucous cells. These include the following:

1. Neuroendocrine cells, which appear as small cells with round nuclei and clear cytoplasm interspersed between other cells (Figure 3–43). They can be highlighted by the use of immunoperoxidase markers, such as synaptophysin or chromogranin.
2. Chief cells, which are basophilic cells seen with the parietal cells (Figure 3–44).

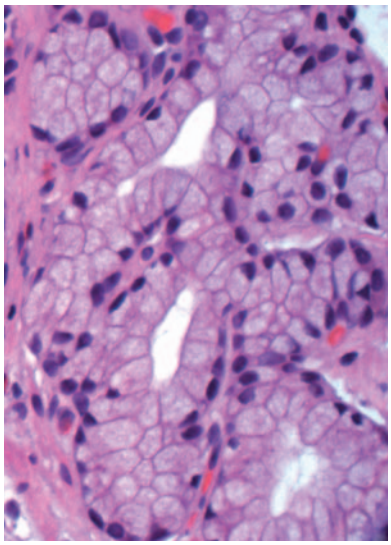

Figure 3–41 Appearance of mucous cells in the glands. These have vacuolated, foamy, eosinophilic cytoplasm.

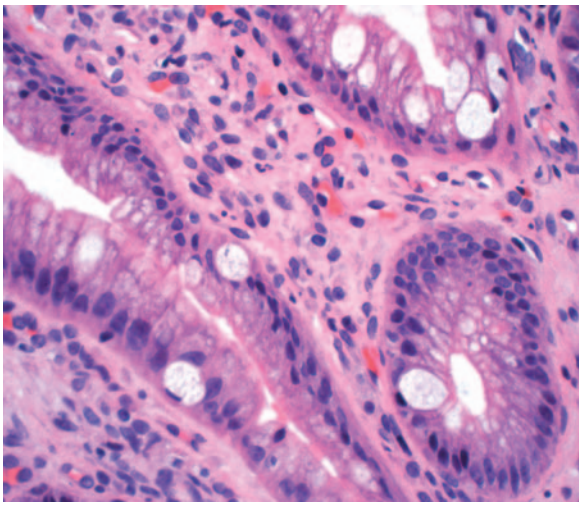

Figure 3–42 Appearance of goblet cells in cardiac mucosa. These cells have a mucin vacuole that is less basophilic and clearer and appears empty. The absence of basophilia does not negate the fact that this is a goblet cell.

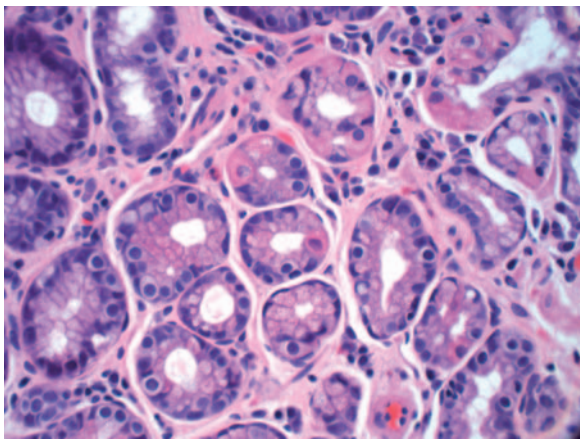

Figure 3–43 Oxyntocardiac mucosa with glands composed of a mixture of mucous cells and parietal cells. Scattered in the gland are round cells with central round nuclei, which are dense and clear cytoplasm. These are neuroendocrine cells and can be specifically identified by neuroendocrine markers.

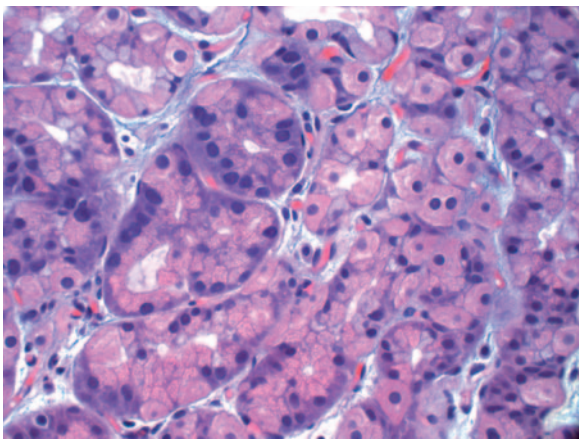

Figure 3–44 Deep glandular region of gastric oxyntic mucosa showing the presence of numerous parietal cells with an admixture of the more basophilic chief cells. Note that although there are no mucous cells, the differentiation of mucous and chief cells is based almost entirely on the tincture of the cytoplasm.

3. Paneth cells, which are usually seen in the deep regions of the gland and are columnar cells with basal nuclei and intensely eosinophilic granular cytoplasm (Figures 3–45, 3–46, and 3–47).
4. Serous, or pancreatic cells, which resemble the acinar cells of the pancreas with basophilic granular cytoplasm (Figures 3–48, 3–49, and 3–50).

Classification

The classification of columnar epithelial types given here follows the excellent definitions used by Paull et al in 1976.[11] They described the defining criteria: "When columnar epithelium was present in esophageal biopsies the following features were assessed: surface architecture; surface cell types—whether consisting only of gastric surface cells or gastric surface combined with intestinal

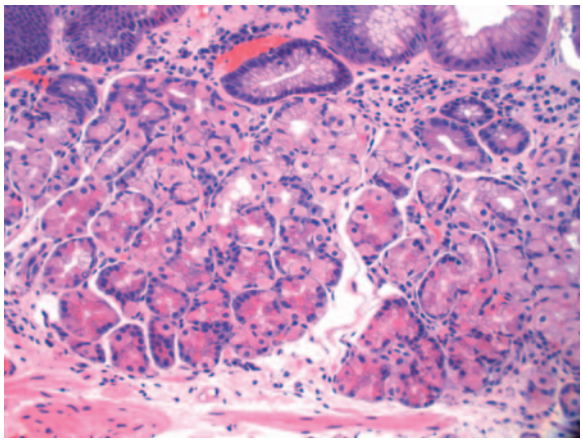

Figure 3–45 Metaplastic esophageal epithelium of oxyntocardiac type with lobulated glands containing mucous cells, parietal cells, and numerous Paneth cells. The Paneth cells are seen largely in the deeper half of the gland.

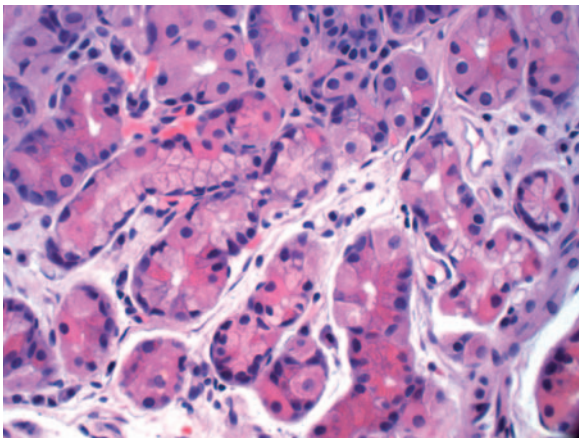

Figure 3–46 Higher magnification of Figure 3–45, showing the deeper part of the gland in oxyntocardiac mucosa. The three cell types are easily recognized. The mucous cells have pale, foamy cytoplasm; the parietal cells are large and round with glassy eosinophilic cytoplasm; and the Paneth cells are columnar cells with deeply eosinophilic cytoplasm.

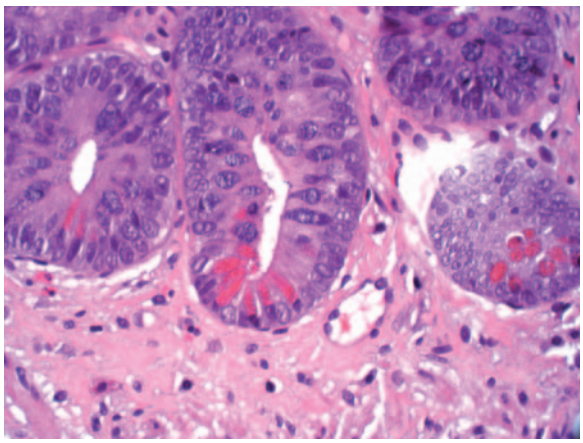

Figure 3–47 Paneth cells at the base of the foveolar pit in metaplastic columnar epithelium, showing the typical columnar cells with deeply eosinophilic granular cytoplasm.

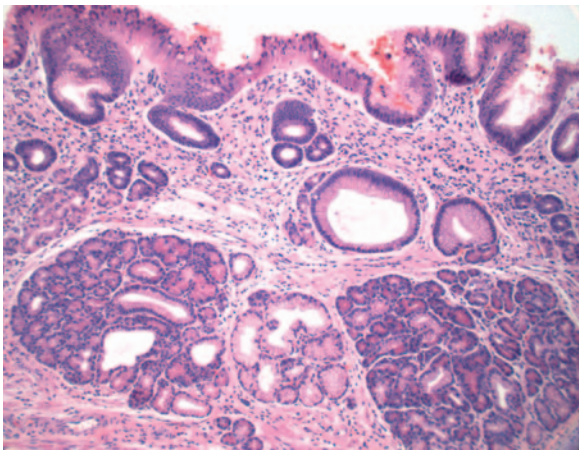

Figure 3–48 Metaplastic esophageal epithelium of oxyntocardiac type with serous or pancreatic metaplasia. Three lobulated glands are shown in the deep mucosa. The central gland consists of mucous cells. The other two contain serous cells. Note the presence of scattered parietal cells in the glands outside the lobulated glands.

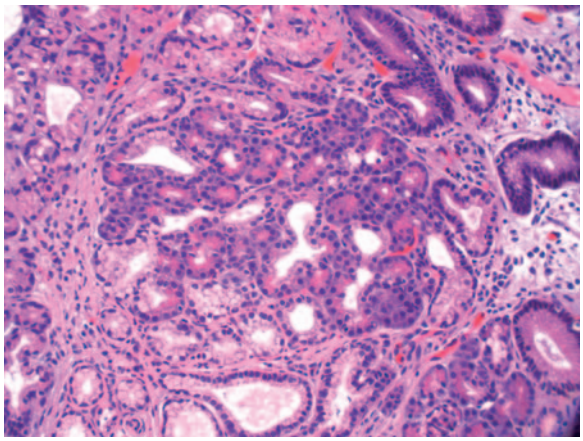

Figure 3–49 Higher magnification of Figure 3–48, showing serous cells with basophilic cytoplasm admixed with mucous cells in this focus of pancreatic metaplasia within oxyntocardiac mucosa.

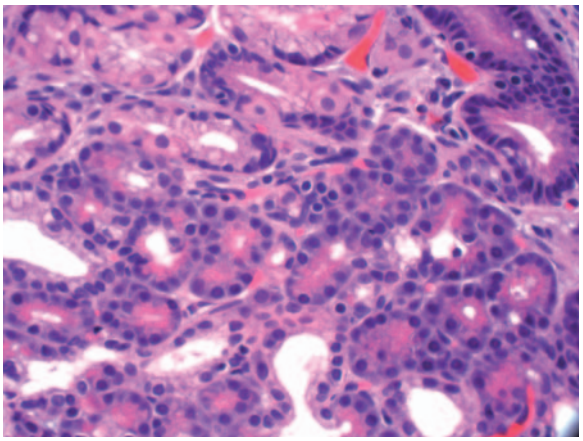

Figure 3–50 Higher magnification of Figure 3–49, showing pancreatic metaplasia. The serous cells have deeply basophilic cytoplasm. There are admixed cells that have more eosinophilic cytoplasm, which may be Paneth cells. The presence of pancreatic and Paneth cells has no known significance, and their specific identification is not important.

type goblet cells; and composition of glandular layers—whether containing mucous cells only or also parietal (oxyntic) and chief cells." Using these features, they define the following three epithelial types:

1. Gastric-fundic-type epithelium whose surface layer is negative for villiform folds and goblet cells and positive for foveoli. It contains mucous cells, parietal cells, and chief cells in the glandular layer.
2. Junctional-type epithelium whose surface layer is negative for villiform folds and goblet cells and positive for foveoli. It contains mucous cells only in the glandular layer, which is devoid of parietal cells and chief cells.
3. Specialized columnar-type epithelium whose surface layer is positive for villiform folds and goblet cells and negative for foveoli. It contains mucous cells only in the glandular layer, which is devoid of parietal cells and chief cells.

This classification, although accurate, has superfluous features that can be deleted in the interest of simplicity, recognizing the fact that simplicity of definition almost always results in improved reproducibility. The nature of the surface epithelium (villiform versus foveolar) and the presence of chief cells (which coexist with parietal cells) can be deleted without consequence. This results in a simplified histologic classification of the three epithelial types. The terms used for these epithelia have changed in general usage since the time of Paull et al.[11] The following more modern terminology and definitions are recommended[12–14] (Table 3–2).

The definitions of the four columnar epithelial types are as follows:

1. Cardiac mucosa: an epithelium containing only mucous-type columnar cells and no parietal or goblet cells (Figure 3–51). Cardiac mucosa may consist only of a surface layer (see Figure 3–25), have a foveolar region (see Figure 3–27), or contain glands. The glands are usually lobulated.
2. Cardiac mucosa with intestinal metaplasia: an epithelium containing goblet cells admixed with the mucous cells (Figure 3–52). No parietal cells are present.

TABLE 3–2 Recommended Terminology and Definitions for Columnar Epithelia Found in the Esophagus and Proximal Stomach

Epithelial type	Mucous cells in glands	Parietal cells in glands	Goblet cells in surface and foveolar region
Cardiac mucosa	+	–	–
Oxyntocardiac mucosa	+	+	–
Intestinal epithelium	+	–	+
Gastric oxyntic mucosa	–	+	–*

*Goblet cells are not found in normal gastric oxyntic mucosa but may be found in chronic atrophic gastritis. This is different than intestinal metaplasia occurring in columnar-lined esophagus.
+, Present; –, absent.

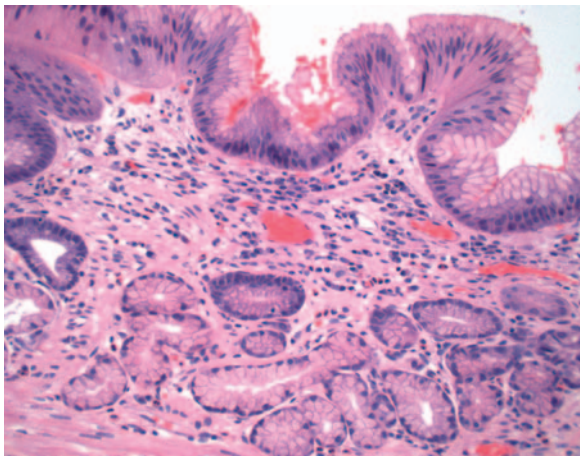

Figure 3–51 Cardiac mucosa, composed entirely of mucous cells. There are no parietal or goblet cells. This photo shows the entire thickness of the mucosa with fibers of the muscularis mucosae visible at the bottom left half. The diagnosis of cardiac mucosa cannot be made without seeing the full thickness of the mucosa, because it depends on the absence of parietal and goblet cells. Note the lack of organization and chronic inflammation in the lamina propria.

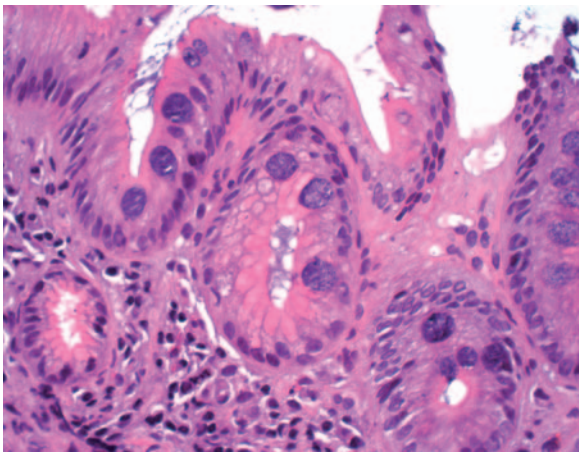

Figure 3–52 Intestinal metaplasia in cardiac mucosa, characterized by the presence of goblet cells. Only the superficial region of the mucosa is seen, but this is adequate because the diagnosis of intestinal metaplasia depends on the presence of goblet cells.

3. Oxyntocardiac mucosa: an epithelium containing a mixture of parietal cells and mucous cells in the glands (Figure 3–53). The glands are usually lobulated.
4. Gastric oxyntic mucosa: an epithelium containing parietal cells but no mucous cells in the glands. Mucous cells are limited to the surface, foveolar pit, and the isthmus of the gland (Figures 3–40, 3–54, and 3–55). The glands are usually straight and tubular.

The following differences are established between Paull et al's classification and the one suggested here:

1. Paull et al's definitions were limited to columnar-lined esophagus above the proximal limit of the lower esophageal sphincter; they did not find gastric oxyntic mucosa in the esophagus. I have extended the anatomic area to include the entire region by including gastric oxyntic mucosa within the classification. It is only when this is done that the gastroesophageal junction is certain to be included because gastric oxyntic mucosa lines the entire stomach up to the pyloric antrum.
2. Chief cells are excluded from the definitional criteria. The reason for this is that chief cells and parietal cells usually coexist, and parietal cells are

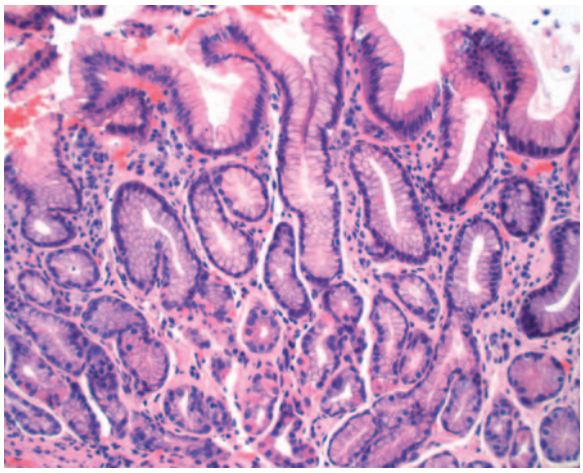

Figure 3–53 Oxyntocardiac mucosa, showing a mixture of parietal cells and mucous cells in the glands under the foveolar region. The surface and foveolar region are lined by mucous cells. Note the mild chronic inflammation in the superficial lamina propria.

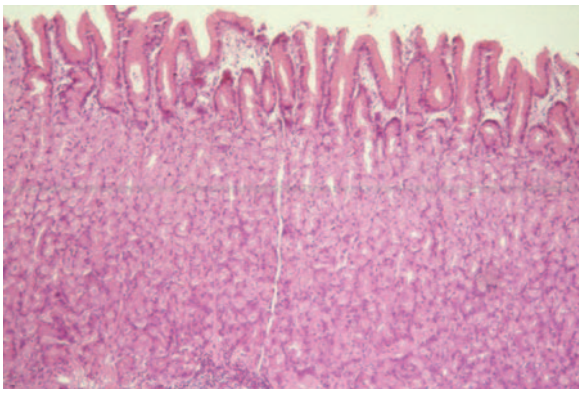

Figure 3–54 Normal gastric oxyntic mucosa, showing a surface and very short foveolar region composed of mucous cells with long tubular glands arising from the base of the foveolar pit. The straight, unbranching, tubular glands contain only parietal and chief cells. The glands are tightly packed with minimal lamina propria. There is no inflammation.

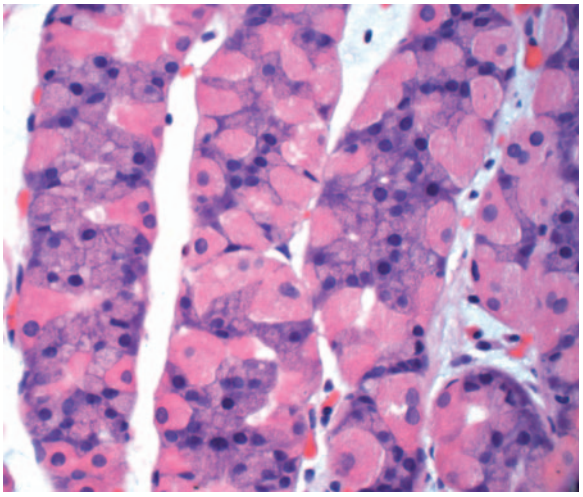

Figure 3–55 High magnification of the deep region of three tubular glands of gastric oxyntic mucosa. These are composed entirely of parietal and chief cells without mucous cells. The stroma between the glands shows blood vessels and a few connective tissue cells only.

much easier to identify. Chief cells may be difficult to differentiate from mucous cells; in fact, the mucous cells that move down into the glands from the foveolar region (mucous neck cells) frequently have prezymogenic granules on electron microscopy (see Figure 3–40).

3. Paull et al's "junctional epithelium" is called *cardiac mucosa*. This term is currently used more commonly than *junctional mucosa*. Also, the gastroesophageal junction is not a structure with any length; it is an imaginary line drawn between the end of the esophagus and the beginning of the stomach. The word *junctional* therefore has no meaning.
4. Paull et al's "gastric-fundic-type epithelium" is renamed *oxyntocardiac mucosa*. The reason for this is that "gastric-fundic-type" epithelium, as described by Paull et al, was clearly esophageal in location; the term promotes the incorrect view that gastric epithelium lines the esophagus. The gastric fundus is lined by gastric oxyntic mucosa, not "gastric-fundic-type" or oxyntocardiac mucosa. The term *oxyntocardiac epithelium* is gaining

acceptance, although it is not universally used; some authorities use the term *mixed mucous and parietal cell epithelium*.[15] In my opinion, the term *oxyntocardiac mucosa* is easier and better and should be used.

5. Paull et al's "specialized columnar epithelium" is called *cardiac mucosa with intestinal metaplasia*. This is much more commonly used at the present time.

Diagnosis of Columnar Epithelial Types

There are only four columnar epithelial types in this region: cardiac mucosa without intestinal metaplasia, cardiac mucosa with intestinal metaplasia, oxyntocardiac mucosa, and gastric oxyntic mucosa. All other terms used are synonymous with one of these epithelial types. The profusion of terms may give some the impression of multiple epithelial types. For example, the terms *specialized columnar epithelium* (*SCE*), *specialized intestinal epithelium* (*SIM*), *incomplete and complete intestinal metaplasia occurring in the esophagus*, and *cardiac intestinal metaplasia* (*CIM*) occurring in cardiac mucosa all refer to intestinal metaplasia of the esophagus as defined here. This is different than gastric intestinal metaplasia occurring in atrophic gastritis. Similarly, *mixed mucous and parietal cell epithelium*, *transitional epithelium,* and *gastric-fundic-type epithelium* are all generally synonymous with oxyntocardiac mucosa, and *junctional epithelium* and *mucous cell-only epithelium* are generally synonymous with cardiac mucosa. It would be a great advantage if all terms other than those recommended here were discontinued to reduce confusion, but I fear this is too much to ask of a large medical community.

Gastric Oxyntic Mucosa

Gastric oxyntic mucosa (synonyms: gastric body and gastric fundic mucosa) consists of a surface epithelial layer and short foveolar region that is composed of mucous cells with basal nuclei and apical mucin (see Figures 3–40 and 3–54). Below the foveolar region is a straight, unbranching tubular gland composed of acid-secreting parietal (i.e., oxyntic) cells and pepsin-secreting chief cells (see Figures 3–54 and 3–55). The gastric gland is long and ends at the muscularis mucosae. No mucous cells are present below the deep foveolar region and the isthmus of the gland where there are mucous neck cells (see Figure 3–40). The lamina propria in normal gastric mucosa is minimal. Inflammatory cells are not normally present, and the vascular stroma between the glands is so small that the sides of the gastric glands are in close apposition to each other (see Figure 3–55).

Gastric oxyntic mucosa may show pathologic changes that include chemical injury with erosion and reactive change, commonly caused by drugs (such as non-steroidal anti-inflammatory drugs) and bile reflux, and true inflammation (gastritis). There are two major etiologies for gastritis: *Helicobacter pylori* infection and autoimmune gastritis; both of these cause a chronic gastritis, with active inflammation commonly superimposed in *H. pylori* infection. *H. pylori* gastritis tends to maximally involve the distal stomach (antral gastritis) but in a majority of patients extends into the proximal stomach to cause a pangastritis. Chronic autoimmune gastritis, on the other hand, is an immune destruction of parietal cells and typically produces chronic gastritis that maximally involves gastric oxyntic mucosa of the body and fundus of the stomach. In both these forms of gastritis, the process can extend into the most proximal region of the gastric oxyntic mucosa adjacent to the gastroesophageal junction. Neither of these diseases, however, causes inflammation that is limited to the

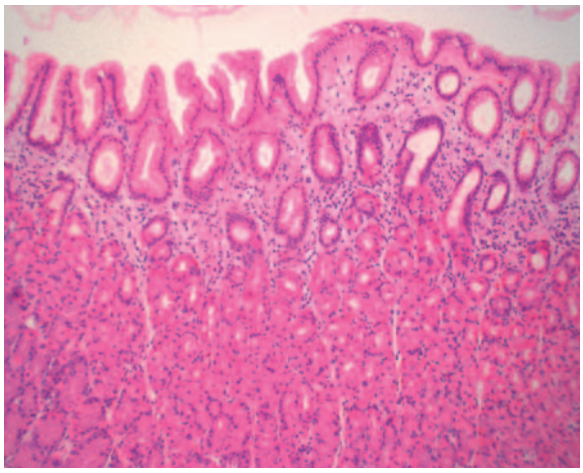

Figure 3–56 Gastric oxyntic mucosa with mild chronic gastritis. The abnormality is limited to the superficial foveolar region with the gastric glands being normal. The foveolar pit is elongated and surrounded by a mild increase in lymphocytes and plasma cells. This patient had a pangastritis with *H. pylori* infection identified.

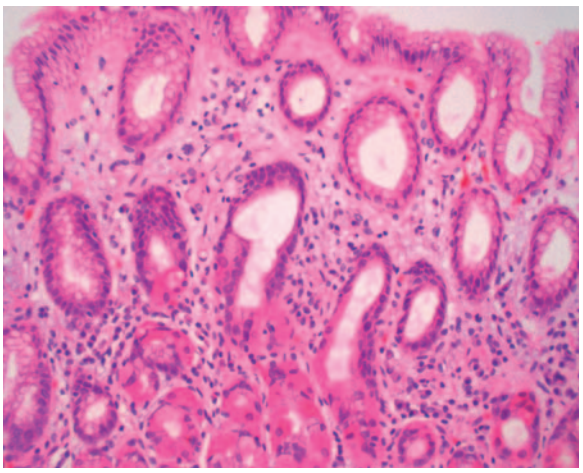

Figure 3–57 Higher magnification of Figure 3–56, showing the inflammatory cells in the superficial lamina propria in mild chronic superficial gastritis. The cells are a mixture of lymphocytes and plasma cells with scattered eosinophils. Neutrophils are not present.

region immediately distal to the gastroesophageal junction. As such, one easy method of excluding the possibility of chronic gastritis involving gastric oxyntic mucosa is to take a biopsy sample from the antrum and body of the stomach; if this is normal, it is highly unlikely that any pathology in the region of the gastroesophageal junction can be attributed to gastritis.

In *H. pylori* gastritis involving gastric oxyntic mucosa, the inflammation is commonly limited to the superficial region around the foveolar pit with sparing of the glandular region (superficial gastritis) (Figures 3–56 and 3–57). In these cases, the cellular composition of the oxyntic mucosal glands is not altered. If the severity of inflammation increases, the inflammatory cells extend deeper into the mucosa, surrounding gastric glands (Figure 3–58). The severity of inflammation in gastritis is graded by the Sydney system[16]; the highest grade of infection includes active inflammation (Figure 3–59). The diagnosis of *H. pylori* gastritis is made by demonstrating the organisms in gastric mucosa; the bacilli are easily seen in routine hematoxylin-stained and eosin-stained sections (Figure 3–60) but can be highlighted in Giemsa (Figure 3–61), Genta (Figure 3–62), and immunoperoxidase stains. In chronic cases, when the number of bacilli may be small and not demonstrable in the gastric biopsy even with special stains, serologic testing for *H. pylori* is helpful to establish the diagnosis. The diagnosis of chronic autoimmune gastritis can be confirmed by demonstrating the presence of anti-parietal cell antibodies in the serum.

The extension of inflammation into the glandular region of oxyntic mucosa is frequently associated with destruction of the glands, resulting in progressive loss of parietal cells (known as *atrophy*) (see Figure 3–58). This process may be accompanied by two types of metaplasia (see Figure 3–62):

1. Pseudo-pyloric metaplasia, in which the glands are replaced by mucous cells, resembling antral mucosa (Figures 3–63 and 3–64). When the gastric glands are completely destroyed, there may be no parietal cells, and the mucosa is composed entirely of mucous cells. When this happens, the atrophic gastric oxyntic mucosa may closely resemble cardiac mucosa in that it is composed of mucous cells only, resulting in much of the confusion that exists in this area (see Figure 3–64). It must be recognized that

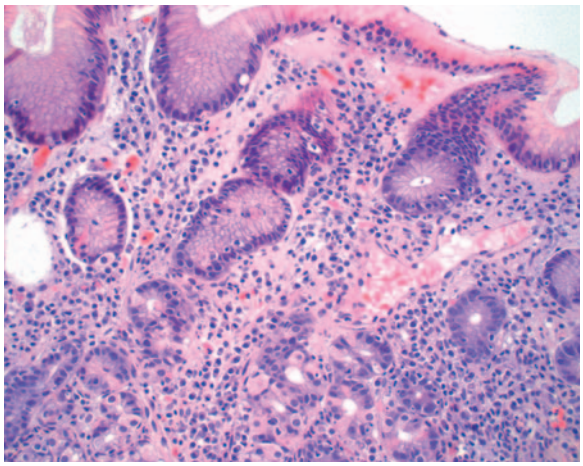

Figure 3–58 Gastric oxyntic mucosa with moderate chronic gastritis, again secondary to *H. pylori*. The inflammation is more severe and extends into the glandular zone. It still consists largely of lymphocytes and plasma cells. Some lymphocytes are seen invading the epithelium.

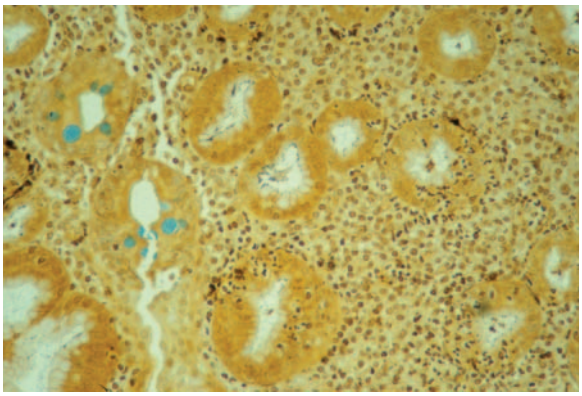

Figure 3–59 Gastric oxyntic mucosa stained with a combined silver and Alcian blue stain. There is severe chronic gastritis with marked active inflammation characterized by the presence of numerous neutrophils, which are seen infiltrating the glands. There is focal intestinal metaplasia, characterized by the blue-staining goblet cells. Numerous *H. pylori* bacilli are present in the glands that do not have intestinal metaplasia. The organisms appear as short black-staining rods abutting the epithelial surface.

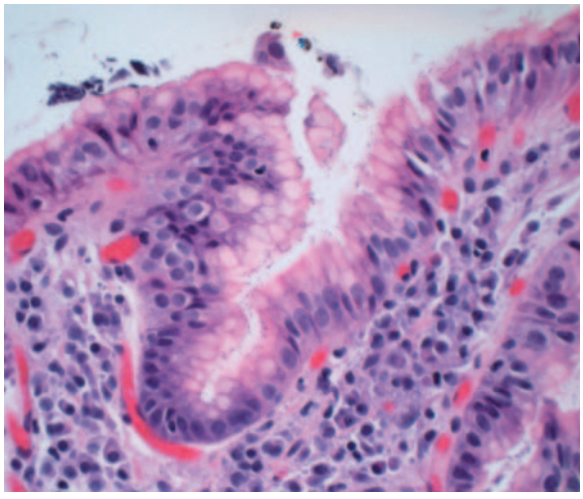

Figure 3–60 *H. pylori* in chronic gastritis. The organisms are easily seen in routine hematoxylin and eosin stain when they are abundant. They are short, curved (seagull shaped) bacilli that occupy the mucous layer at the epithelial cell surface.

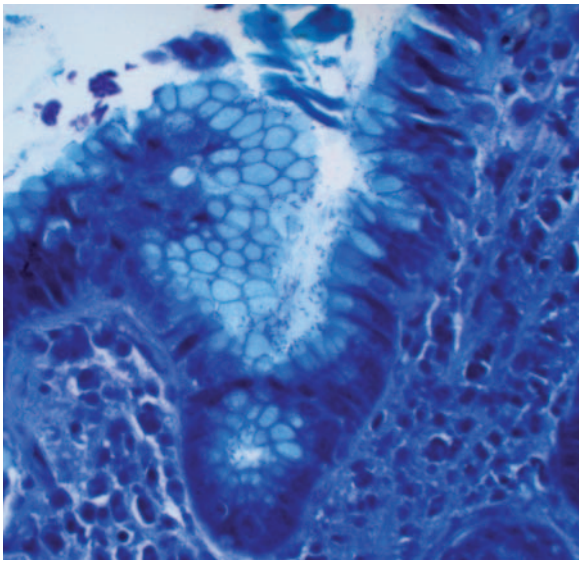

Figure 3–61 *H. pylori,* demonstrated in a Giemsa stain. The blue stain highlights the organism and is valuable in biopsies when the bacilli load is small.

total atrophy of gastric oxyntic mucosa with pseudo-pyloric metaplasia is a different epithelium than cardiac mucosa, despite their similar appearance. Later in this chapter, I will discuss the differential diagnosis between true cardiac mucosa and total atrophy of gastric oxyntic mucosa with pseudo-pyloric metaplasia.

2. Gastric intestinal metaplasia, which involves mainly the surface and foveolar region (Figures 3–63, 3–65, and 3–66). When intestinal metaplasia occurs in gastric oxyntic mucosa that has total atrophy (i.e., no parietal cells) with

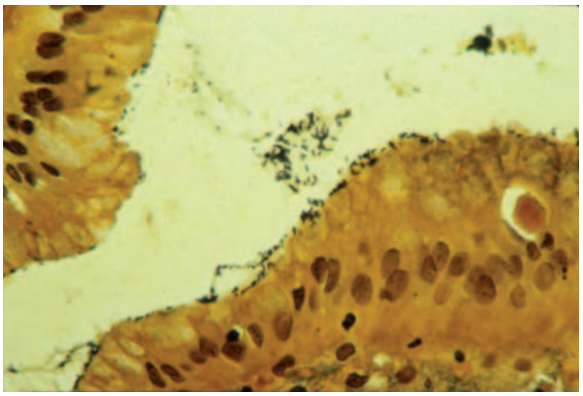

Figure 3–62 *H. pylori,* demonstrated by a Genta *(silver)* stain. The bacilli stain black.

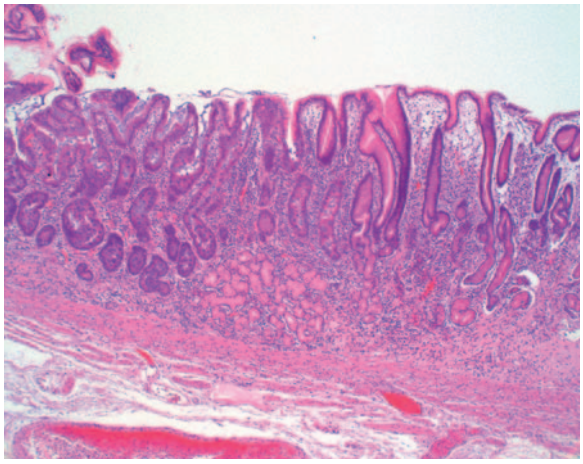

Figure 3–63 Chronic atrophic gastritis involving the gastric body in a patient with autoimmune chronic gastritis. The parietal cell-containing glands have been completely destroyed and replaced by an intestinal metaplasia epithelium in the left half of the photo and a mucous cell-only epithelium with mucous glands in the center and right half. The latter resembles pyloric antral mucosa and is termed *pseudo-pyloric metaplasia*.

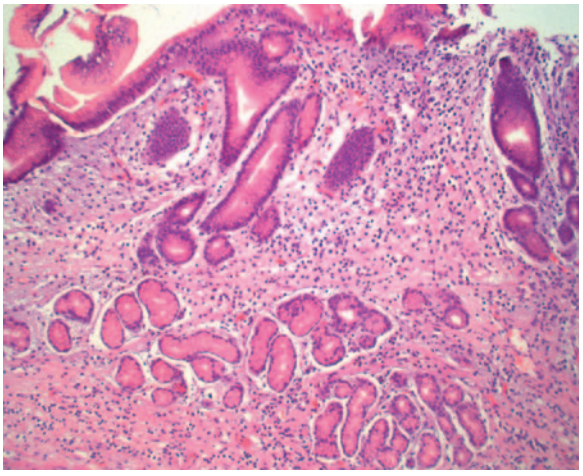

Figure 3–64 Chronic atrophic gastritis with pseudo-pyloric metaplasia involving the gastric body in chronic autoimmune gastritis. The parietal cell-containing glands are lost and replaced by a disorganized mucous cell-only epithelium that resembles both pyloric antrum and cardiac mucosa.

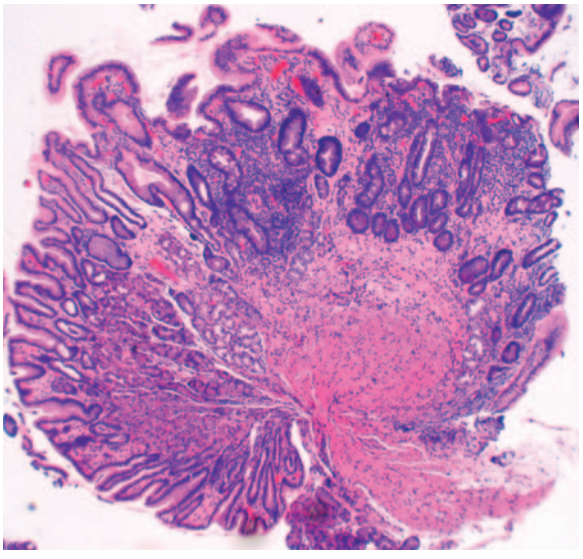

Figure 3–65 Biopsy of gastric body showing multifocal chronic atrophic gastritis of *H. pylori* infection. The left half shows oxyntic mucosa with mild chronic inflammation. In the right half, there is severe chronic inflammation, and the glandular region has been completely destroyed and replaced by a foveolar epithelium that shows extensive intestinal metaplasia.

pseudo-pyloric metaplasia, it resembles intestinal metaplasia occurring in cardiac mucosa (i.e., Barrett esophagus). The differentiation between these two entities will be discussed later in this chapter.

Cardiac Mucosa

Cardiac mucosa (synonyms: junctional mucosa, mucous cell-only epithelium) is defined as an epithelium that is devoid of parietal cells and goblet cells and composed of mucous cells only (see Figure 3–51). The presence of neuroendocrine cells, chief cells, Paneth cells, and pancreatic cells does not change the definition of cardiac mucosa as long as there are no parietal cells and goblet cells.

Cardiac mucosa includes a wide variety of morphologic epithelial types. Rarely, it is seen as a flat epithelium composed of a single surface layer of mucous cells (see Figure 3–25). This most likely represents surface erosion that is healing by columnar regeneration. Cardiac mucosa may consist of a surface epithelium with a foveolar pit without glands under the foveolar pit (see Figure 3–27). The foveolar pit can vary in length from rudimentary to elongated. When glands are present below the foveolar region, they are disorganized, lobulated, and composed of mucous cells and have no parietal cells or goblet cells (Figure 3–67).

In most cases, the surface epithelium of cardiac mucosa is a single-layered columnar epithelium with basal nuclei and apical mucin, resembling the surface cells of gastric mucosa (see Figures 3–51 and 3–67). On occasion, the surface layer is multi-layered, consisting either of multiple layers of columnar cells (see Figure 3–38) or a mixture of columnar cells and basaloid squamous

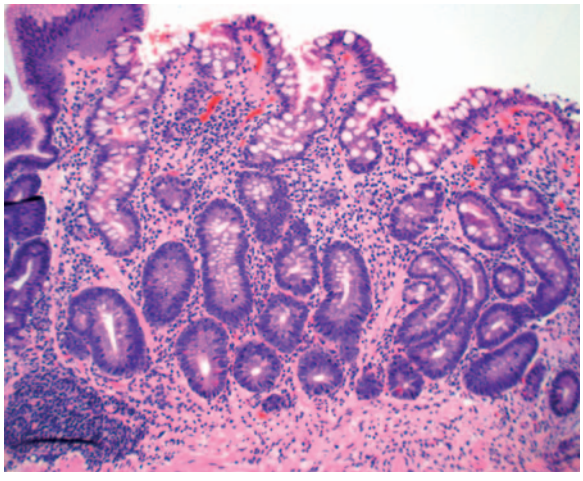

Figure 3–66 Chronic atrophic gastritis involving the gastric body in a patient with multifocal *H. pylori* pangastritis. The mucosa is flat, shows marked chronic inflammation, and consists entirely of an elongated foveolar pit and surface in which there is intestinal metaplasia.

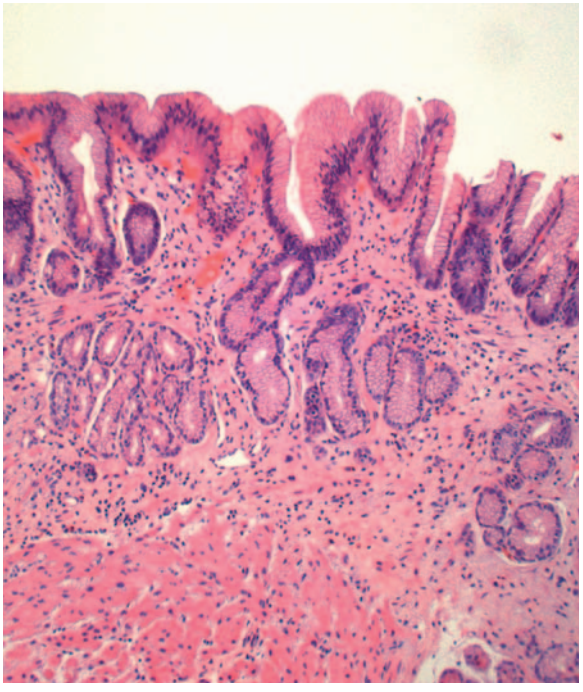

Figure 3–67 Cardiac mucosa, composed of mucous cells only and characterized by disorganized and lobulated glands. Note the hyperplastic muscularis mucosae with a few muscle fibers extending upward into the lamina propria.

cells resembling reserve cells[17,18] (see Figure 3–37). Multi-layered epithelium is a feature of cardiac mucosa, but it can be found in oxyntocardiac mucosa and cardiac mucosa with intestinal metaplasia; it is not seen in gastric oxyntic mucosa and is a reliable marker of esophageal location of a biopsy. We reported that 68 (14.4%) of 471 biopsies composed of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa contained foci of multi-layered epithelium.[9] Multi-layered epithelium most likely represents an unstable reactive change in reflux-induced columnar epithelium. It has been suggested that multi-layered epithelium is a precursor of Barrett esophagus; this distinction is not necessary when one recognizes that all cardiac mucosa is a precursor of Barrett esophagus.

Cardiac mucosa is always inflamed and frequently shows reactive hyperplasia of the foveolar region. Inflammatory cells are lymphocytes, plasma cells, and eosinophils (Figures 3–68 and 3–69). Neutrophils are usually absent unless there is an erosion or secondary infection with *H. pylori* (Figure 3–70). Reactive change is characterized by foveolar elongation and serration and can mimic a hyperplastic polyp (Figures 3–71, 3–72, and 3–73). Smooth muscle

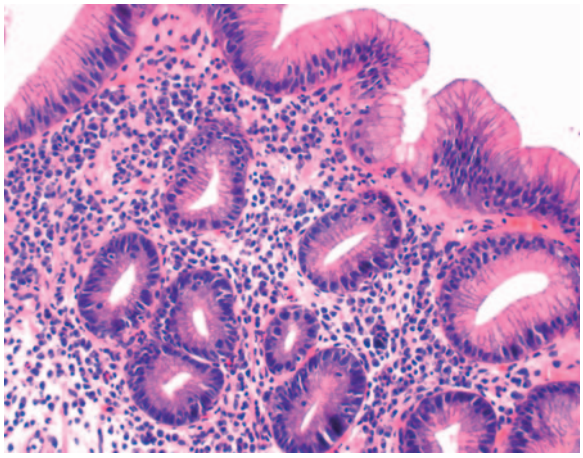

Figure 3–68 Cardiac mucosa, showing chronic inflammation in the lamina propria. The plasma cell is the dominant cell here with scattered eosinophils and lymphocytes.

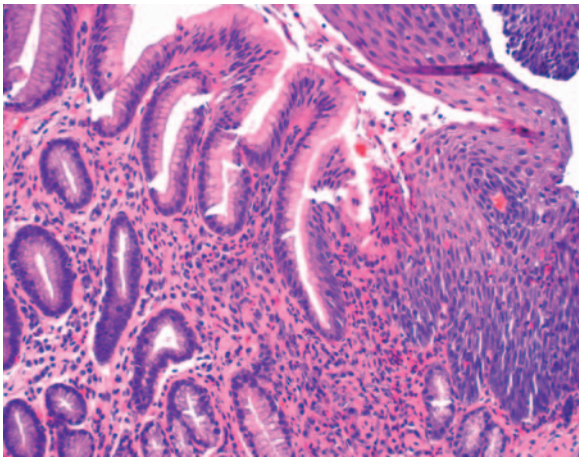

Figure 3–69 Cardiac mucosa distal to the squamocolumnar junction, characterized by a villiform surface and inflammation dominated by eosinophils in addition to the usual plasma cells and lymphocytes. Note the basal cell hyperplasia and eosinophil infiltration of the squamous epithelium, indicative of reflux.

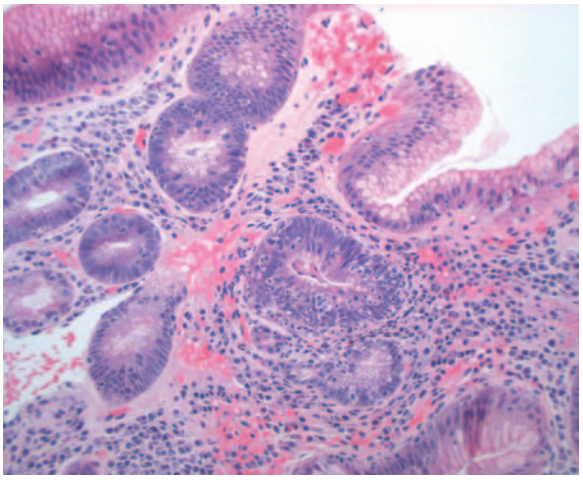

Figure 3–70 Cardiac mucosa with active inflammation, characterized by neutrophils, which are seen infiltrating the glandular epithelium. This patient had *H. pylori* pangastritis with extension of the inflammation to cardiac mucosa.

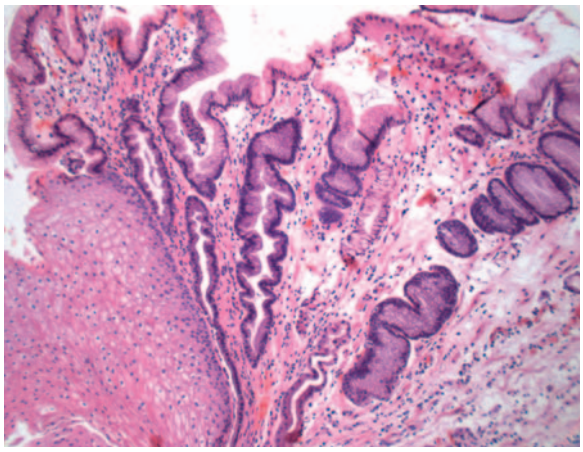

Figure 3–71 Cardiac mucosa with marked reactive changes in addition to the chronic inflammation. There is marked foveolar elongation with serration of the lumen, lamina propria edema, and smooth muscle proliferation. Numerous smooth muscle fibers are seen oriented vertically and extending up toward the surface. This was submitted as a polypoid lesion at the endoscopic gastroesophageal junction.

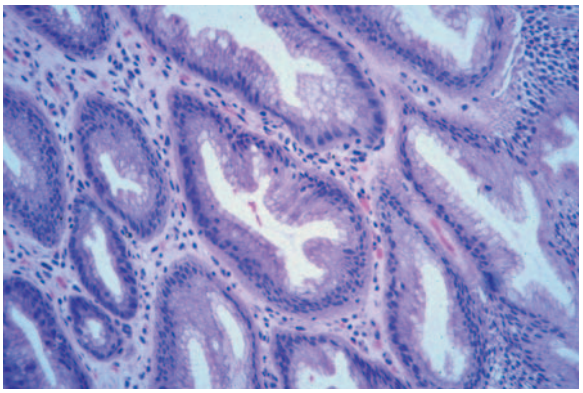

Figure 3–72 Cardiac mucosa, tangentially sectioned through the foveolar region showing the hyperplastic features characterized by serration of the lumen.

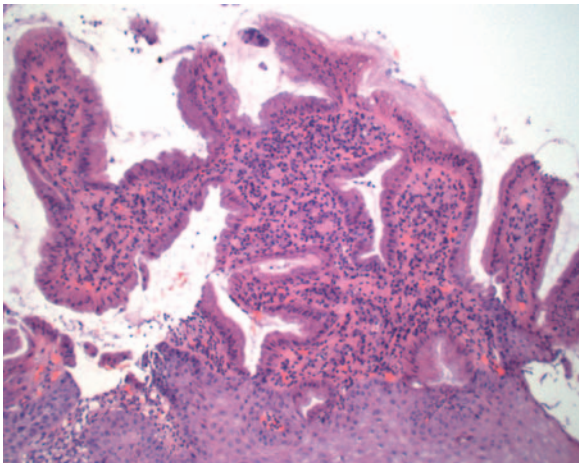

Figure 3–73 Cardiac mucosa, tangentially sectioned, showing severe inflammation and a villiform appearance of the hyperplastic foveolar region.

proliferation is often present with fibers passing vertically into the lamina propria from the muscularis mucosae (see Figure 3–71). Cardiac mucosa can form small polypoid lesions in the distal esophagus; the most common cause of a polypoid lesion encountered at endoscopy of the gastroesophageal junction region is reactive, inflamed cardiac mucosa.

In patients with concomitant *H. pylori* infection of the stomach with pangastritis, the *H. pylori* can extend into cardiac mucosa. Infection with *H. pylori* increases the severity of chronic inflammation and adds active inflammation with neutrophils into the mix (see Figure 3–70). *H. pylori* infection is a secondary phenomenon; it does not produce cardiac mucosa because this is a metaplastic epithelium derived from squamous epithelium, and squamous epithelium is not infected by *H. pylori*. In general, the prevalence of *H. pylori* in cardiac mucosa is similar to its prevalence in the population being studied. For example, in our population at the University of Southern California, the prevalence of *H. pylori* in cardiac mucosa is around 15%.[19] The effect of *H. pylori* secondarily infecting cardiac mucosa is to increase the

inflammatory reaction within it and add active inflammation. If the Sydney grading system is used for cardiac inflammation, the highest grades will be seen in patients with secondary infection with *H. pylori,* because active inflammation is not commonly seen in reflux disease unless there is erosion or *H. pylori* infection. This leads to a positive association between the grade of inflammation and the presence of *H. pylori* in cardiac mucosa if the Sydney system is used. However, if one evaluates acute and chronic inflammation separately, the severity of acute inflammation does not correlate with reflux, although there is a strong correlation between chronic inflammation and reflux.

Oxyntocardiac Mucosa

Oxyntocardiac mucosa (i.e., fundic-type and mixed mucous-parietal cell epithelium) is an epithelium consisting of glands composed of a mixture of parietal cells and mucous cells (Figure 3–74). The glands differ from cardiac mucosal glands because of the presence of parietal cells. The glands differ from gastric oxyntic mucosa by the fact that they are lobulated (Figure 3–75) and contain mucous cells in addition to parietal cells. In addition, oxyntocardiac mucosa may contain mucosal mucous glands (see Figure 3–14) or gland ducts draining the esophageal submucosal glands (see Figure 3–15); these are not seen in gastric oxyntic mucosa.

Oxyntocardiac mucosa is usually inflamed, but to a lesser extent than cardiac mucosa. In patients with cardiac, oxyntocardiac, and gastric oxyntic mucosa in the same biopsy level, the inflammation is almost always maximal in cardiac mucosa, intermediate in oxyntocardiac mucosa, and absent in gastric oxyntic mucosa. Obviously, this is only true when gastric mucosa is normal. When severe gastritis is present in gastric oxyntic mucosa, the inflammation levels in the three mucosal types are reversed.

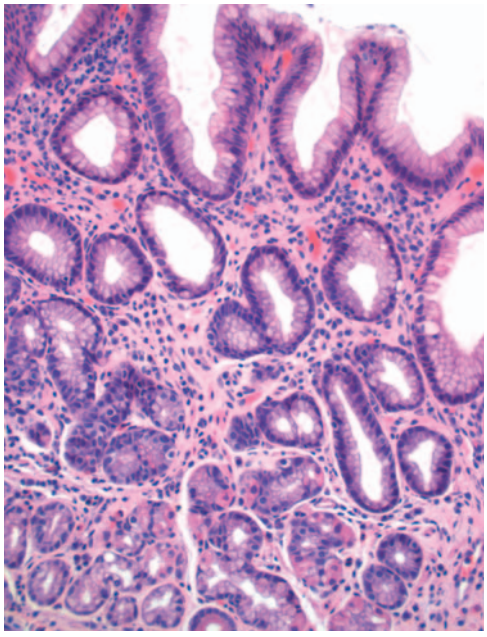

Figure 3–74 Oxyntocardiac mucosa, showing mild foveolar hyperplasia, mild chronic inflammation, and disorganized glands containing mucous and parietal cells.

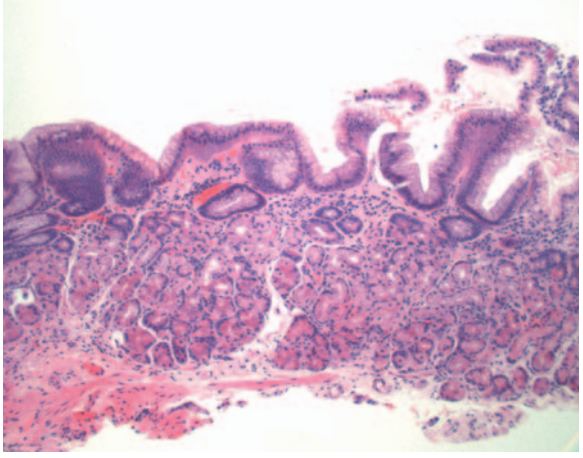

Figure 3–75 Oxyntocardiac mucosa with numerous parietal cells in the glands. The mucosa is better organized but still shows lobulation of the glands, which is different than the straight glands seen in gastric oxyntic mucosa.

CASE STUDY

A 38-year-old female underwent endoscopy for recurrent heartburn that had lasted 5 years. This was associated with episodes of regurgitation. Endoscopy was interpreted as normal (Figure 3–76), despite the fact that the rugal folds did not reach all the way to the Z-line in some parts of the circumference. Biopsies were taken from the region of the squamocolumnar junction and the proximal limit of the rugal folds.

The biopsies, all taken from the same level, showed variable features in three separate pieces. The first piece (from the area labeled A in Figure 3–76, lowest biopsy) showed cardiac mucosa with severe foveolar hyperplasia and severe inflammation (Figure 3–77). The second piece (from the area labeled B, central biopsy, in Figure 3–76) showed oxyntocardiac mucosa with a much lesser degree of chronic inflammation and foveolar hyperplasia (Figure 3–78). The third piece (from the area labeled C, highest biopsy, in Figure 3–76) showed oxyntic mucosa, which was essentially normal (Figure 3–79).

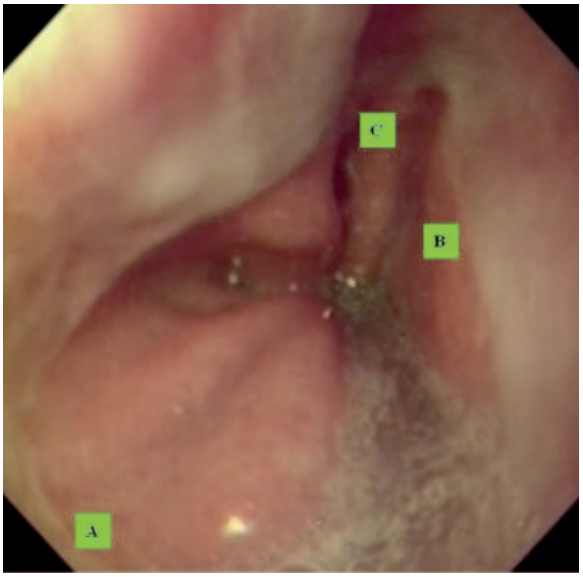

Figure 3–76 Endoscopic appearance showing features that were interpreted as normal despite the suggestion of mild separation of the Z-line and the proximal limit of the rugal folds in some parts of the circumference, particularly in the lower part of the photo. Three biopsy sites at this level are shown as green squares labeled *A*, *B,* and *C*. *A* is shown in Figure 3–77, *B* is shown in Figure 3–78, and *C* is shown in Figure 3–79.

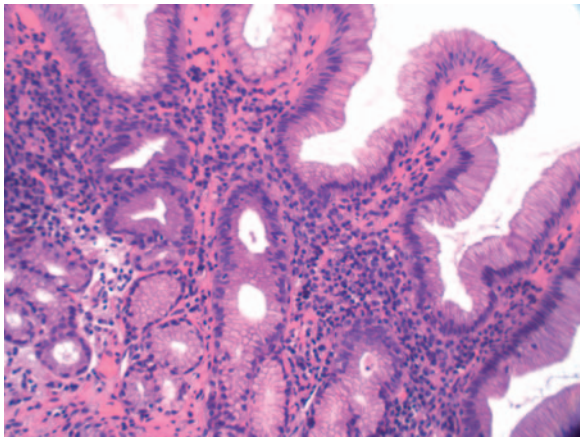

Figure 3–77 Biopsy from location *A* in Figure 3–76 showing cardiac mucosa with marked chronic inflammation and foveolar hyperplasia manifesting as a villiform surface. The glands contain no parietal cells.

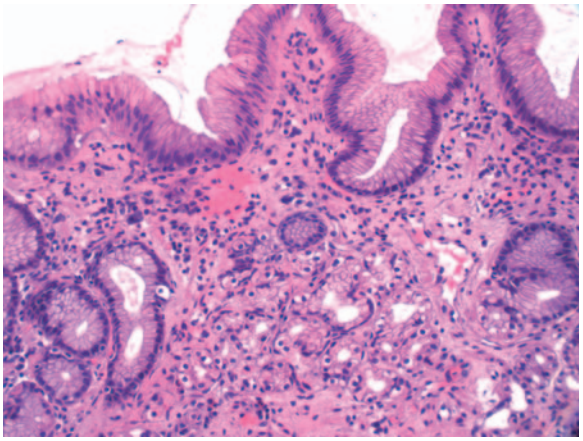

Figure 3–78 Biopsy from location *B* in Figure 3–76 showing oxyntocardiac mucosa characterized by glands showing a mixture of parietal and mucous cells. The chronic inflammation is mild, and there is no significant foveolar hyperplasia.

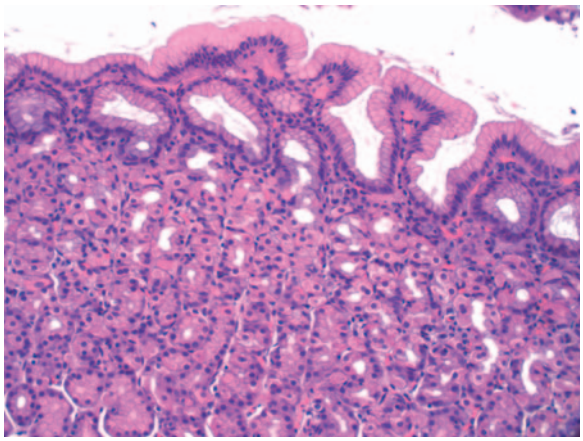

Figure 3–79 Biopsy from location *C* in Figure 3–76 showing essentially normal oxyntic mucosa. The foveolar region is very short with the parietal cell containing straight glands arising very near the surface. A few lymphocytes without any plasma cells are present in the superficial lamina propria.

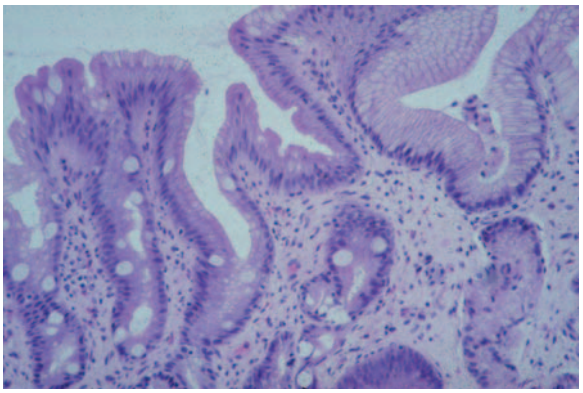

Figure 3–80 Intestinal metaplasia in cardiac mucosa. There are numerous goblet cells with a relatively clear mucous vacuole in the left half. A foveolar-gland complex at the right edge shows cardiac mucosa without intestinal metaplasia.

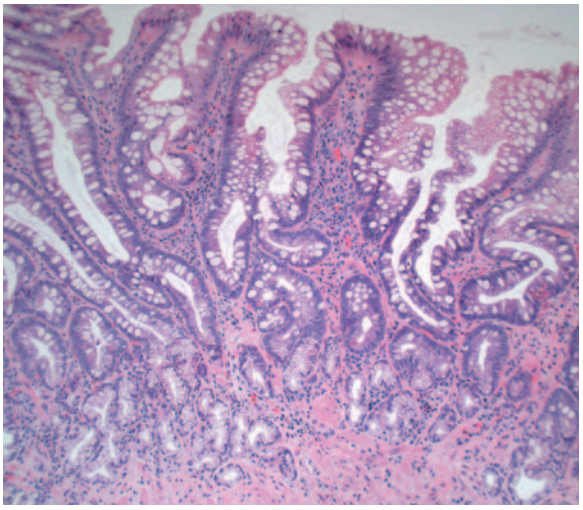

Figure 3–81 Intestinal metaplasia in cardiac mucosa. Numerous goblet cells are present in the surface and foveolar region. The deep glands in the mucosa do not show goblet cells.

This is a typical finding in biopsies of this region. It illustrates the huge variation in both mucosal types and degree of inflammation and reactive change over a very short distance in this region. The potential for sampling error is very high, and adequate sampling is essential.

Intestinal Metaplasia in Cardiac Mucosa

Intestinal metaplasia (i.e., specialized columnar epithelium) is defined by the presence of goblet cells in cardiac mucosa (see Figures 3–39 and 3–42). The diagnosis can be made with just one definite goblet cell; it does not depend on a specific number (Figures 3–80, 3–81, and 3–82). In columnar-lined esophagus, intestinal metaplasia occurs only in cardiac mucosa and tends to occur in the most proximal region of the columnar-lined segment, immediately adjacent to the squamocolumnar junction (Figures 3–83 and 3–84). With very rare exceptions, intestinal metaplasia does not occur in oxyntocardiac mucosa (i.e., goblet cells and parietal cells do not coexist in a single foveolar-gland complex in columnar-lined esophagus).

Intestinal metaplasia is diagnosed in routine hematoxylin-stained and eosin-stained sections by the presence of definite goblet cells. Goblet cells have a single, large, and round mucinous vacuole that distends the cell and pushes the nucleus to the base. The vacuole frequently has a basophilic tinge (see Figures 3–39 and 3–82) but may be empty (see Figures 3–42 and 3–81). Goblet cells are variably interspersed in the cardiac mucosa. Alcian blue stain at pH 2.5 stains acid mucin and is positive in goblet cells (Figure 3–85).

Intestinal metaplasia is not defined by the presence of acid mucin or Alcian blue positivity. Significant overdiagnosis of intestinal metaplasia occurs if Alcian blue stain is used because of the positive staining of non-goblet cells of cardiac mucosa (see the discussion of differential diagnosis between goblet cells and pseudo-goblet cells later in this chapter). I do not use Alcian blue stain routinely. The use of a combined periodic acid Schiff-Alcian blue (PAS-

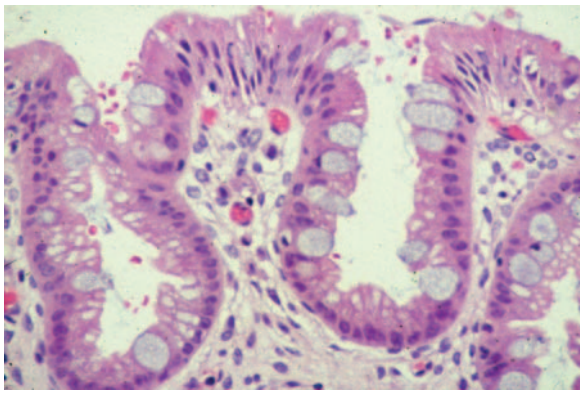

Figure 3–82 Intestinal metaplasia in cardiac mucosa showing goblet cells interspersed in cardiac mucosa. These goblet cells have a distinct basophilic tinge in the mucous vacuole.

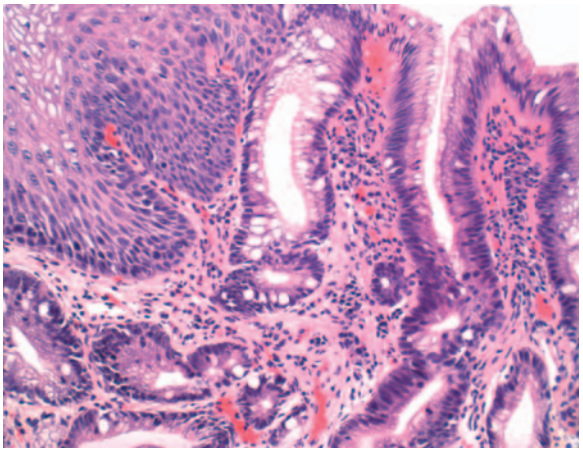

Figure 3–83 Intestinal metaplasia occurring in the columnar epithelium immediately adjacent to squamous epithelium. This is the preferred and typical location for intestinal metaplasia.

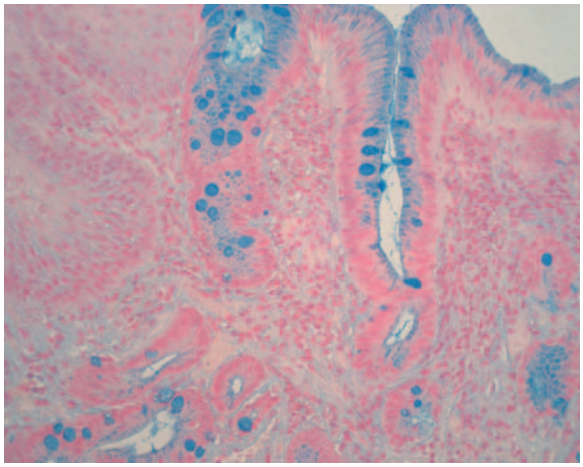

Figure 3–84 Alcian blue stain of Figure 3–83, showing positive *(blue)* staining of the goblet cells of intestinal metaplasia, indicating their acid mucin content.

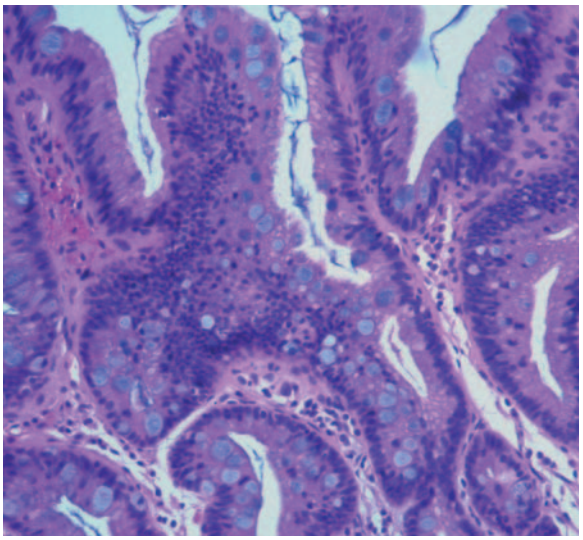

Figure 3–85 Intestinal metaplasia in cardiac mucosa, Alcian blue stain, showing the typical hyperplastic villiform foveolar region with scattered Alcian blue-positive goblet cells interspersed in the cardiac mucosa.

AB) is also popular. This stains neutral mucin-containing cells with PAS (magenta) and acid mucin-containing cells with Alcian blue (deep blue). Cells with both neutral and acid mucin take on a color that is a mixture of the two stains (Figure 3–86). Although it looks beautiful, this stain is not diagnostically valuable and actually results in overdiagnosis of intestinal metaplasia if one takes any blue staining as a positive stain. I will discuss the differentiation of true goblet cells from pseudo-goblet cells later in the chapter.

Classifying intestinal metaplasia in the esophagus into incomplete and complete categories (by evaluating biopsies for sulfated and sialated acid mucins with the use of high-iron diamine stain) has little value.[20] Most patients with intestinal metaplasia in the esophagus have incomplete intestinal metaplasia. There has not been a clear demonstration of a differential cancer risk based on these stains. I do not use the high-iron diamine stain.

Application of Histologic Definitions

The histologic terms just discussed are defined for each foveolar-gland complex of columnar epithelium. A single biopsy specimen may therefore contain one or more columnar epithelial types, with and without squamous epithelium (Figure 3–87; see Figures 3–33 and 3–34). Adjacent foveolar gland complexes may be classified as intestinal, cardiac, oxyntocardiac, or gastric oxyntic. If adequately biopsied, all patients will have squamous epithelium and gastric oxyntic mucosa, which are recognized as the normal epithelia lining the esophagus and stomach. The finding of oxyntocardiac, cardiac, and intestinal epithelia, on the other hand, varies from patient to patient.

Three methods of biopsy reporting are available. The first is to record all the columnar epithelial types present and to provide a detailed estimate of the percentage of each epithelial type that exists in all biopsies at each level. This is valuable only when the significance of the amounts of these epithelial types is researched. For example, in studies designed to evaluate the cancer risk associated with intestinal metaplasia, we use a grading system that quantitates the number of goblet cells as a percentage of the total columnar cells. This method is clearly overkill for clinical use.

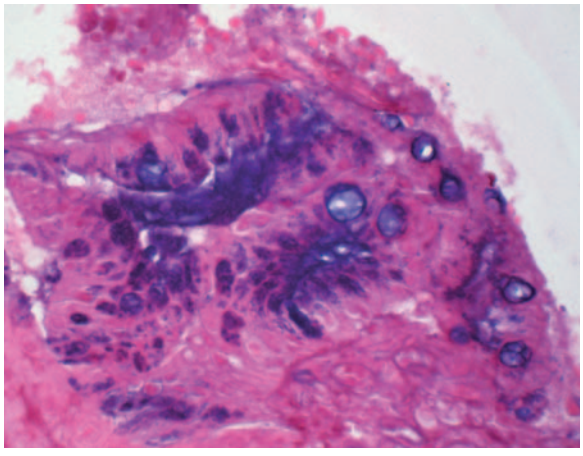

Figure 3–86 Periodic acid Schiff-Alcian blue stain (PAS-AB) of intestinal metaplasia in cardiac mucosa, showing the round goblet cells staining blue. Cells with both acid and neutral mucin stain a color between blue and magenta.

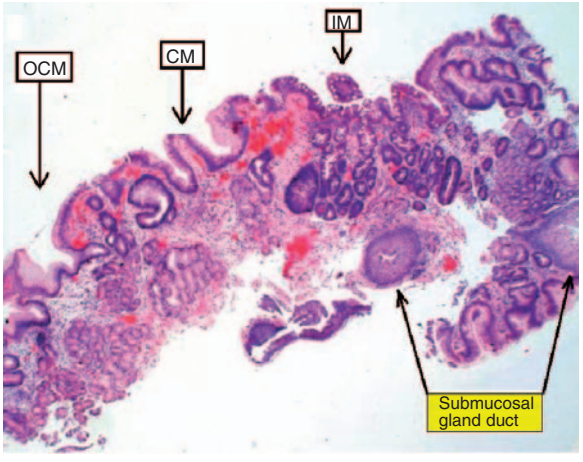

Figure 3–87 Biopsy showing multiple epithelia over a very short distance. From left to right are oxyntocardiac mucosa (*OCM*, most distal), cardiac mucosa without intestinal metaplasia (*CM*), and cardiac mucosa with intestinal metaplasia (*IM*). A submucosal gland duct lined by squamous epithelium is seen, opening at the surface of the epithelium.

The second method is to simply record all the epithelial types without quantitation. It is important to precisely define all of them. This is a reasonable method if one is not convinced about the significance of the different epithelial types. The record is accurate and can be interpreted by whatever opinion the clinician uses.

The third method is to establish a priority of epithelial types; this is the method I routinely use to report esophageal biopsies (Table 3–3). When intestinal metaplasia is present, it is not necessary to report the coexistence of cardiac and oxyntocardiac mucosa; the diagnosis line can simply read: "intestinal (Barrett) metaplasia." However, I frequently indicate: "reflux carditis; intestinal (Barrett) metaplasia" when there are significant amounts of cardiac mucosa without goblet cells. I also use the term *reflux carditis with focal intestinal metaplasia* when the number of goblet cells is small and cardiac mucosa without goblet cells dominates. These subtleties are designed to indicate the quantity of goblet cells in cardiac mucosa and are probably not necessary.

When cardiac and oxyntocardiac mucosa are present together, the diagnosis line can simply state "reflux carditis." When oxyntocardiac mucosa is present alone without cardiac and intestinal epithelium, the diagnosis line can state "oxyntocardiac mucosa with inflammation." When only squamous and gastric oxyntic mucosae are present and are histologically unremarkable, the diagnosis line can state: "no pathologic abnormality," because these are undisputedly normal epithelia in the esophagus and stomach, respectively. A sample pathology report at the University of Southern California is presented in Table 3–4. It details the epithelial types in the microscopic description and what the diagnosis line reads.

In Chapter 7, I will describe how these epithelial types are used to define a new grading system for the diagnosis and management of patients with gastroesophageal reflux disease. The third reporting method described here will become more intelligible with that system.

To make the report more sophisticated, a drawing that outlines biopsy findings can be added. An example is shown in Figure 3–88. It is a diagrammatic representation of the findings reported in Table 3–4. Biopsy images can also be included in the report, as required. I do not presently include any of these items in my practice.

Problems in Differential Diagnosis Between Columnar Epithelial Types

In the vast majority of cases, diagnosing epithelial types is easy. There are, however, situations that cause difficulty because of overlap of definitional

TABLE 3–3 Methods of Reporting a Biopsy Specimen from a Single Level

Epithelia present	Method 1	Method 2	Method 3
Normal SQ only	Normal SQ	Normal SQ	No pathologic abnormality
SQ only with reflux changes	Reflux esophagitis	Reflux esophagitis	Reflux esophagitis
SQ + GOM only	Normal* SQ (v%) + GOM† (w%)	Normal* SQ + GOM†	No pathologic abnormality*/†
SQ + GOM + OCM	Normal* SQ (v%) + GOM† (w%) + OCM (x%)	Normal* SQ + GOM† + OCM	Oxyntocardiac mucosa with chronic inflammation*/†
SQ + GOM + OCM + CM	Normal* SQ (v%) + GOM† (w%) + OCM (x%) + CM (y%)	Normal* SQ + GOM† + OCM + CM	Reflux carditis*/†
SQ + GOM + OCM + CM + IM	Normal* SQ (v%) + GOM† (w%) + OCM (x%) + CM (y%) + IM (z%)	Normal* SQ + GOM† + OCM + CM + IM	Intestinal (Barrett) metaplasia*/†

SQ, Squamous epithelium; *GOM*, gastric oxyntic mucosa; *OCM*, oxyntocardiac mucosa; *CM*, cardiac mucosa; *IM*, intestinal metaplasia in cardiac mucosa.
*If there is any pathologic finding in squamous epithelium, this must be recorded in the diagnosis.
†If there is any pathologic finding in gastric oxyntic mucosa, this must be recorded in the diagnosis.

TABLE 3–4 Sample of Pathology Report in a Patient with a 6-cm Segment of Columnar-Lined Esophagus*

LABORATORY INFORMATION (deleted)
DEMOGRAPHIC DATA AND DATES (deleted)

SPECIMENS: (a) antrum and body; (b) fundus; (c) retrograde at GEJ; (d) 40 cm; (e) 38 cm; (f) 36 cm; (g) 34 cm; (h) 32 cm

GROSS DESCRIPTION (deleted)

MICROSCOPIC DESCRIPTION:

A. Sections show unremarkable antral and body mucosa. There is no significant inflammation, intestinal metaplasia, dysplasia or malignancy. *H. pylori* is absent, confirmed with a negative Giemsa stain.
B. Sections show unremarkable gastric oxyntic mucosa. There is no significant inflammation, cardiac mucosa, intestinal metaplasia, dysplasia, or malignancy. *H. pylori* is absent.
C. Sections show gastric oxyntic mucosa and oxyntocardiac mucosa, the latter with mild chronic inflammation. There is no cardiac mucosa, intestinal metaplasia, dysplasia, or malignancy.
D. Sections show oxyntocardiac and cardiac mucosa, the latter with chronic inflammation and foveolar hyperplasia. There is no intestinal metaplasia, dysplasia, or malignancy.
E. Sections show oxyntocardiac and cardiac mucosa, the latter with chronic inflammation, foveolar hyperplasia, and focal intestinal metaplasia characterized by the presence of goblet cells. There is no dysplasia or malignancy.
F. Sections show cardiac and intestinal epithelium, the latter with goblet cells. There is no dysplasia or malignancy.
G. Sections show unremarkable squamous epithelium without criteria of reflux and intestinal epithelium with goblet cells. There is no dysplasia or malignancy.
H. Sections show unremarkable squamous epithelium without criteria of reflux. There is no glandular epithelium, dysplasia, or malignancy.

DIAGNOSIS:

A. ANTRUM AND BODY, BX: No significant pathologic abnormality.
B. FUNDUS, BX: Unremarkable gastric oxyntic mucosa.
C. RETROGRADE BX AT GEJ: Oxyntocardiac mucosa with chronic inflammation.
D. ESOPHAGUS, 40 CM, BX: Reflux carditis.
E. ESOPHAGUS, 38 CM, BX: Reflux carditis; intestinal (Barrett) metaplasia.
F. ESOPHAGUS, 36 CM, BX: Reflux carditis; intestinal (Barrett) metaplasia.
G. ESOPHAGUS, 34 CM, BX: Intestinal (Barrett) metaplasia.
H. ESOPHAGUS, 32 CM, BX: Unremarkable squamous epithelium.

*Diagnosed at the Keck School of Medicine, University of Southern California.
GEJ, Gastroesophageal junction; *BX,* biopsy.

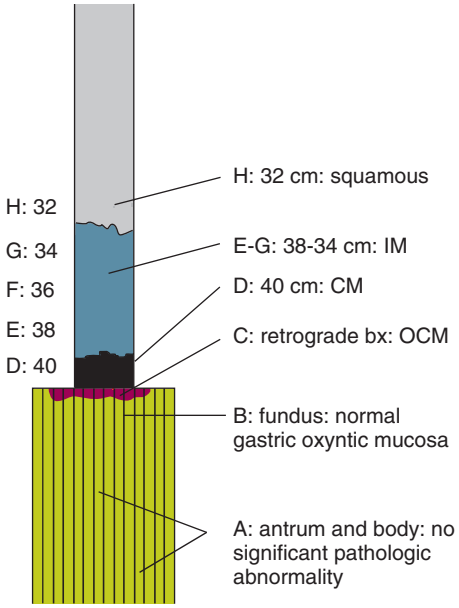

Figure 3–88 Diagrammatic representation of a sample pathology report in a patient with a 6-cm segment of columnar-lined esophagus biopsied according to our protocol. This illustrates the sample pathology report shown in Table 3–4. *CM,* Cardiac mucosa; *IM,* intestinal metaplasia; *OCM,* oxyntocardiac mucosa. *Blue*, Intestinal metaplasia; *black*, cardiac mucosa; *red*, oxyntocardiac mucosa; *gray*, squamous epithelium; *yellow*, gastric oxyntic mucosa with lines denoting rugal folds.

characteristics and similarity of epithelia types. For example, this question frequently arises: When is a goblet cell a goblet cell? Problems are encountered because cardiac mucosa can have cells with acid mucin and cytoplasmic vacuolation (pseudo-goblet cells). The similarity between atrophic gastritis, when parietal cells are destroyed, and cardiac mucosa creates problems. This

becomes more complex in atrophic gastritis associated with intestinal metaplasia. Difficulty arises separating this from Barrett-type intestinal metaplasia in cardiac mucosa. These entities should be studied with a clear understanding that they are different; as a result, better criteria for distinguishing them will emerge. Until then, we must do the best we can with the present definitions.

Cardiac Mucosa with Pseudo-Goblet Cells Versus Intestinal Metaplasia in Cardiac Mucosa

The diagnosis of intestinal metaplasia is very important and depends on the presence of goblet cells in cardiac mucosa. The diagnostic criterion is the presence of a single definite goblet cell in routine hematoxylin-stained and eosin-stained sections (Figure 3–89). Unfortunately, cardiac mucosa frequently shows mucin-distended cells called *pseudo-goblet cells* (Figures 3–90, 3–91, and 3–92). These show varying amounts of vacuolation of the cytoplasm that mimic true goblet cells to varying degrees. In most cases, the vacuoles tend to be clear, apical, not perfectly round, multiple within one cell, affect many adjacent cells, and do not cause bulging of the lateral cell border (see Figure 3–90 and 3–91). It is not rare, however, for pseudo-goblet cells to have a blue tinge in the vacuoles (see Figure 3–92).

In some cases, mucin-distended pseudo-goblet cells of cardiac mucosa can be difficult to differentiate from true goblet cells. The pathologist must be absolutely certain of the presence of a true goblet cell before designating a biopsy as intestinal metaplasia (Figure 3–93). When in doubt, do not diagnose the condition as intestinal metaplasia. The objective is to make the diagnosis of intestinal metaplasia on the basis of only definitive criteria for

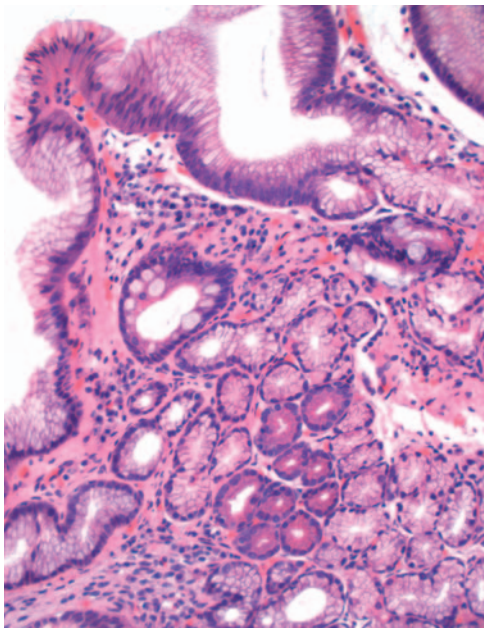

Figure 3–89 Cardiac mucosa with focal intestinal metaplasia limited to a few goblet cells in one foveolar complex. The epithelium contains Paneth cells in addition to the mucous cells. The diagnosis of intestinal metaplasia is made when the first definitive goblet cell is identified in cardiac mucosa.

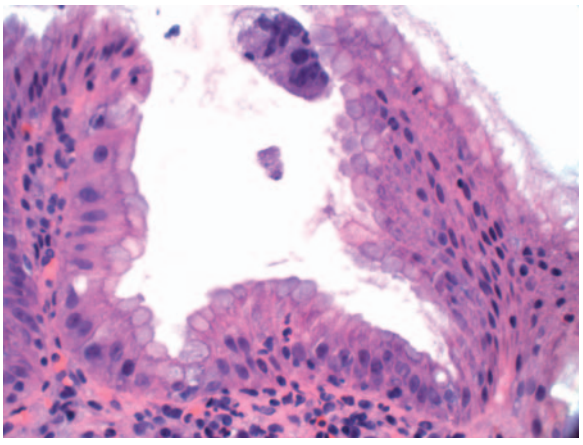

Figure 3–90 Cardiac mucosa with reactive mucin-distended cells. The mucin vacuoles are largely apical and do not satisfy the criteria for goblet cells. They have a basophilic tinge and are likely to be positive in an Alcian blue-stained section.

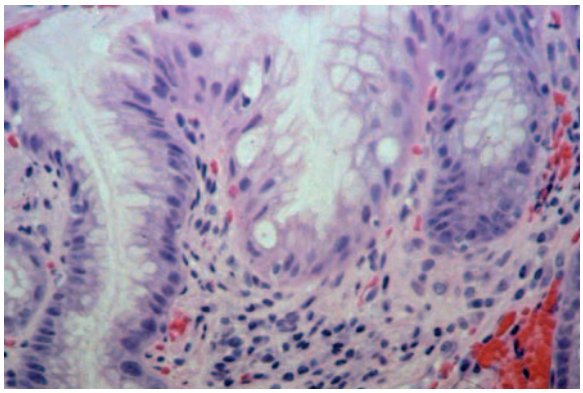

Figure 3–91 Cardiac mucosa with pseudo-goblet cells. Some of the mucin-distended cells in the epithelium are rounded and have a significant resemblance to goblet cells with a clear mucin vacuole. I did not make a diagnosis of true goblet cells on this biopsy. However, it is likely that there will be disagreement among pathologists in this case.

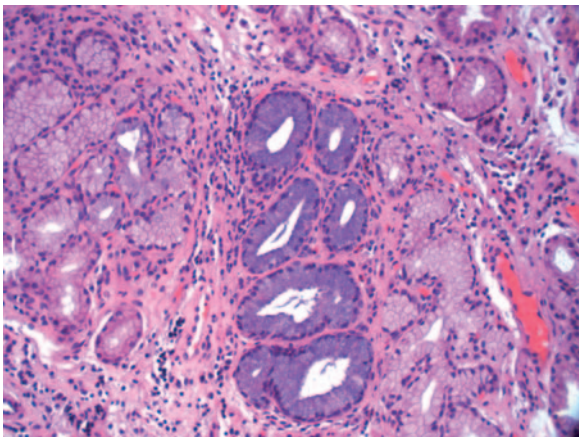

Figure 3–92 Cardiac mucosa with a focus of deeply basophilic cells. These do not satisfy the criteria for true goblet cells even if they are positive in Alcian blue stain.

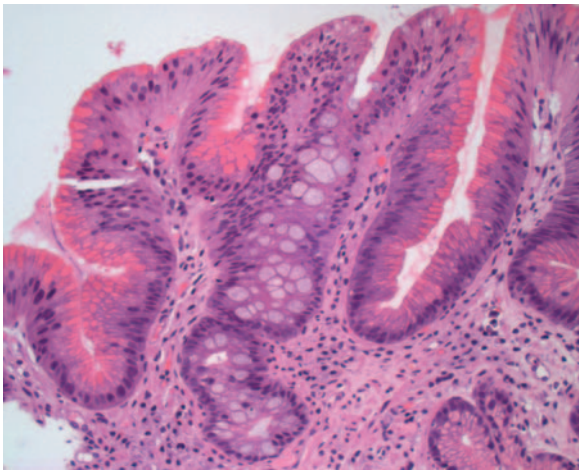

Figure 3–93 Cardiac mucosa with a single foveolar unit that contains goblet cells indicative of intestinal metaplasia. I made a diagnosis of intestinal metaplasia on this biopsy. However, despite the fact that the vacuoles are not perfectly rounded, I believe that there will be observer consensus that this represents true intestinal metaplasia.

goblet cells. This rule makes the diagnosis of intestinal metaplasia highly specific.

The absence of absolute criteria to differentiate pseudo-goblet and true goblet cells results in an inevitable interobserver variation in the sensitivity and specificity of intestinal metaplasia diagnosis. With training and experience, however, pathologists can achieve significant interobserver concordance in the diagnosis of intestinal metaplasia (see Figure 3–93). There is no evidence that pseudo-goblet cells in cardiac mucosa are a precursor of true intestinal metaplasia. It is considered to be a reactive change.

The use of Alcian blue stain at pH 2.5 (or periodic acid Schiff-Alcian blue) has been advocated in the literature as a means of diagnosing intestinal metaplasia. This is based on the fact that true goblet cells contain acid mucin (see Figures 3–85 and 3–86). However, acid mucin is frequently present in pseudo-goblet cells of cardiac mucosa (so-called *columnar blue cells*) (Figures 3–94 and 3–95). As such, a positive Alcian blue stain is not specific for true goblet cells, and Alcian blue positivity does not define intestinal metaplasia. The use of Alcian blue stains is discouraged because it tends to increase the false-positive diagnosis of intestinal metaplasia.

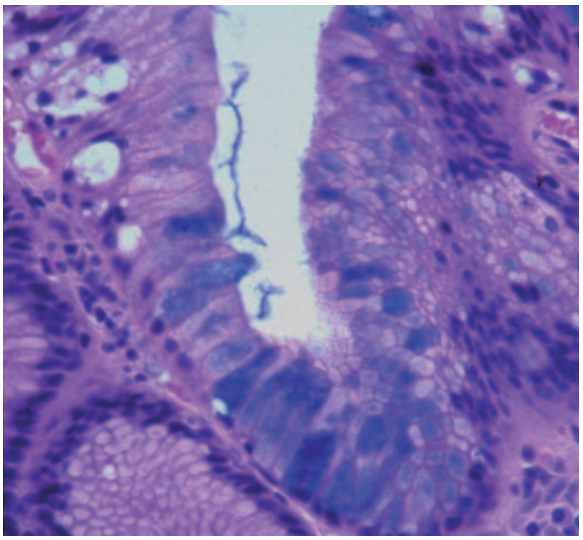

Figure 3–94 Cardiac mucosa, stained with Alcian blue, showing the typical appearance of Alcian blue staining in columnar cells of cardiac mucosa (i.e., "columnar blue cells"). The staining is intense in some cells. This should not be interpreted as representing intestinal metaplasia.

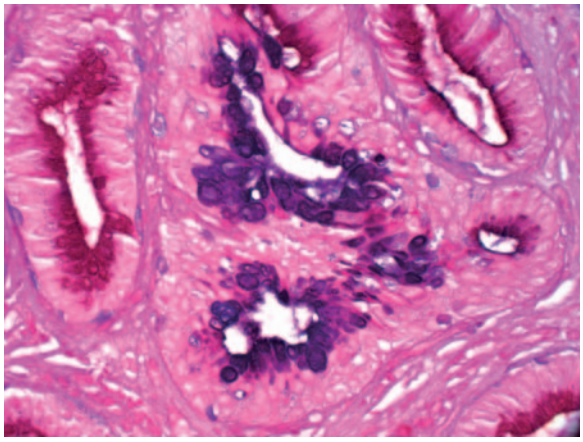

Figure 3–95 Cardiac mucosa, stained with periodic acid Schiff-Alcian blue (PAS-AB) stain. The gland on the side shows the typical magenta stain of neutral mucin in cardiac mucosal cells. The glands in the center show cells that have somewhat round shapes with a color that is between blue and magenta, indicating a mixed neutral and acid-mucin content. These are not goblet cells and should not be used to define intestinal metaplasia.

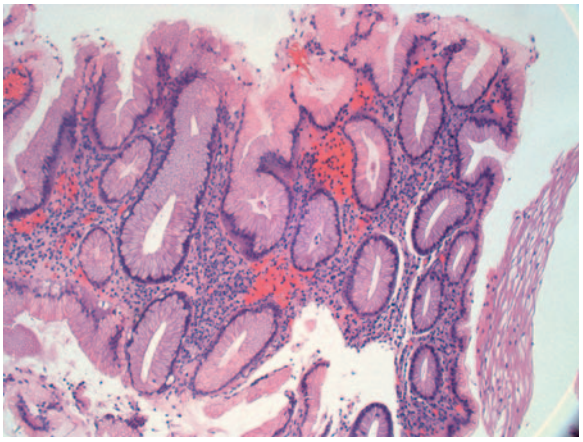

Figure 3–96 Tangentially sectioned superficial biopsy of metaplastic columnar epithelium, showing foveolar hyperplasia and chronic inflammation. If a biopsy sample excludes the deep part of the mucosa, a diagnosis is not possible, because it is unknown whether the deep region contains parietal cells.

Cardiac Mucosa Versus Oxyntocardiac Mucosa

There is no difficulty in differentiating cardiac mucosa, which has no parietal cells, from oxyntocardiac mucosa, which has parietal cells (see Figure 3–33). The presence of a single parietal cell precludes using the term *cardiac mucosa* for that foveolar-gland complex. In addition, cardiac mucosa almost always shows greater severity of chronic inflammation and reactive foveolar hyperplasia than coexisting oxyntocardiac mucosa (see Figures 3–77 and 3–78). The glands of cardiac mucosa are also more variable and disorganized than oxyntocardiac mucosa.

Difficulty arises when differentiating cardiac from oxyntocardiac mucosa in biopsies that are superficial or tangentially sectioned (Figure 3–96). Because the surface and foveolar region of both cardiac and oxyntocardiac mucosa are composed of mucous cells, a biopsy that does not sample the deep

glandular region of oxyntic and oxyntocardiac mucosa can be mistaken for cardiac mucosa. This is not a common problem; most biopsies of this region are adequate. Deeper sections are helpful in this situation because they may show the deeper part of the mucosa. When faced with a superficial or tangential biopsy, I use a somewhat pragmatic approach; I call the epithelium *cardiac mucosa* if there is significant chronic inflammation and foveolar hyperplasia (see Figure 3–96). If it appears normal, I label it "superficial columnar epithelium" without a statement of inadequacy of the biopsy.

Oxyntocardiac Versus Gastric Oxyntic Mucosa

The relative number of parietal and mucous cells in oxyntocardiac mucosa varies. When the glands contain few parietal cells, oxyntocardiac mucosa resembles cardiac mucosa, from which it is reliably differentiated by the presence of easily recognizable parietal cells. There is also significant chronic inflammation and lobulation of the glands in oxyntocardiac mucosa that permits easy distinction from gastric oxyntic mucosa (Figure 3–97).

However, when the number of parietal cells increases in the glands of oxyntocardiac mucosa, the inflammation and lobulation tend to decrease and the glands become straighter (Figure 3–98). In this situation, the differentiation of oxyntic mucosa from gastric oxyntic mucosa depends on the presence of mucous cells in the glands or the presence of gland ducts (see Figure 3–98). Mucous cells are always present but can be few in number. In such cases, it can be quite difficult to draw a line through the exact point where oxyntocardiac mucosa meets gastric oxyntic mucosa. When oxyntocardiac mucosa coexists with chronic gastritis associated with atrophy and pseudopyloric metaplasia of gastric oxyntic mucosa, the distinction can be even more difficult.

The significance of an error in this differential diagnosis is minimal. As will be shown later, oxyntocardiac mucosa is a benign epithelium with no risk of developing intestinal metaplasia or esophageal adenocarcinoma.

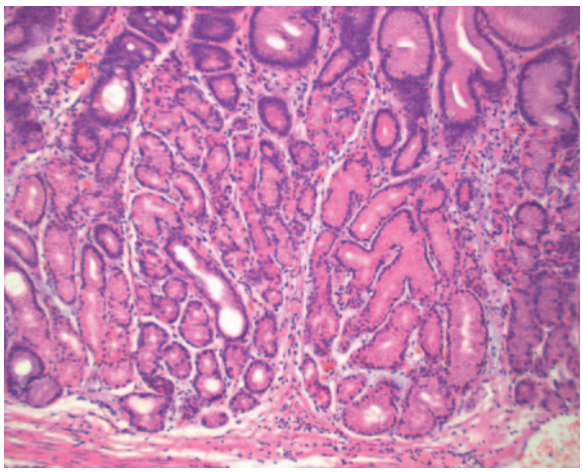

Figure 3–97 Oxyntocardiac mucosa. Despite the presence of large numbers of parietal cells in the glands, the mucous cell admixture is obvious. This, and the lobulated appearance of the glands, makes distinction from gastric oxyntic mucosa relatively easy.

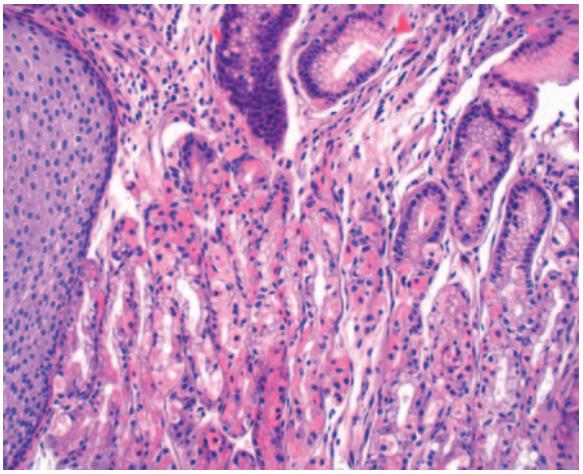

Figure 3–98 Oxyntocardiac mucosa. The number of parietal cells is greater, mucous cells are fewer, and the glands have lost their lobular shape and become more straight. The resemblance to gastric oxyntic mucosa is greater. In this case, the presence of a squamous-lined gland duct (seen partially at the left edge) establishes the esophageal location of this oxyntocardiac mucosa.

Cardiac Mucosa Versus Normal Gastric Oxyntic Mucosa

There is no difficulty in differentiating cardiac mucosa, which has disorganized and lobulated glands composed of mucous cells with no parietal cells (see Figure 3–51), from normal gastric oxyntic mucosa, which has straight tubular glands containing parietal cells and no mucous cells (see Figure 3–54).

Cardiac mucosa invariably shows lymphocytes, plasma cells, and eosinophils in the lamina propria; normal gastric mucosa is uninflamed. In patients with chronic gastritis, gastric oxyntic mucosa is inflamed. In non-atrophic gastritis, the inflammation is in the superficial foveolar region and spares the glands, which remain as straight tubular glands with parietal and chief cells (see Figure 3–56). There is no difficulty in differentiating cardiac mucosa from gastric oxyntic mucosa with chronic non-atrophic gastritis.

Chronic gastritis is caused by *H. pylori* and autoimmunity and is a diffuse change in the stomach that is commonly associated with atrophy, which can result in loss of parietal cells and pseudo-pyloric or intestinal metaplasia. *H. pylori* gastritis primarily involves the antrum and extends into the proximal stomach in a majority of cases (Figure 3–99). The availability of a biopsy sample from the distal stomach is very useful in the diagnosis of pathologic changes in the proximal stomach. Chronic gastritis of all types is a diffuse gastric mucosal inflammation (see Figure 3–99); there is no evidence that *H. pylori* or autoimmune gastritis causes inflammation in gastric mucosa that is restricted to the proximal stomach.

Cardiac Mucosa Versus Atrophic Gastric Mucosa with Pseudo-Pyloric Metaplasia

Chronic gastritis, resulting from both *H. pylori* and autoimmunity, often leads to atrophy of gastric oxyntic mucosa, which is associated with a loss of parietal cells. In many cases, the destroyed parietal cells are replaced by mucous cells (pseudo-pyloric metaplasia). The pseudo-pyloric metaplastic type of chronic atrophic gastritis in its end stage, with complete loss of parietal cells,

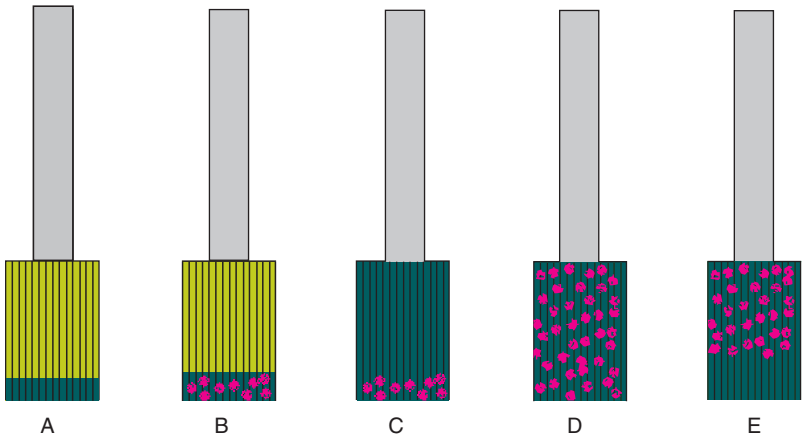

Figure 3–99 Patterns of gastric involvement in chronic gastritis. *Green*, Gastritis; *yellow*, normal stomach; *purple*, atrophy. **A**, Chronic antral gastritis without atrophy, typical of *H. pylori*. **B**, Chronic atrophic antral gastritis, typical of *H. pylori*. **C**, Chronic pangastritis with atrophy limited to the antrum, typical of *H. pylori*. **D**, Chronic atrophic pangastritis, typical of *H. pylori*. **E**, Antral-sparing chronic atrophic gastritis, typical of autoimmune gastritis, but also seen in *H. pylori* infection. Note that there is no chronic gastritis that is limited to the proximal 2–3 cm of the stomach.

is composed only of mucous cells and contains chronic inflammatory cells (see Figure 3–64). In a limited biopsy from the gastroesophageal junction region, this can be impossible to distinguish from cardiac mucosa (see Figure 3–67).

The following morphologic differences exist between cardiac mucosa and gastric oxyntic mucosa with atrophy and pseudo-pyloric metaplasia:

1. Cardiac mucosa is associated with reactive foveolar hyperplasia, which typically gives it a villiform surface with elongation and serration of the foveolar lumen and mucin distension of the foveolar cells (see Figures 3–69 and 3–73). This is in contrast to atrophic gastritis, which tends to have a flat surface with a non-reactive foveolar region (see Figures 3–63 and 3–64).
2. Smooth muscle proliferation into the mucosa is present in cardiac mucosa (see Figure 3–71; Figure 3–100) and usually absent in chronic atrophic gastritis, where the muscularis mucosae retain their its horizontal appearance (see Figure 3–63). Cardiac mucosa commonly shows smooth muscle fibers oriented in a perpendicular direction in the lamina propria, extending up from the hyperplastic muscularis mucosae toward the surface (see Figure 3–71). This is uncommon in chronic atrophic gastritis, but it may still occur.
3. The presence of gland ducts in the mucosa indicates cardiac mucosa (see Figure 3–20). Gland ducts are not present in gastric oxyntic mucosa.
4. The presence of multi-layered surface epithelium indicates cardiac mucosa (see Figures 3–37 and 3–38); multi-layered epithelium is not seen in gastric oxyntic mucosa. Despite these differences, the distinction between the two can be quite difficult in cases with limited biopsy sampling.

Most cases of chronic atrophic gastritis with pseudo-pyloric metaplasia are caused by *H. pylori* infection. *H. pylori* often involves cardiac mucosa when it is present, causing an increase in the severity of the chronic inflammation in cardiac mucosa and active inflammation. The presence of *H. pylori* in the epithelium, therefore, is of no value in distinguishing cardiac mucosa from chronic atrophic gastritis. The presence of *H. pylori* in cardiac mucosa

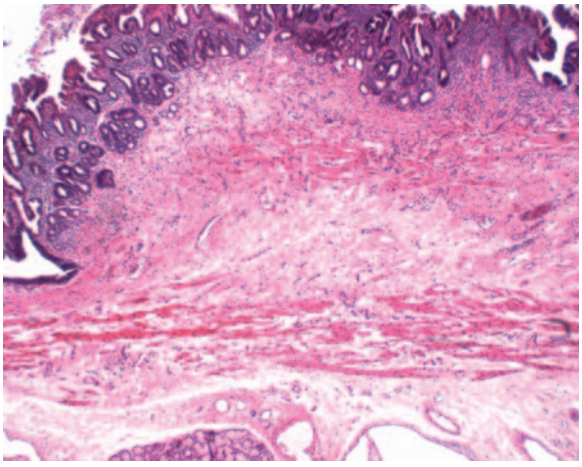

Figure 3–100 Cardiac mucosa with hyperplasia of the muscularis mucosae. The muscularis mucosae has split into two layers. The submucosa begins at the deep edge of the lower layer of muscularis mucosae and contains a submucosal gland, indicating an esophageal location.

does not mean that cardiac mucosal inflammation is caused by *H. pylori* infection. Cardiac mucosal inflammation exists without *H. pylori* and is aggravated when it is infected with the organism.

The fact that the differentiation of these two "mucous cell only" epithelia is difficult is not evidence that they are identical epithelial types. Cardiac mucosa results from columnar metaplasia of esophageal squamous epithelium because of gastroesophageal reflux and is very different etiologically from chronic atrophic gastritis with pseudo-pyloric metaplasia. It is not uncommon in pathology to encounter two completely different pathologic processes that cannot be distinguished from one another by routine histologic examination. An adenocarcinoma in the liver could represent a primary cholangiocarcinoma or a metastasis; the fact that they cannot be distinguished does not equate cholangiocarcinoma to metastatic adenocarcinoma.

Differentiating cardiac mucosa from chronic atrophic gastritis with pseudo-pyloric metaplasia in a biopsy from the proximal stomach region is easily accomplished in the majority of cases by evaluating the entire clinical picture. This is similar to using the example of the patient with an adenocarcinoma in a liver biopsy who also has a pancreatic mass and the clinican having to determine whether the diagnosis is metastatic pancreatic adenocarcinoma versus cholangiocarcinoma. Taking appropriate biopsy samples (the importance of having routine biopsy samples from the distal stomach cannot be overemphasized) and applying the following rules greatly reduces the number of problem cases.

1. If the biopsy in question is from an endoscopically visualized columnar-lined esophagus, the diagnosis is cardiac mucosa, regardless of whether the patient has atrophic gastritis with pseudo-pyloric metaplasia (Figure 3–101). *H. pylori* infection and autoimmune gastritis do not affect esophageal squamous epithelium and cause columnar metaplasia of the esophagus. If there are normal distal gastric biopsies, the patient has only cardiac mucosa with no pathology in gastric oxyntic mucosa (Patient *A* in Figure 3–101). If there is chronic atrophic gastritis in the distal gastric biopsies, the patient has coexisting cardiac mucosa and chronic atrophic gastritis with or without pseudo-pyloric metaplasia (Patient *B* in Figure 3–101).
2. If the patient has no columnar-lined esophagus at endoscopy and biopsies of the distal stomach show no evidence of chronic atrophic gastritis, the presence of a mucous cell-only epithelium in the proximal stomach is

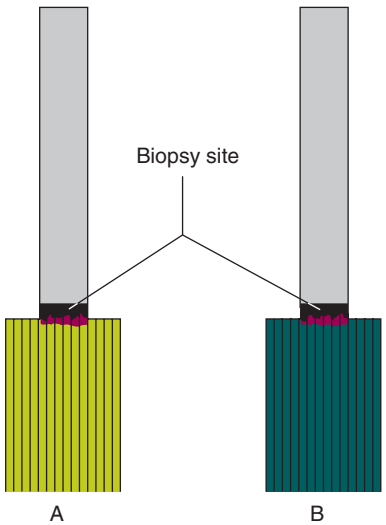

Figure 3–101 Patient with a biopsy from an endoscopically visualized columnar-lined esophagus that shows cardiac or oxyntocardiac mucosa is diagnostic of esophageal cardiac or oxyntocardiac mucosa. *Black*, Cardiac mucosa; *red*, oxyntocardiac mucosa. **A,** Patient has a normal gastric mucosa *(yellow area)*. **B,** Patient has gastritis coexisting with the esophageal cardiac or oxyntocardiac mucosa *(green area)*.

diagnostic of cardiac mucosa (Figure 3–102). *H. pylori* and autoimmunity do not produce atrophic gastritis with pseudo-pyloric metaplasia that is localized to the proximal few millimeters of the stomach. Chronic gastritis is a diffuse gastric epithelial disease that always involves the distal stomach if it has involved the proximal stomach. In Chapter 4, I will show that cardiac mucosa is always esophageal, and when it is called *gastric,* it is because of an error in the present definition of the gastroesophageal junction.

3. If the patient has no columnar-lined esophagus at endoscopy and biopsies of the distal stomach show chronic atrophic gastritis with pseudo-pyloric metaplasia, the diagnosis is one of two things: The patient either has chronic atrophic gastritis extending into the proximal stomach without cardiac mucosa (Patient *A* in Figure 3–103) or the patient has chronic atrophic gastritis coexisting with a small amount of cardiac mucosa distal to the endoscopic gastroesophageal junction (Patient *B* in Figure 3–103). In these cases, careful morphologic study of the proximal gastric biopsy is essential. If there are features distinctive of cardiac mucosa (e.g., multilayered epithelium, gland ducts), a diagnosis of cardiac mucosa coexisting with chronic atrophic gastritis is made. If the histologic features do not permit the characterization of cardiac mucosa separate from chronic atrophic gastritis, the presence of a small amount of coexisting cardiac mucosa may be impossible to identify.

In patients with chronic atrophic gastritis involving the entire stomach with a normal gastroesophageal junction at endoscopy, there is a significant risk of missing a small amount of cardiac mucosa at the most proximal end of atrophic gastritis. This is not clinically significant because there is no real risk of cancer in such a patient.

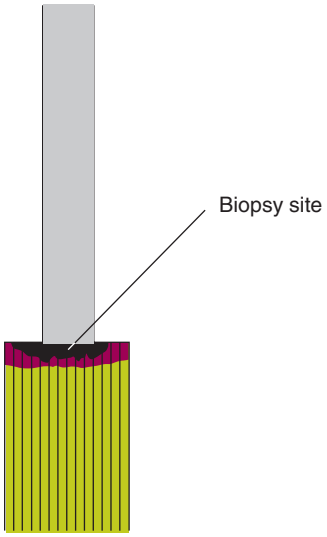

Figure 3–102 Endoscopically normal patient with a biopsy taken immediately distal to the gastroesophageal junction that shows cardiac or oxyntocardiac mucosa. *Black*, cardiac mucosa; *red*, oxyntocardiac mucosa. If this patient has a normal gastric mucosa *(yellow area)* in a biopsy taken at a point 3 cm distal to the endoscopic gastroesophageal junction, the finding in the gastroesophageal junction is diagnostic of cardiac mucosa or oxyntocardiac mucosa.

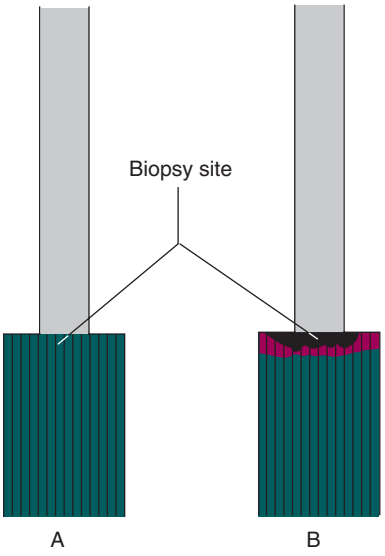

Figure 3–103 When there is diffuse pangastritis with diffuse or multi-focal pseudo-pyloric metaplasia *(green areas)* and the patient is endoscopically normal, the finding of a mucous cell-only or mixed mucous and parietal cell mucosa in a biopsy taken immediately distal to the gastroesophageal junction can be difficult to interpret. It may represent chronic gastritis extending to the gastroesophageal junction with the biopsy representing pseudo-pyloric metaplasia in a patient without cardiac and oxyntocardiac mucosa (**A**). It may also represent cardiac or oxyntocardiac mucosa coexisting with chronic gastritis (**B**). *Black*, cardiac mucosa; *red*, oxyntocardiac mucosa.

CASE STUDY

A 42-year-old white female presented with a history of vague, intermittent dyspepsia for the past 2 months. Her medical history was significant for cholecystectomy for gallstones 5 years previously. Physical examination revealed mild obesity but was otherwise unremarkable.

The upper endoscopy was essentially normal. The tubular esophagus was entirely lined by squamous epithelium (Figure 3–104). The stomach showed moderate amounts of bile in the gastric juice but was otherwise unremarkable without evidence of erythema, ulcers, or mass lesions. The rugal folds extended proximally to the Z-line. No separation was seen between the Z-line and the proximal limit of the rugal folds. The patient had biopsies according to our standard protocol: A–antrum and body; B–retrograde biopsy from the region within 1 cm from the proximal limit of the rugal folds; C–antegrade biopsy from the region of the Z-line, sampling the columnar epithelium immediately distal to the squamocolumnar junction, attempting to straddle the junction; and D–biopsy of squamous epithelium 2 cm above the Z-line.

The antrum and body biopsies showed moderate chronic gastritis with diffuse pseudo-pyloric metaplasia involving both the antral and body mucosa (Figure 3–105). The retrograde biopsy showed gastric oxyntic mucosa with chronic inflammation and pseudo-pyloric metaplasia (Figure 3–106). The antegrade biopsy straddling the squamocolumnar junction showed squamous epithelium without criteria of reflux transitioning into cardiac mucosa (Figure 3–107).

Comparison of the cardiac mucosa in Figure 3–107 and the gastric oxyntic mucosa with chronic atrophy and pseudo-pyloric metaplasia in Figure 3–106 showed all the described differences between these two epithelia. It is easy to recognize not only that these two epithelia are completely different, but also to

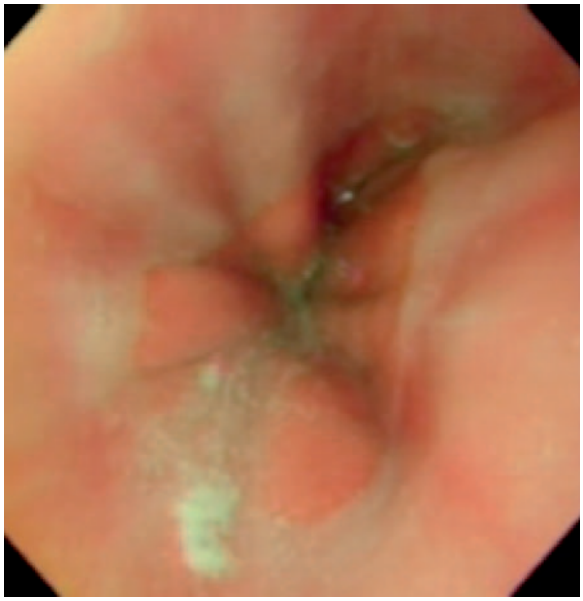

Figure 3–104 Endoscopic appearance of the junctional region. The Z-line is horizontal, and the rugal folds extend all the way to the Z-line. There is bilious refluxate in the lumen.

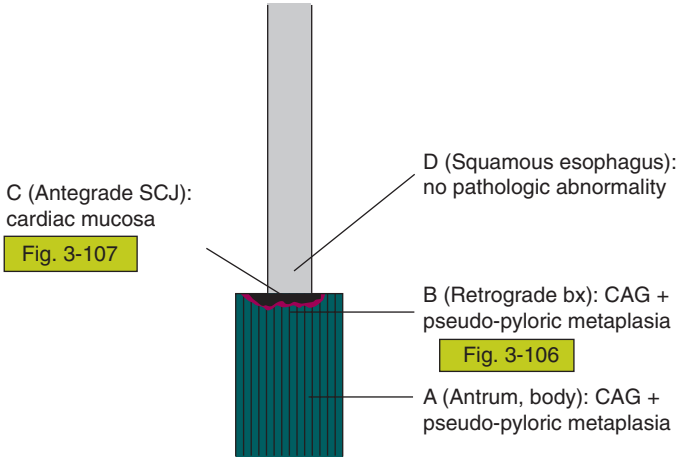

Figure 3–105 Diagrammatic representation of biopsy findings. The stomach showed diffuse chronic gastritis *(CAG) (green area)* with multifocal pseudo-pyloric metaplasia involving the oxyntic mucosa in the retrograde specimen (*B*), shown in Figure 3–106. The antegrade biopsy (*C*) straddling the squamocolumnar junction *(SCJ)* showed cardiac mucosa, shown in Figure 3–107. *Black*, Cardiac mucosa; *red*, oxyntocardiac mucosa.

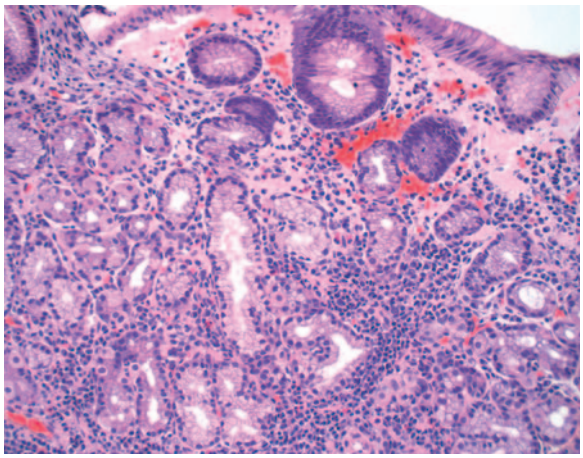

Figure 3–106 Retrograde biopsy (*B* in case study) showing gastric oxyntic mucosa with chronic gastritis and early atrophy with loss of parietal cells and pseudo-pyloric metaplasia. Note the flat surface with minimal foveolar hyperplasia typical of atrophic chronic gastritis. Only the central region is devoid of parietal cells.

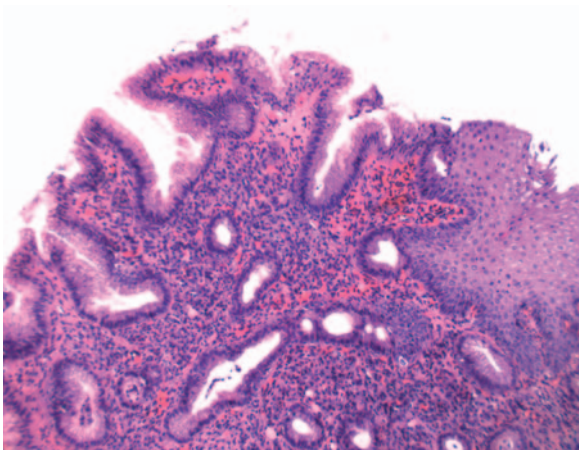

Figure 3–107 Antegrade biopsy (*C* in case study) showing the squamocolumnar junction. The columnar epithelium is cardiac with severe chronic inflammation and marked foveolar hyperplasia and a villiform surface.

identify one as cardiac mucosa and the other as gastric oxyntic mucosa with pseudo-pyloric metaplasia. The cardiac mucosa in this patient was limited to the few millimeters distal to the squamocolumnar junction and accompanied by diffuse chronic gastritis with pseudo-pyloric metaplasia. It should be noted that this is an easy differential diagnosis. When the atrophy in chronic gastritis is more severe and the mucosa becomes mucous cell-only without parietal cells, the distinction can be more difficult.

Intestinal Metaplasia in Cardiac Mucosa Versus Intestinal Metaplasia in Chronic Atrophic Gastritis Involving Gastric Oxyntic Mucosa

The only truly difficult and clinically significant differential diagnosis is that between intestinal metaplasia in cardiac mucosa (Barrett esophagus) and gastric intestinal metaplasia that occurs in gastric oxyntic mucosa in chronic atrophic gastritis. Chronic atrophic gastritis in gastric oxyntic mucosa frequently results in complete loss of parietal cells and intestinal metaplasia (see Figures 3–65 and 3–66). Chronic atrophic gastritis is a diffuse gastric inflammation, with atrophy and intestinal metaplasia being initially patchy and multi-focal with a progression to increasingly diffuse involvement (see Figure 3–99). It frequently is a pangastritis, involving the entire gastric mucosa all the way up to the gastroesophageal junction. Chronic atrophic gastritis caused by *H. pylori* tends to involve the antrum maximally, extends to the gastric body in the majority of cases, and is a pangastritis that commonly involves the most proximal region of the stomach (see Figure 3–99*D*). Autoimmune chronic gastritis is directed primarily at the parietal cell-containing body of the stomach and involves the most proximal stomach in all cases (see Figure 3–99*E*).

The differentiation of intestinal metaplasia in cardiac mucosa from intestinal metaplasia in chronic atrophic gastritis by pure histologic criteria is possible in many cases. Intestinal metaplasia in cardiac mucosa often has a villiform surface with reactive foveolar hyperplasia and smooth muscle proliferation (see Figures 3–81 and 3–86). Chronic atrophic gastritis tends to be a flat mucosa (see Figures 3–65 and 3–66). Residual parietal cells may be present in chronic

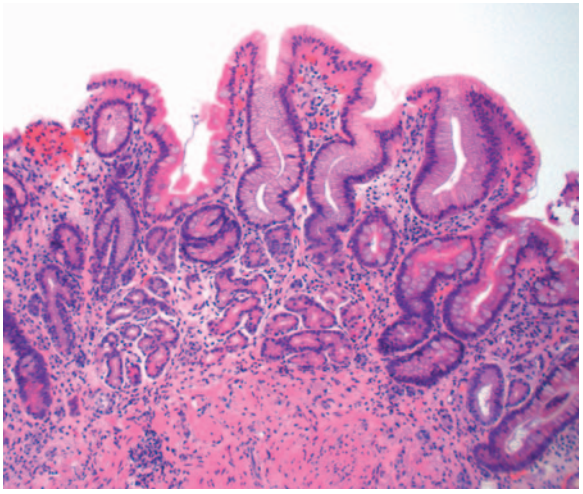

Figure 3–108 Chronic atrophic gastritis with intestinal metaplasia. There are scattered residual parietal cells in the glands of the atrophic mucosa. The combination of intestinal metaplasia and parietal cells almost never occurs in the same foveolar complex in metaplastic esophageal columnar epithelium.

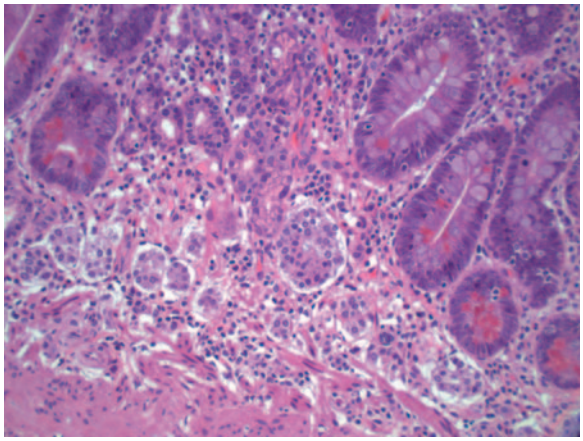

Figure 3–109 Chronic atrophic gastritis with prominent Paneth cells and micronodular neuroendocrine cell hyperplasia. The neuroendocrine cells appear as nests of small round cells with uniform round nuclei in the deepest part of the mucosa.

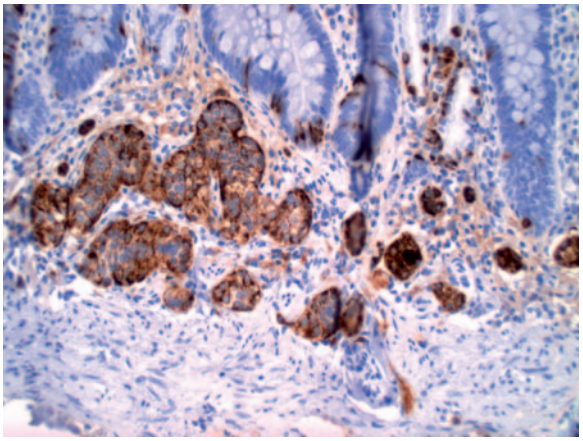

Figure 3–110 Chronic atrophic gastritis, stained by immunoperoxidase technique for chromogranin, shows positive staining in the nests of neuroendocrine cells in the deep mucosa.

atrophic gastritis (Figure 3–108). Intestinal metaplasia does not occur in oxyntocardiac mucosa. Paneth cells, which can be present in both, tend to be more frequent in chronic atrophic gastritis (Figure 3–109). The presence of gland ducts in the mucosa indicates intestinal metaplasia in cardiac mucosa (see Figure 3–16). Gland ducts are not present in gastric oxyntic mucosa. The presence of multi-layered surface epithelium indicates intestinal metaplasia in cardiac mucosa. Multi-layered epithelium is not seen in gastric oxyntic mucosa. Cardiac mucosa with intestinal metaplasia tends to have a hyperplastic muscularis mucosa with irregular extension of smooth muscle fibers into the lamina propria and splitting of the muscularis mucosae (see Figure 3–100). In contrast, atrophic gastritis has a flat muscularis mucosae (see Figure 3–63). Atrophic gastritis with intestinal metaplasia may be associated with neuroendocrine cell hyperplasia, including multiple micro-carcinoid tumors (Figures 3–109 and 3–110). This results from the hypochlorhydria of atrophic gastritis, which causes elevation of serum gastrin that leads to hyperplasia of the neuroendocrine cells of the stomach. Nodular neuroendocrine cell hyperplasia and micro-carcinoid tumors are not seen in cardiac mucosa with intestinal metaplasia. Despite these differences, it is not unusual to encounter difficulty in differentiating between intestinal metaplasia in cardiac mucosa and intestinal metaplasia in chronic

atrophic gastritis when one is faced with a limited biopsy sample from the region of the gastroesophageal junction.

The significance of intestinal metaplasia in cardiac mucosa is that it represents Barrett esophagus. There is controversy here; currently, the diagnosis of Barrett esophagus requires the presence of an endoscopically visualized columnar-lined esophagus in addition to the finding of intestinal metaplasia in cardiac mucosa. When the same histologic change is seen in a biopsy taken distal to the endoscopic gastroesophageal junction, there is confusion and controversy. Despite the confusion, there is concern among most gastroenterologists that this may be the precursor lesion for adenocarcinoma of the gastric cardia. This will be addressed in Chapter 4. In contrast, intestinal metaplasia occurring in chronic atrophic gastritis is believed to have a much lower malignant potential that does not require placing the patient on long-term endoscopic surveillance.

As in the distinction of cardiac mucosa from chronic atrophic gastritis with pseudo-pyloric metaplasia, if one considers the entire picture rather than one limited biopsy, the correct diagnosis of intestinal metaplasia in a proximal gastric region biopsy can be established in the vast majority of cases. The rules here are similar to those established earlier for the distinction between cardiac mucosa and chronic atrophic gastritis with pseudo-pyloric metaplasia.

1. If the biopsy in question is from an endoscopically visualized columnar-lined esophagus, the diagnosis is intestinal metaplasia in cardiac mucosa (Figure 3–111). This is the definition of Barrett esophagus. Atrophic gastritis does not extend into the esophagus to cause columnar metaplasia of squamous epithelium. If there are normal distal gastric biopsies, the patient has only Barrett esophagus with no pathology in gastric oxyntic mucosa (Patient *A* in Figure 3–111). If there is chronic atrophic gastritis in the distal gastric biopsies, the patient has coexisting Barrett esophagus and chronic atrophic gastritis with pseudo-pyloric (Patient *B* in Figure 3–111) or intestinal metaplasia (Patient *C* in Figure 3–111). In patients who have both Barrett esophagus and chronic atrophic gastritis with intestinal metaplasia, it is not uncommon for there to be a gap in the distal esophagus that is devoid of intestinal metaplasia. This is because the intestinal metaplasia in a segment of columnar-lined esophagus tends to occur in the more proximal region of the esophagus with the distal part of the columnar-lined segment composed of non-intestinalized cardiac and oxyntocardiac mucosa (see Figure

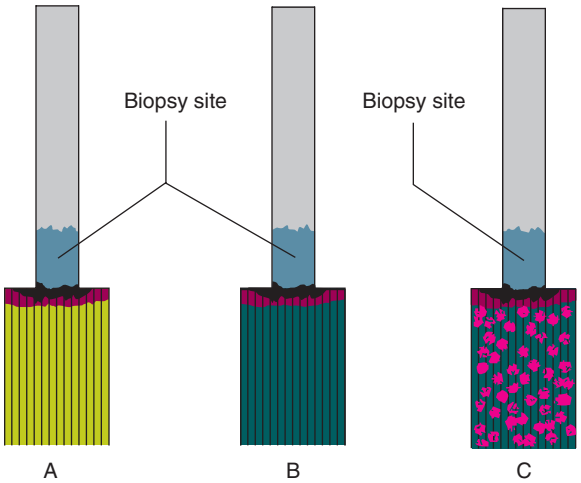

Figure 3–111 When a biopsy from an endoscopically visualized columnar-lined esophagus shows intestinal metaplasia, the diagnosis is always cardiac mucosa with intestinal metaplasia, regardless of any other finding. This may be associated with any finding in the distal gastric biopsies. The patient may have a normal gastric mucosa (*yellow area* in **A**), chronic gastritis without atrophy (*green area* in **B**), or chronic gastritis with multifocal atrophy and intestinal metaplasia (*green with purple areas* denoting atrophy and gastric intestinal metaplasia in **C**). *Blue*, Intestinal metaplasia; *black*, cardiac mucosa; *red*, oxyntocardiac mucosa; *gray*, squamous epithelium; *yellow*, gastric oxyntic mucosa with lines denoting rugal folds.

3–111*C*). This phenomenon is seen only in patients with long segments of columnar-lined esophagus and is detected only with a strict and extensive biopsy protocol.

2. If the patient has no columnar-lined esophagus at endoscopy and biopsies of the distal stomach show no evidence of chronic gastritis, the presence of intestinal metaplasia in a mucous cell-only epithelium in the proximal stomach is diagnostic of intestinal metaplasia in cardiac mucosa (Figure 3–112). *H. pylori* and autoimmunity do not produce a gastritis that is localized to the proximal few millimeters of the stomach. Chronic gastritis is a diffuse gastric epithelial disease that always involves the distal stomach if it has involved the proximal stomach (see Figure 3–99). In Chapter 4, I will show that the reason this is presently called *intestinal metaplasia of the gastric cardia* is because the present definition of the gastroesophageal junction is incorrect. Cardiac mucosa with intestinal metaplasia is always esophageal and always represents Barrett esophagus.
3. If the patient has no columnar-lined esophagus at endoscopy and biopsies of the distal stomach show evidence of chronic atrophic gastritis with intestinal metaplasia, the presence of intestinal metaplasia in a mucous cell-only epithelium in the proximal stomach may mean one of two things: (1) the patient has chronic atrophic gastritis with intestinal metaplasia extending into the proximal stomach without any cardiac mucosa with intestinal metaplasia being present (Patient *A* in Figure 3–113) or (2) the patient has chronic atrophic gastritis coexisting with a small amount of intestinal metaplasia in cardiac mucosa distal to the endoscopic gastroesophageal junction. In these cases, careful morphologic study of the

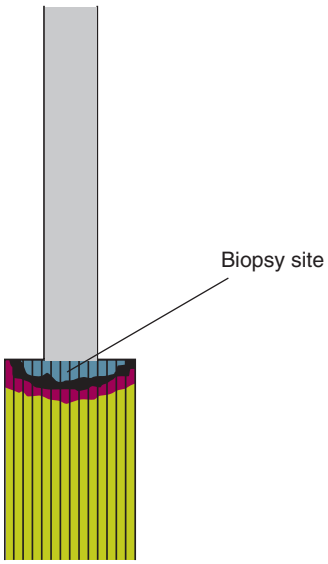

Figure 3–112 The finding of intestinal metaplasia limited to the region within 3 cm distal to the endoscopic gastroesophageal junction with the remaining stomach showing no inflammation *(yellow area)* is diagnostic of intestinal metaplasia in cardiac mucosa. *Blue*, Intestinal metaplasia; *black*, cardiac mucosa; *red*, oxyntocardiac mucosa; *gray*, squamous epithelium; *yellow*, gastric oxyntic mucosa with lines denoting rugal folds.

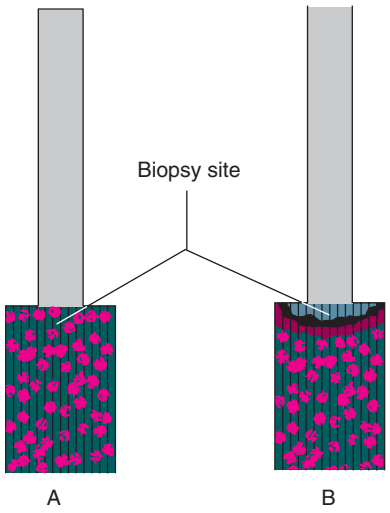

Figure 3–113 In a patient who is normal endoscopically and has distal chronic atrophic gastritis with intestinal metaplasia, the finding of intestinal metaplasia in a mucous cell-only epithelium in a biopsy distal to the endoscopic gastroesophageal junction can mean one of two things: chronic atrophic gastritis with multi-focal intestinal metaplasia without cardiac mucosa (patient *A*) or intestinal metaplasia in cardiac mucosa coexisting with chronic atrophic gastritis with intestinal metaplasia (patient *B*). *Blue*, Intestinal metaplasia; *black*, cardiac mucosa; *red*, oxyntocardiac mucosa; *gray*, squamous epithelium; *green with purple areas*, gastric oxyntic mucosa with chronic atrophic gastritis and multi-focal intestinal metaplasia.

proximal gastric biopsy is necessary. If there are features that are distinctive for intestinal metaplasia in cardiac mucosa, a diagnosis of intestinal metaplasia in cardiac mucosa coexisting with chronic atrophic gastritis is made. If the histologic features do not permit the characterization of cardiac mucosa separate from the chronic atrophic gastritis, the intestinal metaplasia in cardiac mucosa may be missed.

In such a patient with chronic atrophic gastritis involving the stomach and a normal gastroesophageal junction at endoscopy, there is a significant risk of missing a small amount of intestinal metaplasia in cardiac mucosa at the most proximal end of atrophic gastritis. Unlike in pseudo-pyloric metaplasia, this is a significant error because there is a greater likelihood of a malignant potential for intestinal metaplasia in cardiac mucosa than chronic atrophic gastritis. This is the only situation in which I use clinical information to aid in the pathologic diagnosis. If a patient with this problem has typical symptoms of reflux disease, Barrett esophagus is very likely as a second pathology in a patient with chronic atrophic gastritis.

Immunoperoxidase testing has been recommended for this differential diagnosis. Das-1 monoclonal antibody is reported to be positive in intestinal metaplasia complicating cardiac mucosa but not gastric intestinal metaplasia.[21] Differential staining with cytokeratin-7 and 20 shows a "Barrett-type pattern" in intestinal metaplasia occurring in cardiac mucosa, which shows superficial staining with cytokeratin 20 (Figure 3–114) and both superficial and deep staining with cytokeratin 7 (Figure 3–115). This is different than the "gastric-type pattern" in chronic atrophic gastritis.[22] My experience with these immunoperoxidase stains is not positive. I find them to be very difficult to interpret and rarely useful in the few cases in which I have had significant doubt about the diagnosis based on morphologic features. Immunoperoxidase staining should be reserved for those few cases in which there is significant doubt, because their value in this setting is not established. I rarely perform any immunostains for this differential diagnosis.

In the few cases when doubt exists after exhaustive analysis, it is appropriate to call the presence of intestinal metaplasia in cardiac mucosa only when there is reasonable certainty that this coexists with chronic atrophic gastritis. When there is doubt, I call it chronic atrophic gastritis. This approach

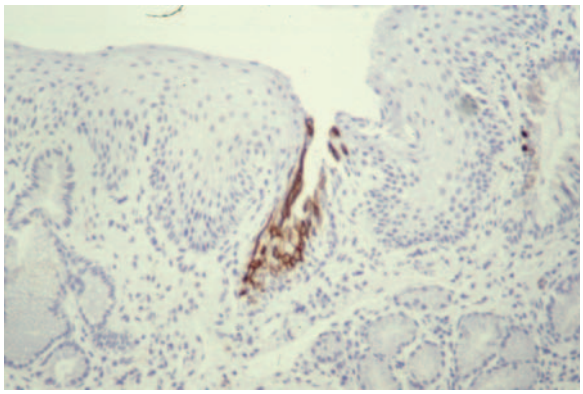

Figure 3–114 Intestinal metaplasia in cardiac mucosa in an esophageal biopsy stained by immunoperoxidase technique for cytokeratin 20, showing staining limited to the superficial region of the glandular epithelium.

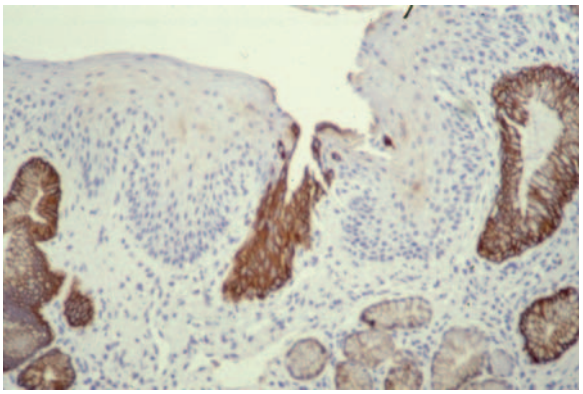

Figure 3–115 Intestinal metaplasia in cardiac mucosa in an esophageal biopsy stained by immunoperoxidase technique for cytokeratin 7, showing strong staining of both the deep and superficial regions of the glandular epithelium.

will result in the false-negative diagnosis of a few patients with small amounts of Barrett-type intestinal metaplasia in cardiac mucosa. This is currently appropriate, because the actual risk associated with small amounts of intestinal metaplasia in cardiac mucosa is not established. If the data suggest a significant cancer risk, one can adjust the criteria to make the diagnosis of intestinal metaplasia in cardiac mucosa more sensitive, but this will result in false-positive diagnoses until more accurate criteria for differentiating the two emerge.

CASE STUDY

A 46-year-old female presented with intermittent chest pain, dyspepsia, and nausea. There was no weight loss. There was no other significant history. Upper endoscopy was essentially unremarkable, with the entire tubular esophagus lined by squamous epithelium, which ended at a horizontal Z-line. The gastric mucosa was somewhat flattened with a focal cobblestone appearance, and the rugal folds were not well defined. Biopsies were taken as follows: A–antrum and body; B–retrograde in the region within 1 cm distal to the endoscopic gastroesophageal junction; C–antegrade biopsies attempting to straddle the squamocolumnar junction; D–biopsy of squamous-lined esophagus 2 cm above the Z-line.

The stomach biopsy, including the antrum, body, and retrograde, showed severe chronic atrophic pangastritis with extensive intestinal metaplasia (Figures 3–116 and 3–117). The antegrade biopsy showed intestinal metaplasia immediately distal to the squamous epithelium (Figure 3–118). The squamous epithelium was unremarkable.

The morphologic features of the intestinal metaplasia adjacent to the squamous epithelium in the antegrade biopsy (see Figure 3–118) showed the typical

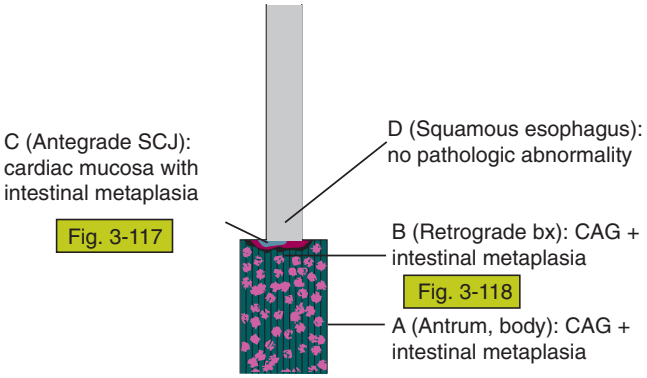

Figure 3–116 Diagrammatic representation of biopsy findings. The stomach showed diffuse chronic gastritis *(CAG)* with multifocal atrophy and intestinal metaplasia *(green with purple areas)* involving the oxyntic mucosa in the retrograde specimen (**B**), shown in Figure 3–117. The antegrade biopsy (**C**) straddling the squamocolumnar junction *(SCJ)* showed cardiac mucosa with intestinal metaplasia shown in Figure 3–118. *Blue*, Intestinal metaplasia in cardiac mucosa; *black*, cardiac mucosa; *red*, oxyntocardiac mucosa.

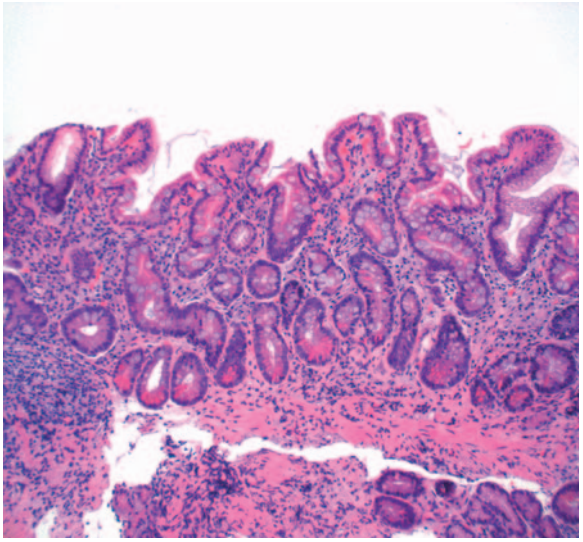

Figure 3–117 Retrograde biopsy (*B* in case study) showing chronic atrophic gastritis with intestinal metaplasia. Note the relatively flat surface and prominent Paneth cells in the deep foveolar region.

villiform appearance of intestinal metaplasia in cardiac mucosa. This was different than the appearance in the retrograde biopsy with chronic atrophic gastritis and gastric intestinal metaplasia (see Figure 3–117) in which the epithelium had a flat surface with numerous Paneth cells. An attempt was made to use the differential staining pattern with cytokeratin 7 and 20. The epithelium at the squamocolumnar junction showed mainly superficial staining with cytokeratin 20 (Figure 3–119) and strong superficial and deep staining with cytokeratin 7 (Figure 3–120), which is the typical pattern of Barrett esophagus. Staining of the chronic atrophic gastritis (the antral biopsy was chosen for the staining) showed a somewhat different staining pattern with superficial and deep staining with cytokeratin 20 (Figure 3–121) and weaker staining with cytokeratin 7. There was positivity in both superficial and deep regions of the mucosa (Figure 3–122). It is probable, although it may be my bias, that the morphologic differences are more definitive than the differences in the cytokeratin staining. Certainly, they are much more cost-effective.

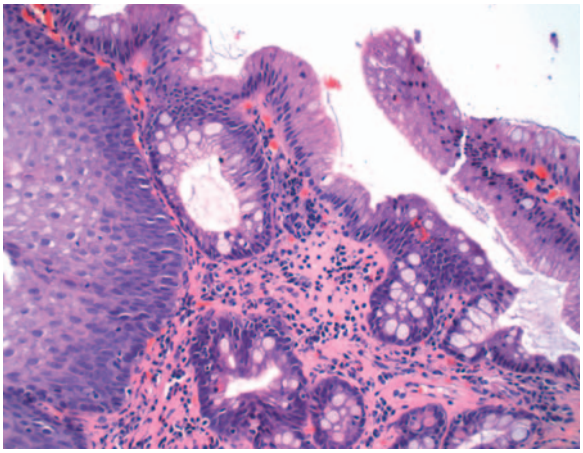

Figure 3–118 Antegrade biopsy (*C* in case study) showing the squamocolumnar junction. The squamous epithelium is unremarkable. The glandular mucosa is intestinal and shows a villiform surface.

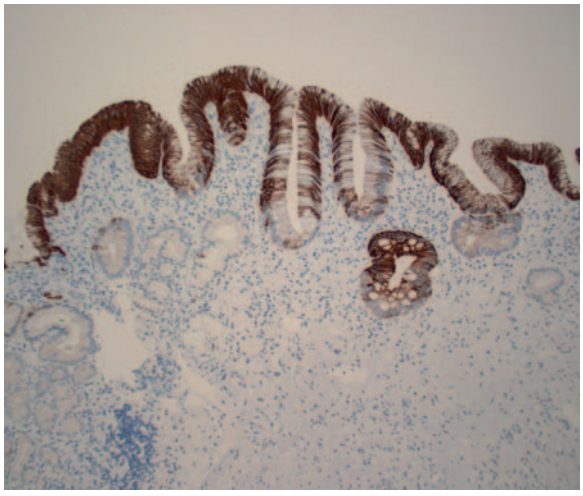

Figure 3–119 Immunoperoxidase stain for cytokeratin 20 in the biopsy from the squamocolumnar junction, showing positive staining limited to the superficial glands.

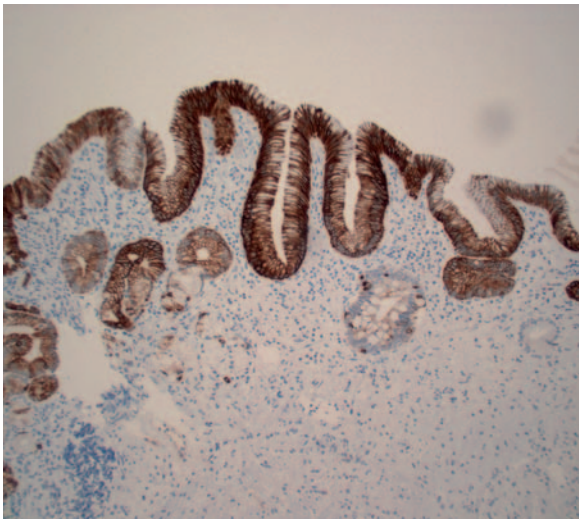

Figure 3–120 Immunoperoxidase stain for cytokeratin 7 in the biopsy from the squamocolumnar junction, showing superficial and deep staining.

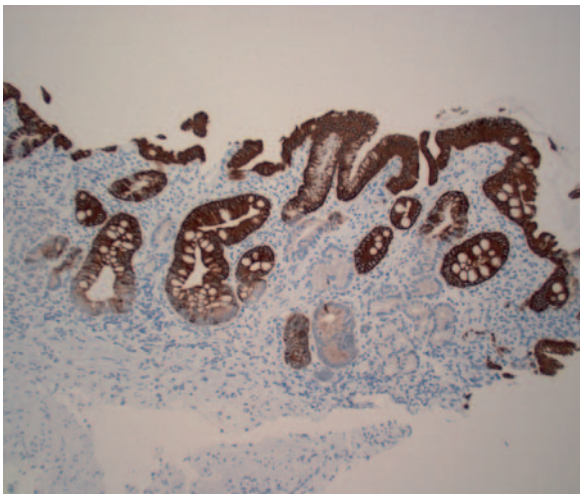

Figure 3–121 Immunoperoxidase stain for cytokeratin 20 in the antral biopsy, showing positive staining in superficial and deep glands.

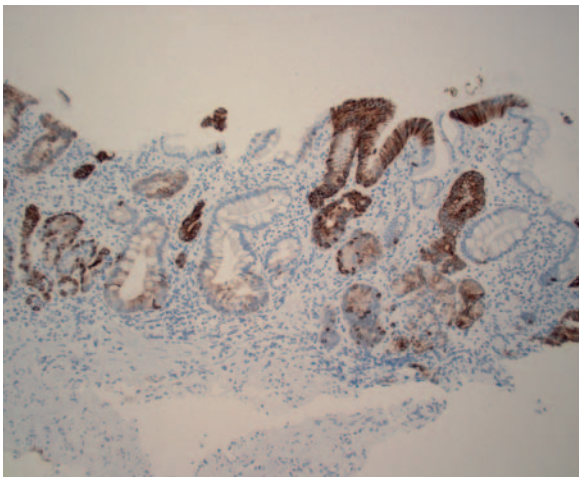

Figure 3–122 Immunoperoxidase stain for cytokeratin 7 in the antral biopsy, showing positive staining in superficial and deep glands.

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CHAPTER 4

Definition of Normal and Reflux-Induced Anatomy and Histology

Every human disease must be founded in accurate and reproducible anatomy and histology. Much of the confusion about gastroesophageal reflux disease is the failure to define it anatomically and histologically. In this chapter, I will explore the reasons for this confusion and show that its resolution is based on the accurate recognition of the gastroesophageal junction (Figure 4–1). For 50 years we have failed to recognize the devastation caused in the most distal esophagus by the effects of reflux disease. We have expected it to retain our concept of what an esophagus should look like. Instead, the damage produced by reflux causes the esophagus to dilate and show columnar metaplasia. The confusion results from mistaking this dilated, end-stage reflux-damaged distal esophagus with columnar metaplasia for the proximal stomach. When we understand how this damage happens, the confusion disappears.

Normal Anatomy

There are only two anatomic structures within this defined area of damage–the esophagus and the stomach. The two organs are separated by an imaginary line, which is called the *gastroesophageal junction* (Figure 4–2). There is no third organ here. The gastroesophageal junction is not a "region" or a "zone." No diseases can arise from, or occur in, an imaginary line. Thus, the term *adenocarcinoma of the gastroesophageal junction* is a misnomer and an expression of the uncertainty about the exact relationship of the adenocarcinoma to the true gastroesophageal junction. If this uncertainty did not exist, we would simply call a tumor in this region either *esophageal* or *gastric adenocarcinoma,* not *adenocarcinoma of the gastroesophageal junction.* The gastric cardia is part of the stomach; it cannot express pathologic changes in the esophagus by gastroesophageal reflux.

The Normal Esophagus

The normal esophagus is the organ that transports food from the pharynx to the stomach by the act of swallowing. Swallowing is effected by a peristaltic wave that propels the bolus of food rapidly down the esophagus. The peristaltic wave is coordinated with relaxation of the lower esophageal sphincter, which permits passage of the food bolus into the stomach (Figure 4–3).

The esophagus traverses the neck and mediastinum (cervical and thoracic esophagus), passes through the diaphragmatic hiatus, and becomes an abdom-

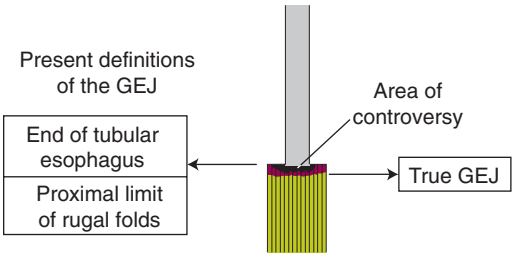


Figure 4–1 Diagrammatic representation of the controversial region. The gastroesophageal junction *(GEJ)* is presently defined as either the end of the tubular esophagus (on gross examination) or the proximal limit of rugal folds (endoscopy). When cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa are found distal to the gastroesophageal junction, they are, by definition, gastric in location. I will show in this chapter that this is incorrect. The true gastroesophageal junction cannot be defined by gross or endoscopic examination. It can only be defined histologically as the proximal limit of gastric oxyntic mucosa. *Gray,* Squamous epithelium; *black*, cardiac mucosa; *red,* oxyntocardiac mucosa; *yellow,* gastric oxyntic mucosa with rugal folds shown as *stripes*.

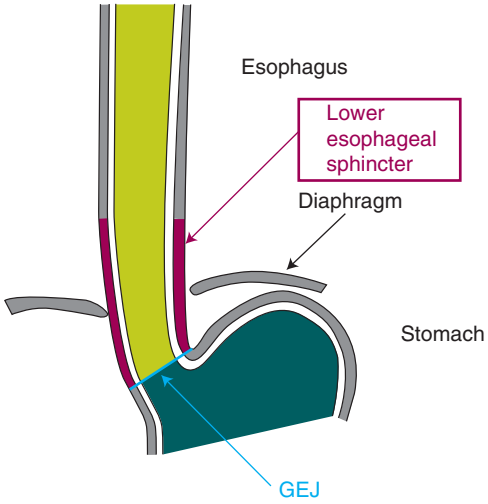


Figure 4–2 Diagram of normal anatomy of the esophagus and proximal stomach. The lower esophageal sphincter *(red areas)* includes the distal 3 to 4 cm of the esophagus, straddling the diaphragm. The normal gastroesophageal junction *(GEJ)* is the distal limit of the tubular esophagus, the distal limit of the sphincter *(red areas),* the distal limit of squamous epithelium *(yellow area),* and the proximal limit of gastric oxyntic mucosa *(green area).*

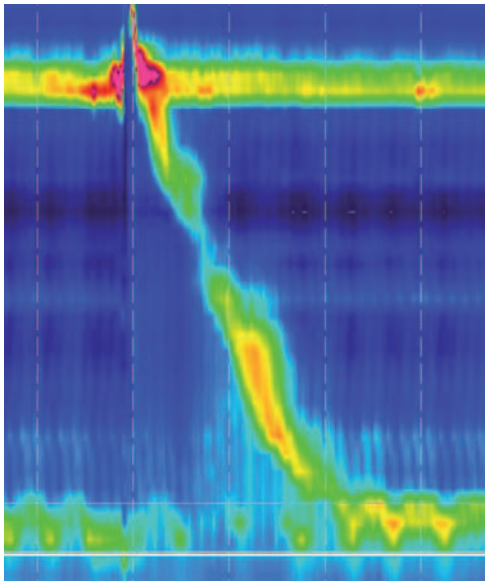


Figure 4–3 A normal swallow with complete high-resolution manometry depiction of motor function from the upper esophageal sphincter *(UES)* to the proximal stomach using the Manoscan 360 system. Pressures are expressed in color intensity (*red, orange, yellow, green, dark blue; blue* indicates decreasing pressure levels). This shows the relaxation of the upper esophageal sphincter *(upper horizontal band)* at the beginning of the swallow, and the propagated high-pressure peristaltic wave passing down the esophagus. The lower esophageal sphincter *(lower horizontal band)* relaxes at the onset of the swallow and regains its resting pressure when the peristaltic wave has passed. (Reproduced with permission from Sierra Scientific Instruments. Special thanks to James L. Pitman for providing the images.)

inal organ (abdominal esophagus) before it ends at the gastroesophageal junction (Figures 4–2 and 4–4). The abdominal esophagus is normally 2 to 3 cm long. Anatomically, the normal esophagus is a tubular structure that transitions into the saccular stomach at the gastroesophageal junction (see Figure 4–2). This point of transition is marked externally by the peritoneal reflection. The lesser curvature of the stomach passes straight down and to the right at the junction, but the greater curvature of the stomach on the left side passes acutely upward and to the left from the junction, forming the acute angle of His. The muscle wall of the abdominal esophagus is equivalent

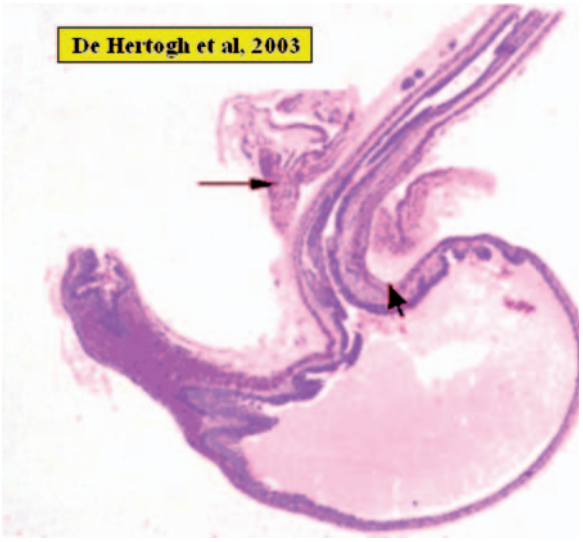


Figure 4–4 Fetal gross specimen of esophagus and stomach showing the diaphragm *(long arrow)* and the angle of His *(short arrow).* The area between the two arrows is the abdominal portion of the esophagus. (Reproduced with permission from De Hertogh G, Van Eyken P, Ectors N, et al: *Gut* 52:791–796, 2003.)

to the abdominal part of the lower esophageal sphincter, which is therefore 1 to 3 cm long (see Figure 4–2).

The Lower Esophageal Sphincter

A competent lower esophageal sphincter normally prevents gastroesophageal reflux. The sphincter is a high-pressure zone (resting pressure is normally 15 to 40 mm Hg) resulting from tonic contraction of the muscle wall of the distal esophagus (Figures 4–5 and 4–6). The sphincter straddles the diaphragmatic hiatus; it has a thoracic segment above the diaphragm that is 1 to 3 cm long and an abdominal segment below the diaphragm that is 1 to 3 cm long (see Figures 4–5 and 4–6). The sphincter ends at the end of the esophagus. The lower esophageal sphincter is a manometrically defined entity. It cannot be accurately defined anatomically or endoscopically, despite claims by some gastroenterologists that it can be clearly seen at endoscopy and claims by some pathologists that it can be identified at gross examination. There is no muscle thickening or other easy and reproducible criterion for the anatomic definition of the sphincter.

For the lower esophageal sphincter to function normally in preventing gastroesophageal reflux, the following three components are essential[1]:

1. Adequate resting high pressure; when this decreases to below approximately 8 mm Hg, sphincter competence is impaired, regardless of any other factor.
2. Adequate total length; when this is less than approximately 3 cm, sphincter competence is impaired.
3. Adequate abdominal segment length; when this is less than 1 cm, sphincter competence is impaired.

Lesser magnitude of abnormality in these three factors may result in sphincter failure when they are combined. In gastroesophageal reflux disease, lower esophageal sphincter abnormalities that impair sphincter competence occur early and increase in severity with the severity of reflux disease.[2] In general, the degree of sphincter abnormality correlates with the amount of reflux as measured in the 24-hour pH test and the multichannel impedance test. The earliest detectable sphincter abnormality is generally a decrease in

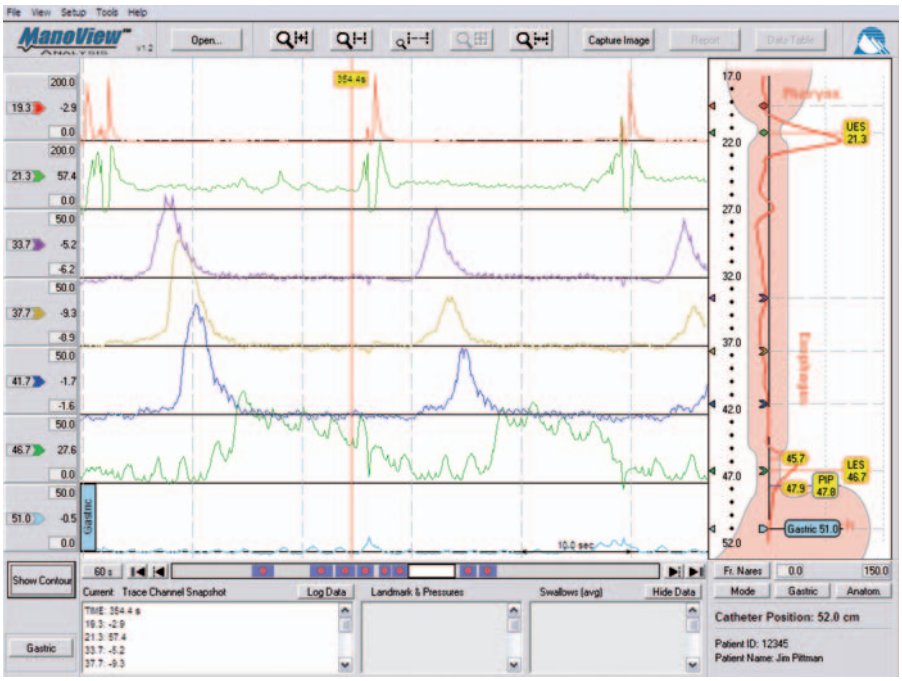


Figure 4–5 Esophageal manometry tracing showing two separate swallows. The upper channel *(red line)* shows the upper esophageal sphincter, which is 20 to 23 cm from the nares. The middle four channels are in the body of the esophagus and show the propagated peristaltic wave. The bottom channel *(green line)* is the lower esophageal sphincter, which extends from 45 to 49 cm from the nares. The lower sphincter relaxes at the beginning of the swallow and returns to its high resting pressure at the end of the passage of the peristaltic wave. The anatomic depiction of the tracing is on the right with the distances from the nares. (Reproduced with permission from Sierra Scientific Instruments.)

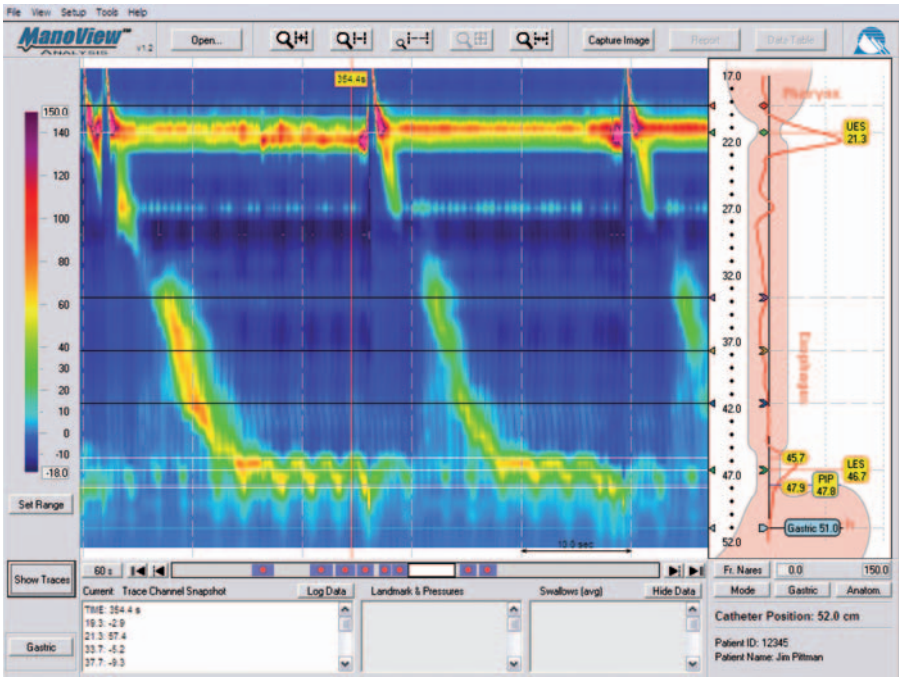


Figure 4–6 The same normal swallows as the tracing in Figure 4–5 in a high-resolution color format. The color code for the pressure range is shown at the left. Note the lower esophageal sphincter *(horizontal band)* with the high resting pressure *(orange and yellow areas)* between the swallows and relaxation *(blue and light green areas)* during the swallow. The length of the sphincter is approximately 3 to 4 cm, corresponding to the height of the resting pressure wave as marked on the right as distance from nares next to the anatomic depiction of the waveform. Note also the background negative pressure *(dark blue area)* in the thoracic esophagus and the positive pressure *(lighter blue area)* in the stomach. (Reproduced with permission from Sierra Scientific Instruments.)

sphincter length. Both total length and abdominal segment length decrease, suggesting that the sphincter length loss begins distally.

It is important to understand that "loss of sphincter length" is defined by manometry and is a physiologic abnormality. What is lost is the ability of this part of the esophageal wall to maintain tonic contraction and a high pressure. The part of the sphincter that has lost its function still retains its basic anatomic structure unless pathologic abnormalities occur in these structural elements; its wall is still the esophageal muscle wall, it is lined by squamous epithelium, it has submucosal glands, and it is above the peritoneal reflection. I will show that changes to this part of the abdominal esophagus that has "lost" the sphincter are the changes that have caused much of the confusion about the recognition of the early stages of gastroesophageal reflux disease.

The lower esophageal sphincter masks the normal intraluminal pressure in the distal esophagus (Figure 4–7). Above the sphincter, the esophageal luminal pressure is –0.5 mm Hg, which is usual for intrathoracic organs. Below the sphincter, intraluminal gastric pressure is 5 mm Hg, which is typical for intra-abdominal organs. The baseline intraluminal pressure of the distal esophagus changes from thoracic (–0.5 mm Hg) to abdominal (5 mm Hg) at the diaphragmatic hiatus (the "respiratory or pressure inversion point" at manometry). In a normal person, this baseline intraluminal pressure is masked by the normal high pressure of the sphincter zone. When the sphincter is lost, this masked baseline pressure will be manifested. Therefore, one can expect a dilatory tendency of the esophagus below the diaphragm, because its intraluminal pressure is positive; one can also expect a tendency to collapse above the diaphragm, because the thoracic intraluminal pressure is negative.

The Normal Stomach: What Is the Gastric Cardia?

The stomach is a saccular structure that begins at the gastroesophageal junction and ends at the gastroduodenal junction (see Figures 4–2 and 4–4). It is a true reservoir and is in a normally collapsed state until there is food intake, at which time it distends. Until normal gastric capacity is reached, gastric distension is associated with only a minimal rise in the intragastric pressure from its baseline of 5 mm Hg, which is normal for intra-abdominal organs.

The stomach is traditionally divided into the cardia, fundus, body, and antrum. The gastric cardia is one of the most confusing structures in the human body. Anatomically, the *gastric cardia* is defined as the proximal part of the

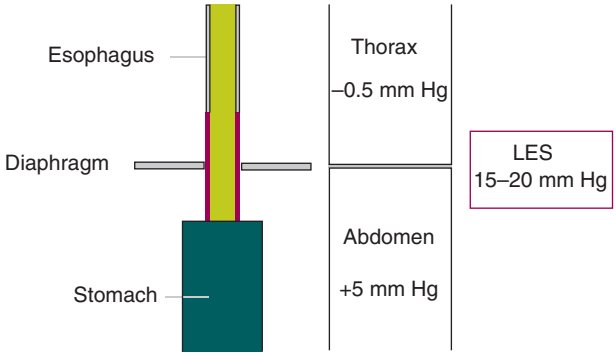


Figure 4–7 Diagrammatic representation of the pressures in the distal esophagus and proximal stomach. The normal background positive pressure in the abdominal esophagus is usually masked by the resting high pressure tone of the lower esophageal sphincter *(LES)*. *Yellow,* Squamous epithelium; *red,* lower esophageal sphincter; *green,* gastric oxyntic mucosa.

stomach distal to the gastroesophageal junction (Figure 4–8). This viewpoint is well expressed by De Hertogh et al[3]:

> Anatomists have applied the term "cardia" to that part of the stomach which lies around the orifice of the tubular oesophagus. There is no anatomical landmark for the distal margin of the so-defined cardia. Its proximal margin is the gastro-oesophageal junction which, according to anatomists, is localized at the level of the angle of His.

Although its distal limit is undefined, most people will assume that the gastric cardia is somewhere between 1 to 3 cm in length and that this is lined by cardiac mucosa (Figure 4–8*A*).

The only purpose of recognizing a "gastric cardia" is to differentiate it from the body and fundus of the stomach. In the past, this was not a problem, because it was assumed that this area was normally lined by the histologically distinct cardiac mucosa for a distance that was 1 to 3 cm. This is now known to be false and has created problems. What do we call the anatomic "gastric cardia" when it is not lined by cardiac mucosa?

When cardiac and oxyntocardiac mucosa are found in this region, they are regarded as normal gastric mucosa, and it is believed that these epithelia normally line the proximal stomach (Figure 4–9*B*). When inflammation occurs, it is called *carditis,* with the implication that this is an inflammation of proximal gastric mucosa. When cardiac mucosa with intestinal metaplasia is found in this region, it is called *intestinal metaplasia of the gastric cardia* (Figure 4–9*C*). When adenocarcinoma arises in this region, it is called *adenocarcinoma of the gastric cardia* and classified as a gastric cancer (Figure 4–10). If this is correct, there should be no concern or confusion.

The confusion results from two factors:

1. These diseases of the "gastric cardia" are often restricted to the most proximal 3 cm of the stomach; the remainder of the stomach is often normal. It is difficult to understand how a gastric disease such as inflammation or intestinal metaplasia can be limited to this region without involving the rest of the stomach.
2. These diseases have a demonstrated etiologic association with gastroesophageal reflux. Patients with inflammation, with and without intestinal

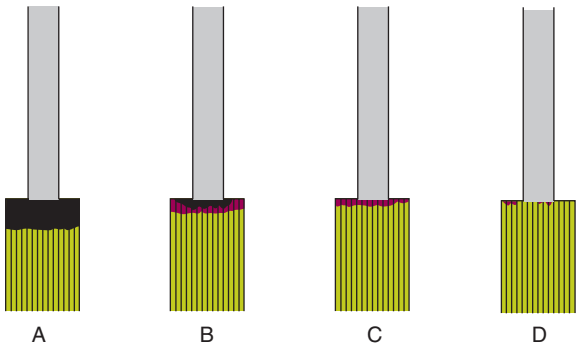
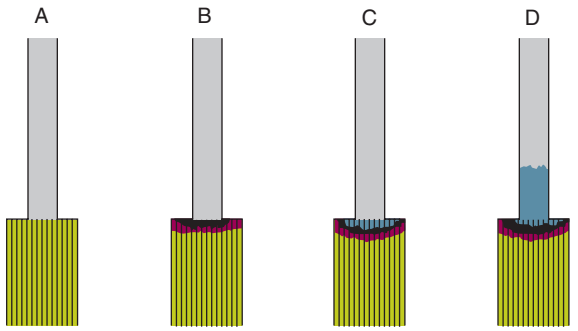


Figure 4–8 The evolving definition of the gastric cardia. Until recently, the gastric cardia was believed to be the proximal 2 to 3 cm of the stomach lined normally by cardiac mucosa (**A**). Recent evidence indicates this is not correct. In most people, there is less than 5 mm of combined cardiac and oxyntocardiac mucosa separating the squamous epithelium of the esophagus and gastric oxyntic mucosa (**B**). In many patients, only a very short segment of oxyntocardiac mucosa is present, with cardiac mucosa being absent (**C**). In still others, the oxyntocardiac mucosa found is only seen in part of the circumference (**D**). This means that in other parts of the circumference, squamous epithelium transitions directly into gastric oxyntic mucosa (**D**). *Gray,* Squamous epithelium; *black,* cardiac; *red,* oxyntocardiac; *yellow,* gastric oxyntic mucosa with rugal folds shown as *stripes.*



	A	B	C	D
CM/OCM in tubular esophagus	No	No	No	Yes
CM/OCM distal to present GEJ	No	Yes	Yes	Yes/No
CM with IM in tubular esophagus	No	No	No	Yes
CM with IM distal to present GEJ	No	No	Yes	Yes
Present view	Does not exist	Normal	CIM	BE
Correct view	Normal	Micro-CLE	Micro-BE	BE

Figure 4–9 Four patients (**A-D**) are shown with varying composition of columnar epithelia. *Blue,* Intestinal; *black,* cardiac; *red,* oxyntocardiac; *gray,* squamous; *yellow,* gastric oxyntic. The present diagnosis in these patients is compared with the corrected diagnosis as suggested by new evidence. *BE,* Barrett esophagus; *Micro-BE,* microscopic Barrett esophagus, which is an unrecognized entity; *CLE,* columnar-lined esophagus; *CIM,* intestinal metaplasia of the cardia.

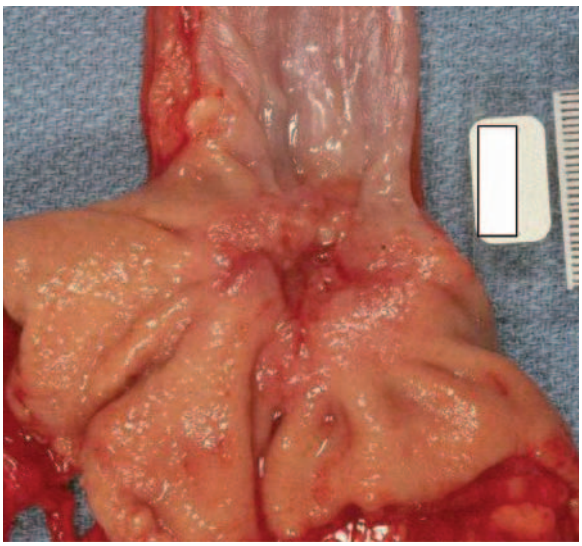


Figure 4–10 Ulcerated adenocarcinoma occurring immediately distal to the end of the tubular esophagus. At present, this will be designated an "adenocarcinoma of the gastric cardia" and will be classified as a gastric cancer. In reality, this is an esophageal adenocarcinoma arising in the dilated, reflux-damaged distal esophagus.

metaplasia in cardiac mucosa, who have biopsies taken distal to the endoscopic gastroesophageal junction frequently have both gastroesophageal reflux and *Helicobacter pylori* ascribed as etiologies.[4] There is an epidemiologic association between adenocarcinoma of the gastric cardia and gastroesophageal reflux disease.[5] Confusion results because it is difficult to

understand how gastroesophageal reflux can cause pathology in the proximal stomach. It seems almost oxymoronic to state that intestinal metaplasia and cancer of the proximal stomach result from gastroesophageal reflux.

The gastroenterologic community has developed an interesting method to deal with this confusion. They have produced practice guidelines that discourage biopsy of this region in endoscopically normal patients.[6] This is designed to avoid the problem: one cannot be confused by what one does not see. If these practice guidelines are followed, there will not be a problem, except in the approximately 10,000 patients who will present with reflux-induced adenocarcinoma in the "gastric cardia" each year.

Because of this complication, some gastroenterologists disregard the practice guidelines and biopsy the controversial area, even when they do not see an abnormal columnar-lined esophagus. When cardiac mucosa, inflammation, and particularly intestinal metaplasia are found in the biopsy, confusion is created (see Figure 4–9*C*). There is a fear that intestinal metaplasia of the gastric cardia is more similar to Barrett esophagus than gastric intestinal metaplasia in chronic atrophic gastritis because it has a higher risk of malignancy. This fear causes gastroenterologists to place these patients under surveillance similar to that for Barrett esophagus, even though the patient's condition does not fit into the present definition of Barrett esophagus. These same gastroenterologists will not place a patient with chronic atrophic gastritis with intestinal metaplasia under surveillance because the risk is known to be extremely small.

Normal Histology of the Esophagus and Proximal Stomach

With few exceptions, squamous epithelium is entirely esophageal, and pure oxyntic mucosa is entirely gastric in location. The exact location (i.e., whether distal esophagus or proximal stomach) and significance of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa as defined in Chapter 3 are presently controversial (Table 4–1).

There is no disagreement that these three epithelial types are *always* interposed between esophageal squamous epithelium and the proximal limit of gastric oxyntic mucosa (see Figure 4–9). There is disagreement, however, about whether these epithelia are found in all people, where they are located

TABLE 4–1 Location and Significance of the Five Epithelial Types as Presently Accepted Compared to What Will Be Proven

Epithelial type and endoscopic location	Present belief	Truth (future)
Squamous in the esophagus	Normal lining of esophagus; damaged in reflux	Normal lining of esophagus; damaged in reflux
Squamous in the proximal stomach by present definition	Rare; "esophageal reaction to gastric injury"	Normal lining of esophagus; damaged in reflux
Oxyntic in the esophagus	Not found	Not found
Oxyntic in the stomach	Not damaged by reflux; proximal stomach damaged by reflux?	Not damaged by reflux
Cardiac and oxyntocardiac in the esophagus	Abnormal when seen at endoscopy; "normal gastric" when seen in biopsies; no significance?	Columnar-lined esophagus; caused by reflux-induced metaplasia of squamous epithelium
Cardiac and oxyntocardiac in the proximal stomach by present definition	Normal epithelial lining of proximal stomach	Columnar-lined esophagus; caused by reflux-induced metaplasia of squamous epithelium
Cardiac mucosa with intestinal metaplasia in the esophagus	Barrett esophagus; caused by reflux-induced metaplasia of squamous epithelium	Barrett esophagus; caused by reflux-induced metaplasia of squamous epithelium
Cardiac mucosa with intestinal metaplasia in the proximal stomach by present definition	"Intestinal metaplasia of the gastric cardia;" caused by either reflux or *H. pylori* gastritis	Barrett esophagus; caused by reflux-induced metaplasia of squamous epithelium

(esophagus, stomach, or both), whether they are normal or abnormal, and what their significance is when they are found in a biopsy.

According to what is presently accepted, cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa are known to be the components of columnar-lined esophagus (see Figure 4–9*D*). Cardiac mucosa without intestinal metaplasia and oxyntocardiac mucosa are also believed to be the normal lining of the proximal stomach, known as the *gastric cardia*[7] (see Figure 4–9*B*). Cardiac mucosa is believed to appear in all people, despite evidence to the contrary (see Figure 4–9*A*). When intestinal metaplasia occurs in cardiac mucosa in the area distal to the presently defined gastroesophageal junction, it is called *intestinal metaplasia of the gastric cardia* (cardiac intestinal metaplasia [CIM]; see Figure 4–9*C*). There is no histologic difference among these three epithelial types when they occur in the esophagus as abnormal metaplastic epithelia and when they are believed to occur normally in the proximal stomach.

Discrepancy Between the Anatomic Gastric Cardia and Cardiac Mucosa

If one defines the anatomic gastric cardia as that area of the stomach lined by cardiac mucosa, the situation becomes complicated. If one adheres to the strict definition of cardiac mucosa, it is frequently completely absent in this region. In our autopsy series,[8] cardiac mucosa was absent in 56% of patients. In Marsman et al,[9] it was absent in 38% of patients. In these patients, only oxyntocardiac mucosa separated squamous from gastric oxyntic mucosa (see Figure 4–8*C;* Figure 4–11). It is only by including oxyntocardiac mucosa within the definition of cardiac mucosa that one can make a case for the universal presence of cardiac mucosa. Even then, the majority of patients have less than 0.5 mm of the combined cardiac and oxyntocardiac mucosa (see Figure 4–8*B;* Figures 4–12 and 4–13). It is also clear that at least in a part of the circumference of the squamocolumnar junction, some patients have a direct transition of squamous epithelium to gastric oxyntic mucosa (see Figure 4–8*D;* Figure 4–14).

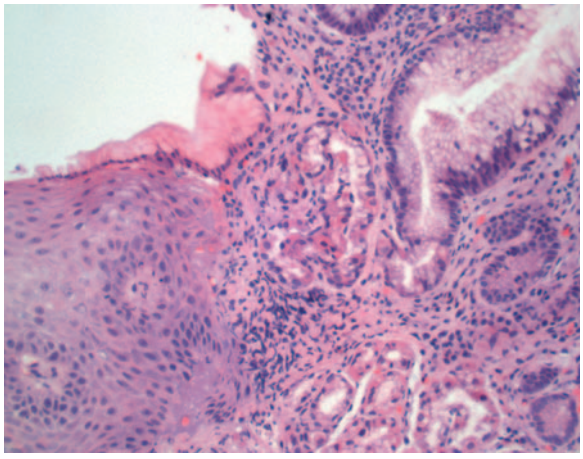


Figure 4–11 Squamocolumnar junction showing transition of squamous epithelium to oxyntocardiac mucosa with parietal cells. There is no intervening cardiac mucosa.

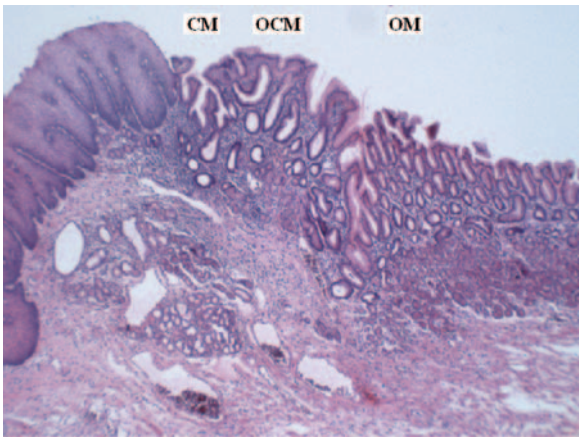


Figure 4–12 Squamocolumnar junction showing squamous epithelium on the left with basal cell hyperplasia and papillary elongation indicative of reflux. This transitions to a very short length of cardiac mucosa *(CM)* and oxyntocardiac mucosa *(OCM)* before gastric oxyntic mucosa *(OM)* begins.

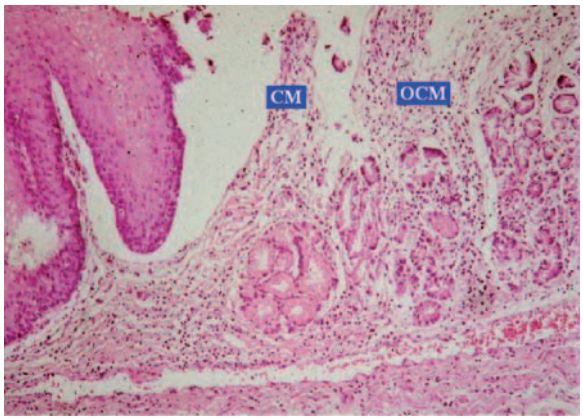


Figure 4–13 Squamocolumnar junction in an autopsy specimen showing squamous epithelium followed by one foveolar complex of cardiac mucosa *(CM),* followed by one lobulated complex of oxyntocardiac mucosa *(OCM),* followed by gastric oxyntic mucosa.

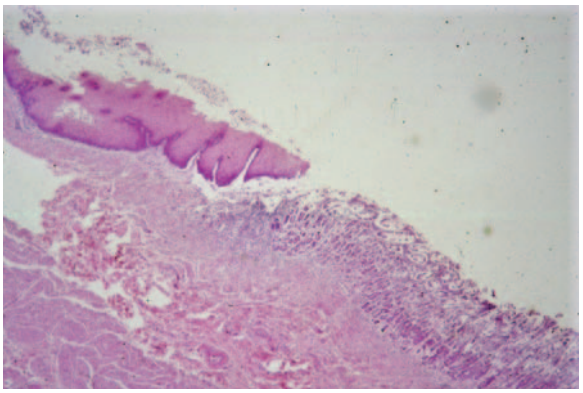


Figure 4–14 Squamocolumnar junction in an autopsy from a child showing direct transition of squamous epithelium to gastric oxyntic mucosa. The latter is characterized by straight tubular glands composed of parietal cells.

Recently, Odze[7] suggested a reproducible definition of the distal limit of the gastric cardia as the proximal limit of gastric oxyntic mucosa, as defined by histology. Odze's "true" gastric cardia is defined as "the area of mucosa located distal to the anatomic gastroesophageal junction (defined as the proximal limit of the gastric folds) and proximal to the portion of the stomach (corpus) that is composed entirely of oxyntic glands." According to Odze,[7] the normal extent of the true gastric cardia is less than 0.4 cm (see Figure 4–8*B, C*). It must be recognized that 0.4 cm (4 mm) is a very short length, and the question must be asked whether the use of the endoscopic gastroesophageal junction to define the proximal limit of the "true gastric cardia" is sufficiently accurate within this 4-mm range. Odze's preamble to this definition suggests that this is not so: "At the time of endoscopy, it is difficult, if not impossible to detect a minor proximal displacement of the Z-line. . . ." Most gastroenterologists will agree that the proximal limit of rugal folds is difficult to determine within the 0.4-cm range of accuracy. The technical error for the criterion that defines the proximal limit of the "true gastric cardia" is larger than the maximum extent of the defined entity!

The gastric cardia, however it is defined, is not necessarily lined by an epithelium that falls within the definition of cardiac mucosa. Odze[7] states:

". . . the true gastric cardia is composed of surface mucinous columnar epithelium and either pure mucous glands or a mixture of mucous/oxyntic glands in most individuals. However, the length of cardiac mucosa with this histologic appearance is variable, and ranges from 1.0 to 4.0 mm. . . . A paradoxical observation is that a small proportion of patients have mucosa composed of pure oxyntic glands only, without mucous glands, in the true gastric cardia. . . . This finding, however, is often focal, and does not usually involve the entire circumference of the true gastric cardia."

Thus, Odze's "true gastric cardia" can be lined by cardiac and/or oxyntocardiac mucosa, despite its extremely short length of less than 0.4 cm. It can "paradoxically" be lined in part of its circumference by gastric oxyntic mucosa, which defines its distal limit (see Figure 4–14), in which case the "true gastric cardia" disappears because its proximal and distal limits are coincidental. This madness is the only answer to circumvent accepting the truth (see Figure 4–9*A*): *Cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa does not exist as normal epithelia in either the esophagus or the stomach.*[10,11]

The Importance of Precise Histologic Definitions

At present, the definitions of epithelial types used in Chapter 3 are generally followed in a significant body of literature, permitting conclusions to be drawn. Even when synonyms are used, the definitions provided in the methods usually, but not always, permit the epithelial type to be determined. For example, the Harvard group[12] generally uses the terms *mucous cell-only* and *mixed mucous and parietal cell* in place of *cardiac* and *oxyntocardiac*. The problem with this is that it is not clear whether *mucous cell-only* refers to both cardiac mucosa and atrophic gastric oxyntic mucosa with pseudopyloric metaplasia. Confusion also results when researchers lump all intestinal metaplasia in the gastric cardia without attempting to separate intestinal metaplasia of Barrett-type occurring in cardiac mucosa from gastric intestinal metaplasia occurring in atrophic gastric oxyntic mucosa.

Another problem in the literature is the profusion of terms used for these five epithelial types. This profusion does not indicate an abundance of epithelial types. There are only five: squamous, cardiac mucosa with intestinal metaplasia, cardiac mucosa without intestinal metaplasia, oxyntocardiac mucosa, and gastric oxyntic mucosa (normal and with all the pathologic lesions associated with gastric oxyntic mucosa, including gastritis and gastric intestinal metaplasia). We should restrict the terminology of these five epithelial types in biopsies of the esophagus and proximal stomach; if pyloric antral mucosa is added, the epithelial types found in the entire esophagus and stomach are covered.

Confusion also results when the definitions are not followed precisely. The most common twist is to include oxyntocardiac mucosa within the definition of cardiac mucosa. Marsman et al,[9] in a study of cardiac type mucosa at the esophagogastric junction, looked at whether the type of columnar mucosa immediately distal to the squamocolumnar junction was "purely cardiac, oxyntocardiac, or fundic mucosa." They found that, of 63 patients who had the squamocolumnar junction in one biopsy sample, "purely cardiac mucosa was present in 39 (62%) biopsies, and oxyntocardiac mucosa was present in 24 (38%) biopsies." There is no study that more effectively shows that cardiac mucosa is absent in a significant number of people. However, the authors conclude that "cardiac mucosa was uniformly present adjacent to the squamous epithelium at the esophagogastric junction." This conclusion is reached by combining cardiac and oxyntocardiac mucosa within what these authors call cardiac mucosa. To them, cardiac mucosa includes "purely cardiac mucosa" and oxyntocardiac mucosa; the whole point of distinguishing between the two vanishes. If data are to be uniformly assessed, it is crucial that we adhere to strict definitions of the epithelial types rather than twisting them to fit the needs of the moment. Why is it difficult for Marsman et al[9] to correctly conclude from their data: "Cardiac mucosa was present in 39 (62%) biopsies and *absent in 24 (38%) of biopsies?*"

Another source of confusion in the literature is the use of the word *carditis* in two completely different ways. If carditis is defined as "inflammation of the histologically defined cardiac mucosa," it will always show a strong association with gastroesophageal reflux disease.[13] If carditis is defined as "inflammation in a biopsy taken from the anatomically defined gastric cardia," there will be a mixed association, because there is variation in the histology of the anatomic gastric cardia.[4] Those among this group who have cardiac mucosa will show an association with reflux, whereas those with gastric oxyntic mucosa will show an association with gastritis.

Definition of the Gastroesophageal Junction

Historical Background (Figure 4–15)

Defining the gastroesophageal junction has been problematic ever since Allison and Johnstone described the entity of columnar-lined esophagus in 1953.[14] Before this, the gastroesophageal junction was defined endoscopically, grossly, and histologically as the squamocolumnar junction. Norman Barrett, in 1950,[15] expressing the viewpoint of the time, stated: ". . . the oesophagus is that part of the foregut, distal to the cricopharyngeal sphincter, which is lined by squamous epithelium." By this definition anything distal to the squamocolumnar junction was "gastric." The columnar-lined esophagus was misclassified as a tubular intrathoracic stomach (Figure 4–16). By histology, any columnar epithelium distal to the squamocolumnar junction was designated as "gastric." The concept that cardiac mucosa lined the proximal stomach is

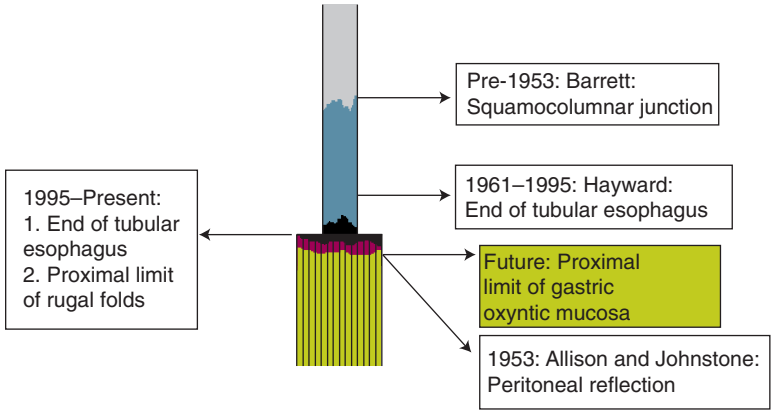


Figure 4–15 Various historical definitions of the gastroesophageal junction. At present, the gastroesophageal junction is defined by the unvalidated end of tubular esophagus and proximal limit of rugal folds. The validated definitions of the gastroesophageal junction are the peritoneal reflection and the proximal limit of gastric oxyntic mucosa.

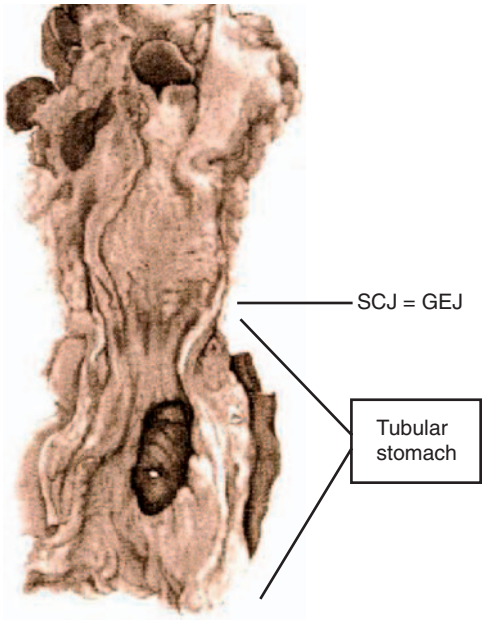


Figure 4–16 Norman Barrett's (1950) interpretation of the columnar-lined esophagus. By using the squamocolumnar junction *(SCJ)* to define the end of the esophagus, Barrett designated the entire columnar-lined esophagus as an intrathoracic tubular stomach. *GEJ,* Gastroesophageal junction. (Reproduced with permission from Barrett NR: *Br J Surg* 38:175–182, 1950.)

rooted in this old histologic dogma, which is based on the incorrect definition of the gastroesophageal junction as the squamocolumnar junction.

In their landmark paper of 1953, Allison and Johnstone[14] proved that in some patients, there is a columnar-lined esophageal segment interposed between the squamocolumnar junction and the gastroesophageal junction (Figure 4–17). To convince Barrett that what he was calling an intrathoracic tubular stomach was actually a columnar-lined esophagus, the authors state:

> Careful examination of such a specimen shows that it has no peritoneal covering, that the musculature is that of normal oesophagus, that there may be islands of squamous epithelium within it, that there are no oxyntic cells in the mucosa, and that in addition to gastric glands there are present typical oesophagael mucous glands (Figure 4–18).

This argument was so persuasive that Barrett abandoned his concept of the tubular intrathoracic stomach and completely embraced Allison and Johnstone's (1953) concept of columnar-lined esophagus in 1957.[16]

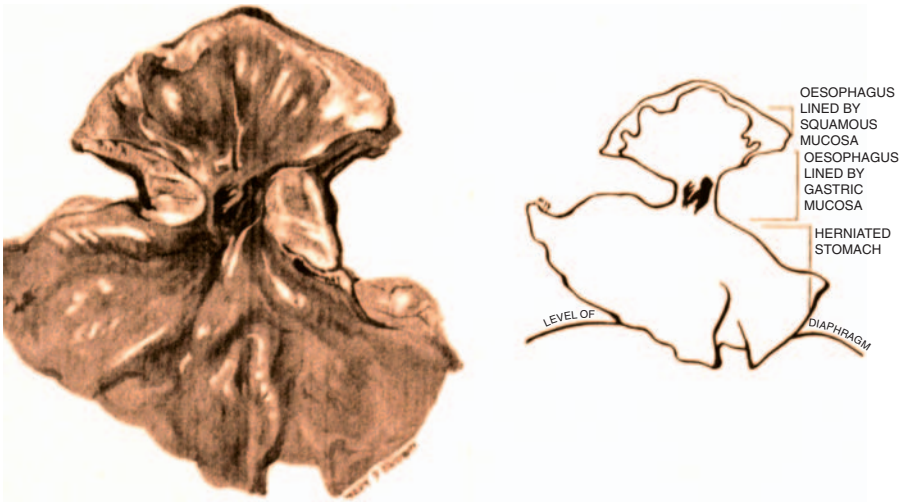


Figure 4–17 One of the first illustrations of the columnar-lined esophagus ("oesophagus lined with gastric mucous membrane"). (Reproduced with permission from Allison PR, Johnstone AS: *Thorax* 8:87–101, 1953.)

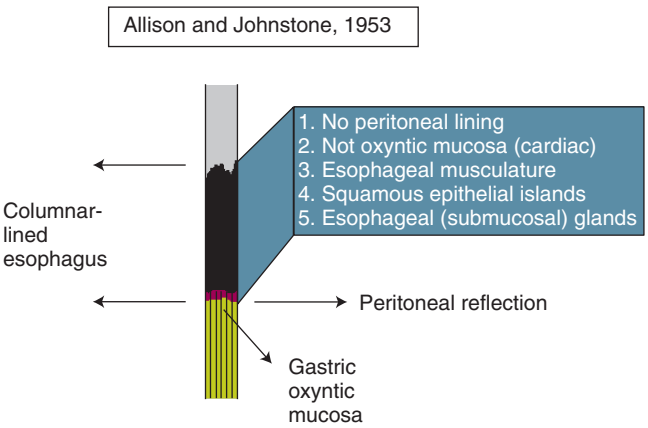


Figure 4–18 Allison and Johnstone's reasons for interpreting the columnar-lined segment as esophagus rather than a tubular stomach. Note that they report the presence of gastric fundal (oxyntic) mucosa at the peritoneal reflection.

Allison and Johnstone[14] showed that the columnar-lined esophagus was lined by a columnar epithelium that was largely lacking in oxyntic cells and contained squamous islands. This is cardiac and, very likely, oxyntocardiac mucosa. However, because of the definitions existing at the time, they called this "gastric epithelium" and titled their paper, "The Oesophagus Lined with Gastric Mucous Membrane." While agreeing with Allison and Johnstone about the existence of the entity, Barrett in 1957[16] suggested that the name of the entity be changed from "oesophagus lined by gastric mucous membrane" to "columnar-lined esophagus." He was pointing out the obvious: the esophagus is lined by esophageal epithelia, never gastric epithelia.

Allison and Johnstone[14] provide detailed descriptions of the histology in seven cases; these show that the proximal part of the columnar-lined segment was lined by cardiac mucosa, oxyntic cells were seen in the more distal part, goblet cells were present in one patient, and one patient had an adenocarcinoma. All these were reported as "gastric mucosa." The pathology report by D.H. Collins on the resected specimen of the first case is so masterful to be worthy of repeating:

> The specimen comprises a substantial portion of the body and cardia of stomach . . . together with 5 cm of oesophagus. . . . The oesophagus was separated by a knife from the stomach along the line of peritoneal reflection. A vertical slice was then made through the centre of the reconstituted specimen, (see Figure 4–18) i.e., up the posterior wall, and three vertically contiguous blocks were prepared. . . . The stomach below the anatomical junction with the oesophagus is lined by gastric mucosa of fundal type. . . . Cardiac glands and cardiac gastric mucosa do not appear until 0.6 cm up the anatomical oesophagus, and the oesophageal glands appear at 2 cm up the oesophagus (see Figure 4–18).

Allison and Johnstone[14] had no problem in accurately defining the extent of columnar-lined esophagus when it was present. It was limited proximally by the squamocolumnar junction and distally by the gastroesophageal junction. They used a validated definition of the gastroesophageal junction (the line of the peritoneal reflection) to define the histology (see Figure 4–18). This produced an accurate result: the entire stomach distal to the peritoneal reflection is lined by gastric fundal mucosa. The major part of the columnar-lined esophagus is lined by cardiac mucosa with squamous islands. Although they did not define histologic criteria to define the gastroesophageal junction, they showed that the mucosa at and distal to the junction was gastric oxyntic mucosa.

All the confusion associated with columnar-lined esophagus is based on applying incorrect and invalidated definitions of the gastroesophageal junction (Table 4–2). Unfortunately, the peritoneal reflection is not easy to identify in anything other than esophagectomy and autopsy specimens. Problems began emerging when attempts were made to define the gastroesophageal junction at endoscopy. This has largely been done without correlation with the true anatomic gastroesophageal junction; Allison's and Johnstone's finding that gastric fundal (i.e., oxyntic) mucosa is present at and distal to the peritoneal reflection has been lost.

The most influential paper with regard to defining the gastroesophageal junction is that by Hayward in 1961.[17] Hayward defines the gastroesophageal junction as the point of transition of the tubular esophagus into the saccular stomach. He states that "The oesophagus is a tube and all of this tube is oesophagus, regardless of its lining. The true junction is where the conducting tube changes to the digesting pouch." The transition of the tube to the pouch can be determined endoscopically. This became the first universally accepted endoscopic definition of the gastroesophageal junction after columnar-lined esophagus was recognized as an entity. This currently persists as the recommended definition for pathologists to use for the gastroesophageal junction

TABLE 4–2 Historical Definitions of the Gastroesophageal Junction*

Period	GEJ definition	Clinical impact
VALIDATED DEFINITIONS		
1953–1961; Allison and Johnstone, 1953	GEJ = peritoneal reflection; mucosa at and distal to this was gastric oxyntic mucosa.	1. CLE defined accurately as the zone interposed between the SCJ and gastric oxyntic mucosa. 2. CLE composed of cardiac and oxyntocardiac mucosa.
The predicted future; Chandrasoma et al, 2006	GEJ = proximal limit of gastric oxyntic mucosa; the entire stomach is lined by gastric oxyntic mucosa; cardiac mucosa is CLE (back to Allison!).	1. End of CLE is proximal limit of gastric oxyntic mucosa; histology defines GEJ; endoscopy cannot define GEJ. 2. True GEJ is 0–3 cm distal to the end of tubular esophagus and proximal limit of rugal folds. 3. Biopsy all patients, including those whose endoscopy is normal, to define CLE accurately.
UNVALIDATED DEFINITIONS		
Before 1953; Barrett, 1950	The SCJ	1. CLE mistaken for tubular intrathoracic stomach. 2. Pathology in the CLE interpreted as gastric pathology.
1961–1994; Hayward, 1961	GEJ = end of tubular esophagus; CLE in distal 2 cm of esophagus is normal; cardiac mucosa is present in proximal stomach.	1. CLE known to be acquired as a result of gastroesophageal reflux. 2. CLE could not be differentiated from proximal stomach; histology could no longer be used to define the GEJ. 3. Biopsy limited to patients with >2 cm CLE.
1987–present; McClave et al, 1987	GEJ = proximal limit of rugal folds; Any visible CLE is abnormal; Cardiac mucosa is present in proximal stomach.	1. End of CLE is proximal limit of rugal folds. 2. CLE cannot be differentiated from proximal stomach; histology cannot be used to define the GEJ. 3. Biopsy limited to patients with any endoscopically visible CLE; distal CLE missed.
1980s–present; not in the literature, but used in practice.	GEJ = end of the lower esophageal sphincter, seen as a tightness around the endoscope on retrograde view.	1. End of CLE is the end of the lower esophageal sphincter. 2. Endoscopic determination of the end of the sphincter has been shown to have a large error. 3. Lower esophageal sphincter is damaged in patients with reflux and therefore unreliable.

SCJ, Squamocolumnar junction; *GEJ*, gastroesophageal junction; *CLE*, columnar-lined esophagus.
*This will also determine the distal limit of the columnar-lined esophagus and affect how columnar-lined esophagus is defined at the time.

when they dissect gross esophagectomy specimens.[18] By this endoscopic and gross definition, the extent of the columnar lined-esophagus was now defined as the area between the squamocolumnar junction and the end of the tubular esophagus. Hayward[17] expanded this error when he suggested that the distal 2 cm of the tubular esophagus was normally lined by cardiac mucosa (Figure 4–19).

Although the junction between the tubular esophagus and saccular stomach was clear in normal patients, this point was frequently not well defined, particularly in patients with hiatal hernia.[19] For this reason, endoscopists sought a more reliable marker for the endoscopic gastroesophageal junction. In 1987, McClave et al[20] reported that the proximal limit of the rugal folds was a reliably defined endoscopic landmark (see Figure 2–5). In normal patients, the rugal folds lined the entire saccular region distal to the tubular esophagus. Over the next decade, the proximal limit of the rugal folds supplanted the end of the tubular esophagus as the endoscopic gastroesophageal junction and is now almost universally accepted.[21]

In addition to these commonly used definitions, some gastroenterologists use their own definitions of the gastroesophageal junction, even though they do not even appear in the literature. One example of this states that the end of the lower esophageal sphincter defines the gastroesophageal junction. In 1995, Kim et al[22] showed that there was a substantial error in the endoscopic determination of the lower esophageal sphincter. However, even if the sphincter can be identified at endoscopy, its lower end represents the true gastroesophageal junction only in normal people. One of the early manifestations of reflux-induced distal esophageal damage is shortening of the abdominal

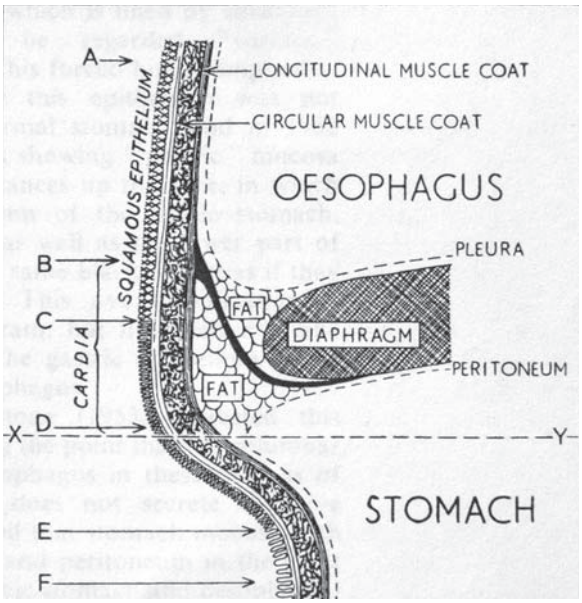


Figure 4–19 Hayward's (1961) interpretation of normal anatomy and histology. This is the basis of the long-held belief that cardiac mucosa lines the distal 2 cm of the esophagus as well as "a variable part" of the proximal stomach. **B–D,** "Cardia," which appears to be the area between the peritoneal reflection and insertion of the phreno-esophageal ligament. **C–E,** Extent of "normal" cardiac mucosa. According to Hayward, the cardia is esophageal, not gastric.

segment of the sphincter, which causes the end of the low esophageal sphincter to move proximally as it is destroyed progressively at the distal end.

Clinical Impact of Validated and Unvalidated Definitions of the Gastroesophageal Junction

Two validated definitions have been used for the gastroesophageal junction in the literature. The first is by Allison and Johnstone,[14] who used the line of the peritoneal reflection. The second is a study of fetal autopsies by De Hertogh et al[3]; these authors used the angle of His to define the gastroesophageal junction (see Figure 4–4). In this study, as in the study by Allison and Johnstone, the epithelium at and distal to the gastroesophageal junction was gastric oxyntic mucosa with parietal cells. The angle of His is valid as the gastroesophageal junction in fetal and neonatal specimens. In patients with reflux disease, particularly when hiatal hernia is present, the angle of His becomes progressively obliterated and therefore unreliable as a marker of the gastroesophageal junction.

When validated definitions of the junction are used, therefore, three segments are recognized (see Figure 4–18):

1. The squamous-lined esophagus.
2. The columnar-lined esophagus, which ends at the gastroesophageal junction; this is lined by cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa.
3. The stomach, which begins at the gastroesophageal junction and is lined entirely by gastric oxyntic mucosa.

The end of the tubular esophagus and the proximal limit of rugal folds are not validated definitions of the gastroesophageal junction. The end of the

tubular esophagus was defined as a result of Hayward's[17] edict, and the proximal limit of rugal folds transformed from its original description of an endoscopic landmark to become the universal definition of the gastroesophageal junction. Neither of these has ever been validated against the true gastroesophageal junction.

When either the end of the tubular esophagus or the proximal limit of the rugal folds is used to define the gastroesophageal junction, the truth of the three segments defined here earlier changes to the falsehood of the following four segments (Figure 4–20):

1. The squamous-lined esophagus.
2. The columnar-lined esophagus, which ends at the gastroesophageal junction, which is lined by cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa.
3. The gastric cardia (proximal stomach), which is an area of the proximal stomach lined by cardiac and oxyntocardiac mucosa.
4. The rest of the stomach, which begins at the distal limit of the gastric cardia and is lined by gastric oxyntic mucosa.

These new and incorrect definitions of the gastroesophageal junction have split the columnar-lined esophagus defined by Allison and Johnstone[14] into two segments that straddle the false gastroesophageal junction (see Figure 4–20). Cardiac mucosa has shifted from being always proximal to the gastroesophageal junction, and therefore abnormal columnar-lined esophagus, to an epithelium that is found "normally" in the proximal stomach. The "gastric cardia" lined by cardiac mucosa represents a mythical structure that has been created by an invalidated and incorrect definition of the gastroesophageal junction.

This has enormous implications for the diagnosis of biopsies of this region. According to Allison and Johnstone's definition, the columnar-lined esophagus can be distinguished histologically from the stomach because the latter is lined entirely by gastric oxyntic mucosa that is different from the cardiac and oxyntocardiac mucosa that line the columnar-lined esophagus (see Figure 4–18). By the presently accepted definitions, histology cannot distinguish the columnar-lined esophagus from normal stomach because both are lined by cardiac and oxyntocardiac mucosa (see Figure 4–20). This has

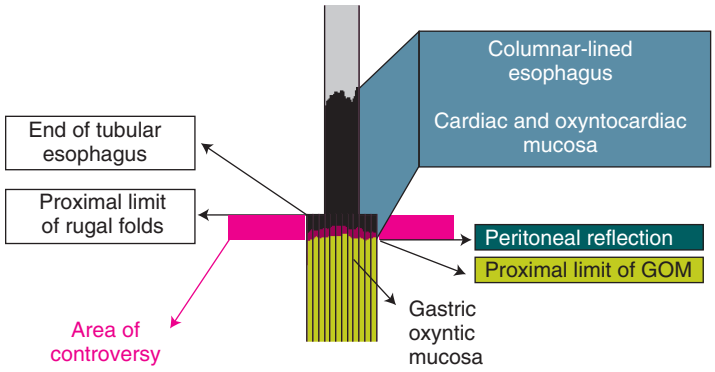


Figure 4–20 The result of using incorrect definitions of the gastroesophageal junction (end of tubular esophagus and proximal limit of rugal folds) is to divide the columnar-lined segment into a visible columnar-lined esophagus and an area distal to the junction, which is called *gastric cardia.* Use of a validated definition of the gastroesophageal junction (proximal limit of rugal folds and peritoneal reflection) corrects this error. *GOM,* Gastric oxyntic mucosa.

resulted in the inability to develop and use histologic criteria in the biopsy diagnosis of reflux disease for more than 50 years.

Definition of the True Gastroesophageal Junction by Histology: The Proof

We have accepted the end of the tubular esophagus and the proximal limit of the rugal folds as definitions of the gastroesophageal junction too easily and without requiring any validation or proof that they correspond to the true anatomic gastroesophageal junction. One is reminded of Barrett's[15] proclamation that the squamocolumnar junction was the gastroesophageal junction, which was made because of his strong opinion and the agreement of the community (but without validation).

In a recently published study,[23] we attempted to validate the present definitions of the gastroesophageal junction, using some of the methodology used by Allison and Johnstone in 1953. We carefully selected 10 esophagectomy specimens that had a sharp demarcation between the tubular and saccular parts and had the rugal folds extending all the way to this point (Figure 4–21). We excluded patients who had any gastric pathology. Like Allison and Johnstone, who divided the specimen along the line of the accepted gastroesophageal junction (peritoneal reflection), we divided the specimen along the line of the presently accepted gastroesophageal junction (the end of the tubular esophagus and the proximal limit of the rugal folds). By selecting cases in which these two criteria were coincident, we were able to test both in the same specimen. We then took vertical sections from this line distally for 3 cm, examining the entire region distal to the gastroesophageal junction (Figure 4–22). We mapped

Figure 4–21 Esophagogastrectomy specimen selected for study, showing a well-defined end of the tubular esophagus coinciding with the proximal limit of rugal folds.

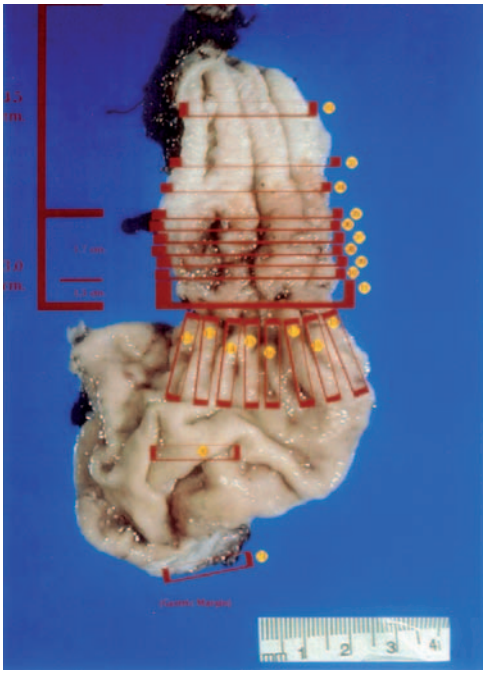


Figure 4–22 Method of sectioning the specimen in Figure 4–21. The specimen is divided across the line of the presently defined gastroesophageal junction. The area immediately distal to this is completely submitted for microscopic examination by serial vertical sections. This permits direct measurement of changes distal to the presently defined gastroesophageal junction.

the epithelial types according to strict definitions. We found cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa in all patients to a length that varied from 0.31 cm to 2.05 cm (Figure 4–23). By currently accepted standards and Odze's[7] definition, this would be the "true gastric cardia," which is much larger than Odze's maximum of 0.4 cm.

To test whether this was esophagus or stomach, we evaluated these full-thickness sections for the presence of submucosal glands, a criterion used by Allison and Johnstone and shown by the embryologic study of Johns in 1952[24] to be found only in squamous lined-esophagus and not in the stomach. Submucosal glands varied in number and were found in 8 of 10 specimens distal to the presently accepted gastroesophageal junction (Figures 4–23, 4–24, and 4–25). The submucosal glands were always found under cardiac, oxyntocar-

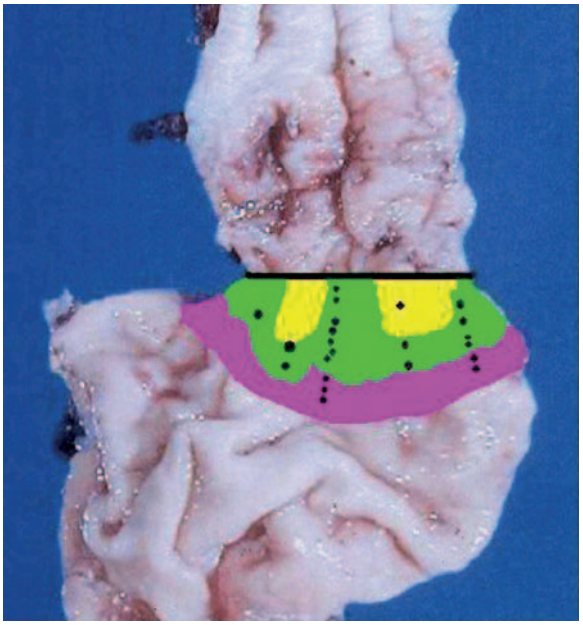


Figure 4–23 Summary of histologic findings in the specimen shown in Figure 4–21. Cardiac mucosa with intestinal metaplasia *(yellow areas),* cardiac mucosa *(green area),* and oxyntocardiac mucosa *(pink area)* line the area distal to the presently defined gastroesophageal junction to a distance of 2.05 cm. Esophageal submucosal glands *(black dots)* are present in this area, coincident with these three epithelial types.

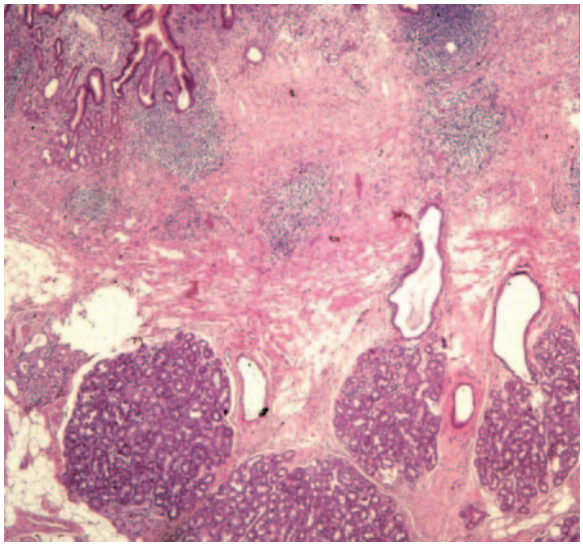


Figure 4–24 Submucosal glands under cardiac mucosa in the region distal to the end of the tubular esophagus.

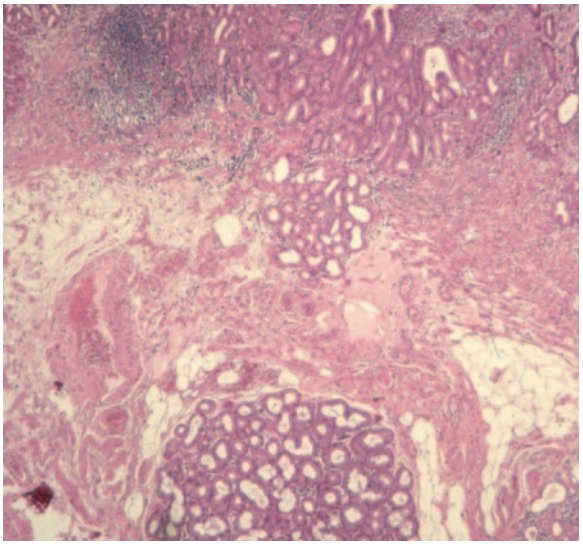


Figure 4–25 Submucosal glands under oxyntocardiac mucosa in the region distal to the end of the tubular esophagus.

diac, and intestinal epithelium and extended to within 0.5 cm from the proximal limit of gastric oxyntic mucosa. Submucosal glands were never seen under gastric oxyntic mucosa. We concluded from this study that the presently accepted definitions of the gastroesophageal junction (the end of the tubular esophagus and the proximal limit of rugal folds) are incorrect and that up to 2.05 cm of the region presently thought to be proximal stomach is actually distal, reflux-damaged esophagus (Figure 4–26).

The extent of the segment distal to the end of the tubular esophagus that contained submucosal glands and was lined by cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa varied in our study from 0.31 to 2.05 cm (Figure 4–27). In a similar study of esophagectomy specimens by Sarbia et al,[25] cardiac and oxyntocardiac mucosa were present up to 2.8 cm distal to the end of the tubular esophagus. Sarbia et al[25] also reported the presence of submucosal glands and gland ducts in this part of the specimen distal to the end of the tubular esophagus. 2.8 cm is the maximum length of the "proximal stomach" lined by cardiac and oxyntocardiac mucosa in the literature.

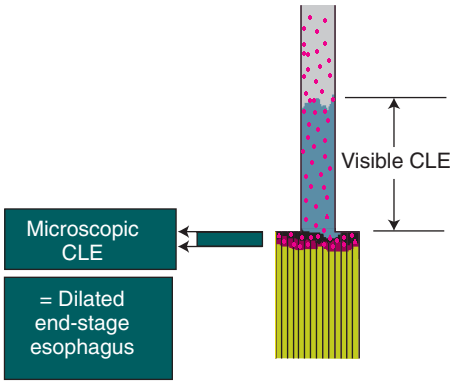


Figure 4–26 The presence of submucosal glands characterizes the area distal to the end of the tubular esophagus as end-dilated stage esophagus rather than part of the stomach. This permits the recognition of the distal microscopically defined columnar-lined esophagus *(CLE)* (by the presence of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa and submucosal glands) that is currently missed because of the use of incorrect definitions of the gastroesophageal junction. *Pink dots,* Submucosal esophageal glands.

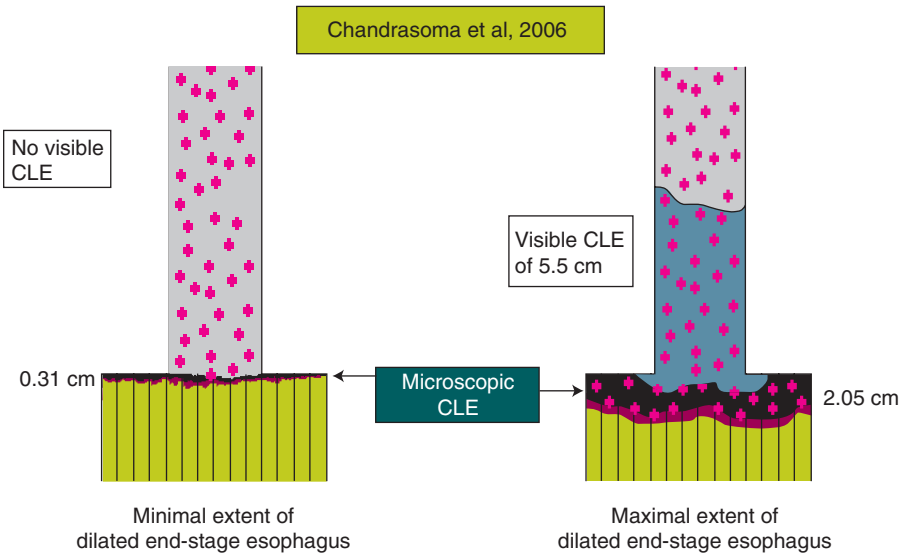


Figure 4–27 All 10 patients in this study had evidence of a dilated end-stage esophagus. The extent of this area varied from a minimum of 0.31 cm in one patient with squamous carcinoma of the esophagus to 2.05 cm in one patient with adenocarcinoma in long-segment Barrett esophagus (specimen shown in Figure 4–21). *CLE,* Columnar-lined esophagus. *Pink dots,* Submucosal esophageal glands.

The most common cause of significant error in medical research is overextension of technical capability. The endoscope and the naked eye at gross examination cannot see the true gastroesophageal junction. Overextending the capability of the endoscope and the naked eye and attempting to use these modalities to localize and define the true gastroesophageal junction results in significant error and significant diagnostic failure. The true gastroesophageal junction can only be defined histologically as the proximal limit of gastric oxyntic mucosa. Gastric oxyntic mucosa cannot be reliably differentiated endoscopically or by the naked eye from cardiac and oxyntocardiac mucosa. This requires histology; the best scope is the microscope, which has the required resolution of a few micrometers.

Pathogenesis of Reflux Disease

Gastroesophageal reflux disease occurs as a result of damage produced in esophageal squamous epithelium by exposure to gastric juice. A common error implicit in the very name of the disease is to believe that reflux of gastric juice into the esophagus is necessary for reflux disease. The proximity of the squamous epithelium at the end of the esophagus to gastric juice makes it feasible for the squamous epithelium to be exposed to gastric juice without reflux. This can occur during gastric overdistension, which is very likely the primary event that causes squamous epithelial damage[1] (Figure 4–28). Once reflux damage begins, it sets up a vicious cycle of pathologic events that results in the later stages of the disease, which are more readily recognized.

Reflux Versus Reflux Disease

Gastroesophageal reflux is extremely common, at least in the Western world. When a pH electrode is placed in the distal esophagus for a 24-hour period (in the 24-hour pH test), the vast majority of individuals will have episodes in which gastroesophageal reflux causes the esophageal pH to dip below 4.

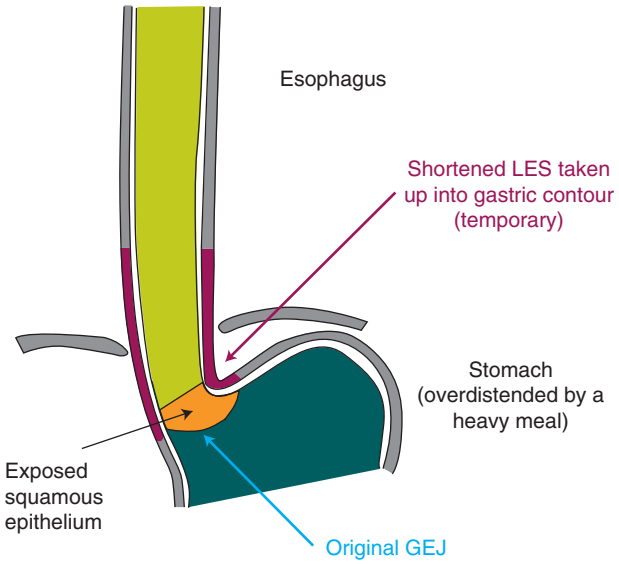


Figure 4–28 Pathogenesis of early reflux change. During gastric distension, the intragastric pressure increases, and the lower esophageal sphincter *(LES) (red areas)* shortens, being "taken up" into the contour of the stomach. The squamous epithelium of the most distal esophagus associated with this sphincter shortening *(orange area)* is now exposed to the gastric contents and can be damaged by gastric juice. *GEJ,* Gastroesophageal junction. *Yellow,* Squamous epithelium; *green,* gastric oxyntic mucosa.

Acid exposure is considered abnormal in the 24-hour pH test only when the pH in the esophagus is less than 4 for greater than 4.5% of the 24-hour period[26]; this amounts to an astonishing 64 minutes per day.

Most "normal" people will experience an acid exposure in this test between zero and 4.5% of the 24-hour period; very few people will have absolutely no acid exposure. In the 24-hour pH test, the measuring electrode is placed 5 cm above the proximal limit of the lower esophageal sphincter; this is 8 to 10 cm above the gastroesophageal junction. If a point so high in the esophagus is exposed to so much acidity, even in the "normal" population, it is likely that most, if not all, people experience some acid exposure in their distal esophagus.

It should therefore not be surprising if epithelial changes caused by reflux are present in most people. Changes of reflux can be expected to be as common as aortic atherosclerosis or anthracosis of the lung. Failure to understand this simple fact has resulted in the early changes of reflux disease being mistaken as "normal" for many decades.

The Mechanism of Gastroesophageal Reflux

Ingesting a meal involves swallowing masticated food and air is frequently swallowed with the food, causing gastric distension. With small meals, this is not a problem. However, with large meals, the gas distends the stomach and increases intragastric pressure. Kahrilas et al,[27] in an experimental study in which air was introduced into the stomach, showed that distension and increased intragastric pressure were associated with progressive shortening of the lower esophageal sphincter (see Figure 4–28). When the sphincter shortened to a critical level, a transient lower esophageal sphincter relaxation occurred, causing a reflux episode and acid exposure of the lower esophagus. The number of transient lower esophageal sphincter relaxations was directly related to the degree of shortening of the length of the sphincter (Figure 4–29). Transient lower esophageal sphincter relaxations are believed to be the main mechanism of gastroesophageal reflux.

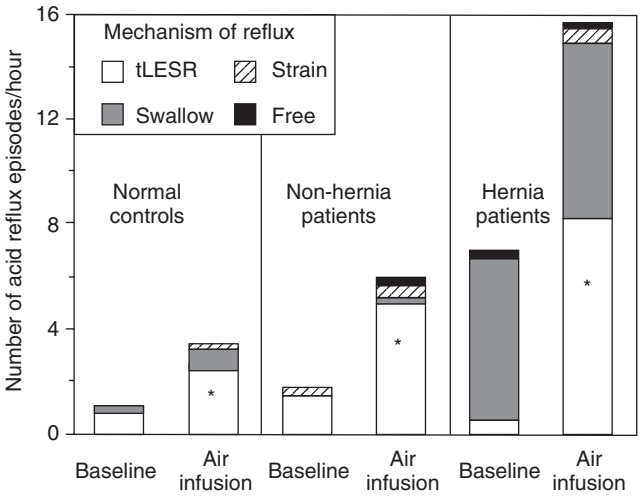


Figure 4–29 The number of acid reflux events related to different mechanisms during baseline recording and during a period of intragastric air infusion among normal controls, non-hernia GERD patients, and hernia patients. Air infusion resulted in a significant increase in reflux events only by the transient lower esophageal sphincter relaxation (tLESR) mechanism. (Reproduced with permission from Kahrilas PJ, Shi G, Manka M, Joehl RJ: *Gastroenterology* 118:688–695, 2000.)

The study by Kahrilas et al[27] had three patient groups: patients without symptomatic reflux disease, patients with symptomatic reflux without hiatal hernia, and patients with symptomatic reflux and hiatal hernia. The baseline sphincter length was lowest in patients with symptomatic reflux with hiatal hernia and increasingly more normal in patients with symptomatic reflux without hiatal hernia and patients without symptomatic reflux (Figure 4–30). This correlated with a larger number of baseline reflux episodes and higher acid exposure in hiatal hernia patients. It decreased in patients with reflux but no hernia and was lowest in patients without symptomatic reflux (see Figure 4–30). When air was infused into the stomach, the sphincter shortened equally in the three groups (see Figure 4–30). However, because the starting sphincter length was lowest in patients with hiatal hernia, the added shortening resulting from induced gastric distension caused a greater increase of reflux episodes in this group (see Figure 4–30; Figures 4–31 and 4–32).

Consider a person without reflux symptoms in this study and assume that the sphincter length is normal. As gastric distension is induced by air insufflation into the stomach, the sphincter shortens until this becomes sufficient to result in a sphincter relaxation, leading to reflux. When the refluxed contents are swallowed air, this is belching; when they are liquid gastric contents, it is reflux.

What is sphincter shortening? Where does the shortened sphincter go? Taking a round balloon and blowing it up can help answer these questions (Figure 4–33). Initially, the collapsed balloon (i.e., the stomach) fills up to capacity; the luminal pressure is not greatly increased, and the neck of the balloon (the sphincter) maintains its length (Figure 4–33*B*). As the balloon becomes overdistended with air, the intraluminal pressure increases, and the neck of the balloon shortens. If one draws a line at the distal end of the original neck, this point extends into the proximal part of the body of the balloon. Similarly, "shortening of the lower esophageal sphincter" during gastric overdistension results in the distal part of the esophagus being taken up into the contour of the stomach (Figure 4–33*C*). This part, which is lined

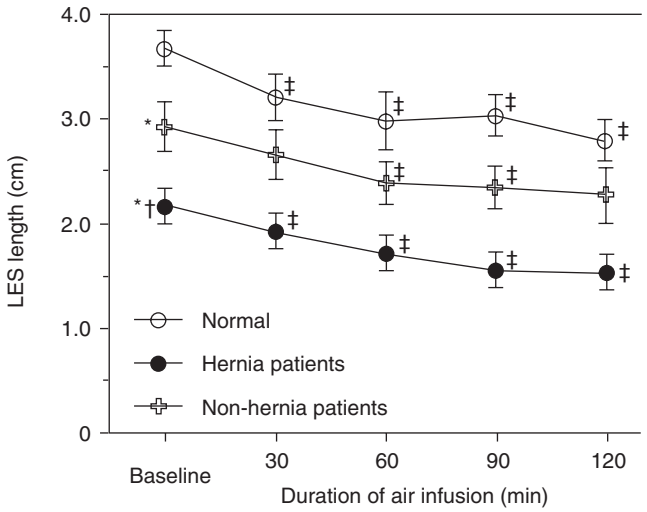


Figure 4–30 Esophagogastric junction (i.e., lower esophageal sphincter) length during recordings averaged over 30-minute periods. This shows that sphincter length at baseline is longest in normal patients, less in non-hernia GERD, and still less in hernia patients. All three groups show a similar decrease in the lower esophageal sphincter length during air infusion. (Reproduced with permission from Kahrilas PJ, Shi G, Manka M, Joehl RJ: *Gastroenterology* 118:688–695, 2000.)

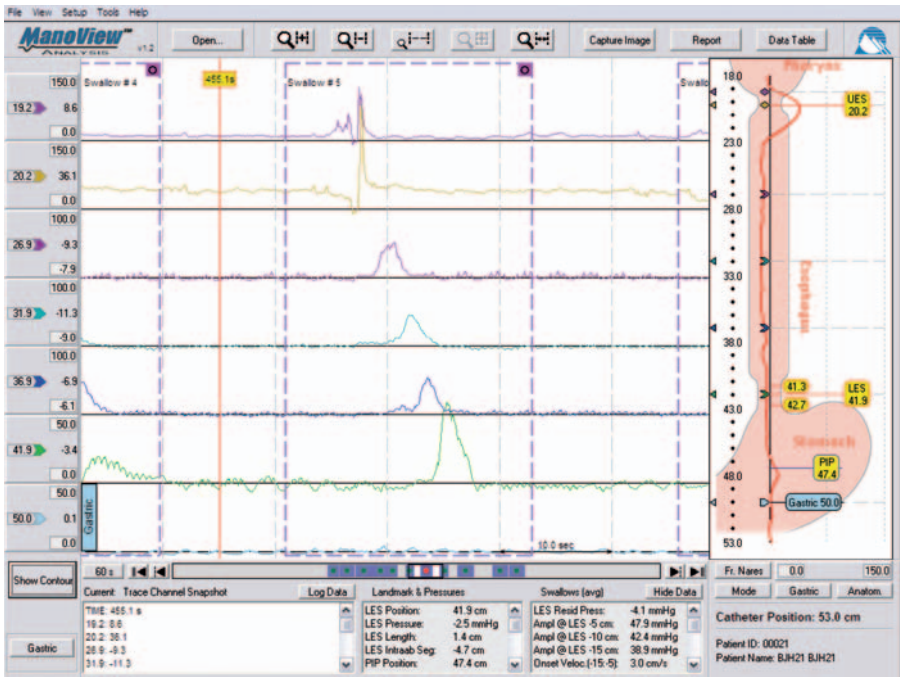


Figure 4–31 Esophageal manometry tracing showing one swallow. This shows a short esophagus (ends at 43 cm) with complete loss of the resting high pressure zone of the lower esophageal sphincter *(green tracing).* The anatomic depiction of the tracing is on the right with the distances from the nares. The high-resolution color format of this same swallow provides a clearer depiction of the changes (see Figure 4–32). (Reproduced with permission from Sierra Scientific Instruments.)

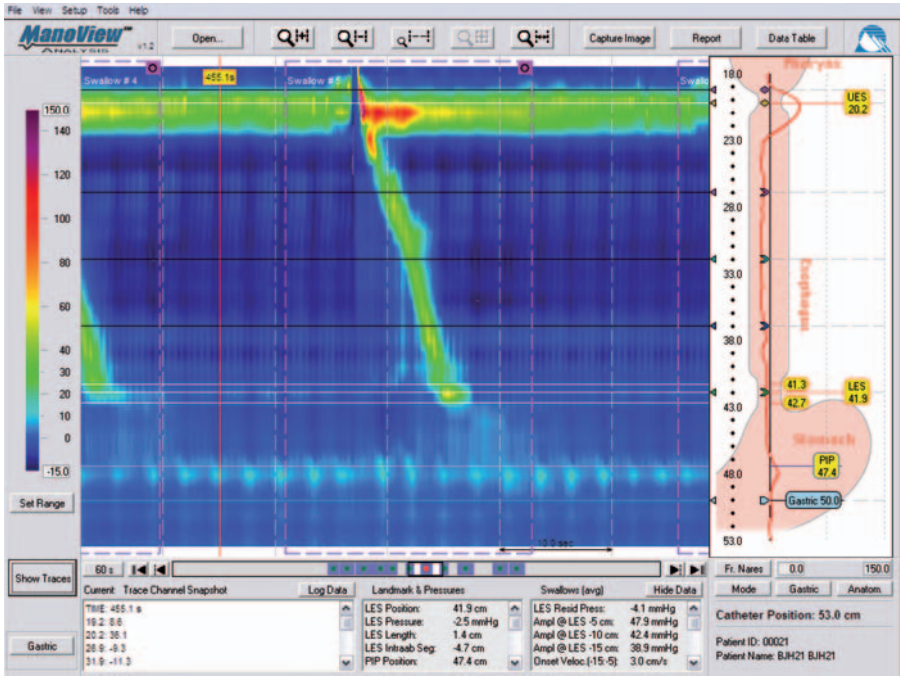


Figure 4–32 The tracing in Figure 4–31 shown in high-resolution manometry format. The propagated peristaltic wave ends 43 cm from the nares; this is the end of the tubular esophagus in this patient. There is complete loss of high-pressure zone of the lower esophageal sphincter. The diaphragmatic pinch *(intermittent green line)* is at 47.4 cm. The segment between the end of the peristaltic (at 43 cm) and the diaphragmatic pinch (at 47.4 cm) represents the esophagus associated with the destroyed lower esophageal sphincter (= dilated end-stage esophagus) with a probable sliding hiatal hernia. Note that this entire area has the same light blue pressure coloration as intragastric pressure (+ 5 mm Hg). This contrasts with darker blue coloration in the esophageal body, which corresponds to a more negative pressure in the color chart on the left. The anatomic depiction of the changes is shown on the right with the distances from the nares. (Reproduced with permission from Sierra Scientific Instruments.)

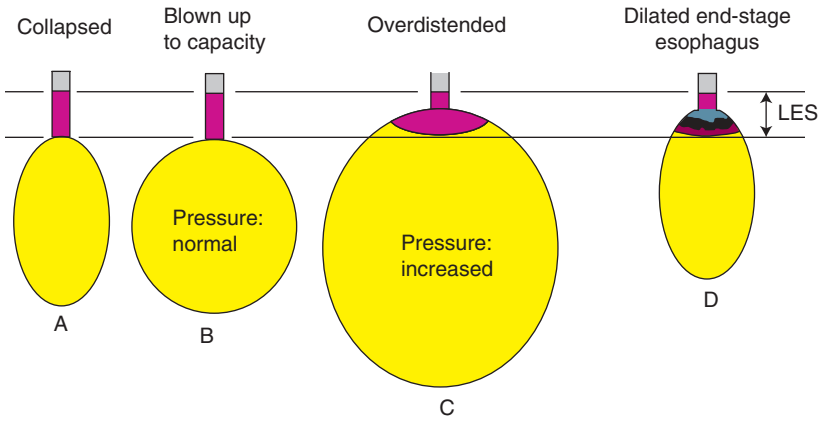


Figure 4–33 The effect of blowing up a balloon resembles the change produced by gastric distension. In the collapsed state (**A**) and when blown to capacity (**B**), the pressure is low and the neck *(purple areas)* remains long. As the balloon overdistends (**C**), the pressure increases and the neck shortens, with its distal part being taken up into the contour of the stomach. **D**, The similarity to the dilated end-stage esophagus with loss of the distal part of the lower esophageal sphincter is shown.

by squamous epithelium, is now exposed to gastric luminal contents. Reflux-induced damage can now occur in this exposed distal esophagus.

The Dilated End-Stage Esophagus: The Earliest Stage of Reflux Disease

The earliest changes to the squamous epithelium occur during periods of postprandial gastric distension. This is a temporary change because the postprandial gastric distension resolves as the stomach empties. It is very likely that the normal squamous epithelium can resist minor damage that occurs during this temporary exposure to postprandial gastric contents, which are likely to be less acidic because of the high percentage of ingested food in the stomach. However, when damage is prolonged with an exceptionally heavy meal or repeated with frequent large meals, the distal esophagus can be permanently damaged by this acid exposure. This damage is limited to the most distal few millimeters of the esophagus and is characterized by three important clinicopathologic events:

1. Esophageal pain or heartburn can occur; this explains why heartburn is typically postprandial in early reflux disease.
2. The squamous epithelium undergoes columnar metaplasia into cardiac mucosa.
3. The lower esophageal sphincter is "lost," resulting in sphincter shortening (Figures 4–34 and 4–35).

All these changes occur without any overt gastroesophageal reflux. It is likely that the 24-hour pH test, which only detects free reflux into the esophageal body, is normal in some of these patients.

This correlates well with changes observed in studies of patients with minimal reflux disease. In our autopsy study, the range of mean length of cardiac and oxyntocardiac mucosa was less than 5 mm in 17 of the 18 patients studied completely. In the pediatric autopsy study by Kilgore et al,[28] the mean cardiac mucosal length was 1.8 mm. In the study by Oberg et al[29] of clinical patients who were endoscopically normal, 88 (26%) of 334 patients had such

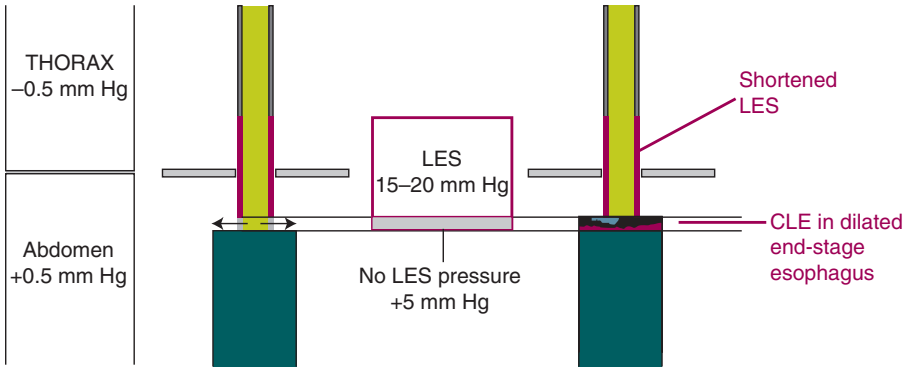


Figure 4–34 Diagrammatic representation of loss of the most distal part of the lower esophageal sphincter *(LES) (red wall).* This part of the esophagus dilates, and the squamous epithelium *(yellow areas)* undergoes columnar metaplasia. *Blue,* intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa. This microscopic columnar-lined (Barrett) esophagus *(CLE)* is interposed between the squamocolumnar junction and gastric oxyntic mucosa *(green areas).*

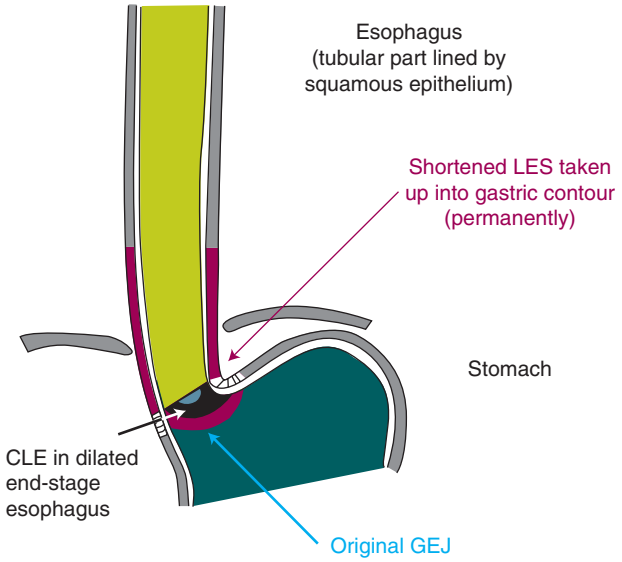


Figure 4–35 Early reflux disease at the microscopic phase. The most distal esophagus that has lost the sphincter effect *(black- and white-striped wall)* has become dilated and has taken the contour of the stomach. This area commonly develops rugal folds. Endoscopy and gross examination are normal, and the dilated end-stage esophagus will be mistaken for proximal stomach unless the proximal limit of gastric oxyntic mucosa *(green area)* is used to define the gastroesophageal junction *(GEJ)*. This patient has microscopic Barrett esophagus and is at risk for developing adenocarcinoma, which will be mislabeled "adenocarcinoma of the gastric cardia." *LES,* Lower esophageal sphincter. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa.

a small amount of cardiac and oxyntocardiac mucosa that it was not present in extensive biopsies from this region. This is the baseline reflux damage that occurs in the "normal" population; this is the acid exposure equivalent to the small amount of atherosclerosis that occurs in most people because of the lipid-rich diet so common in the Western world.

For nearly half a century, we have been confused by the severity of the damage to the distal esophagus by reflux. It is incorrect to believe that the esophagus retains its normal shape when damaged by reflux. The reflux-damaged distal esophagus loses its sphincter, dilates to become continuous with the gastric contour, and becomes lined by metaplastic columnar epithelia. Rugal folds do not indicate gastric mucosa. Rugal folds occur in all organs that act as reservoirs (e.g., the stomach, urinary bladder, gall bladder). When the distal reflux-damaged esophagus dilates, it ceases to function as the tube that transmits food; instead, it becomes part of the reservoir that distends with meals. It therefore develops rugal folds. However obvious it may seem that rugal folds are gastric, the presence of submucosal glands

under rugal folds indicates that mucosa with rugal folds can be esophageal (see Figure 4–23).

The reflux-damaged distal esophagus can be recognized histologically by the fact that it is lined by metaplastic columnar epithelia (cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa) and has submucosal glands. I call this *dilated end-stage esophagus*. Like the end-stage kidney that becomes "thyroidized," the end-stage esophagus has become "gastricized." The dilated end-stage esophagus is limited distally by the proximal limit of gastric oxyntic mucosa (the true gastroesophageal junction) and proximally by the end of the tubular esophagus. In some patients, the dilated end-stage esophagus represents the only pathologic abnormality associated with reflux disease (see Figure 4–27, patient on the left). In others with more severe reflux disease, the columnar metaplasia extends into the tubular esophagus to a variable length (see Figure 4–27, patient on the right).

In normal people without reflux damage to the distal esophagus, there is no columnar-lined esophagus (i.e., no cardiac or oxyntocardiac mucosa). The entire esophagus is tubular and lined by squamous epithelium, which transitions to gastric oxyntic mucosa at the gastroesophageal junction (see Figure 4–2). In these patients without reflux-induced damage, the anatomic gastric cardia is lined by gastric oxyntic mucosa. In normal people, every definition ever used for the gastroesophageal junction is correct. The normal junction is the distal limit of squamous epithelium, the proximal limit of gastric oxyntic mucosa, the end of the lower esophageal sphincter, the end of the tubular esophagus, the angle of His, the peritoneal reflection, and the proximal limit of the gastric rugal folds.

Let us consider a patient with reflux disease affecting the most distal 1 mm of the esophagus. The distal lower esophageal sphincter has lost 1 mm of the normal high-pressure zone (this shortening is too small be detectable at manometry). The squamous-lined tubular esophagus is shortened by 1 mm, being replaced by 1 mm of metaplastic columnar epithelia in the dilated end-stage esophagus; this is below the resolution capacity of the endoscope, and endoscopy is normal. This is equivalent to a 1-mm cephalad migration of the squamocolumnar junction. This explains the findings by Glickman et al[12] that 21% of children with less than 1 mm of cardiac mucosa had active esophagitis, compared to 55% of children with greater than 1 mm of cardiac mucosa. The presence of cardiac mucosa is an exquisitely sensitive indicator of reflux. It can also identify patients with cellular changes of reflux who are asymptomatic; many patients with 1 mm of columnar metaplastic epithelia limited to dilated end-stage esophagus will be asymptomatic.

This patient, however, can show all the changes and complications of reflux disease in this abnormal 1-mm area. He or she can develop microscopic Barrett esophagus in this segment (which will be misdiagnosed as "intestinal metaplasia of the gastric cardia") and reflux-induced adenocarcinoma of the dilated end-stage esophagus (which will be misdiagnosed as "adenocarcinoma of the gastric cardia").

Because the dilated end-stage esophagus results from destruction of the 1- to 3-cm abdominal segment of the lower esophageal sphincter, its maximal extent must be less than 3 cm. This correlates with the 2.8-cm maximum reported length of cardiac and oxyntocardiac mucosa distal to the end of the tubular esophagus. Additional sphincter loss in reflux disease affects the thoracic part of the sphincter, which is an intrathoracic organ with a negative intraluminal pressure that prevents it from dilating even when the sphincter is destroyed.

Dilated end-stage esophagus is the earliest stage of reflux disease and columnar-lined esophagus. Although these patients may have classical symptoms, endoscopy is normal because this area is distal to the end of the tubular

esophagus and is often lined by rugal folds. By present definitions, this will be called non-erosive reflux disease (NERD). According to current practice guidelines, this area is not subject to biopsy. Dilated end-stage esophagus, involving the most distal region of the esophagus, is the most common type of reflux disease and is present in a majority of the population. Present definitions ignore this most common manifestation of gastroesophageal reflux disease.

Visible Columnar-Lined Esophagus and Hiatal Hernia: The Later Stage of Reflux Disease

The study by Kahrilas et al[27] shows the occurrence of permanent sphincter shortening that occurs as gastroesophageal reflux progresses. Compared with asymptomatic patients, the baseline sphincter length shortens in the group with symptomatic reflux and shortens even more when a hiatal hernia develops (see Figure 4–30). As baseline sphincter shortening occurs, baseline reflux episodes and acid exposure increase, and the patient becomes increasingly susceptible to gastric distension. The vicious cycle is well demonstrated here where the initial sphincter damage sets the stage for further damage and increasing reflux.

At the level of sphincter shortening that accompanies minimal disease, sphincter competence is largely retained except during gastric distension in the postprandial period. With increasing sphincter shortening, sphincter incompetence increases, and free reflux occurs into the body of the esophagus. This is associated with columnar metaplasia in the tubular esophagus above the dilated segment (Figure 4–36). This is endoscopically visible columnar-lined esophagus (Figure 4–37). In these patients, the diagnosis is not missed. However, the endoscopic measurement of the length of the columnar-lined segment commonly ignores the invisible dilated end-stage esophagus distal to the visible segment of columnar-lined esophagus in the tubular esophagus.

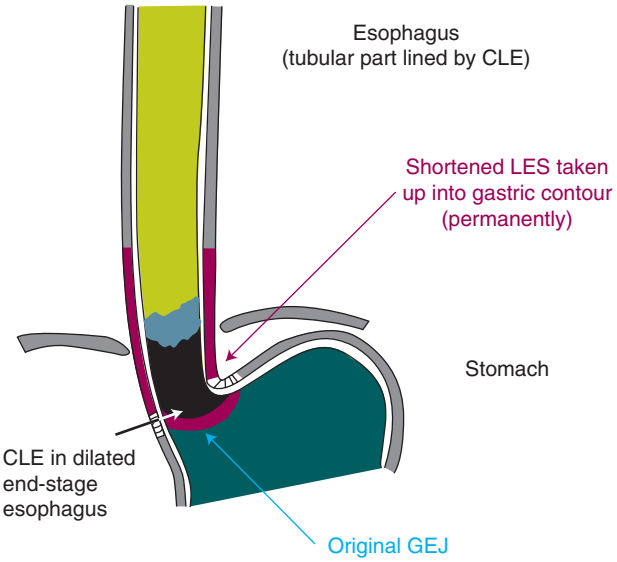


Figure 4–36 Later stage of reflux damage in which the permanent shortening of the lower esophageal sphincter *(black- and white-striped wall)* has resulted in an incompetent sphincter and free reflux into the body of the esophagus. The columnar-lined esophagus *(CLE)* has extended beyond the dilated end-stage esophagus into the tubular esophagus and is now visible endoscopically. *GEJ,* Gastroesophageal junction. *Blue,* intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *yellow,* squamous epithelium; *green,* gastric oxyntic mucosa.

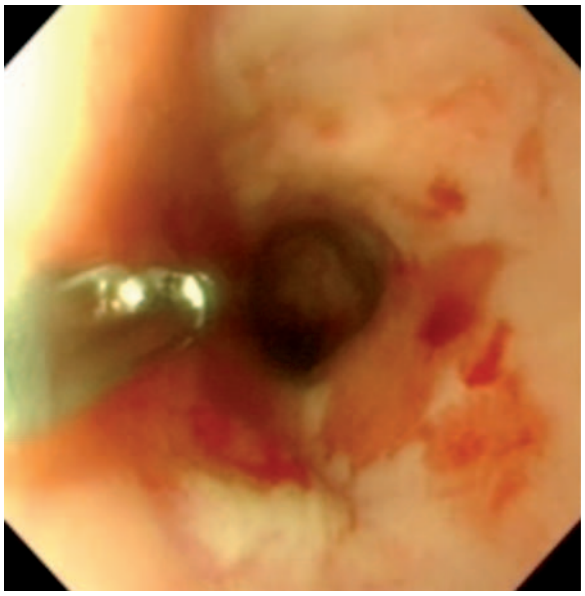


Figure 4–37 Endoscopic appearance of the diagrammatic esophagus shown in Figure 4–36, demonstrating a long segment of columnar-lined esophagus in the tubular esophagus.

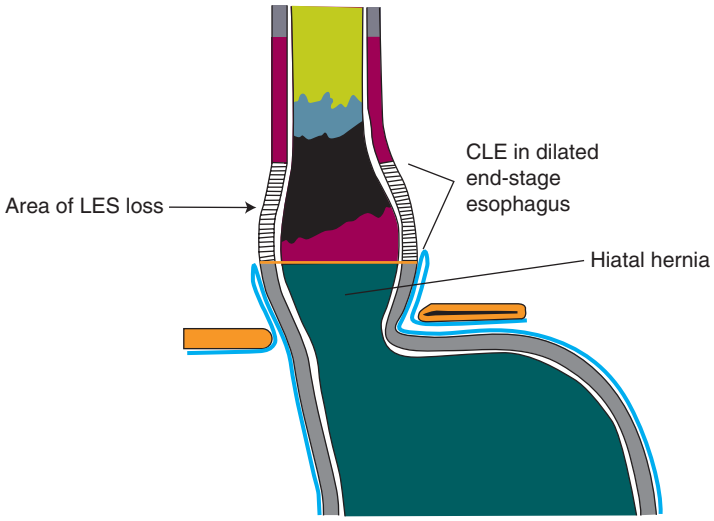


Figure 4–38 Final and advanced stage of reflux-induced damage, associated with esophageal shortening due to longitudinal contraction of the esophagus. This is possible because the angle of His has become obliterated by the loss of the sphincter and dilatation of the distal esophagus. The entire dilated end-stage esophagus (area where the wall is shown as the black and white stripes representing the lost sphincter and lined by metaplastic epithelium) and part of the stomach (*green area,* oxyntic mucosa) lie above the diaphragm. Note that the proximal part of the dilated segment above the diaphragm is the dilated end-stage esophagus. *LES,* Lower esophageal sphincter; *CLE,* columnar-lined esophagus.

As the extent of the dilated end-stage esophagus increases, there is a progressive shortening of the tubular component of the abdominal esophagus. This causes the angle of His to become progressively less acute. When the entire abdominal segment of the lower esophageal sphincter is lost, the end of the tubular part of the esophagus is close to the diaphragmatic hiatus, and the angle of His is close to being a right angle. The resistance to upward movement of the dilated esophagus and stomach has decreased. When there is shortening of the esophagus due to fibrosis resulting from severe reflux, a sliding hiatal hernia occurs (see Figures 4–31 and 4–32; Figure 4–38). Hiatal

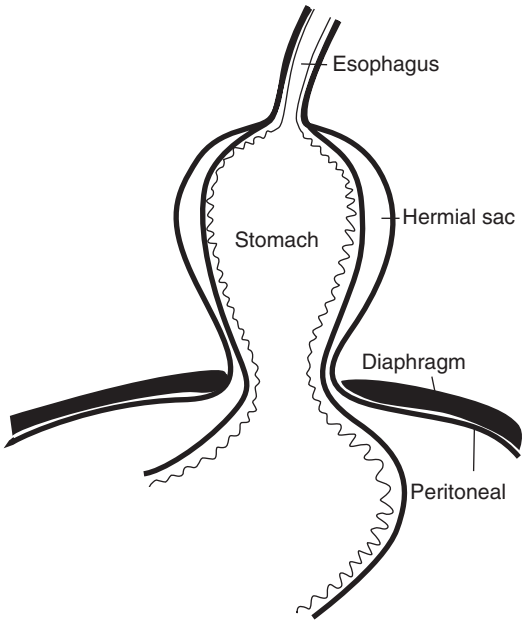


Figure 4–39 Sliding hiatal hernia as illustrated by Allison in 1948. The sliding hiatal hernia is covered by a sac of peritoneum, and the squamous epithelium *(straight line)* ends at the end of the tubular esophagus at the point of the peritoneal reflection. At this point, gastric mucosa *(serrated line)* begins. There is no columnar-lined esophagus or dilated end-stage esophagus shown here. (Reproduced with permission from Allison PR: *Thorax* 3:20–42, 1948.)

hernia has been accurately defined for a long time; Allison's (1948) description and illustration of a sliding hiatal hernia is perfect (Figure 4–39).

It should be recognized that the more proximal 2 to 3 cm of what is called *hiatal hernia* very likely represents the dilated end-stage esophagus. This can be proved by biopsy, in which the proximal region of a hiatal hernia is frequently lined by cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa (and not by gastric oxyntic mucosa).

Anatomic Location and Significance of Epithelial Types: Resolution of Controversy

It is clear that when one examines the vertical extent of the five epithelial types, the following conclusions are always true:

1. Squamous epithelium is always the most proximal of the five epithelial types and is the normal lining of the tubular esophagus.
2. Gastric oxyntic mucosa is always the most distal of the five epithelial types and is the normal lining of the body of the stomach.
3. A variable amount of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa is interposed between squamous epithelium and gastric oxyntic mucosa in most, if not all, patients. The extent of involvement varies from zero to the entire esophagus in rare cases.

The anatomic location of this segment of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa depends on where the line is drawn that defines the gastroesophageal junction:

1. When the line is drawn at the peritoneal reflection[14] (see Figure 4–18) or the angle of His in fetal specimens[3] (see Figure 4–4), the entire area at and distal to the line (i.e., stomach) is lined by gastric oxyntic mucosa, and the other three columnar epithelial types are located entirely in the esophagus.

2. When the line for the gastroesophageal junction is drawn at the end of the tubular esophagus or the proximal limit of the rugal folds, this line straddles the segment of columnar epithelium composed of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa. This results in part of this columnar epithelium being regarded as esophageal and part as proximal gastric (see Figure 4–20).

We have shown that the end of the tubular esophagus and proximal limit of rugal folds are incorrect definitions of the gastroesophageal junction, because the area distal to it and extending up to the proximal limit of gastric oxyntic mucosa contains submucosal mucous glands and gland ducts, which characterize this part as esophageal. What is called "gastric cardia" by these definitions is reflux-damaged dilated end-stage esophagus. As soon as this fact is understood, everything falls into place (see Figure 4–26).

Squamous Epithelium

Squamous epithelium is the normal epithelial lining of the esophagus and is present in all people. In the vast majority of patients, squamous epithelium of the esophagus is continuous with the squamous epithelium of the pharynx proximally and stops at the end of the tubular esophagus. This is currently accepted as the norm, at least from an endoscopic point of view, in which the coincidence of squamous epithelium at the end of the tubular esophagus with the proximal limit of the rugal folds is defined as the normal gastroesophageal junction. In a study of patients presenting for screening colonoscopy (mean age 59 years; 60% male; 78% white), Rex et al[30] showed that the squamous epithelium extended all the way to the end of the tubular esophagus and to within 5 mm of the proximal limit of the rugal folds in 785 (81.7%) of 961 patients; the other 176 patients had a visible columnar-lined segment in the lower esophagus. This percentage was higher in patients without heartburn than those with heartburn.

In rare cases, squamous epithelium extends into the proximal region of the pouch distal to the end of the tubular esophagus (Figures 4–40*C* and 4–41). This usually occurs as tongues of squamous epithelium distal to the end of the tubular esophagus between rugated columnar epithelial folds.[31] The maximum extent to which squamous epithelium has been reported to extend distal to the proximal limit of rugal folds is 3 cm. The prevalence of squamous epithelium distal to the proximal limit of the rugal folds was 16 (3%) of 547 patients. If the

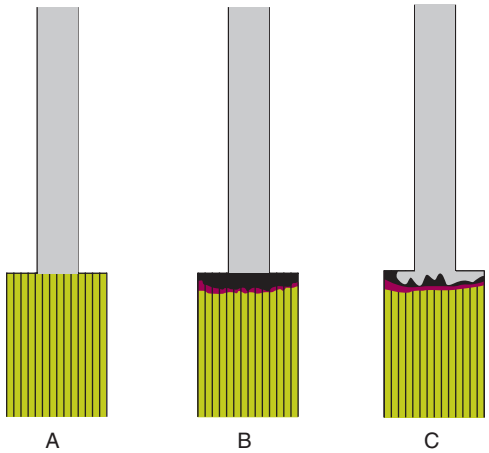


Figure 4–40 Epithelial composition of the area immediately distal to the tubular esophagus (lined entirely by squamous epithelium *[gray areas]*). **A**, Normal patient without dilated end-stage esophagus or columnar-lined esophagus. The squamous epithelium transitions directly to gastric oxyntic mucosa (*yellow striped areas* represent rugal folds). **B**, Patient with approximately 1 cm of microscopic columnar-lined esophagus composed of cardiac mucosa without intestinal metaplasia *(black areas)* and oxyntocardiac mucosa. This area is often lined by rugal folds. **C**, Patient with approximately 1 cm of microscopic columnar-lined esophagus composed of cardiac and oxyntocardiac mucosa where residual squamous epithelial islands *(gray areas)* are present in the dilated end-stage esophagus.

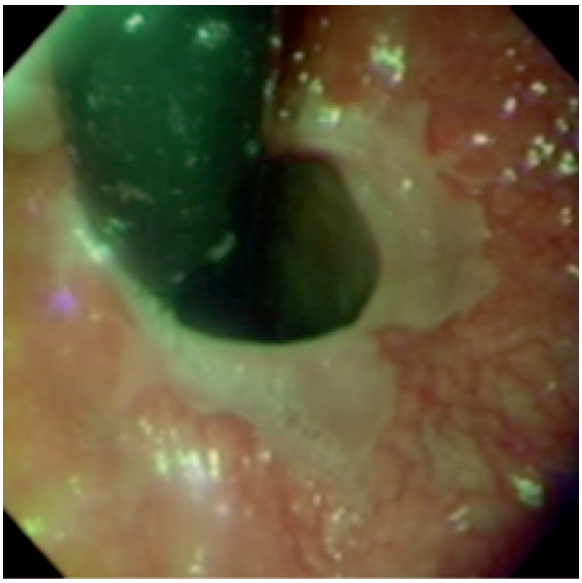


Figure 4–41 Endoscopic appearance of the patient discussed in Figure 4–40*C*, showing a retrograde view of the region immediately distal to the end of the tubular esophagus. Squamous epithelium extends down as irregular tongues between columnar epithelium, which represent metaplastic columnar epithelia lining the dilated end-stage esophagus.

definition of the gastroesophageal junction used by the authors (i.e., the proximal limit of rugal folds) is correct, the only possible conclusion is that in these rare patients, squamous epithelium lines the proximal stomach. This would not be impossible. In many ruminant and herbivorous animals, a varying part of the proximal stomach is normally lined by squamous epithelium.

However, Fass and Sampliner[31] showed that most, if not all, their patients with squamous epithelium extending into the "proximal stomach" had features suggesting gastroesophageal reflux disease. They all had hiatal hernias and heartburn was reported in 12 (75%), acid regurgitation in 8 (50%), Barrett esophagus was present in 6 (38%), and esophageal stricture in 4 (25%). These data make it unlikely that the presence of squamous epithelium in the proximal stomach represents a congenital anomaly. When attempting to explain the relationship between the finding of squamous epithelium in the proximal stomach and gastroesophageal reflux disease, the authors suggest two explanations. In their abstract, they conclude: "Squamous cell extension into the proximal stomach . . . may represent an esophageal mucosal response to proximal gastric injury." In the paper, they write: "These findings suggest that acid reflux may be one of the culprits responsible for the development of squamous epithelium in the proximal stomach." Both these explanations are difficult to comprehend.

In the authors' Figure 4, the squamous epithelium abuts inflamed cardiac mucosa. By our definition, this area is the dilated end-stage esophagus proximal to the true gastroesophageal junction (the proximal limit of gastric oxyntic mucosa). The authors are actually describing squamous islands within tongues of columnar-lined esophagus extending up into the dilated end-stage esophagus (see Figures 4–40 and 4–41). Their blind trust in the accuracy of the endoscopic gastroesophageal junction prevents them from seeing the obvious. As Allison and Johnstone[14] suggested, squamous islands are typical of columnar-lined esophagus, not stomach; squamous epithelium almost never occurs in the human stomach.

Gastric Oxyntic Mucosa

Gastric oxyntic mucosa with straight, tubular, unbranching glands composed of parietal and chief cells is present in all humans. It is the normal lining of that part of the stomach proximal to the point at which it transforms into antral mucosa in the distal stomach. In general, it is accepted that typical gastric oxyntic mucosa is not seen in the esophagus. The oxyntocardiac mucosa, which is found in columnar-lined esophagus, has parietal cells and, when these are numerous, this epithelium can resemble gastric oxyntic mucosa. However, oxyntocardiac mucosa is generally thinner and has lobulated and less organized glands that distinguish it from gastric oxyntic mucosa (Figure 4–42).

Gastric oxyntic mucosa is normally continuously exposed to gastric juice. It is an epithelium that is designed to withstand gastric juice exposure. It cannot, therefore, show pathologic changes in gastroesophageal reflux disease. Gastric oxyntic mucosa shows pathologic changes in the numerous diseases that affect the stomach. These include inflammation (gastritis) resulting mainly from infection with *H. pylori* and autoimmunity, and chemical injury (acute erosive gastropathy and reactive gastropathy) resulting from drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) and bile reflux. In most patients with these gastric diseases, there is a diffuse involvement of the gastric mucosa, and the proximal stomach is involved only when there is a pangastritis. Malignant epithelial neoplasms arising in gastric oxyntic mucosa are adenocarcinomas; they have a strong association with *H. pylori* infection. Gastric adenocarcinomas are histologically indistinguishable from esophageal adenocarcinomas.

Cardiac Mucosa with and Without Intestinal Metaplasia and Oxyntocardiac Mucosa

These three epithelial types, when present, are always interposed between the squamocolumnar junction and gastric oxyntic mucosa (Figure 4–43). Not all three occur in all patients; oxyntocardiac mucosa is the most prevalent; next is cardiac mucosa without intestinal metaplasia; cardiac mucosa with intestinal metaplasia is the least prevalent. Most adult patients have at least

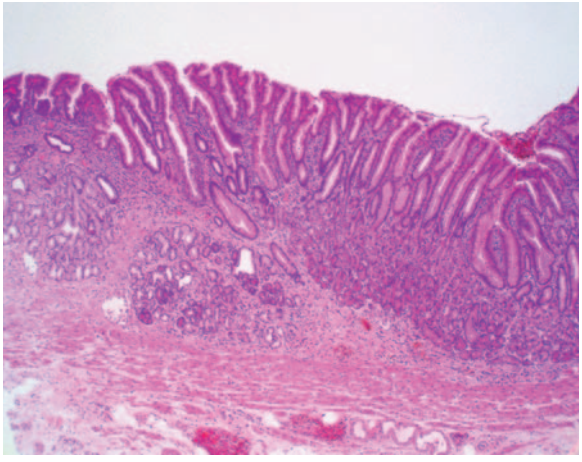


Figure 4–42 The true gastroesophageal junction in a patient with a columnar-lined esophagus. The gastroesophageal junction is the proximal limit of gastric oxyntic mucosa (right half of the field), which transitions into the lobulated oxyntocardiac mucosa. This is almost always the most distal of the types of columnar epithelia in the esophagus.

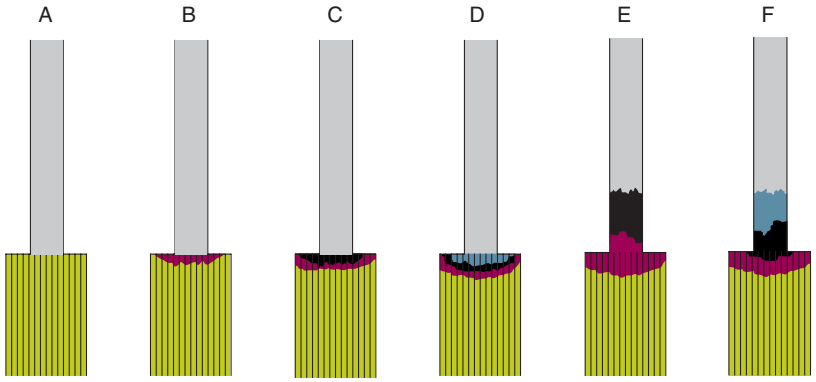
one of these epithelial types, usually oxyntocardiac mucosa. The amount of the three epithelial types varies greatly among patients in whom all three types are found.

When more than one of these epithelial types is present, there is a consistent zonation[32,33] (see Figure 4–43). Oxyntocardiac mucosa tends to be most distal immediately adjacent to gastric oxyntic mucosa (see Figures 4–42 and 4–43); cardiac mucosa with intestinal metaplasia is usually found proximally, adjacent to the squamous epithelium (Figure 4–44); cardiac mucosa without intestinal metaplasia is intermediate in location.

This zonation is maintained in all patients when the entire region between the squamocolumnar junction and the proximal limit of gastric oxyntic mucosa is considered. In patients who have these three epithelia straddling the end of the tubular esophagus and the proximal limit of the rugal folds, the zonation generally holds true across these lines (see Figure 4–43). In patients who have these epithelia limited to the region distal to the end of the tubular esophagus, the same zonation is seen when all three epithelia are present (see Figure 4–35).

Prevalence and Extent—Present Viewpoint

Paull et al[32] showed that columnar-lined esophagus consists of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa. Since the



Present belief	Does not exist	Normal cardia	Normal cardia	CIM	?Normal	SSBE
Truth	Normal	CLE in End-S E	CLE in End-S E	BE in End-S E	CLE	BE

Figure 4–43 Present interpretation of the findings of six patients compared with the new correct interpretation based on the accepted concept of the dilated end-stage esophagus. **A,** This is the normal state; currently, it is not believed to exist. **B** and **C,** Presence of small amounts of oxyntocardiac *(red areas)* or cardiac *(black areas)* and oxyntocardiac mucosa distal to the end of the tubular esophagus in a patient with normal endoscopy. This is presently designated *normal gastric cardia*. It represents reflux-induced columnar-lined esophagus *(CLE)* in dilated end-stage esophagus *(End-S E)*. **D,** Presence of intestinal metaplasia distal to the end of the tubular esophagus in a patient with normal endoscopy. This is presently designated *cardiac intestinal metaplasia (CIM)*. It represents microscopic Barrett esophagus *(BE)* in dilated end-stage esophagus. **E,** Patient with 2 cm of columnar-lined esophagus at endoscopy who has no intestinal metaplasia on biopsy. There is no diagnosis for this patient using current criteria. This represents moderate reflux disease manifesting as columnar-lined esophagus. **F,** Patient with 2 cm of columnar-lined esophagus at endoscopy with intestinal metaplasia on biopsy. This is correctly diagnosed as Barrett esophagus. *SSBE,* Short-segment Barrett esophagus.

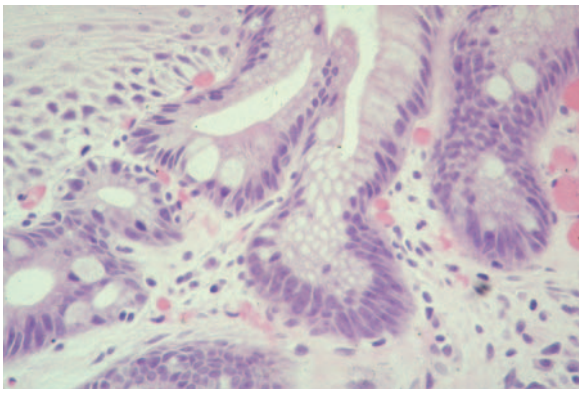


Figure 4–44 The proximal limit of the columnar-lined esophagus in a patient with intestinal metaplasia. The squamous epithelium *(left)* usually transitions into intestinalized cardiac mucosa.

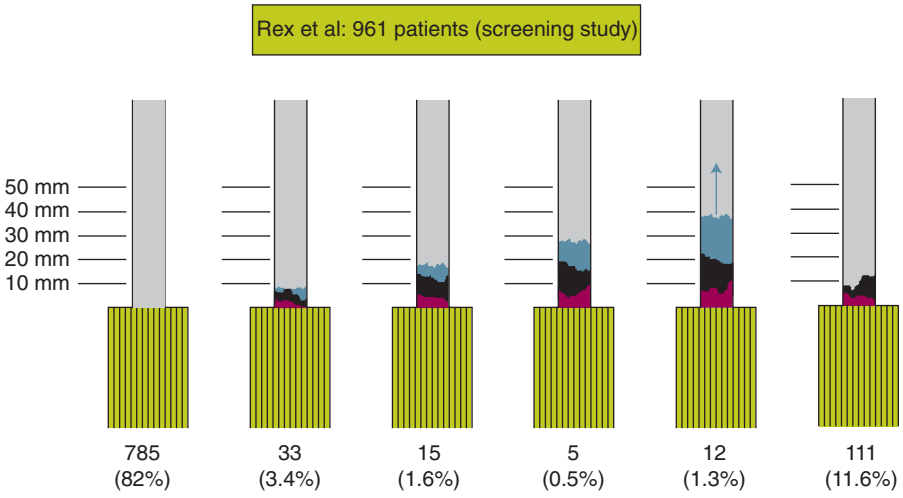


Figure 4–45 Findings in 961 patients in the screening study by Rex et al, 2003. The length of the columnar-lined segment is shown on the scale at the left. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

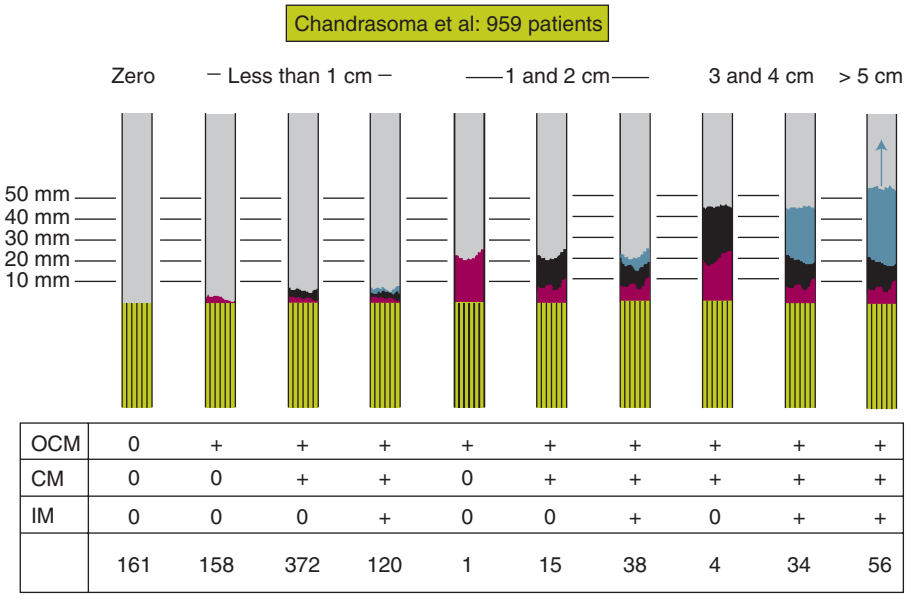
1960s, this has been considered an abnormal metaplasia of the esophagus resulting from the effect of reflux disease on esophageal squamous epithelium. Columnar-lined esophagus involves a variable extent of the tubular esophagus; in rare cases, the metaplasia extends to the most proximal region below the cricopharyngeal sphincter.

The amount of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa varies greatly depending on the population being studied. In a screening population of 961 patients that included patients with symptoms of reflux disease, Rex et al[30] showed that 176 (18.3%) patients had a visible columnar-lined segment in the tubular esophagus (Figure 4–45). This was defined as the presence of columnar-lined esophagus equal to or greater than 5 mm above the end of the tubular esophagus and the proximal limit of rugal folds. Sixty-five (6.8% of the total population and 36.9% of the 176 patients with a visible columnar-lined esophagus) of these patients had intestinal metaplasia and were diagnosed as Barrett esophagus. The columnar epithelial segment lengths in these 65 patients were 5 to 9 mm in 33, 10 to 19 mm in 15, 20 to 29 mm in 5, 30 to 39 mm in 9, 40 to 49 mm in 1, 50 mm in 1, and 80 mm in 1 patient. Unfortunately, the segment lengths in the 111 patients who had columnar-lined esophagus without intestinal metaplasia (i.e., patients with cardiac mucosa without intestinal metaplasia and oxyntocardiac mucosa) are not reported. This is because these patients currently do not fall

into a diagnostic category and are ignored despite the fact that there was a clearly defined endoscopic abnormality that led to biopsy.

Although Rex et al[30] is a screening study of patients presenting for colonoscopy who were offered upper endoscopy without the existence of a clinical indication, this is not a normal population. The patients presented for screening colonoscopy, which excluded patients under 40 years; they had a mean age of 59 years. It included patients with symptoms of reflux such as heartburn. The study clearly shows the impact of including patients with heartburn in the study. The 384 patients with heartburn had a prevalence of Barrett esophagus and long-segment Barrett esophagus that were 8.3% and 2.6%, significantly higher than the 5.6% and 0.36%, respectively, in patients without any heartburn. This study is selected, however, because it is probably the most normal population studied clinically and represents one end of the spectrum.

This contrasts with our study of a clinical population of 959 patients who presented to a foregut surgery unit for potential reflux disease surgery[34] (Figure 4–46). Our measurements were gathered with histologic mapping biopsies that assessed the separation of gastric oxyntic mucosa from squamous epithelium, regardless of endoscopic landmarks. They are not directly comparable to the numbers in the study by Rex et al.[30] The data provide much more detailed information regarding patients with very small amounts of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa. There were 148 (15.4%) patients who had 1 cm or more of these three epithelial types. The segment lengths were determined by the measured biopsies and not by the endoscopic length. The lengths were 1 or 2 cm in 54 patients, 3 or 4 cm in 38 patients, and 5 cm or greater in 56 patients. A total of 811 (84.6%) of the patients had 0 to 1 cm of separation between squamous epithelium and gastric oxyntic mucosa; 161 (19.9%) of these had only gastric oxyntic mucosa and squamous epithelium; 158 (19.4%) had only oxyntocardiac mucosa between gastric oxyntic mucosa and squamous epithelium; and 492 (60.7%) had cardiac mucosa with and without intestinal metaplasia. The prevalence of intestinal metaplasia in the columnar epithelium was 120 (14.8%) of the 811 patients who had less than 1 cm; 38 (70.4%) of the 54



OCM	0	+	+	+	+	+	+	+	+	+
CM	0	0	+	+	0	+	+	+	+	+
IM	0	0	0	+	0	0	+	0	+	+
	161	158	372	120	1	15	38	4	34	56

Figure 4–46 Findings in 959 patients in the study by Chandrasoma et al, 2005, of mapping biopsies. This is a clinical population biased toward having patients with severe reflux disease. *CM,* Cardiac mucosa; *IM,* intestinal metaplasia; *OCM,* oxyntocardiac mucosa. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

patients with 1 and 2 cm; 34 (89.5%) of the 38 with 3 and 4 cm; and 56 (100%) of those with 5 cm or greater.

This population is highly biased toward patients with complicated reflux disease being referred for surgery and reflects the distribution of these epithelia in the most abnormal setting. This study is the opposite end of the spectrum to that by Rex et al.[30] Most other clinical studies will have data that are between these two studies in terms of prevalence and extent of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa.

The medical community has always had difficulty in determining how much of this cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa is abnormal. One of the most incredible phenomena of the past five decades has been the change in what is considered the normal extent of cardiac mucosa. Before Allison and Johnstone[14] described the columnar-lined esophagus, all cardiac mucosa was considered a normal part of the stomach. The initial viewpoint about columnar-lined esophagus, until it was recognized as a reflux-induced metaplasia, was that it was just a congenital anomaly. In 1961, Hayward[17] defined normal cardiac mucosa as lining the distal 2 cm of the tubular esophagus and extending a variable distance into the proximal stomach. In the most recent (1997) edition of the standard histology text used by pathologists, DeNardi and Riddell[35] state that "the distal 2 cm of the esophagus may be lined by columnar cells of the gastric cardia." Owen,[36] discussing gastric histrology, states that, "Pure cardiac mucosa and cardiofundic mucosa are normal findings but that the extent of the mucus-secreting mucosa is less than was previously thought.

The viewpoint still remains that there are 3 to 4 cm of cardiac mucosa straddling the gastroesophageal junction and partially in the esophagus and partially in the proximal stomach. The presence of columnar epithelium in the tubular esophagus is endoscopically abnormal; this is an indication for biopsy. However, it is only when intestinal metaplasia is present in the biopsy that this columnar epithelium is considered abnormal; this is the definition of Barrett esophagus. If no intestinal metaplasia is found in the biopsy, most people will revert to the viewpoint that this columnar epithelium in the distal esophagus is "normal" or "gastric," regardless of the endoscopic length of columnar epithelium (see Figure 4–43). This viewpoint is clearly seen in Rex et al,[30] in which 111 patients with columnar-lined esophagus who did not have intestinal metaplasia were essentially ignored in the data.

It is believed that cardiac mucosa normally lines the proximal stomach. A biopsy distal to the gastroesophageal junction that shows cardiac mucosa is accepted as normal despite the presence of significant inflammation and reactive change in the mucosa. Currently, no attempt is made to quantitate this cardiac mucosa during biopsy interpretations of this region; there is no limit to the amount of cardiac mucosa that is accepted as normal in a gastric biopsy.

When the accepted normal amount of cardiac mucosa separating the squamocolumnar junction and gastric oxyntic mucosa was in the 3- to 4-cm range, all these opinions made sense. However, recent evidence suggests that the amount of cardiac mucosa present between squamous and oxyntic mucosa is much smaller in the vast majority of the population. In the mid-1990s, we suggested that the evidence indicated that there was no normal cardiac mucosa in this region[37]; this still remains a controversial opinion. However, the concept of normalcy has shifted dramatically from the 3- to 4-cm range to an amount much closer to the zero that I predicted. In a recent review of the literature, Odze[7] suggests that the normal amount of cardiac mucosa is "less than 0.4 cm," and most studies of normal people show that the amount of cardiac mucosa is either zero or less than 0.5 cm. The medical community is very slowly but inexorably accepting this amount as the normal length of cardiac mucosa.

When this accepted number shrinks, it becomes increasingly difficult to place this minute amount of cardiac mucosa normally in both esophagus and stomach and to regard this as a normal epithelium. The tissue accessed by the standard biopsy forceps is approximately 3 to 4 mm, which means that unless the actual squamocolumnar junction is present in the biopsy sample, there is a significant risk that any cardiac mucosa present will not be sampled. Marsman et al[9] showed this to be the case. In a study of endoscopically normal patients, they showed that 62% of patients who had the squamocolumnar junction in one biopsy specimen had cardiac mucosa, compared with only 2% of patients when the squamocolumnar junction was not present in one biopsy sample.

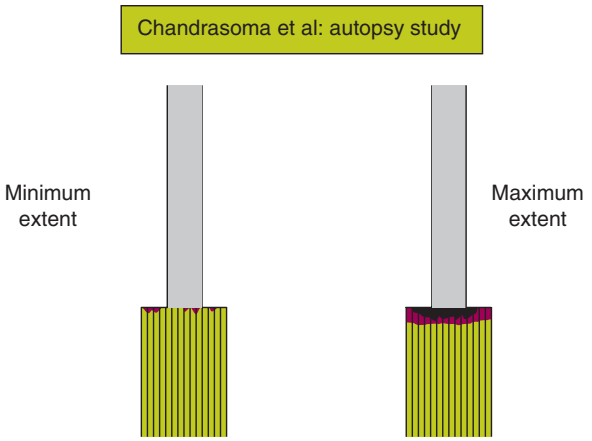
If the accepted maximal length of normal cardiac mucosa is "less than 4 mm" as suggested by Odze,[7] the finding of cardiac mucosa entirely involving one biopsy sample (which is 4 mm) or more must be abnormal. However, pathologists interpreting biopsies of this region will accept any amount of cardiac mucosa in this region and call it "normal" without any attempt at quantitation. This is obviously an error. This situation will only change when the medical community accepts my viewpoint that cardiac mucosa is always abnormal. At that time, the presence of cardiac mucosa in any biopsy will be regarded as the pathologic state that it truly represents.

Prevalence and Extent—New Data in Autopsy Populations

One reason the amount of cardiac mucosa has been greatly exaggerated in the historic literature is because the data have been derived from studies of esophagectomies and endoscopic biopsies. By definition, these are highly abnormal cases that are not likely to provide accurate data on the normal state. When this region is studied at autopsy in people who had no esophageal disease, the data that emerge are very different. The first autopsy study of the gastroesophageal junctional region was not reported until after the turn of this century.[8]

Cardiac mucosa is not seen in all patients. The maximum amount of cardiac and oxyntocardiac mucosa encountered in the 18 patients who were completely examined ranged from 0.48 to 8.05 mm (Figure 4–47). Autopsy studies are not able to accurately identify intestinal metaplasia. We first reported this in an autopsy study of the gastroesophageal junctional region; although this study was published 2000, the data were available many years before, when the study was being rejected by multiple journals. In 10 (56%) of 18 patients in whom the entire circumference of the junction was examined by vertical sections, there was no cardiac mucosa. In eight patients, the cardiac mucosa had a mean length of 0.036 to 1.038 mm and a maximum length of 0.25 to 2.75 mm. Note that 0.36 mm is 36 μm, which is equivalent to a single foveolar-gland complex. Oxyntocardiac mucosa was present in all 18 patients, but only in a part of the circumference of the squamocolumnar junction in nine patients. The length of oxyntocardiac mucosa in the 10 patients without cardiac mucosa was a mean of 0.40 to 1.92 mm, a maximum of 1.00 to 7.25 mm. In the eight patients who had cardiac mucosa, the combined cardiac plus oxyntocardiac mucosal length was a mean of 0.16 to 6.95 mm and a maximum of 0.48 to 8.05 mm. In patients who had no oxyntocardiac or cardiac mucosa in some part of the circumference of the squamocolumnar junction, the squamous epithelium transitioned directly to gastric oxyntic mucosa (see Figure 4–14).

Only one study, by Kilgore et al,[28] found that cardiac mucosa was universally present distal to the squamous epithelium. The reason for this unduplicated finding is that the authors used a unique and flawed definition of cardiac mucosa: "In each case, 5 μm sections were stained with hematoxylin and eosin as well as Alcian blue/periorid acid-Schiff (PAS). . . . All slides were



Oxyntocardiac mucosa	Yes	Yes
Cardiac mucosa	No	Yes
CM + OCM length	0.48 mm	8.05 mm

Figure 4–47 Findings in the autopsy study by Chandrasoma et al, 2000. The patient on the left represents the minimum separation of squamous and gastric oxyntic mucosa, represented by oxyntocardiac mucosa *(OCM)* only in a part of the circumference measuring a maximum of 0.48 mm. The patient on the left is the maximum separation, represented by 8.05 mm of combined cardiac and oxyntocardiac mucosa). *CM,* Cardiac mucosa. *Black,* Cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

evaluated in a blinded fashion by two observers looking for the presence of cardiac-type mucosa characterized by unequivocal PAS-positive mucous glands arranged in lobular configuration."

This is the first and only time in the literature that cardiac mucosa was primarily defined by the PAS stain and the first time that the definition was made by the presence of mucous glands rather than the absence of parietal cells. The authors suggest in the next sentence that parietal cells were absent in their cardiac mucosa: "The length of the cardiac-type mucosa, the distance between the most distal portion of the squamous mucosa and the identification of the most proximal parietal cell, was measured. . . ." However, because the cytoplasm of parietal cells frequently stains weakly with PAS, exclusion of parietal cells is not always clear. Careful examination of the illustrations is revealing. In their Figure 4, they show an admixture of PAS-positive glands and parietal-cell containing glands, indicative of oxyntocardiac mucosa (which they call *transitional mucosa*). When their Figure 2 is examined, it shows a low magnification view of the squamocolumnar junction where "squamous mucosa. . . . is found adjacent to cardiac-type mucosa characterized by a lobular configuration of PAS-positive mucous-secreting glands." First, the glands appear more straight tubular than lobulated; second, not all the cells of the gland are strongly PAS-positive; third, there appears to be a population of smaller, PAS-negative cells between the surface and the deep glands that look identical to the parietal cells.

The critical point here is that cardiac mucosa is not defined by the presence of PAS-positive mucus-secreting cells; it is defined by the fact that all the cells must be mucous cells in a hematoxylin- and eosin-stained section. PAS-stained sections have not been used in any other paper to define cardiac mucosa. If PAS-stained sections are used, all the cells must be strongly PAS-positive mucus-secreting cells, and the entire mucosa must be lobulated. Every colum-

nar epithelium in the esophagus and stomach has a surface-lining epithelium composed of mucous cells containing neutral mucin and therefore is strongly PAS-positive. The report by Kilgore et al[28] is important because it is the only study that reports the universal presence of cardiac mucosa at the junction.

Additional dissent with the statement that cardiac mucosa is not universally present comes from two autopsy studies of fetuses and neonates, which claim to find cardiac mucosa in all patients. The study by De Hertogh et al[3] is extremely interesting. What these authors call "cardiac mucosa" is clearly located above the gastroesophageal junction and therefore in the esophagus. The epithelium at the gastroesophageal junction contains parietal cells. The authors actually show the reverse of their conclusion that cardiac mucosa is normally present in the proximal stomach in human fetuses. No one at this time will suggest that cardiac mucosa is normally found in the distal esophagus. What the authors call "cardiac mucosa" is actually the non-ciliated columnar epithelium present in the distal esophagus as the last fetal columnar epithelium to disappear during epithelial development. Providing data that essentially prove this, the authors show that the length of this "cardiac mucosa" decreases with increasing fetal age, a feature that defines a fetal structure destined to disappear when development is completed. Derdoy et al[38] also incorrectly designate fetal columnar epithelium "cardiac mucosa" and find that it is universally present; this study also shows that this "fetal cardiac mucosa" decreases in length as fetal age increases, a characteristic feature of fetal tissue. In a third similar fetal and neonatal study from South Korea, Park et al[39] designated fetal columnar epithelium as "transitional epithelium" and concluded that cardiac mucosa was not present in fetuses. This study contained an excellent illustration of a direct transition from squamous epithelium to gastric oxyntic mucosa in a neonate.

Prevalence and Extent—Data from Clinical Populations

The finding that cardiac mucosa is frequently absent at the squamocolumnar junction, which was initially received with skepticism, has now been amply confirmed. In studies with extensive sampling of the normal squamocolumnar

TABLE 4–3 Prevalence of Cardiac Mucosa at the Endoscopically Normal Squamocolumnar Junction in Different Studies with Adequate Histologic Data

Study	Prevalence of cardiac mucosa	Comments
Chandrasoma et al, 2000	44%	Circumferential vertical sections at autopsy
Jain et al, 1998	35%	Extensive endoscopic sampling
Kilgore et al, 2000	100%	Pediatric autopsies; flawed; incorrect definition of cardiac mucosa was used
Marsman et al, 2002	62%	Endoscopic sampling; authors conclusion contradicted their data
Glickman et al, 2003	19%	Pediatric endoscopies; high prevalence of reflux
De Hertogh et al, 2003	100%	Fetal autopsies; fetal columnar epithelium mistaken for cardiac mucosa
Derdoy et al, 2003	100%	Fetal autopsies; fetal columnar epithelium mistaken for cardiac mucosa
Park et al, 2003	0	Fetal autopsies; fetal columnar epithelium called transitional mucosa
Zhou et al, 2000	45%	Autopsy
Oberg et al, 1997	74%	Endoscopic sampling in clinical population with a bias toward reflux

junction at endoscopy, in biopsies that have the actual squamocolumnar junction in one biopsy piece, and in vertical sections taken across the squamocolumnar junction in esophagectomy specimens, cardiac mucosa is absent in a variable number of patients. In these studies, the incidence of cardiac mucosa generally increases when the population studied is older, has a higher rate of symptomatic reflux disease, and has endoscopically visible columnar-lined esophagus.

There is no argument that columnar-lined mucosa can extend proximally into the tubular esophagus from the gastroesophageal junction; in rare cases, this reaches the upper esophagus.

Evidence shows that up to approximately 3 cm of the presumed proximal stomach distal to the end of the tubular esophagus and/or proximal limit of the rugal folds can be lined by cardiac and oxyntocardiac mucosa. In our autopsy study,[8] which is the closest to a normal population, 0.05 to 0.8 cm of the region distal to the end of the tubular esophagus was lined by cardiac and oxyntocardiac mucosa. In our esophagectomy study,[23] we reported the 0.31 to 2.05 cm of the area distal to the end of the tubular esophagus and the proximal limit of rugal folds was lined by these three epithelial types. Sarbia et al,[25] in a study of esophagectomy specimens in patients with squamous carcinoma, reported the presence of cardiac and oxyntocardiac mucosa to a maximum extent of 2.8 cm distal to the end of the tubular esophagus. Jain et al[40] showed that cardiac mucosa was present 2 cm distal to the proximal limit of the rugal folds by endoscopic biopsy in one of 31 patients. This confirms the contention in many histology textbooks that approximately 2 cm of the "proximal stomach" is lined by cardiac mucosa. When combined with the data that cardiac mucosa can frequently be absent at the junction, it can be stated that an area distal to the end of the tubular esophagus measuring 0 to 30 mm in length can be lined by cardiac (and oxyntocardiac) mucosa (Table 4–4). This is the maximum extent of the dilated end-stage esophagus.

Significance of Cardiac Mucosa with and Without Intestinal Metaplasia and Oxyntocardiac Mucosa

The presence of cardiac mucosa in the tubular esophagus (i.e., columnar-lined esophagus) has long been known to result from metaplasia caused by squamous epithelial damage induced by gastroesophageal reflux. Despite this, columnar-lined esophagus has never been used as a diagnostic criterion for reflux disease. I have suggested in Chapter 2 that this is inexplicable and should be changed. The question remains as to how much cardiac

TABLE 4–4 Studies that Provide Measurement of the Extent of Cardiac Mucosa with and without Oxyntocardiac Mucosa Distal to the Gastroesophageal Junction*

Study	Patients without cardiac mucosa	Maximum length of cardiac mucosa	Maximum length of CM + OCM
Chandrasoma et al, 2000	56%	2.75 mm	8.05 mm
Jain et al, 1998	65%	3% had 20+ mm	Data not provided
Glickman et al, 2002	19%	43% had >1 mm	Data not provided
Kilgore et al, 2000	0	1–4 mm (mean 1.8 mm)	Data not provided
Sarbia et al, 2003	3%	1–15 mm (mean 5 mm)	28 mm

*As presently defined.
CM, Cardiac mucosa; *OCM*, oxyntocardiac mucosa.

mucosa with and without intestinal metaplasia and oxyntocardiac mucosa is necessary before its presence becomes associated with gastroesophageal reflux (Figure 4–48).

In 1993, Csendes et al[41] reported that the extent of columnar-lined esophagus correlated with the severity of reflux disease; the longer the columnar-lined segment, the greater the likelihood and severity of reflux disease, and the greater the likelihood and severity of lower esophageal sphincter abnormality.

In a histologic study, we compared a population of patients who had less than or greater than 2 cm of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa separating the squamous epithelium and gastric oxyntic mucosa in mapping biopsies.[42] Patients with greater than 2 cm of these columnar epithelia were significantly more likely to have an abnormal acid exposure and abnormalities in the lower esophageal sphincter than patients with less than 2 cm of these epithelial types (see Figure 4–48).

This association between the presence of these three columnar epithelia and gastroesophageal reflux disease has been shown at even very short lengths. Oberg et al,[29] in a study of 334 endoscopically normal patients, showed that the 246 patients who had cardiac and/or oxyntocardiac mucosa in their biopsies were more likely to have an abnormal 24-hour pH test with higher acid exposure of the lower esophagus. In addition, they were more likely to have lower esophageal sphincter incompetence such as decreased total and abdominal length (see Figure 4–48).

In a study of pediatric patients who had the squamocolumnar junction in one biopsy sample, many of whom had symptomatic reflux, Glickman et al[12] showed that patients with greater than 1 mm of cardiac mucosa were more likely to have reflux symptoms than those with less than 1 mm (see Figure 4–48). This suggests that even minute amounts of cardiac mucosa are a manifestation of gastroesophageal reflux. If cardiac mucosa was a normal structure, the findings would have been the reverse. If cardiac mucosa was unassociated

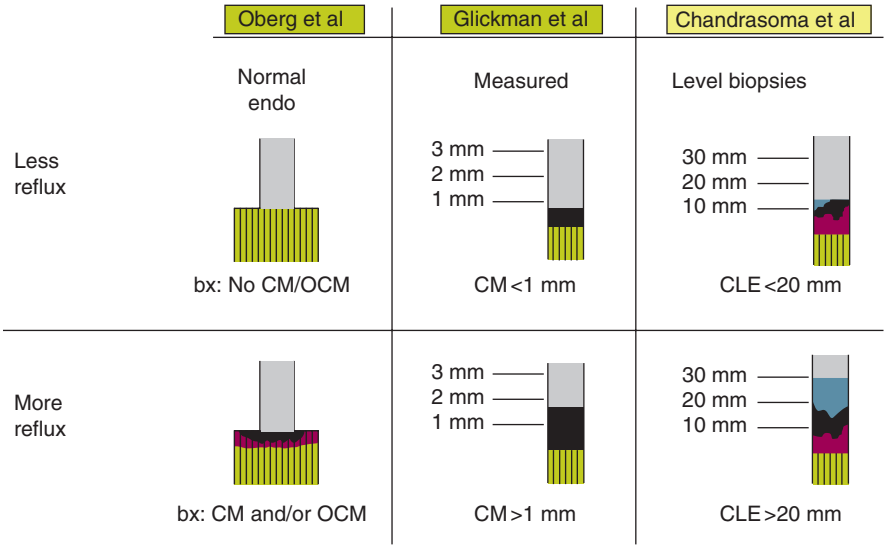


Figure 4–48 Results of three studies that compare the severity of reflux disease in patient groups that differ in the amount of cardiac and/or oxyntocardiac mucosa *(CM/OCM)* present between the squamous epithelium and gastric oxyntic mucosa. In all the studies, the presence of cardiac mucosa indicated more evidence of reflux, and greater lengths of cardiac mucosa indicated greater severity of reflux. *Black,* Cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

TABLE 4–5 New Histology-Based Definitions

Esophagus (histologic)	**That part of the foregut lined by squamous epithelium or metaplastic esophageal columnar epithelia.**
Metaplastic esophageal columnar epithelia	Cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa.
Columnar-lined esophagus	That part of the esophagus lined by metaplastic esophageal columnar epithelia.
Stomach	That part of the foregut lined by gastric oxyntic mucosa.
Gastroesophageal junction	The proximal limit of gastric oxyntic mucosa.
Normal GEJ	The coincidence of esophageal squamous epithelium with gastric oxyntic mucosa without intervening columnar-lined esophagus.
Esophagus (anatomic)	The tubular esophagus (only in normal patients) plus the dilated end-stage esophagus (in patients with reflux disease).
Dilated end-stage esophagus	The dilated segment distal to the end of the tubular esophagus lined by metaplastic esophageal columnar epithelia.

with reflux, there is no reason for a statistically significant relationship between the amount of cardiac mucosa and reflux.

These data prove beyond any reasonable doubt that cardiac mucosa is an abnormal epithelium associated with gastroesophageal reflux. It is not a normal epithelium—even at a length of 1 mm. In Chapter 5, I will show that cardiac mucosa is the first columnar metaplastic epithelium that arises from squamous epithelium in the esophagus. Depending on the milieu in the esophagus, cardiac mucosa can transform into oxyntocardiac mucosa (by developing parietal cells) or develop goblet cells, which represent intestinal metaplasia in cardiac mucosa. The three columnar epithelial types–cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa–are all derived from reflux-induced columnar metaplasia of the esophageal squamous epithelium.

New Definitions of the Normal State and Gastroesophageal Reflux Disease

The understanding of the changes associated with early reflux in anatomic and histologic terms finally permits the clear, unambiguous, and easily reproducible definition of the esophagus and stomach (Table 4–5). Cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa represent reflux-induced columnar metaplastic esophageal epithelia. They are never gastric and never normal (see Figures 4–2, 4–9, and 4–43).

The acceptance and use of these new definitions are essential for gastroesophageal reflux disease to be understood and appropriately treated. Until this happens, confusion is inevitable.

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CHAPTER 5

Cellular Changes of Non-Neoplastic Gastroesophageal Reflux Disease

The cellular events that occur with gastroesophageal reflux result from interaction of the cells that are exposed and the nature of the refluxate. Ultimately, every change must be explained on the basis of a cellular interaction between a cell present in the patient and a molecule or combination of molecules in the refluxate. Such interactions are theoretically of two types (Figure 5–1):

1. *Destructive or injurious,* in which a molecule causes cell damage by a chemical reaction with cell components. Acid in a high enough concentration has the potential to induce direct cell damage in all types of esophageal epithelia, whether squamous or metaplastic columnar. It is likely that molecules in the refluxate other than acid also contribute to cell injury.
2. *Interactive,* in which a molecule in the refluxate combines with a cell component, usually a receptor, and induces a change in the structure and/or function of the cell. Interactive mechanisms generally preserve the altered cell in contrast to the destructive influences, which damage and destroy the cells.

The most important result of molecule-cell interactions is an alteration in the genetic control of the cell. All the genetic changes in the stem cells of the esophagus must result from such molecule-receptor interactions. Conceptually, two types of genetic changes are produced:

1. Genetic switches, which are reversible changes that direct the differentiation of the stem cell. Normally, the direction of differentiation in the adult esophagus is squamous. Genetic switches due to reactivation of suppressed columnar signaling genes may cause the stem cell to differentiate into all the columnar cell types seen in the esophagus. This is metaplasia.
2. Genetic mutations, which are irreversible changes in the genetic structure. It is likely that multiple mutations are necessary to give the cells the characteristics that we recognize as cancer.

Destructive injuries tend to be the mechanism of physical agents and simple chemicals such as highly ionic compounds (the coagulative heat of a laser, the hydroxyl ions of lye, the free radicals generated by radiation, and the free hydrogen ions of acid). It is very unlikely that any cell has receptors to simple ionic compounds. Cell receptors are generally complex and interact with larger

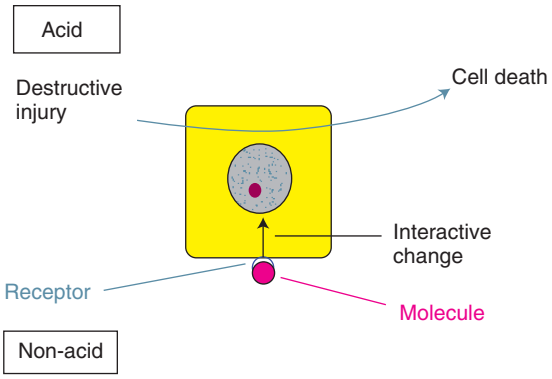


Figure 5–1 Diagram showing the two basic types of injury to cells in gastroesophageal reflux disease. In the first mechanism, the agent of injury (exemplified by acid) damages the cell directly, resulting ultimately in cell destruction. In the second mechanism, changes result from interactions between complex (non-acid) molecules in the refluxate and cell receptors.

molecules. It is therefore likely that larger molecules, such as complex nitrogenous compounds and bile salt derivatives, are responsible for interactive changes (see Figure 5–1).

Squamous Epithelial Injury

Reflux disease must begin as a cellular change in squamous epithelium because the entire esophagus is lined by squamous epithelium. Squamous epithelial damage resulting from reflux progresses in two directions. The first is an injury caused by toxic luminal molecules, mainly acid. Acid causes surface epithelial damage, resulting in increased cell loss and increased proliferation of the epithelium, recognized as basal cell hyperplasia. Acid entering the epithelium very likely causes cell damage, resulting in the release of chemokines such as interleukins. These attract neutrophils and eosinophils into the epithelium. When severe, it is characterized by erosions and ulcerations. When untreated, this may lead to perforation of the ulcers and fibrosis of the wall with strictures. Problems resulting from this severe squamous epithelial injury have declined with the availability of efficient acid suppression.

The manifestations of squamous epithelial injury represent the presently recognized criteria for the diagnosis of reflux disease. These have been described in Chapter 2 (Figures 2–2 to 2–4 and 2–17 to 2–28).

Sequence of Columnar Metaplasia of the Esophagus

The second direction of change in squamous epithelium is more chronic with interactive cellular changes that result in columnar metaplasia. Columnar metaplasia results from genetic switches in the progenitor stem cells of the esophagus (Figure 5–2). Each genetic switch produces a phenotypically different epithelial type with different clinical significance. Study of the sequence and mechanism of these interactions provides understanding of the pathogenesis of reflux-induced adenocarcinoma.

Cardiac Metaplasia of Squamous Epithelium: The First Genetic Switch

One of the important changes in squamous epithelium associated with reflux is the increase in epithelial permeability that results from the separation of tight junctions between the cells ("dilated intercellular spaces").[1] This is an acid-induced change. It permits luminal molecules to enter the epithelium and permeate downward (Figure 5–3). With increasing severity of acid-induced

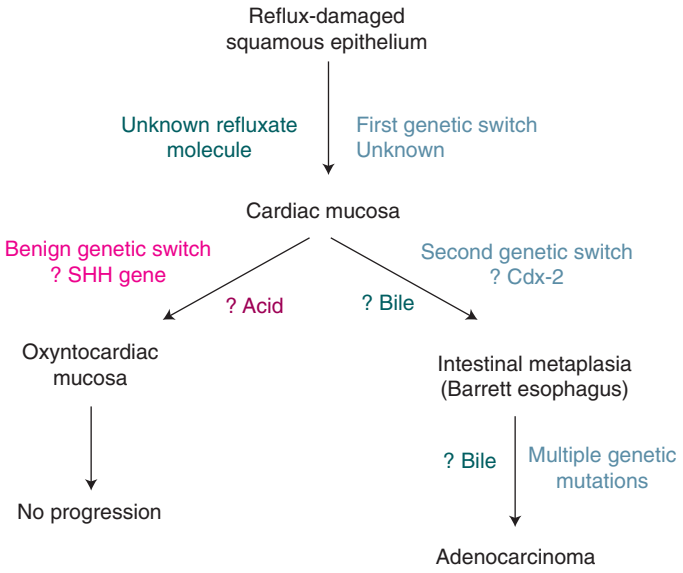


Figure 5–2 The reflux-to-adenocarcinoma sequence. This involves conversion of squamous epithelium to cardiac mucosa, conversion of cardiac mucosa to intestinal metaplasia, and finally, the occurrence of multiple carcinogenic mutations in intestinal metaplasia. The pathway where cardiac mucosa switches to oxyntocardiac mucosa is benign, because oxyntocardiac mucosa does not progress to intestinal metaplasia or cancer. The possible genes and molecules involved in each step are shown. *SHH,* Sonic hedgehog gene.

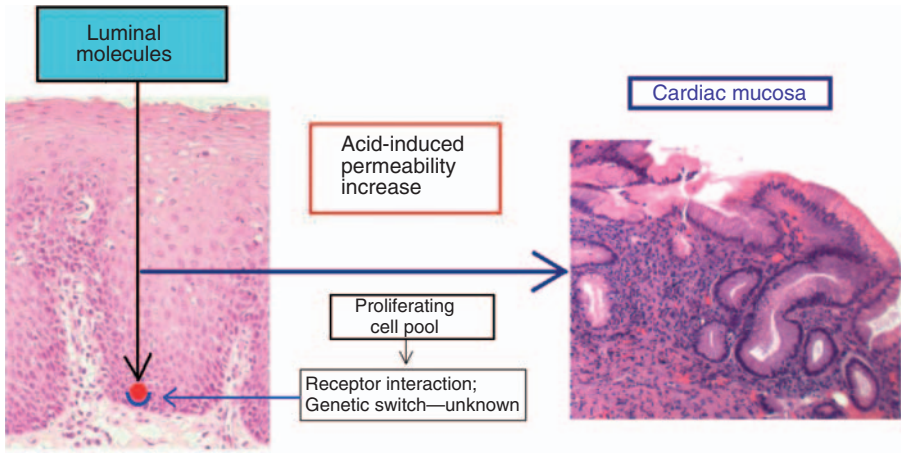


Figure 5–3 The first genetic switch, which results in the conversion of squamous epithelium to cardiac mucosa. Acid damage of the squamous epithelium leads to increased permeability. Refluxate molecules enter and filter down to encounter the proliferating stem cell pool in the suprabasal region. Interaction between cell surface receptors and complex molecules induces the genetic switch that causes the stem cell to change its differentiation from squamous to columnar.

permeability, progressively larger luminal molecules reach greater depths of the epithelium. Tobey et al[2] showed that severely acid-damaged squamous epithelium permitted molecules up to 20 kD in size to enter and permeate the full thickness of the squamous epithelium. Stimulation of nerve endings by these molecules is very likely responsible for the pain associated with reflux disease. Although acid is the most potent stimulant of pain-sensitive nerve endings, it is likely that other molecules can also induce pain in this manner. This would explain why non-acid reflux episodes can cause pain in some patients who are on acid-suppressive drugs.

The progenitor esophageal stem cells are located in the basal layer of the squamous epithelium. Normally sequestered from the lumen, these cells proliferate to continually renew the epithelium. In normal esophageal epithelium, the proliferating cell pool is limited to the basal two to three cell layers. In patients with acid-induced increased permeability of the epithelium, these proliferating cells become exposed to permeating luminal molecules. The interaction between cell receptors of proliferating cells and extrinsic refluxate molecules is essential for significant genetic changes to occur. Genetic changes produced in terminally differentiated surface cells are irrelevant, except for promoting cell death. Acid in the refluxate is the key that unlocks the esophageal squamous epithelium and exposes its normally sequestered stem cells and proliferating cells to the effect of all the luminal molecules that have been permitted access.

The first recognizable evidence of a change in the genetic control of the esophageal epithelial stem cell is a shift in the direction of differentiation from squamous to columnar. This is columnar metaplasia. Columnar transformation has been recognized as a complication of gastroesophageal reflux for some time. In 1961, Hayward[3] described the process well:

> When the normal sphincteric and valvular mechanism in the lower esophagus and oesophagi-gastric junction. . . . fails, . . . reflux from the stomach occurs and acid and pepsin reach the squamous epithelium and begin to digest it. . . . In quiet periods some healing occurs, and in these periods the destroyed squamous epithelium may re-form, often with. . . . junctional (= cardiac) epithelium, usually not very healthy-looking. . . . Further reflux therefore attacks principally the squamous epithelium higher up. In the next remission it may be replaced by more junctional (= cardiac) epithelium. . . . With repetition over a long period the metaplastic junctional (= cardiac) epithelium may creep higher and higher. . . .

When the esophageal stem cell in the base of the epithelium shifts its differentiation from squamous to columnar, the columnar daughter cell that is produced has none of the typical cell attachments that bridge it with the adjacent squamous cells immediately above (Figure 5–4). The stratified squamous epithelium changes to a single- or multi-layered columnar epithelium composed of mucous cells. This is cardiac mucosa of surface type (see Figures 3–25 and 3–26). This rapidly progresses to develop a foveolar region, seques-

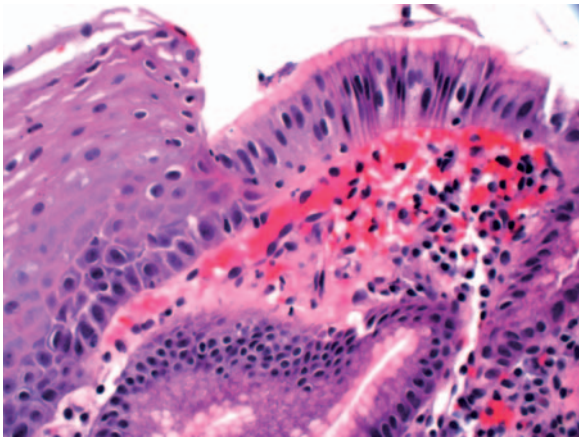


Figure 5–4 The zone of transition from squamous to the single-layered columnar epithelium. Note the line of cleavage in the suprabasal region of the squamous epithelium. This is the expected change resulting from a change in the differentiation of the stem cell to columnar. The lack of cell attachments between the new columnar cell and the superficial squamous cells leads to separation of the superficial part of the squamous epithelium.

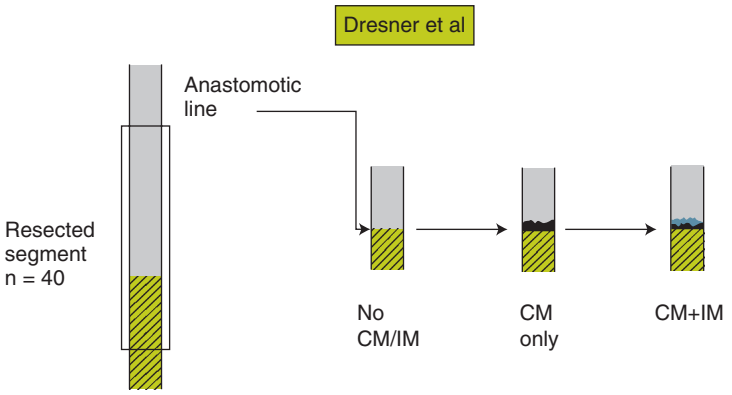
tering the esophageal epithelial stem cells in the deep part of the foveolar pit, separating them from the lumen (see Figures 3–27 and 3–28). Glands may form under the foveolar region. In the first phase of columnar metaplasia, there are no differentiated cells, and this mucosa consists only of mucous cells, falling within the definition of cardiac mucosa.

Two pieces of direct evidence support the statement that cardiac mucosa is the first epithelium to arise from squamous epithelium as a result of reflux:

1. The type of metaplastic epithelium encountered in children with reflux disease is cardiac. Intestinal metaplasia is rare in children.[4]
2. In patients who have undergone esophagogastrectomy with gastric pull-up, cardiac mucosa is the first columnar epithelium to develop in the esophagus above the anastomotic line as a result of the reflux that is very common in these patients (Figure 5–5).[5–8] In both situations, cardiac mucosa precedes the occurrence of intestinal metaplasia by many years, if not decades.

Cardiac mucosa resembles the late fetal columnar epithelium that occurs in the distal esophagus,[9] being composed of columnar mucous cells and mucosal mucous glands (fetal columnar epithelium, type III; see Chapter 3, Figures 3–1 to 3–3). Cardiac metaplasia probably results from reactivation of a genetic signal that is innate to esophageal stem cells and is expressed during fetal life. It is significant that this is the last esophageal columnar genetic signal that is suppressed during development. Earlier genetic signals responsible for ciliated (type II) and more primitive (type I) fetal columnar esophageal epithelia are rarely, if ever, reactivated in the metaplastic process that occurs in reflux disease.

Columnar transformation of the esophageal squamous epithelium to form cardiac mucosa is the result of a complex series of changes highly specific for reflux. It requires reflux-induced damage of the squamous epithelium to cause increased permeability, followed by a genetic switch resulting from an



Number of cases:	21	10	9
Time from surgery (months):	N/A	14 (3–22)	27 (11–118)

Figure 5–5 Study by Dresner et al of esophagogastrectomy patients. On follow-up, these patients sequentially develop cardiac and then intestinal metaplastic epithelium in the squamous epithelium above the anastomotic line. The likelihood of developing metaplasia is significantly related to duodenogastroesophageal reflux in these patients. *CM,* Cardiac mucosa; *IM,* intestinal metaplasia. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

interaction between an unknown and probably specific molecule in the refluxate and the esophageal progenitor cell. Although the squamous epithelial damage is not specific for reflux and can occur in other diseases such as allergic esophagitis, the actual genetic switch that causes columnar metaplasia in the squamous epithelium appears to be highly specific for reflux. It is not reproduced by any other known agent producing injury in the esophagus–not by chemicals, pills, corrosives, or infectious agents.

Although acid acts as the key that permits access to the squamous epithelium, it is likely that a molecule other than acid is responsible for the actual genetic switch that leads to columnar transformation in the esophageal progenitor cell. The exact molecule in the gastric refluxate, the progenitor cell receptor, and the genetic change that causes cardiac metaplasia in esophageal squamous epithelium are unknown.

Cardiac transformation of squamous esophageal epithelium is a cumulative change. As the number of reflux episodes increases, so too does the amount of squamous epithelium that transforms into cardiac mucosa. Cameron et al[10] reported that the length of cardiac mucosa in any given individual increases until a steady state is reached at around 20 years of age. In the vast majority of autopsy studies, the amount of cardiac mucosa is less than 0.5 cm.[11,12] The length of columnar transformation found in the esophagus in any patient at any point in time is a function of the amount of exposure to reflux, the duration of exposure, and the susceptibility of that individual to reflux-induced damage (Figure 5–6). In any individual, columnar transformation will tend to increase with age and increasing severity of reflux (Figure 5–6*D*).

There is much evidence that toxic molecules in the gastric refluxate cause damage to cardiac mucosa. Cardiac mucosa almost always shows inflamma-

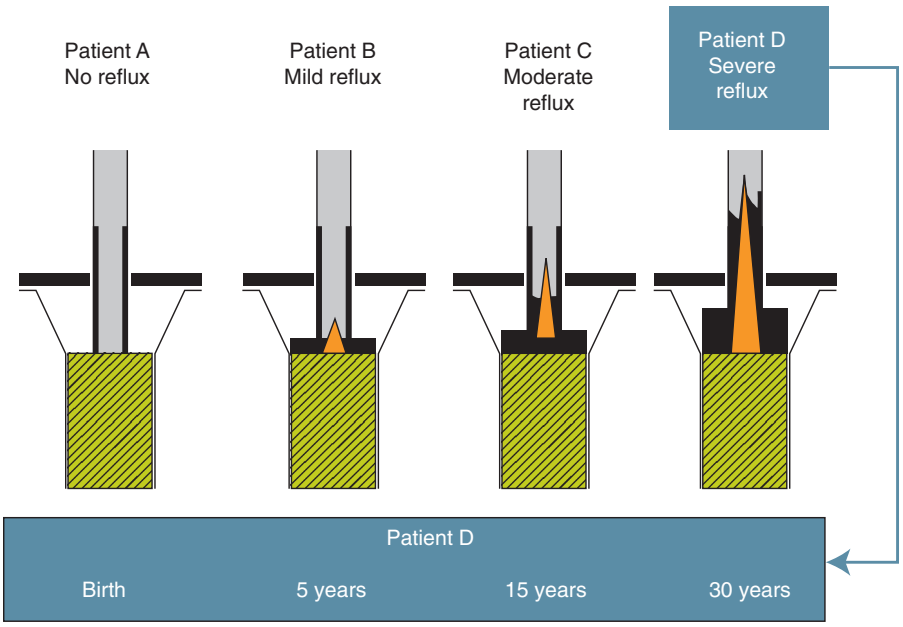


Figure 5–6 Four patients with different and constant levels of reflux are shown. **A,** Patient without reflux has only squamous epithelium *(gray)* and gastric oxyntic mucosa *(yellow).* **B,** Patient with mild reflux (column of reflux shown as an *orange triangle*) who has a short segment of metaplastic columnar epithelium *(black),* shown here to be limited to the dilated end-stage esophagus. **C,** Patient with moderate reflux, who has a longer segment of columnar-lined esophagus, extending into the tubular esophagus from the dilated end-stage esophagus. **D,** Patient with severe reflux with a long segment of columnar-lined esophagus. The bottom box shows the possible evolution of the esophageal abnormality with increasing age in the patient shown in **D,** showing a progressive worsening of the severity of reflux with age.

tion, with the number of eosinophils and plasma cells correlating with the severity of reflux. Reactive hyperplasia of the foveolar region with elongation, serration, mucin distension of the cells, and smooth muscle proliferation is almost invariably seen. We call this reflux carditis.[13]

In addition to remaining as cardiac mucosa with evidence of damage, there are three interactions that may cause cardiac mucosa to change to other phenotypically different epithelial types:

1. It can reverse to squamous epithelium (unlikely without treatment).
2. It can develop goblet cells, becoming intestinal metaplasia, which defines Barrett esophagus (uncommon, but critical).
3. It can develop parietal cells, becoming oxyntocardiac mucosa (very common) (see Figure 5–2).

These changes are the result of complex interactions between molecules in the refluxate and cardiac mucosal cells. It is very unlikely that they are acid-induced changes. Other specialized cells, such as pancreatic cells, Paneth cells, neuroendocrine cells, and chief cells, also arise in esophageal columnar epithelium. These are ignored because they have no known clinical significance.

Cardiac Mucosa to Intestinal Metaplasia: The Second Genetic Switch

The proliferating stem cells in cardiac mucosa are located in the basal region of the foveolar pit, where they multiply to renew the epithelium. Luminal refluxate molecules have relatively easy access to the progenitor cells in cardiac mucosa through the open foveolar pit (Figure 5–7). Intestinal metaplasia, characterized by the appearance of goblet cells in cardiac mucosa (see Figure 5–7), is the most important change in cardiac mucosa. This defines Barrett esophagus. This occurs in a relatively small number of patients and is a necessary precursor to progression to cancer. It is believed, and correctly

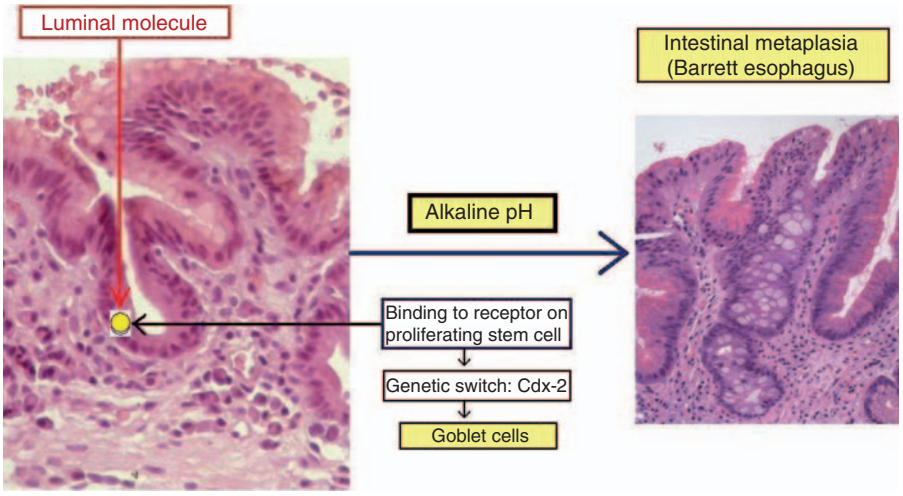


Figure 5–7 The second genetic switch whereby cardiac mucosa undergoes intestinal metaplasia. Refluxate molecules have relatively easy access to the proliferating stem cell pool in the deep region of the foveolar pit. When the appropriate receptor-molecule interaction occurs, the Cdx-2 gene is activated, resulting in intestinal metaplasia. This change appears to be promoted in an alkaline pH.

so, that the only metaplastic columnar epithelium that is susceptible to reflux-induced cancer is intestinal metaplasia.

There is strong evidence that the genetic switch that causes intestinal metaplasia in cardiac mucosa is activation of the Cdx homeobox transcription gene system, which includes Cdx-1 and Cdx-2. These genes are suppressed in normal esophagus and stomach. However, they are expressed in the normal small and large intestine and are believed to drive differentiation in these sites.[14] Cdx-1 and Cdx-2 are expressed in most cases of intestinal metaplasia of the esophagus.[15] Cdx-2 can be demonstrated by immunohistochemistry in most cases of intestinal metaplasia and some cases of cardiac mucosa in the esophagus.[16] Vallbohmer et al,[17] from our group, using a laser capture microdissection technique to measure Cdx-2 mRNA expression levels by quantitative real-time polymerase chain reaction, showed that there was a significant stepwise increase in Cdx-2 expression from squamous to cardiac to Barrett's epithelium.

Goblet cells are not expressed in the esophagus during fetal life, except in rare cases in which they occur transiently in the second trimester.[18] Induction of Cdx-2, which is the normal genetic signal directing small and large intestinal differentiation, is to be regarded as the reactivation of an aberrant columnar signal in the esophageal stem cell.

The exact molecule responsible for intestinal metaplasia in cardiac mucosa is unknown. There is a strong correlation between Barrett esophagus and an abnormal 24-hour pH test. This has been taken as evidence that acid is responsible for Barrett esophagus. Correlation of Barrett esophagus with the 24-hour pH test only means that Barrett esophagus has an association with the severity of reflux. Acid is measured in the 24-hour pH test as a marker of the severity of reflux. Every other molecule in the refluxate other than acid will be increased equally with acid in patients with an abnormal 24-hour pH test. Any one of these refluxate molecules can be responsible for Barrett esophagus.

What is more relevant is a strong correlation between Barrett esophagus and an abnormal Bilitec test.[19] This test measures esophageal exposure to bilirubin. Just as acid is a marker for gastric juice, bilirubin is a marker for duodenal contents in the refluxate and therefore indicates the presence of duodenogastric reflux. The association between Barrett esophagus and duodenogastric reflux has led some authorities to believe that compounds in bile, mainly bile acid metabolites, are the molecules responsible for intestinal metaplasia in cardiac mucosa. Bile acid metabolites have been shown to enter esophageal cells, become concentrated within the cell, and induce a variety of cellular changes in experimental models.[20]

Cardiac to Oxyntocardiac Mucosa: The Benign Genetic Switch

Oxyntocardiac mucosa is formed when cardiac mucosa develops a genetic signal that causes its progenitor cells to differentiate into parietal cells and move downward into the glands in the deeper part of the mucosa (Figure 5–8). Review of the embryology of the esophagus indicates that this event is also aberrant for the esophagus. At no point during embryogenesis does the fetal stem cell in the esophagus produce parietal cells.[9] Gastric mucosa, on the other hand, develops parietal cell-containing glands very early in fetal life. It therefore appears that oxyntocardiac transformation of cardiac mucosa represents the acquisition of an aberrant genetic signal that resembles the normal gastric genetic signal (see Figure 5–2).

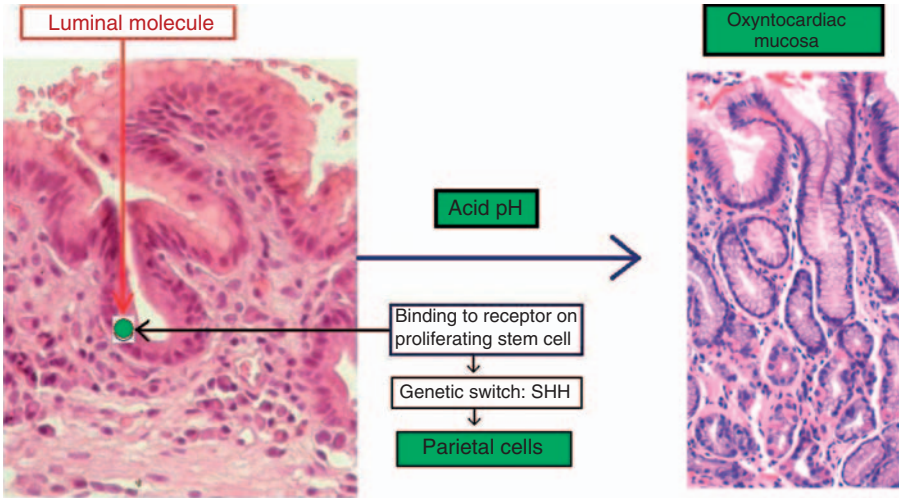


Figure 5–8 The third (and benign) genetic switch whereby cardiac mucosa converts to oxyntocardiac mucosa. Refluxate molecules interact with proliferating stem cell receptors in the deep foveolar region. The appropriate receptor-molecule interaction leads to activation of the Sonic hedgehog gene *(SHH)*, resulting in parietal cell differentiation and oxyntocardiac mucosa. This change appears to be promoted in an acidic pH.

Recent studies indicate that the Sonic hedgehog gene directs epithelia in the gastrointestinal tract to differentiate into parietal cells.[21] This gene is maximally expressed in normal adult gastric oxyntic mucosa. It is also expressed in heterotopic gastric mucosa in Meckel diverticula and has been shown to be expressed in metaplastic columnar epithelia of the esophagus that contains parietal cells (i.e., oxyntocardiac mucosa). The genetic signal acquired by cardiac mucosa that results in oxyntocardiac mucosa appears to be the Sonic hedgehog gene (see Figure 5–8).

As first reported by Paull et al[22] and confirmed by us,[23] parietal cells are almost never associated with goblet cells in the same foveolar-gland complex. What this means is that when cardiac mucosa gets the gastric-type (Sonic hedgehog) genetic signal to produce parietal cells, it precludes the simultaneous development of the genetic signal that causes intestinal metaplasia (Figure 5–9). The gastric-type genetic signal appears to block the occurrence of the intestinal-type genetic signal in the same foveolar-gland complex. As such, it is a benign epithelium. Conversion of other types of metaplastic columnar epithelium in the esophagus, such as cardiac and intestinal epithelia, to oxyntocardiac mucosa will decrease the risk of carcinoma. As such, it can be regarded as one mechanism of "histologic cure" of columnar metaplasia.

Distribution of Columnar Epithelial Types

Intestinal metaplasia develops in cardiac mucosa in a highly consistent and non-random manner. This was shown by Paull et al,[22] who mapped the distribution of the three different types of epithelia: "When present, specialized columnar-type (intestinal) epithelium was always the most proximally located, and the gastric-fundic-type (oxyntocardiac) always the most distally located columnar epithelium. Junctional-type (cardiac) epithelium, when present, was interposed between the gastric-fundic-type (oxyntocardiac) and the specialized columnar (intestinal) type or squamous epithelium."

In a more recent study,[23] we confirmed the findings of Paull et al. In a detailed mapping of goblet cells within the columnar-lined segment, we showed

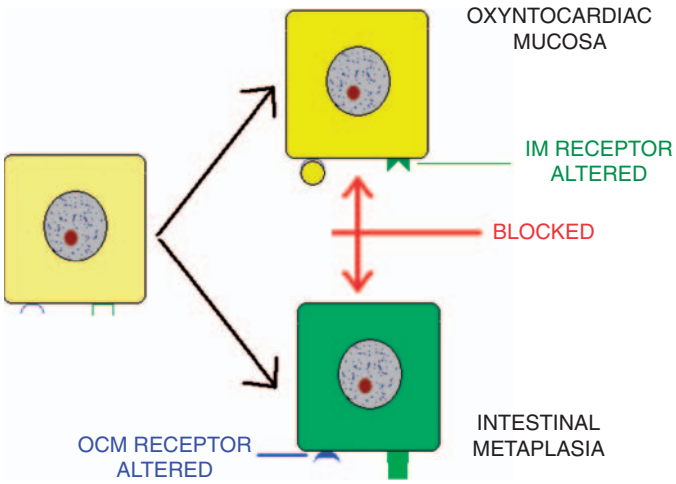


Figure 5–9 The genetic switches that result in oxyntocardiac and intestinal metaplasia appear to mutually exclude each other. In some way, activation of the receptor that causes oxyntocardiac mucosa precludes activation of the receptor that causes intestinal metaplasia. In this figure, the receptors are shown to be blocked. *IM,* Intestinal metaplasia; *OCM,* oxyntocardiac mucosa.

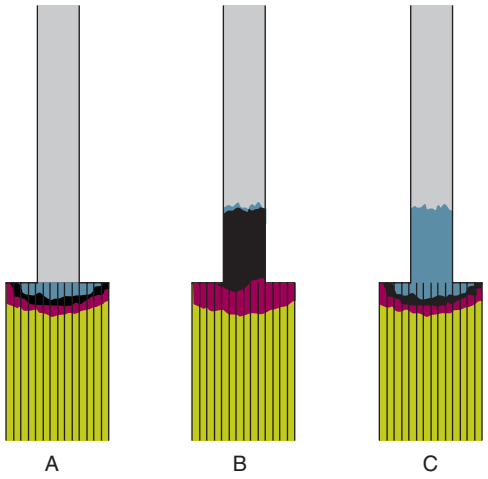


Figure 5–10 Distribution of the three types of metaplastic columnar epithelia in the esophagus. Regardless of the length of the columnar-lined segment and whether the metaplasia is in the tubular or dilated end-stage esophagus, intestinal metaplasia (when present) tends to be proximal, cardiac mucosa intermediate, and oxyntocardiac mucosa most distal. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

TABLE 5–1 Frequency of Intestinal Metaplasia in Biopsies from the Most Proximal and Most Distal Levels in 32 Patients with Columnar-Lined Esophagus Studies by Mapping Biopsies[23]

	Number of patients with IM (%)	Number of biopsies with IM (%)	Number of biopsies without IM (%)
Total	32	311/424 (73%)	113/424 (27%)
Most proximal level	32 (100)	64/68 (94%)	4/68 (6%)
Most distal level	22 (69)	40/102 (39%)	62/102 (61%)

that intestinal metaplastic epithelium occupies the most proximal segment of the columnar-lined esophagus (Figure 5–10). This was true regardless of the length of columnar-lined esophagus. It was also true when the columnar metaplastic epithelium extended into the dilated end-stage esophagus.

The distribution of intestinal metaplasia in 424 biopsies from the columnar-lined esophagus in 32 patients is shown in Table 5–1. The mean density of goblet cells in biopsies at the most proximal and most distal levels are shown in Table 5–2. These show that intestinal metaplasia favors the more proximal regions of a segment of columnar-lined esophagus.

The distribution of oxyntocardiac mucosa was the exact reverse of intestinal metaplasia; the number of parietal cells was maximal at the distal end and progressively decreased in the more proximal regions of the columnar-lined segment.

Relationship Between Prevalence of Intestinal Metaplasia and Length of Columnar-Lined Esophagus

There is an increasing prevalence of intestinal metaplasia with increasing length of columnar-lined esophagus (Figure 5–11). In a study that mapped the different epithelial types in 959 patients,[24] 100% of patients with a columnar epithelium segment of more than 5 cm had intestinal metaplasia, compared with 90% when the length was 3 to 4 cm, 70% when the length was 1 to

TABLE 5–2 Goblet Cell Density in Biopsies at Most Proximal and Most Distal Levels in 32 Patients with Columnar-Lined Esophagus Studies by Mapping Biopsies[23]

	Grade 0	Grade 1	Grade 2	Grade 3
Most proximal level	0	5	6	21
Most distal level	10	8	13	1

Grade 0, No goblet cells; *Grade 1,* less than one-third of glands contain goblet cells; *Grade 2,* one- to two-thirds of glands contain goblet cells; *Grade 3,* more than two-thirds of glands contain goblet cells.

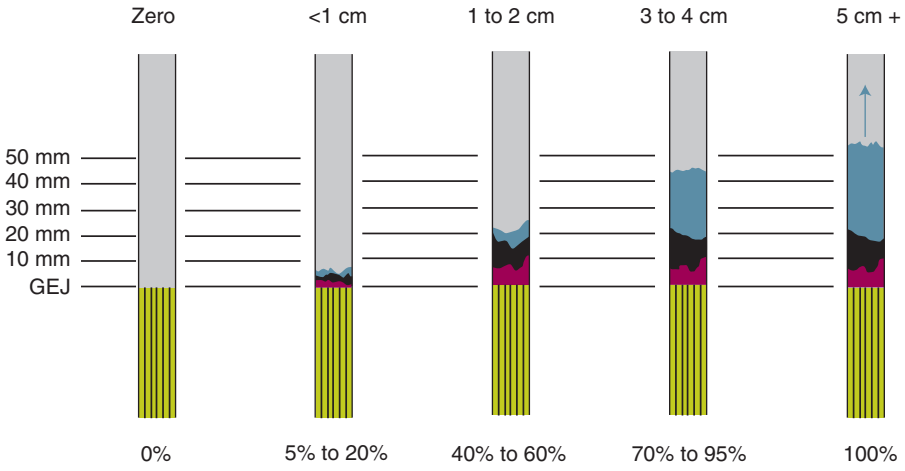


Figure 5–11 Prevalence of intestinal metaplasia in different lengths of columnar-lined esophagus, showing a progressive increase in prevalence, reaching 100% when the length of columnar-lined esophagus is 5 cm. *GEJ,* Gastroesophageal junction. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

2 cm, and 15% with a length less than 1 cm. This study consisted of patients presenting for complicated reflux disease to a foregut surgery unit. Although the overall numbers of different epithelial types are skewed toward a higher prevalence of the more severe manifestations of reflux disease, the prevalence of intestinal metaplasia at the various lengths of columnar-lined esophagus is likely to be accurate (Table 5–3).

This linear relationship between the prevalence of intestinal metaplasia and length of columnar-lined esophagus suggests that intestinal metaplasia is not a random event. In some way, the likelihood of intestinal metaplasia appears to increase the farther away the squamocolumnar junction moves from the true gastroesophageal junction. This suggests that factors causing intestinal metaplasia are most active at points increasingly more proximal in the esophagus. The fact that intestinal metaplasia occurs in all patients who have a columnar epithelial length of 5 cm suggests that the occurrence of intestinal metaplasia in cardiac mucosa is the result of a refluxate molecule found in all humans. This event appears more related to milieu (i.e., the presence of cardiac mucosa at a particular point in the esophagus) than by the presence of a specific molecule in the refluxate.

The distribution of intestinal metaplasia and oxyntocardiac mucosa within the columnar-lined segment is exactly opposite. Oxyntic mucosa favors the more distal part of the columnar-lined esophagus and is almost always present immediately above the true gastroesophageal junction at the distal limit of the dilated end-stage esophagus, where it transitions into gastric oxyntic mucosa. This suggests that the factors involved in the generation of oxyntocardiac

TABLE 5–3 Prevalence of Epithelial Types in Patients Classified According to Length of Columnar-Linded Esophagus†

Group	Definition	Significance	Number (%)
1	**Abnormal columnar epithelium 0–0.9 cm**		**811**
1a	Only oxyntic and squamous epithelia	Normal	161 (19.9)
1b	+ OCM only	Compensated reflux	158 (19.4)
1c	+ CM without IM	Mild reflux disease	372 (45.9)
1d	+ IM	Microscopic BE	120 (14.8)
2	**Abnormal columnar epithelium 1–2 cm**		**54**
2a	Only oxyntic and squamous epithelia	*	0 (0)
2b	+ OCM only	*	1 (3.8)
2c	+ CM without IM	Moderate reflux disease	15 (27.8)
2d	+ IM	BE	38 (70.4)
3	**Abnormal columnar epithelium 3–4 cm**		**38**
3a	Only oxyntic and squamous epithelia	*	0 (0)
3b	+ OCM only	*	0 (0)
3c	+ CM without IM	Severe reflux disease	4 (10.5)
3d	+ IM	BE	34 (89.5)
4	**Abnormal columnar epithelium 5+ cm**		**56**
4a	Only oxyntic and squamous epithelia	*	0 (0)
4b	+ OCM only	*	0 (0)
4c	+ CM without IM	*	0 (0)
4d	+ IM	BE	56 (100)

OCM, Oxyntocardiac mucosa; *CM,* cardiac mucosa; *IM,* intestinal metaplasia; *BE,* Barrett esophagus.
*Too rare to warrant clinical significance.
†The significance of the different categories is based on the new proposed system and is not the recent view.

mucosa from cardiac mucosa are probably related and opposite to those producing intestinal metaplasia.

Historical Differences in Epithelial Composition of Columnar-Lined Esophagus

A long segment of columnar-lined esophagus was common from the time the entity was first described. Allison and Johnstone[25] reported that 21 of 125 patients had columnar-lined esophagus, extending to the level of the aortic arch. Hayward[3] encountered columnar-lined esophagus so frequently that he felt the need to define it as abnormal only when it exceeded 2 cm. Subsequent endoscopists increased the normal amount of columnar epithelium necessary for a diagnosis of columnar-lined esophagus to 3 cm. This evidence strongly suggests that there has been no significant increase in the prevalence of columnar-lined esophagus. In fact, careful evaluation of the historical literature suggests that the very long (15 to 20 cm) segments of columnar-lined esophagus reported by Allison and Johnstone,[25] Barrett,[26] and Paull et al[22] are seen less frequently at the present time. This would be the expected effect of an increased use of more effective acid-suppressive drugs in the early symptomatic stage of reflux disease, which would decrease the amount of squamous epithelium undergoing columnar metaplasia. If true, the fact that this has not caused a decrease in reflux-induced adenocarcinoma must mean that the length of columnar-lined mucosa is not primarily related to the risk of adenocarcinoma.

Detailed descriptions of the histologic types within a columnar-lined segment of esophagus are rare in the literature. The histologic descriptions in Allison and Johnstone's 1953[25] report on columnar-lined esophagus and Barrett's 1957[26] report suggest that goblet cells were rarely seen even in patients who had columnar-lined esophagus extending to the aortic arch. Allison and

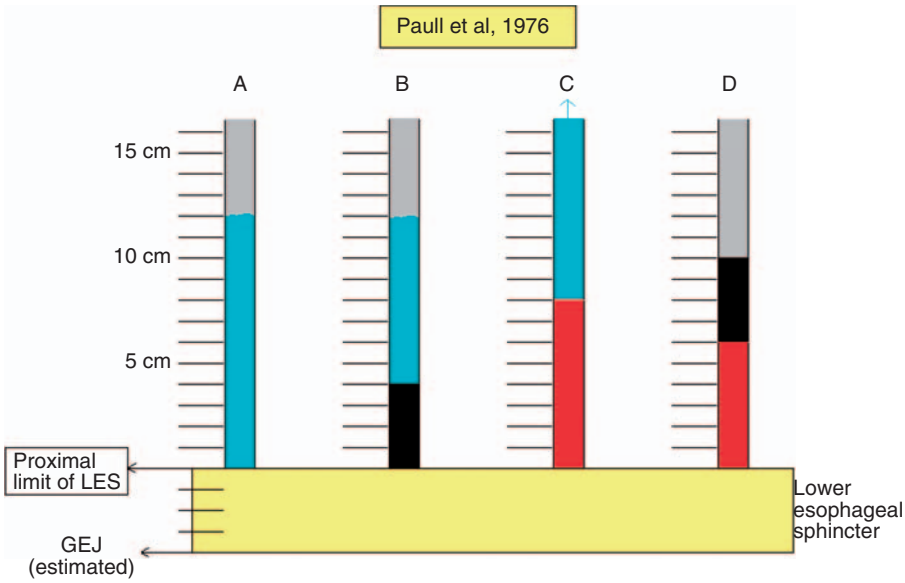


Figure 5–12 Paull et al's (1976) mapping diagrams showing the distribution of intestinal metaplasia *(blue),* cardiac mucosa *(black),* and oxyntocardiac mucosa *(red)* in four patients with long segments of columnar-lined esophagus. The authors made their measurements from the proximal limit of the manometric lower esophageal sphincter *(LES)*. The true gastroesophageal junction *(GEJ)* is 3 to 4 cm distal to this point. *Gray,* Squamous epithelium.

Johnstone[25] described one patient with goblet cells. The dominant epithelium in these early reports is cardiac mucosa with some mention of the presence of "a few parietal cells" in the distal part of the columnar-lined segment.

The only good historical example of mapping of the three epithelial types is found in the report by Paull et al,[22] which is a detailed histologic analysis of 11 patients with long segments of columnar-lined esophagus. The researchers used the manometrically defined proximal end of the lower esophageal sphincter as the primary landmark to define the biopsies as esophageal. Although intestinal metaplastic epithelium (specialized columnar epithelium) was the most prevalent epithelial type, the following data are significant:

Of the 11 patients, two had no intestinal metaplasia, and two had intestinal metaplasia in only one biopsy. Unfortunately, the lengths of columnar-lined esophagus in these patients are not stated. Substantial amounts of oxyntocardiac mucosa were seen fairly high in the body of the esophagus. In the two patients without intestinal metaplasia, oxyntocardiac (gastric-fundic-type) mucosa extended at least 3 and 6 cm above the lower esophageal sphincter. The proximal limit of the lower esophageal sphincter is approximately 4 cm above the true gastroesophageal junction, making these extremely long segments of columnar-lined esophagus.

Paull et al[22] illustrate detailed histologic maps in four patients (Figure 5–12). One patient has a 10-cm length of columnar-lined epithelium above the proximal limit of the sphincter (total length around 13 to 15 cm) and no intestinal metaplasia. In the patients in this study, the intestinal metaplasia appears to spare the more distal part of the esophagus. In only one of four patients did intestinal metaplasia reach the proximal limit of the sphincter. In two patients, oxyntocardiac mucosa was found at a point greater than 5 cm above the proximal limit of the sphincter (see Figure 5–12).

The extent of intestinal metaplasia in the 1953 to 1976 period appears to be different than what is seen at the present time. In our study of the distribution of histologic epithelial types in 32 patients with endoscopically visible

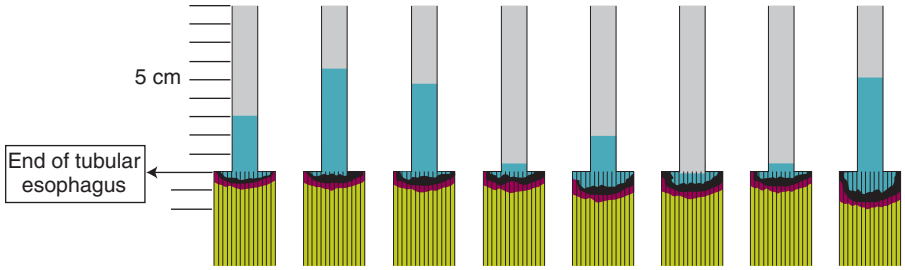


Figure 5–13 Chandrasoma et al's (2006) mapping diagrams of the distribution of the three epithelial types. Note that the entire segment of columnar metaplastic epithelium, including the dilated end-stage esophagus, is shown. *Blue,* intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

columnar-lined esophagus,[23] intestinal metaplasia was present in 64 of 68 biopsies from the most proximal level in all 32 patients. Intestinal metaplasia was present in 40 of 102 biopsies at the most distal level in 22 of 32 patients (see Table 5–1). It should be noted that "the most distal level" in our study is the end of the histologically defined columnar-lined esophagus, which is 3 to 4 cm more distal than that presented in the study by Paull et al,[22] which uses the top of the lower esophageal sphincter as the distal limit. In contrast, oxyntocardiac mucosa was absent at the proximal level in all 68 biopsies; it was present in the most distal level in 16 of 32 patients and in the retrograde (unmeasured) biopsy in another three patients. In a recent study of 10 esophagectomy specimens, we showed that intestinal metaplasia involved the entire columnar-lined segment in the tubular esophagus and extended below the level of the end of the tubular esophagus in all eight of the patients with Barrett esophagus[27] (Figure 5–13).

The data comparing the 1976[22] and 2006[27] studies suggest that there is a much greater dominance of intestinal metaplasia over oxyntocardiac mucosa in the columnar-lined esophagus in today's patient compared with that shown in the study by Paull et al (see Figures 5–12 and 5–13).

One possible cause for the increasing incidence of adenocarcinoma is that there has been a shift in the direction of cardiac mucosal transformation from oxyntocardiac mucosa to intestinal metaplasia, while the length of columnar-lined esophagus has remained constant or actually decreased. This change will remain undetected by all tests other than careful mapping biopsies and correct histologic classification of the columnar-lined segment of esophagus. Despite the evidence, few researchers recognize that the columnar epithelium in Barrett esophagus is a mixture of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa.

Mechanism of the Genetic Switches in Columnar-Lined Esophagus

A genetic change must be caused by the interaction of a refluxate molecule with an appropriate target cell receptor. The target cell is always the progenitor stem cell in the esophageal epithelium. The first genetic change involves this cell when it is in the basal region of the stratified squamous epithelium. The result of this change is a conversion of the esophageal epithelium from squamous to cardiac (see Figures 5–3 and 5–4). There is no evidence for any genetic switch in the squamous epithelium that directly results in oxyntocardiac mucosa or intestinal metaplasia. These two specialized columnar epithelial types develop from cardiac mucosa (see Figures 5–7 and 5–8), not from squa-

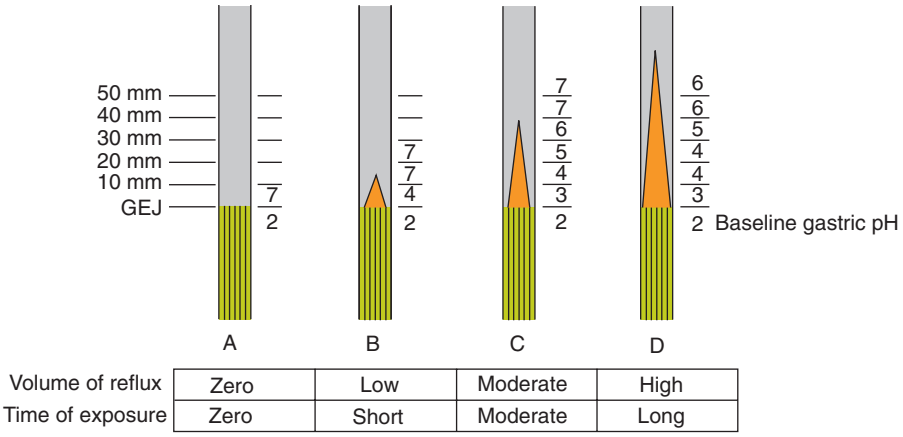


Figure 5–14 Influence of severity of reflux (shown by an *orange triangle*) on the esophageal pH. In a patient with no reflux, there is a sharp pH drop from esophageal neutrality to gastric acidity at the gastroesophageal junction *(GEJ)*. With increasing reflux volume, acid exposure extends over a larger part of the distal esophagus, the exposure time of the cell to refluxate molecules increases, and a pH gradient of increasing length is established in the distal esophagus.

mous epithelium. This is important; the fact that there is an epithelium that precedes Barrett esophagus, often by decades, gives us the opportunity to attack this epithelium and prevent the occurrence of Barrett esophagus. Before this is done, we need to understand the molecular basis of this change.

Two factors are essential to produce a genetic change in the stem cell:

1. The appropriate refluxate molecule must come into contact with the appropriate target cell receptor.
2. There must be sufficient time for the interaction to occur.

Both these factors are related to the severity of gastroesophageal reflux. In patients who have infrequent, small-volume reflux episodes, the exposure of the esophagus is limited to its most distal few millimeters. If cleared rapidly, the cell's exposure time to refluxate molecules is short. With increasing severity and volume of reflux, the refluxate is propelled farther up the esophagus, and the time taken to clear the refluxate increases, thereby increasing the exposure time of the target cell (see Figure 5–6; Figure 5–14).

Gastroesophageal reflux inevitably alters the pH of the distal esophagus (see Figure 5–14). In people who have a competent lower esophageal sphincter and no reflux, there is a sudden pH change from neutral (pH 7) in the distal esophagus to the acid (pH 1–3) milieu of the stomach (see Figure 5–14*A*). When reflux occurs, there is a progressive widening of this pH gradient. The greater the severity and volume of the reflux, the more severe the acid exposure at increasingly more proximal points in the esophagus (see Figure 5–14*B–D*). This factor is responsible for the initial squamous epithelial damage and its conversion to cardiac mucosa and explains why the length of cardiac metaplasia of the esophagus correlates with the severity of reflux (see Figure 5–6).

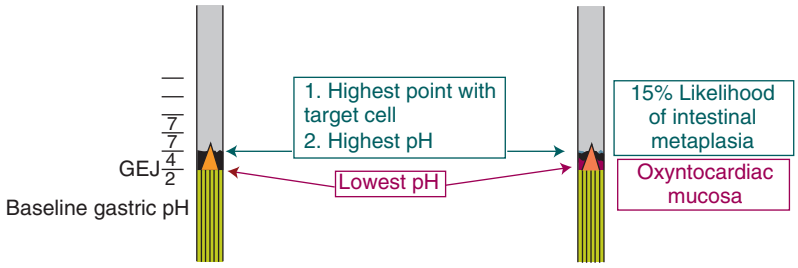
The genetic switches that occur in cardiac mucosa to produce intestinal and oxyntocardiac mucosa appear to be the result of opposing factors. Intestinal metaplasia occurs in a relatively small number of patients with columnar-lined esophagus and favors the more proximal part of the esophagus. This is proof that intestinal metaplasia in cardiac mucosa is not induced by acid; the more proximal region is the site of least acidity in the esophagus. The likelihood of intestinal metaplasia rises with increasing length of cardiac mucosa

and becomes invariable (at the present time) when the cardiac mucosal length reaches 5 cm. This is in contrast to oxyntocardiac mucosa, which is an almost invariable change that occurs in the most distal part of the metaplastic segment.

There are two reasons why intestinal metaplasia may be favored at a more proximal level of the esophagus:

1. Pulse or intermittent exposure to refluxate molecules, such as acid and bile, is more damaging to metaplastic columnar cells than continuous exposure. It is likely that for a given amount of reflux, the more proximal region has a greater pulse exposure, resulting in greater damage and increased likelihood of intestinal metaplasia. This mechanism, however, cannot explain the historical change in the prevalence and distribution of intestinal metaplasia within the columnar-lined segment.
2. The more likely explanation of why intestinal metaplasia is favored proximally is that a higher pH environment promotes it.

Let us consider a patient with mild reflux disease who has generated a length of cardiac metaplasia measuring 1 cm (see Figure 5–6*B;* Figure 5–15). This patient has infrequent episodes of small-volume reflux that exposes cardiac mucosa to the refluxate for a short time. The pH gradient created in the esophagus goes from gastric baseline at the junction, to esophageal neutrality over a relatively short distance (see Figure 5–14*B*). The cardiac mucosa is exposed to the least acidic pH at the most proximal level but only for a very short time, decreasing the likelihood of intestinal metaplasia. If the exposure is sufficient to result in the intestinal metaplasia genetic switch, it will be limited to the most proximal region (see Figure 5–15). The most distal region is exposed to a more acidic pH, which promotes conversion of cardiac mucosa to oxyntocardiac mucosa. This patient will demonstrate the typical distribution of epithelial types associated with a 1-cm length of columnar-lined esophagus with oxyntocardiac mucosa in the most distal region and cardiac mucosa in the most proximal region. There is a 15% probability of intestinal metaplasia in this patient, which is usually limited to the most proximal region of this segment.



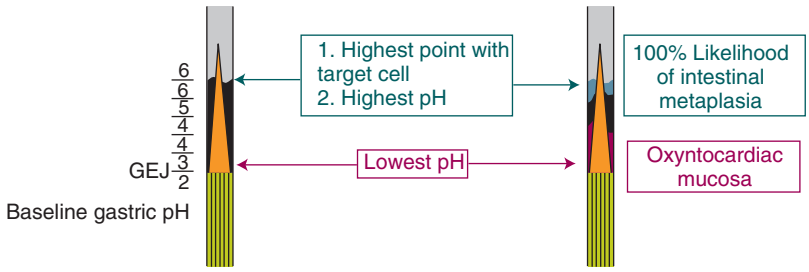
Volume of reflux	Low
Time of exposure	Short
Length of cardiac mucosa	1 cm

Figure 5–15 Factors influencing epithelial changes in the esophagus in a patient with mild reflux that has caused a short (1 cm) segment of cardiac metaplasia. The pH gradient is such that the distal part of the segment is acid, tending to convert cardiac mucosa to oxyntocardiac mucosa. The pH is highest in the most proximal region. With a 1-cm length of cardiac mucosa, there is an approximately 15% probability that the higher pH exposure of the target cell is sufficient to induce intestinal metaplasia. If it happens, intestinal metaplasia will favor the most proximal region. *GEJ,* Gastroesophageal junction. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

A patient with less severe reflux will have a shorter length of cardiac mucosa, a shorter duration of exposure, and early reflux disease that is very likely limited to a short area of dilated end-stage esophagus. This part of the dilated esophagus is continuously exposed to gastric juice. In a patient with normal gastric pH, this predominantly acid exposure in the distal segment appears to favor all the cardiac mucosa being converted to oxyntocardiac mucosa, and the likelihood of intestinal metaplasia is very small. If, however, the baseline gastric pH is more alkaline due to the use of acid-suppressive drugs, this area is continuously exposed to the alkaline gastric baseline pH. This sets the stage for intestinal metaplasia occurring in this dilated end-stage esophagus.

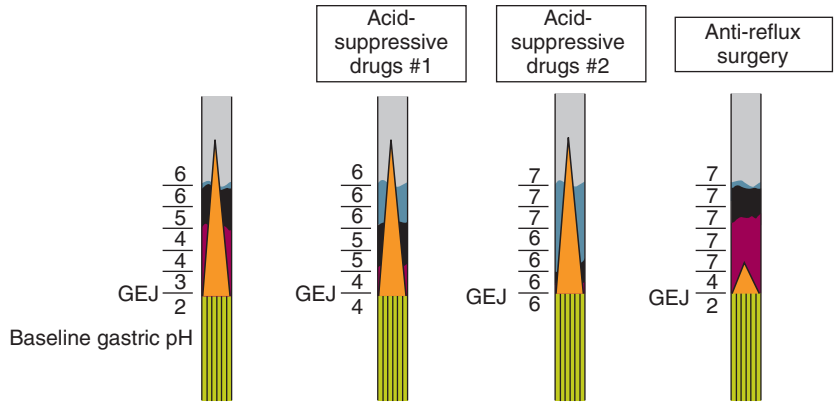
In contrast, a patient with more severe reflux will have a longer segment of cardiac metaplasia in the esophagus (e.g., 5 cm; see Figure 5–6*D;* Figure 5–16). High-volume reflux episodes will expose the entire segment of cardiac metaplasia for a longer duration. The pH gradient is also more spread out in the esophagus, with the region with the highest pH being most proximal. This patient has a 100% prevalence of intestinal metaplasia. This occurs in the most proximal segment, which has correct combination of factors for the intestinal metaplasia switch. The correct target cell (cardiac mucosal stem cell) is exposed to the refluxate molecule at the correct pH (alkaline) for a sufficient length of time.

Acid suppression on this model of genetic switches causes the most distal pH to change from baseline gastric acid pH of 1 to 3 to the acid-suppressed pH of between 4 to 6 or higher (Figure 5–17). As acid suppression increases its effectiveness, the mean baseline gastric pH becomes higher. An equal volume of reflux in such a patient will lead to exposure of increasing lengths of cardiac metaplasia in the esophagus to the correct less acidic pH required for the conversion of cardiac mucosa to intestinal metaplasia. This will result in intestinal metaplasia involving a greater extent of the columnar-lined segment, which always favors the more proximal region but extends progressively more distally in the esophagus (Figures 5–17 and 5–18). This perfectly explains the historical difference in the amount of intestinal metaplasia observed in the study by Paull et al study in 1976 and our study in 2005.



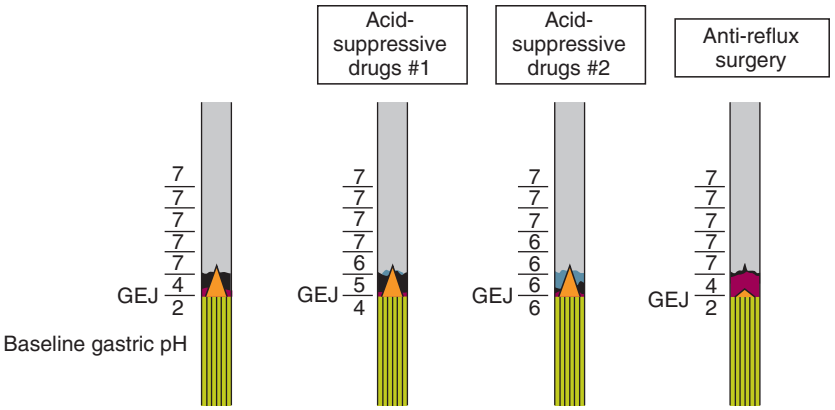
Volume of reflux	High
Time of exposure	Long
Length of cardiac mucosa	5 cm

Figure 5–16 Factors influencing epithelial changes in the esophagus in a patient with severe reflux, which has generated a long segment of columnar-lined esophagus. With high-volume reflux, the time available for receptor-molecule interactions is greater, and the extent of higher pH in the proximal region of a longer segment of cardiac mucosa is greater. This results in a greater likelihood of intestinal metaplasia, which still favors the most proximal region of the esophagus. When the length of columnar-lined esophagus reaches 5 cm, intestinal metaplasia invariably occurs. *GEJ,* Gastroesophageal junction. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.



Volume of reflux	High	Remains high	Remains high	Decreased
Time of exposure	Long	Remains high	Remains high	Decreased
Amount of IM	Small	Increased	More increased	Same or less
Amount of OCM	Moderate	Less	Still less	Increased

Figure 5–17 Influence of acid-suppressive drug therapy and anti-reflux surgery on epithelial changes in columnar-lined esophagus. This shows a patient with severe reflux, a long segment of columnar-lined esophagus with intestinal metaplasia *(IM)* limited to the most proximal region. When this patient is treated with increasingly effective acid-suppressive drugs, the reflux volume remains the same, but the acidity in the esophagus progressively decreases. This promotes intestinal metaplasia to reach more distal regions of the columnar-lined segment because the required higher pH exists much lower as the gastric baseline pH increases. With anti-reflux surgery, the volume of refluxate decreases, and the pH gradient reverts toward normal. The upper region is no longer exposed to refluxate molecules and remains stable. The lower region tends to become a more acid milieu, and because of that, cardiac mucosa tends to convert to oxyntocardiac mucosa. *GEJ,* Gastroesophageal junction; *OCM,* oxyntocardiac mucosa. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.



Volume of reflux	Low	Unchanged	Unchanged	Decreased
Time of exposure	Short	Unchanged	Unchanged	Decreased
Amount of IM	Zero	Low	Increased	Zero
Amount of OCM	Moderate	Less	Still less	Increased

Figure 5–18 Influence of acid-suppressive drug therapy and anti-reflux surgery on epithelial changes in columnar-lined esophagus in a patient with mild reflux, a short segment of columnar-lined esophagus with intestinal metaplasia *(IM)* limited to the most proximal region. The changes are identical to those seen in the patient with severe reflux. *GEJ,* Gastroesophageal junction; *OCM,* oxyntocardiac mucosa. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

TABLE 5–4 Tharalson et al's[28] Study Data with Four Sensors Placed at Four Levels in the Columnar-Lined Segment*

Sensor height (cm)	Total study time	Upright position	Supine position
1	**26.4** (+/–14.6)%	**24.2** (+/–11.4)%	**39.8** (+/–25.5)%
6	**23.2** (+/–15.8)%	**21.4** (+/–15.8)%	**25.8** (+/–20.8)%
11	**12.6** (+/–8.0)%	**10.2** (+/–8.0)%	**15.8** (+/–13.2)%
16	**6.7** (+/–6.9)%	**5.3** (+/–4.5)%	**8.4** (+/–12.0%)

*The data are expressed as the percentage of time that the pH was under 4 during the 24-hour test at each sensor height (expressed as centimeters above the lower esophageal sphincter.) The acid exposure for the total period and in the upright and supine positions are given.

By the same reasoning, the decreased acid milieu of the distal esophagus in the acid-suppressed patient would tend to decrease the conversion of cardiac mucosa to oxyntocardiac mucosa in the distal esophagus (see Figures 5–17 and 5–18). This is exactly as observed.

There is direct evidence for such a relationship between acid exposure along the esophagus and the occurrence of intestinal metaplasia. Tharalson et al[28] studied 17 patients with varying lengths of Barrett esophagus with 24-hour esophageal pH monitoring, using a pH probe with four sensors located 5 cm apart. Barrett esophagus was defined as the presence of intestinal metaplasia on biopsy. Barrett's length was measured from the proximal margin of continuous Barrett's epithelium to the end of the tubular esophagus or the proximal margin of hiatal hernia folds. It should be noted how, even with highly experienced investigators like those in this group, Barrett esophagus is diagnosed when any biopsy shows intestinal metaplasia and the entire length of endoscopic columnar-lined esophagus becomes "Barrett's length," despite absence of any statement regarding the presence of intestinal metaplasia in the entire extent. If histologic mapping is done as in the study by Paull et al, a variable amount of the "Barrett length" will be found to consist of non-intestinalized cardiac mucosa.

A reflux episode was defined as a decrease in pH less than 4 and reflux time as the interval until the pH is more than 4. The data were reported for each of the four sensors as the percentage of time that the pH was under 4 during the 24-hour test. The values for mean acid exposure, expressed as mean percent time pH less than 4 (+ or – one standard deviation) at each sensor height (expressed as centimeters above the lower esophageal sphincter), are shown in Table 5–4.

The authors use a complicated mathematical calculation to show that there was a statistically significant relationship between the rate of change in acid exposure and the length of Barrett esophagus.

The data in the study are more interesting than the conclusion. They show that the acid exposure (and, potentially, exposure to all other molecules in the refluxate that accompanies the acid) progressively decreases from the distal to the proximal esophagus in patients with reflux. The severity of reflux determines the length of columnar-lined esophagus. The constant zonation of epithelial types within this columnar-lined segment has intestinal metaplasia occurring at the most proximal part of the segment. This indicates that factors that promote intestinal metaplasia are most active in the proximal region. Because all the molecular components are either equal to or lower in concentration in the proximal esophagus compared with the distal esophagus, it becomes very likely that the intestinal metaplasia results from a factor other than just the presence of a molecule. If a molecule in the refluxate was solely responsible for the development of intestinal metaplasia in cardiac mucosa, this would tend to be maximal in the distal esophagus, which is the region of highest concentration.

Multiple-level pH electrodes have shown that the pH tends to progressively increase more proximally in the esophagus in patients with columnar-lined esophagus. This suggests that intestinal metaplasia of cardiac mucosa is a pH-dependent phenomenon, with higher pH promoting intestinal metaplasia. Similarly, it suggests that a lower pH stimulates parietal cell differentiation in cardiac mucosa because oxyntocardiac mucosa occurs in the most distal region of the columnar-lined esophagus (see Figures 5–17 and 5–18). We again reach the rather frightening conclusion that increasing the pH of the gastric refluxate may promote intestinal metaplasia over oxyntocardiac transformation in cardiac mucosa.

CASE STUDY

(Contributed by Daniel Oh, MD, Department of Foregut Surgery, USC)

The patient was a 30-year-old male at the time of his first presentation at USC in 1995. He complained of worsening dysphagia with solids and recently also with liquids. He denied any symptoms of reflux disease such as heartburn or regurgitation. He had not experienced any weight loss (body mass index [BMI] was 25).

The patient was told by his mother that he had a problem with vomiting and an inability to eat since infancy. This required parenteral nutrition and dilatations. He did not start eating solid food until age 4. He then experienced stable symptoms from age 8 to his middle 20s, during which time he experienced solid food dysphagia once a month. However, his dysphagia began to increase in frequency to once a day, including episodes of food impaction. He was dilated at this time, and his symptoms improved. He required three subsequent dilatations in the next 5 years for his dysphagia.

Barium swallow at this time showed abnormal liquid bolus transit in five of five swallows, with incomplete propagation of peristalsis and stasis of bolus within the body of the esophagus. There was markedly decreased peristalsis in the distal half of the esophagus with a long segment of narrowing of the distal esophagus 10 cm long, 7 cm above the hiatus (fixed deformity). There was no hernia, and the gastroesophageal junction opened normally.

Upper endoscopy was attempted, but the adult endoscope (9-mm diameter) would not pass the narrowing in the distal esophagus. A pediatric endoscope was then used and could be passed into the stomach. At the gastroesophageal junction, short tongues (1.5 cm) of columnar mucosa were seen (Figure 5–19). Biopsies confirmed the diagnosis of Barrett esophagus limited to biopsies of the most proximal level of columnar-lined esophagus adjacent to the squamocolumnar junction (Figure 5–20). Biopsies at more distal levels showed cardiac mucosa without intestinal metaplasia (Figure 5–21).

Manometric evaluation showed a structurally intact lower esophageal sphincter (total length 3.9, abdominal length 2.8 cm, resting pressure 14.4 mm Hg). The relaxation study showed complete relaxation, but there was abnormal peristalsis in the distal body of the esophagus. The mean contraction amplitudes in the body were: level I: 24 mm Hg, level II: 33 mm Hg, level III: 9 mm Hg, level IV: 40 mm Hg (normal 30 to 180 mm Hg). The peristaltic waves were interrupted from level II to III in 90% of the swallows, with resumption of the wave proximal to the lower esophageal sphincter. This area corresponded to the narrowing seen on barium swallow and endoscopy. The 24-hour pH monitoring was within limits of normal at this time (26 episodes, 2% total time pH <4, DeMeester score 5–7).

In 1995, his main problem was dysphagia due to his congenital esophageal hypoplasia. This esophageal narrowing had two components: fibrous mechanical stenosis and ineffective motility through the abnormal segment.

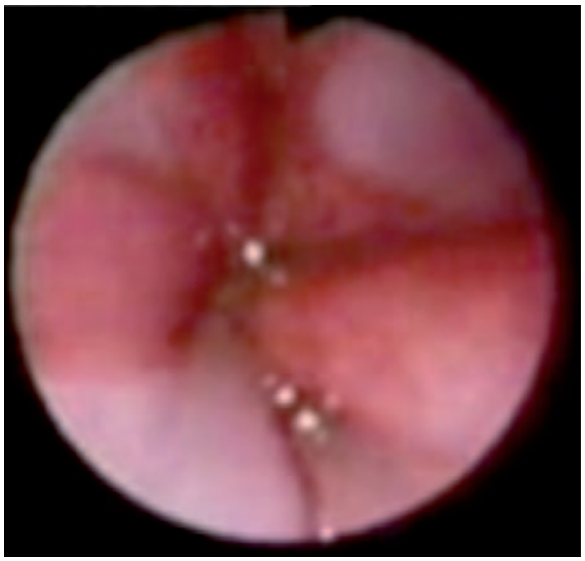


Figure 5–19 Case study patient. Endoscopy in 1995 at age 30 showing short (measured at 1.5 cm) tongues of columnar-lined esophagus in the distal tubular esophagus.

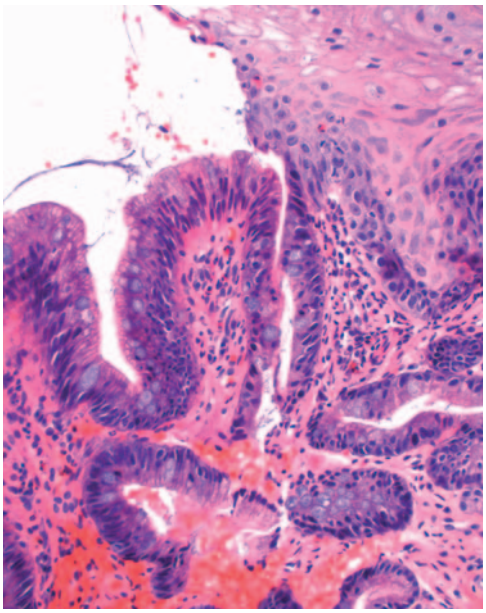


Figure 5–20 Case study patient. Biopsy from the squamocolumnar junction at the high point of one of the tongues of columnar-lined esophagus. The squamous epithelium shows basal cell hyperplasia and intraepithelial eosinophils indicative of reflux. This transitions into cardiac mucosa with intestinal metaplasia, characterized by the presence of goblet cells.

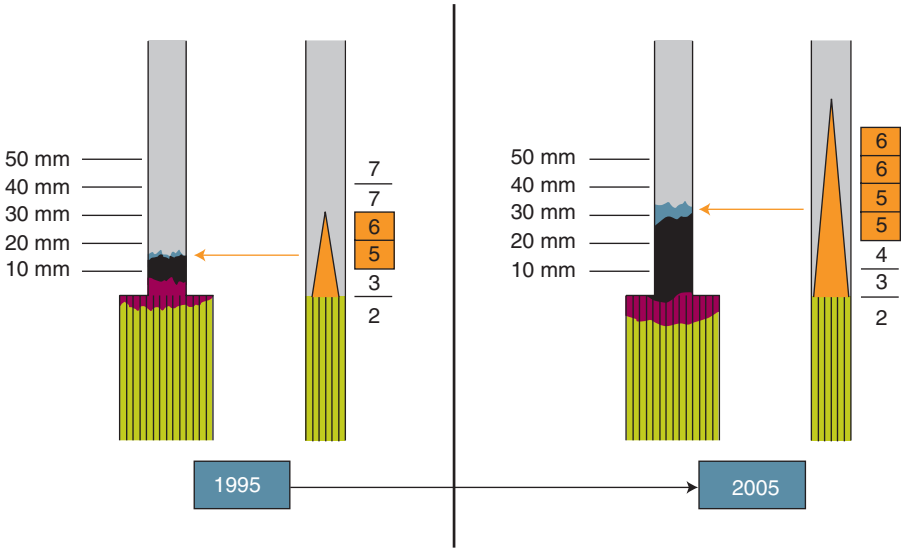


Figure 5–21 Case study patient. Diagrammatic representation of the endoscopic and biopsy features in the patient in 1995 and 2005. Also shown is a representation of the severity of reflux and the pH gradient in the esophagus based on the severity of reflux. The relationship of the location of the intestinal metaplasia to weak acid pH (5 to 6 range, highlighted in orange) is striking. In 2005 *(right),* the point at which intestinal metaplasia was found in 1995 now contains cardiac mucosa, very likely due to the fact that the milieu at that point is more acidic. The intestinal metaplasia at this point has reversed to cardiac mucosa. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

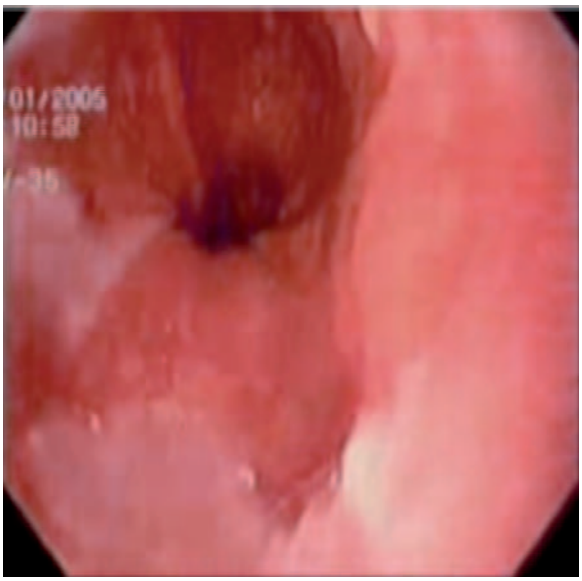


Figure 5–22 Case study patient. Endoscopy in 2005 showing a longer (measured at 3.5 cm) segment of columnar-lined esophagus.

The patient elected to continue dilatation as needed for his dysphagia, which was performed intermittently for the next 10 years.

In 2005, now at age 40 years, the patient returned to USC with new symptoms of heartburn, nocturnal regurgitation, and coughing. Barium swallow again showed failure in five of five liquid swallows with peristaltic wave failure in the esophagus and marked stasis that cleared only with repeated dry swallows. There was a tapered narrowing in the distal esophagus 3 cm below the carina, 8 cm long, and 1.2 cm wide. Hamburger swallows were abnormal with slow transit (delay) through the narrowed region. No hiatal hernia or reflux were seen in the radiologic study.

Endoscopy now showed a columnar-lined segment from 33 cm to the gastroesophageal junction at 36 cm (Figure 5–22); biopsies along the 3.5 cm segment showed intestinal metaplasia only at the top, with the more distal biopsies showing only cardiac and oxyntocardiac mucosa (see Figure 5–21). The crura were at 38 cm (indicating a 2-cm hiatal hernia). On retroflexion he had a Hill grade III gastroesophageal flap valve.

Manometry revealed deterioration of the lower esophageal sphincter over the past decade (overall length 1.2 cm, abdominal length 0.6 cm, resting pressure 8.0 mm Hg). Lower esophageal sphincter relaxation was normal. The body was again abnormal with loss of the peristaltic wave in the distal esophagus and resumption near the lower esophageal sphincter. The 24-hour pH monitoring at this time showed markedly abnormal acid exposure (143 episodes, 23% total time pH <4, and DeMeester composite score of 72).

This patient had a congenital hypoplastic distal esophagus that required repeated dilatations over his lifetime. At age 30, he was without reflux symptoms but was noted to have short tongues of Barrett esophagus. By age 40, the patient's lower esophageal sphincter function had deteriorated significantly. With the increased severity of reflux, he began to experience classic symptoms of reflux disease. His columnar-lined esophageal segment had increased in length to 3 cm, and there was now a hiatal hernia.

Of considerable interest is the fact that his intestinal metaplasia in 2005 was limited to the most proximal biopsy level. Biopsies that were taken more distally showed cardiac mucosa without intestinal metaplasia. This would

TABLE 5–5 Genetic Switches Responsible for Different Directions of Epithelial Differentiation in the Esophagus*

Genetic switch	Caused by	Genetic factors	Effect of acid-suppressive drugs	Effect of anti-reflux surgery
Squamous to cardiac	Acid (?)	Unknown	Prevention; reversal (?)	Prevention; reversal (?)
Cardiac to oxyntocardiac	Acid (?)	Sonic hedgehog gene	Prevention	Promotion
Cardiac to intestinal	Alkalinity	Cdx-2	Promotion (?); reversal (?)	Prevention; reversal

*These are all caused by factors in the refluxate. Changes in the quality of the refluxate resulting from acid-suppressive drugs and the quantity of reflux resulting from successful anti-reflux surgery have different effects on these switches.

indicate that the intestinal metaplasia at the proximal limit of the columnar-lined esophagus in 1995 (i.e., about 2 cm distal to the proximal limit of the present columnar-lined segment) had reversed to cardiac mucosa. Instead, intestinal metaplasia was now seen 2 cm more proximally.

The likely explanation for this sequence of changes is the change in the pH gradient resulting from the change in the severity of reflux during these two examinations (see Figure 5–21). The relatively mild reflux in 1995 caused 1.5 cm of columnar metaplasia in the esophagus. The pH gradient associated with the mild reflux resulted in sufficient alkalinity (shown in Figure 5–21 as a pH of 5 to 6, *orange shaded area*) in the more distal esophagus to produce intestinal metaplasia. As reflux increased over the next 10 years, the amount of columnar metaplasia also increased in length. The pH gradient shift moved the 5 to 6 range pH to the more proximal esophagus. The zone of previous intestinal metaplasia was now exposed to a more acid milieu and reverted to cardiac mucosa and oxyntocardiac mucosa. The correct weak acid milieu to cause intestinal metaplasia in cardiac mucosa was more proximal (see Fig. 5–21, *arrow,* pH 5 to 6).

This patient's case was presented at the USC Foregut Conference held in Hawaii in February 2006. At this time, it was noted that the patient had been recently placed on acid-suppressive drugs to control his reflux symptoms. This was the first time in his life he had taken acid-suppressive drugs. The treatment was expected to control his symptoms but would increase the risk of extension of his intestinal metaplasia as the pH 5 to 6 milieu extended distally with the increased gastric baseline pH induced by acid suppression. This would also increasingly bring the intestinal epithelium into closer proximity to carcinogens in the gastric juice, thereby increasing his risk for cancer.

Reversibility of Genetic Switches

We have discussed three genetic switches that are responsible for the array of metaplasia that converts squamous epithelium to the different types of columnar epithelia (Table 5–5).

Genetic switches result from expression and suppression of normal genetic pathways in the cell as a result of cell surface interactions. They are reversible; removing or altering the surface interactions can drive these differentiation pathways in different directions. If this is true, intestinal metaplasia can revert back to cardiac mucosa if the Cdx gene activation is reversed. Cardiac mucosa can revert to squamous epithelium if it loses the first columnar genetic switch or can become oxyntocardiac mucosa if it can be made to acquire the

"gastric-type genetic signal" associated with the Sonic hedgehog gene. The ability to manipulate the columnar epithelia in the esophagus to move it away from intestinal metaplasia and toward squamous and oxyntocardiac mucosa is equivalent to preventing adenocarcinoma.

The best method of manipulating these genetic shifts in columnar-lined esophagus is to characterize the nature of the interactions that cause the genetic changes and neutralize them. Until these specific interactions are characterized, however, the only logical method of achieving reversal is to alter the damaging environment or abolish reflux completely. Acid-suppressive therapy is unlikely to do either of these; impedance studies have shown that the reflux persists, the refluxate becomes more alkaline, and the pulse effect does not change. The fact that the prevalence of intestinal metaplasia and adenocarcinoma has risen, even as acid suppression has improved, is evidence that acid is a relatively minor factor in these genetic switches.

On the other hand, successful anti-reflux surgery, usually a Nissen or other type of fundoplication, creates a new valve and decreases the amount of gastroesophageal reflux (see Figure 5–17). Anti-reflux surgery is not perfect; it requires a fine balance of tightness of the wrap to ensure that reflux is minimized without causing a physical obstruction that leads to dysphagia. The aim of anti-reflux surgery is to reduce reflux sufficiently to prevent progression of genetic changes to cancer. This requires a level of reflux control that is greater than that necessary to cure the patient of symptoms. Evidence suggests that when a successful anti-reflux surgery is defined as normalization of the 24-hour pH test, the control of reflux is sufficient to prevent progression to adenocarcinoma. What this means at a molecular level is that the exposure of the target cells in the esophagus to refluxate molecules has been reduced to a level that prevents the occurrence of the genetic switches and mutations required for adenocarcinoma.

We have observed the phenotypic expression of some of these reversals; intestinal metaplasia accompanying short-segment Barrett esophagus frequently reverses,[29] and we have observed an increased amount of oxyntocardiac mucosa in post-fundoplication biopsies compared with preoperative biopsies. Both of these are highly beneficial changes that occur at a histologic level without any change in the endoscopic length of the columnar-lined esophagus.

The most promising point of attack when attempting to prevent cancer is the stage of reflux disease before the development of intestinal metaplasia. The patients at risk in the future are those who have cardiac mucosa, which is detectable by screening and biopsy. There is a long lag phase before cardiac mucosa progresses to intestinal metaplasia in most patients. Recognition of the molecular component in the refluxate that drives Cdx-2 activation and the "gastric-type genetic signal" can lead to the production of drugs that have an impact on these molecules and drive differentiation of cardiac mucosa away from intestinal metaplasia and toward oxyntocardiac mucosa. This will theoretically prevent progression to adenocarcinoma.

Barrett Esophagus: Five Decades of Medical Failure

The medical community presently does not give Barrett esophagus the respect it deserves; the disease is belittled. Throughout history, its incidence and importance have been underestimated. Before 1953, its very existence was denied by the simple expedience of defining the end of the esophagus as squamocolumnar junction[30] (Figure 5–23); the columnar-lined esophagus was therefore an intrathoracic tubular stomach. When it was described in 1953,[25]

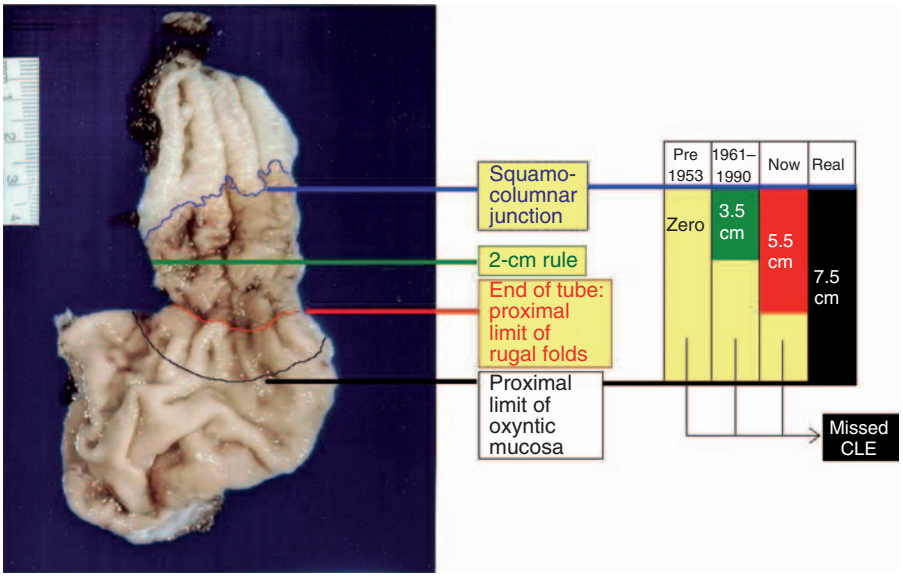


Figure 5–23 The error made over five decades in the diagnosis of columnar-lined esophagus. The true length of columnar-lined esophagus *(CLE)* in this esophagus (see Figure 4–23) is 5.5 cm visible in the tubular esophagus plus 2.05 cm in the dilated end-stage esophagus. If the true gastroesophageal junction (proximal limit of gastric oxyntic mucosa) is used, the total length is 7.5 cm. Using present definitions of the gastroesophageal junctions (end of tubular esophagus and proximal limit of rugal folds), the length of columnar-lined esophagus is 5.5 cm; the 2-cm segment of microscopic disease in the dilated end-stage esophagus is missed. Between 1961 and the mid-1990s, 2 cm of the distal esophagus was believed to be normally lined by columnar epithelium. According to this, the length of abnormality would be 3.5 cm; both short-segment disease and microscopic disease in the dilated end-stage esophagus was missed. Before 1953, the entire columnar-lined segment was believed to be a tubular stomach; the entire entity was missed.

it was declared to be an insignificant congenital anomaly. When it was recognized to be caused by gastroesophageal reflux, the disease was limited to only those patients who had long-segment disease by using the false definition that the distal 2 to 3 cm of the esophagus was lined normally by columnar epithelium.[3] This led to short-segment disease being ignored for three decades between 1961 and the 1990s. We continue to make the same mistake. Today's incorrect criteria and definitions ignore microscopic Barrett esophagus that occurs in the dilated end-stage esophagus. By defining the end of the esophagus as the tops of the rugal folds and the end of the tubular esophagus, we repeat the mistake of 1953, declaring the esophagus as ending more proximally than it does. This results in the majority of patients with Barrett esophagus being declared as having a gastric disease. Today's "intrathoracic tubular stomach" is "normal gastric cardiac mucosa, and intestinal metaplasia and adenocarcinoma of the gastric cardia." We are ignoring the base of the iceberg of Barrett esophagus. This five-decade comedy of errors must be at least partly responsible for the meteoric sixfold rise in the incidence of reflux-induced adenocarcinoma of the esophagus.

Barrett esophagus is treated as if it is a relatively low-risk disease. This is not true. Barrett esophagus currently ranks as one of the most dangerous premalignant conditions. The magnitude of risk for cancer, which is 0.5% per year or 10% in 20 years, is similar to that of chronic ulcerative colitis. The risk is much higher than for colonic adenomas. It is a far more specific indicator of risk than a mammographic abnormality. Yet we treat it like it is not significant. Unlike mammographic abnormalities, we make no attempt to find

it; unlike tubular adenomas of the colon, we do not remove it; and unlike ulcerative colitis, in which prophylactic colectomy is considered when low-grade dysplasia is found, we wait until high-grade dysplasia is found before we do anything at all.

One reason for this inaction is the sense of extreme futility we have about our ability to prevent the occurrence of cancer in a patient with Barrett esophagus. In a recent Barrett esophagus workshop of 18 world experts (15 gastroenterologists, two surgeons, and one pathologist), it was concluded that there was essentially nothing that could be done in a patient with Barrett esophagus to prevent cancer.[30] This pessimistic viewpoint is pervasive and dooms the nearly 25,000 patients who develop reflux-induced cancer to a 85% to 90% mortality. I hope to convince you that this futility is not justified. In Chapter 1, I made a plea for an aggressive attack on the disease by emphasizing cancer prevention. There is strong evidence that successful anti-reflux surgery will prevent Barrett esophagus in patients with cardiac mucosa if it is performed before it occurs. There is significant evidence in the literature and a strong theoretical basis for the statement that decreasing the volume of reflux by a successful anti-reflux operation stops the progression of the sequential change toward cancer (see Figures 5–17 and 5–18 and Chapter 6).

The natural history of reflux-induced adenocarcinoma extends over many decades with epithelial changes that mirror the progression of disease. The correct way to prevent this is to detect these changes and treat the disease at the earliest feasible stage. At the present time, this is the patient with Barrett esophagus. The wrong way is to continue what we do now, which is doing nothing or promoting the progression to cancer with long-term, acid-suppressive drugs.

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CHAPTER 6

Reflux-Induced Adenocarcinoma of the Esophagus

Gastroesophageal reflux disease is the basis for all adenocarcinomas of the esophagus. Except for extremely rare adenocarcinomas that arise in the submucosal glands of the esophagus, adenocarcinomas arise from the surface epithelium that has progressed along the reflux-to-adenocarcinoma sequence. This includes the following:

1. Squamous epithelial damage leading to cardiac metaplasia.
2. Intestinal metaplasia in cardiac mucosa, which defines Barrett esophagus.
3. Carcinogenesis; all esophageal adenocarcinomas pass through this sequence.

Cardiac metaplasia of squamous epithelium occurs early in the course of reflux disease, often during childhood and early adult life (Figure 6–1). There is a long lag phase, measurable in years, and sometimes decades, before intestinal metaplasia occurs in cardiac mucosa. The rate of carcinogenesis in intestinal metaplasia, which likely requires multiple mutations, is variable but frequently takes many years and often decades (see Figure 6–1).

CASE STUDY

(Contributed by Daniel Oh, MD; Case presented at USC Foregut Conference in Hawaii; also included in Lord R et al.[1])

This patient gave a long and eventful history. As a 9-month-old boy, the patient swallowed a penny. This went undetected until progressive dysphagia resulted in a chest x-ray at age 7 years, which showed the penny in the thoracic esophagus. The penny was removed endoscopically. The patient continued to experience dysphagia, mainly with solids. This required multiple esophageal dilatations. Finally at age 15, it was determined that his dysphagia and inability to eat could not be adequately managed with dilatations, and he had a partial esophagectomy with gastric pull-up. As a result, the patient's dysphagia resolved; however, he then experienced heartburn and regurgitation over the next few decades. It was also determined that he was having aspiration events that were leading to progressively worsening pulmonary function.

At 56 years of age (41 years after the esophagectomy) the patient was referred to the USC Foregut Surgery Unit for severe reflux symptoms that were not controlled adequately with medical treatment. The upper endoscopy showed that the cricopharyngeus was at 15 cm, and the esophagogastric

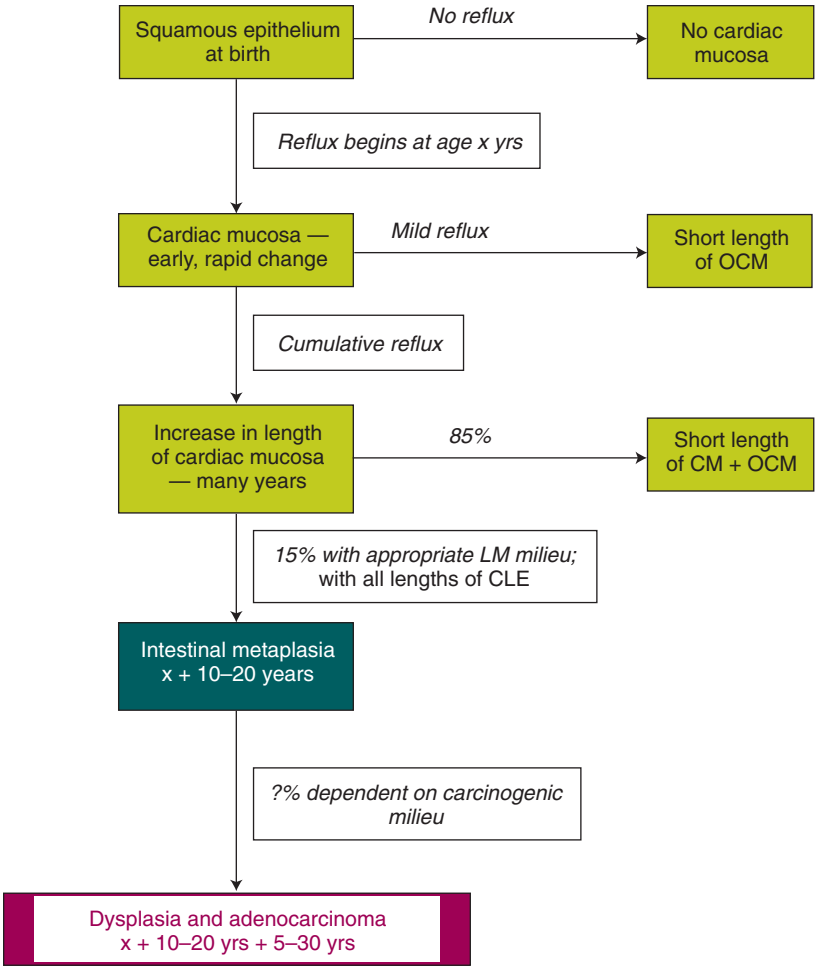


Figure 6–1 Typical lifetime course for a patient traversing the reflux-to-adenocarcinoma sequence. The first part of the sequence, which is conversion of increasing amounts of squamous epithelium to cardiac mucosa *(CM)*, takes two to three decades. Those patients that progress in the sequence go on to develop intestinal metaplasia and adenocarcinoma, again over the course of several decades. This typical time sequence varies such that the age range for different stages can vary significantly. *CLE,* Columnar-lined esophagus; *OCM,* oxyntocardiac mucosa.

anastomosis was intrathoracic in location and 30 cm from the incisors. There was a long segment of columnar-lined esophagus from 30 cm to 23 cm (Figure 6–2). A small nodule was present at 29 cm.

The surgical pathology report was as follows (Figure 6–3):

A. 29 cm, bx: Invasive, moderately differentiated adenocarcinoma.
B. 29 cm, nodule, bx: Invasive, moderately differentiated adenocarcinoma.
C. 26 cm, bx: Reflux carditis; intestinal (Barrett) metaplasia.
D. 25 cm, bx: Intestinal (Barrett) metaplasia with low-grade dysplasia.
E. 24 cm, bx: Intestinal (Barrett) metaplasia with low-grade dysplasia.
F. 23 cm, bx: Reflux esophagitis; intestinal (Barrett) metaplasia.
G. Brushings at 29 cm: Malignant cells present consistent with adenocarcinoma.

This patient demonstrates the typical course of the reflux-to-adenocarcinoma sequence. At the time of surgery, when he was 15 years old,

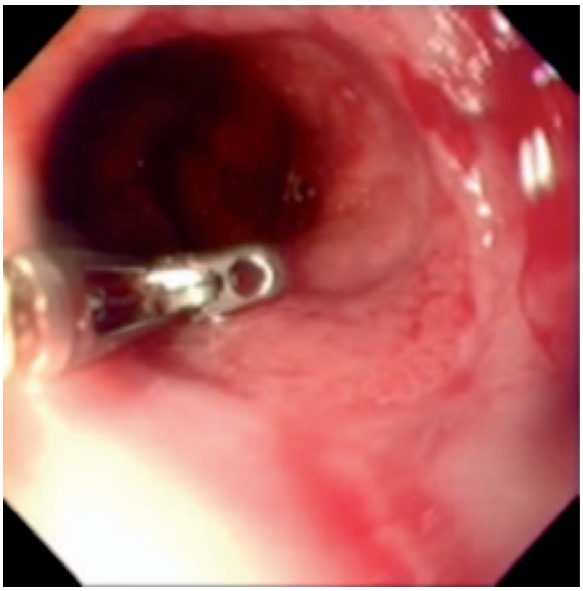


Figure 6–2 Case study. Endoscopic appearance at age 56 years showing the distal esophagus with a long segment of columnar-lined esophagus. The biopsy forceps are shown next to the area of the nodule at 29 cm, 1 cm above the anastomotic line.

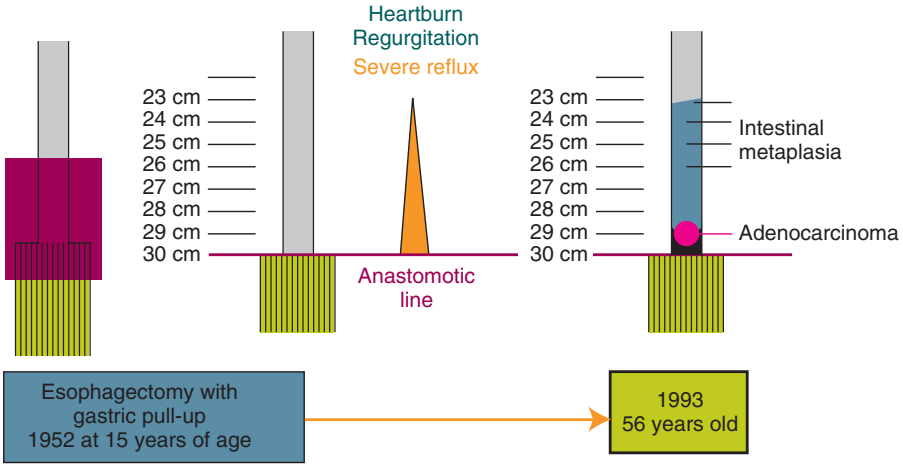


Figure 6–3 Diagrammatic representation of the patient's lifetime course. The area of esophagus and stomach resected at age 15 *(red area)* includes the proximal stomach and lower esophageal sphincter. This sets the stage for chronic and severe symptomatic reflux disease *(orange triangle).* The end result is a 6-cm segment of columnar-lined esophagus composed largely of intestinal metaplastic epithelium. After four decades, an adenocarcinoma develops in the distal part of the area of intestinal metaplasia, 1 cm above the anastomotic line. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

the patient's distal esophagus and proximal stomach were removed. There is no "cardia" or "native cardiac mucosa" in this patient. This surgery is associated with gastroesophageal reflux because the lower esophageal sphincter has also been removed. This patient had symptomatic reflux disease after the surgery. The ravages of this gastroesophageal reflux are clearly limited to his esophagus because the gastroesophageal junction can be recognized clearly as the anastomotic line; 41 years after his esophagectomy, the end result of reflux included a 7-cm segment of columnar-lined esophagus with cardiac mucosa with and without intestinal metaplasia. The intestinal metaplasia

extended to a point 1 cm above the anastomotic line. At this point, where there is maximum contact of the target cell in intestinal metaplasia with the highest dose of carcinogen in the refluxate, an adenocarcinoma developed. In this case, it is clearly documented that the reflux-to-adenocarcinoma sequence took 41 years to evolve.

A cancer with a long premalignant phase characterized by several histologically recognizable steps (cardiac mucosa, intestinal metaplasia) would seem to be very amenable to preventive measures. This is true. However, we currently do nothing to find people at risk for reflux-induced adenocarcinoma; 90% of patients present for the first time with symptomatic and often advanced cancer, which has a mortality rate of approximately 90%. Less than 5% of patients who develop esophageal adenocarcinoma have a known diagnosis of Barrett esophagus.[2] The majority of such patients give a history of symptomatic reflux for a long time preceding the cancer. Many such patients have been "successfully treated" with acid-suppressive drugs, which have controlled their symptoms. Only a small number of patients develop reflux-induced adenocarcinoma while under surveillance because of a prior endoscopic diagnosis of Barrett esophagus; these patients present with early-stage cancer and have a better survival rate, suggesting that this disease's mortality rate can be reduced if we change our attitudes.[3]

Reflux-induced adenocarcinoma includes the following:

1. Adenocarcinoma of the tubular esophagus, the only entity presently accepted universally as being esophageal and definitely reflux induced (Figures 6–4*B,* 6–5, and 6–6). It is also accepted that these tumors are preceded by Barrett esophagus and follow the reflux-to-adenocarcinoma

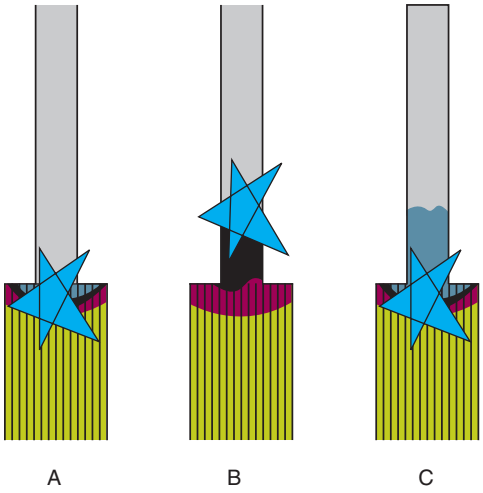


Figure 6–4 Three patients with adenocarcinoma *(blue star)* are shown. **A,** Patient with disease limited to the dilated end-stage esophagus. The tumor will be classified by present criteria as an adenocarcinoma of the gastric cardia. **B,** Patient with a columnar-lined segment in the tubular esophagus. The intestinal metaplasia is limited to the most proximal region of the columnar segment. The tumor arises in that area with intestinal metaplasia and will be a distal esophageal tumor. **C,** Patient with a long segment of columnar-lined esophagus with intestinal metaplasia extending into the dilated end-stage esophagus, where the cancer has occurred. This would be classified as an adenocarcinoma of the gastric cardia occurring in a patient with Barrett esophagus. In reality, it is a distal esophageal tumor arising in the region of maximum risk in Barrett esophagus.

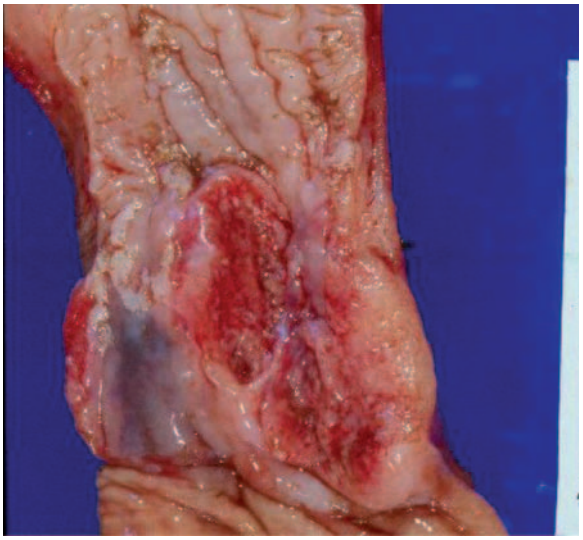


Figure 6–5 Adenocarcinoma of the tubular esophagus. The proximal edge of the tumor consists of squamous epithelium. The columnar-lined esophagus from which the tumor arose has been almost entirely replaced by the tumor, except possibly in the dilated end-stage esophagus distal to the tumor. This can be identified only by histology.

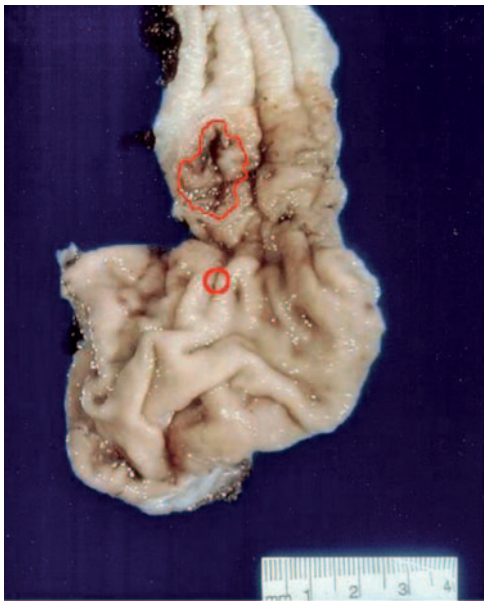


Figure 6–6 Adenocarcinoma arising in columnar-lined esophagus. This is the specimen whose epithelia are mapped in Figure 4–23, showing a 2.05-cm dilated end-stage esophagus distal to the end of the tubular esophagus. There is an obvious ulcerated tumor (outlined in red) in the tubular esophagus. A second intramucosal adenocarcinoma was found in the distal region of the intestinal metaplasia in the dilated end-stage esophagus. This would not be sampled by present endoscopic practice guidelines until it became large enough to be visible. It would be incorrectly classified as an adenocarcinoma of the gastric cardia.

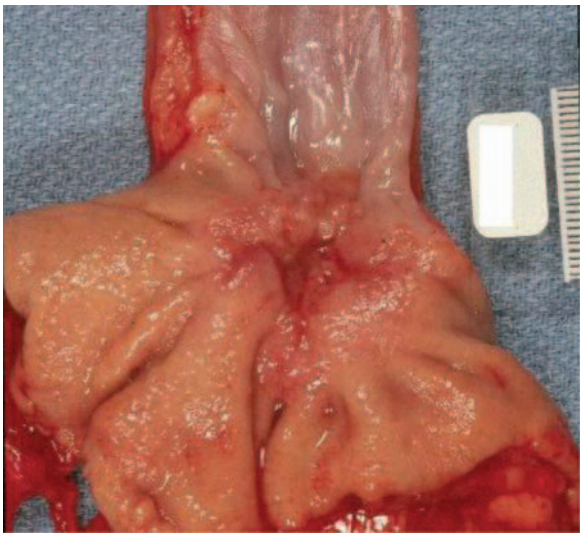


Figure 6–7 Adenocarcinoma arising in disease limited to the end-stage esophagus. The entire tubular esophagus is lined by squamous epithelium. Rugal folds are distorted by the ulcerated tumor. The only way to accurately define the location of the tumor is to histologically map the epithelia around the tumor. This patient had intestinal metaplasia at the lateral edge, cardiac mucosa at the distal edge, and the gastric mucosa was normal. These features allow this to be defined as an adenocarcinoma of the distal esophagus by the newly suggested definitions.

sequence, although the early stages of the sequence as I have described (i.e., cardiac metaplasia) are not universally accepted. Every year in the United States, an estimated 14,000 patients develop adenocarcinoma in the tubular esophagus. The incidence is equal to or higher in Western Europe. Lagergren et al[4] have shown that these tumors are strongly associated with symptomatic gastroesophageal reflux disease, are more common in men, and arise in long-segment Barrett esophagus.

2. Adenocarcinoma of the dilated end-stage esophagus (see Figures 6–4*A*, *C*, 6–6, and 6–7). These tumors arise at or distal to the present definition of the gastroesophageal junction (i.e., the end of the tubular esophagus and/or the proximal limit of the rugal folds). They are presently classified as "adenocarcinoma of the gastroesophageal junction" or "adenocarcinoma of the gastric cardia." Both these designations are currently categorized under "adenocarcinoma of the gastric cardia" in the WHO International Classification of Tumors and are regarded as gastric adenocarcinomas. In a recent study of these tumors, we showed that most, if not all, adenocarcinomas classified as gastric cardia using present criteria occur in metaplastic esophageal columnar epithelium in dilated end-stage esophagus.[5] These tumors are common, with an estimated 11,000 diagnoses every year in the United States. They may arise in patients who have Barrett esophagus limited to the end-stage dilated esophagus (see Figures 6–4*A* and 6–7) or in the distal region of a long segment of Barrett esophagus that involves both tubular and dilated end-stage esophagus (see Figures 6–4*C* and 6–6). In Lagergren et al's[4] study, adenocarcinoma of the cardia, which includes tumors within 3 cm distal to the gastroesophageal junction, was shown to

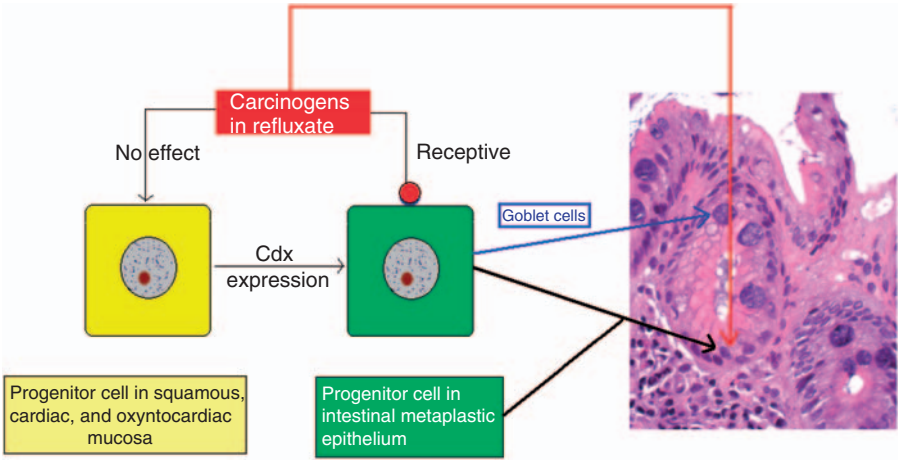


Figure 6–8 The target cell for carcinogens in the refluxate is limited to the progenitor cell in intestinal-type epithelium, which differentiates into goblet cells *(green boxes).* The carcinogens do not produce cancer in squamous, cardiac, and oxyntocardiac mucosa *(yellow boxes).* The target cell is located in the proliferating progenitor stem cell pool in the deep foveolar region.

have an association with symptomatic gastroesophageal reflux disease, albeit less than for adenocarcinomas of the tubular esophagus. The pathogenesis of these tumors is uncertain at this time. If they are adenocarcinomas of the dilated end-stage esophagus, there is no reason to believe that they have a pathway other than the reflux-to-adenocarcinoma sequence (through cardiac mucosa and Barrett esophagus) that leads to all other esophageal adenocarcinomas. The similarities between these tumors and adenocarcinomas of the tubular esophagus support a common pathogenesis.[6] Many of the differences (gender distribution, lesser association with symptomatic reflux) between the two can be explained by the fact that many adenocarcinomas of the dilated end-stage esophagus arise in very short segments of Barrett esophagus. Short-segment Barrett esophagus has an equal gender distribution, as opposed to the male predominant long-segment disease, and has more asymptomatic patients because it is caused by a lesser severity of reflux disease. If it is accepted that adenocarcinomas of the "gastric cardia" are reflux-induced carcinomas of the end-stage dilated esophagus (as it should be), the total incidence of reflux-induced adenocarcinomas in the United States is approximately 25,000 per year.

The Target Cell

The target cells for carcinogens that produce adenocarcinoma in gastroesophageal reflux disease are limited to proliferative cells in columnar-lined epithelium marked by the presence of intestinal metaplasia.[7] The carcinogens do not act on the goblet cells; these are usually terminally differentiated cells. Instead, they act on the proliferative cell pool in the deep foveolar region of intestinal metaplastic epithelium. It is as if the genetic switch that causes the esophageal cell to differentiate into goblet cells makes it receptive to carcinogenic molecules (Figure 6–8).

All other epithelia found in the esophagus, including squamous epithelium, cardiac mucosa, and oxyntocardiac mucosa, are not susceptible to reflux-induced carcinogenesis. In the study by Lagergren et al,[4] there was no association between squamous carcinoma of the esophagus and symptomatic gastroesophageal reflux disease.

If there is no intestinal metaplasia, there is no risk of malignancy, regardless of the length of columnar-lined esophagus or the concentration of carcinogen in the gastric refluxate. Of course, there is the possibility that the target cell may eventually appear. The absence of the target cell in a 50-year-old patient is more highly predictive of a lack of cancer risk than the absence of intestinal metaplasia in a child. The presence of the target cell indicates a risk of cancer, regardless of the length of columnar-lined esophagus (see the section later in this chapter, page 201).

The Carcinogen

Esophageal adenocarcinoma displays characteristics of a tumor caused by the effect of a luminal molecule associated with gastroesophageal reflux. The carcinogen involved is unknown but must reside in the gastric juice. The very low incidence of adenocarcinoma in reflux disease suggests that the carcinogen in *not ubiquitous in gastric juice.*

The rate of progression to cancer varies considerably in patients with Barrett esophagus; data exist only for the 10% of patients who develop cancer while under surveillance for Barrett esophagus. The majority of these patients have stable disease without progression to increasing dysplasia or cancer over many years. However, some patients progress through the sequence quickly. The rate of progression to cancer in the 90% of patients who first present with cancer is unknown. The variable rate of progression to dysplasia and cancer in patients with Barrett esophagus suggests that carcinogen concentration is a dominant factor in the genesis of cancer. Unfortunately, without definitive knowledge regarding the nature of the carcinogen, there is no ability to categorize patients according to the level of carcinogenicity of gastric refluxate.

The carcinogens in the gastric refluxate may be endogenous secretions of the oral cavity, esophagus, stomach, or exogenous molecules in food. If the patient has duodenogastric reflux, the endogenous compounds available to act on the esophageal epithelium greatly increase because all the components of bile and pancreatic juice enter the stomach. In the milieu of the gastric lumen, these molecules interact to produce new molecules that may induce cancer in the esophagus when gastroesophageal reflux occurs.

Salivary Nitrogenous Compounds

Salivary secretions contain significant amounts of nitrate. The normal oral bacterial flora rapidly convert 10% to 90% of this secreted salivary nitrate into nitrite. Under fasting conditions, significant nitrite concentrations can be found in the saliva and esophagus.[8] When nitrite progresses down the esophagus and encounters gastric acid, it is converted to potentially carcinogenic N-nitroso compounds. These compounds are proven experimental carcinogens and have been used to induce gastric and esophageal cancers in animals.

McColl[8] postulates that reflux-induced adenocarcinoma is caused by generation of these carcinogenic compounds when saliva meets gastric acid. Normally, without significant reflux, the site of this saliva-gastric acid interaction is the gastric cardia. In patients with reflux, the location of this interaction is in the distal esophagus and causes cancer in that location. Although this hypothesis is interesting, there is relatively little direct evidence to support it.

Acid

There is almost no clinical or experimental evidence that suggests that H^+ ions in gastric juice are capable of causing genetic mutations. The only pathologic change shown to be caused by acid is related to cellular injury, which in turn results in increased proliferative activity. Increasing the proliferative activity of an epithelium has a secondary effect in facilitating mutations; because mutations occur during cell division, anything that increases proliferative activity will increase the chance of random mutations.

It is highly unlikely that acid is capable of causing genetic changes. H^+ ions are the smallest and simplest particles in nature, and it is highly unlikely that cellular receptors have developed to recognize H^+. In general, cell surface receptors have complex structures that are complementary to large molecules with complex tertiary structures that lend specificity to the molecule-receptor interaction.

Despite the lack of evidence that acid is directly involved in carcinogenesis, as well as the theoretical objections to its action as a molecule capable of interacting with cell surface receptors to cause genetic mutations, most individuals will regard acid as the main factor in the etiology of reflux-induced adenocarcinoma of the esophagus. The entire emphasis of treating reflux disease is on acid suppression. There is a naïve expectation that removing acid from the equation will prevent all the complications of reflux disease. There is no evidence, despite considerable study, that acid suppression decreases the likelihood of either Barrett esophagus or its progression to cancer in a patient with reflux disease.

CASE STUDY

A 64-year-old patient presented with dysphagia for solid food, which progressively worsened over the course of 2 weeks. This was associated with a 10-pound weight loss during the previous month. The patient had a significant history of chronic autoimmune gastritis 5 years previously and was documented at that time to have hypochlorhydria. Except for vitamin B12 injections at intervals, the patient was not on any medications for the gastritis. In particular, there was no history of acid-suppressive drug use. The patient was not under a routine surveillance protocol for the chronic atrophic gastritis and there was no prior diagnosis of Barrett esophagus.

Upper endoscopy showed a short segment of columnar epithelium in the distal 1 cm of the tubular esophagus and a nodular lesion at the gastroesophageal junction (Figures 6–9 and 6–10). The stomach showed diffuse atrophy involving the body and fundus with a flat mucosa showing no rugal folds (Figure 6–11).

Biopsies from the columnar-lined segment of the tubular esophagus showed cardiac mucosa with and without intestinal metaplasia. There was an area of low-grade dysplasia arising in intestinal metaplasia in the distal tubular esophagus in a biopsy taken immediately proximal to the nodular lesion (Figure 6–12). Biopsies from the nodule showed an invasive, poorly differentiated adenocarcinoma arising in intestinal metaplasia (Figure 6–13). There was cardiac mucosa adjacent to the cancer in one of the biopsy pieces, indicating that this carcinoma had cardiac mucosa at one edge. Biopsies of the atrophic body of the stomach showed chronic atrophic gastritis with extensive intestinal metaplasia (Figure 6–14). There was diffuse enterochromaffin cell hyperplasia with multiple microcarcinoid tumors (Figures 6–15 and 6–16).

This case was sent to me for consultation from a pathologist in Los Angeles who wanted to know whether this was a gastric adenocarcinoma

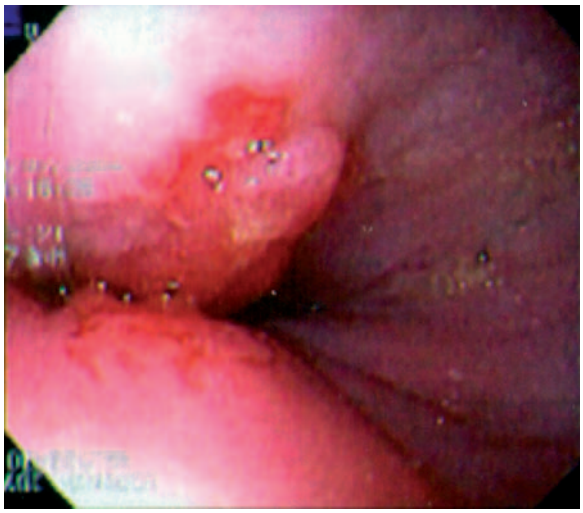


Figure 6–9 Case study. Endoscopy showing a short tongue of columnar-lined esophagus with a small nodular lesion at the gastroesophageal junction. The rugal folds are seen in the far region of the circumference.

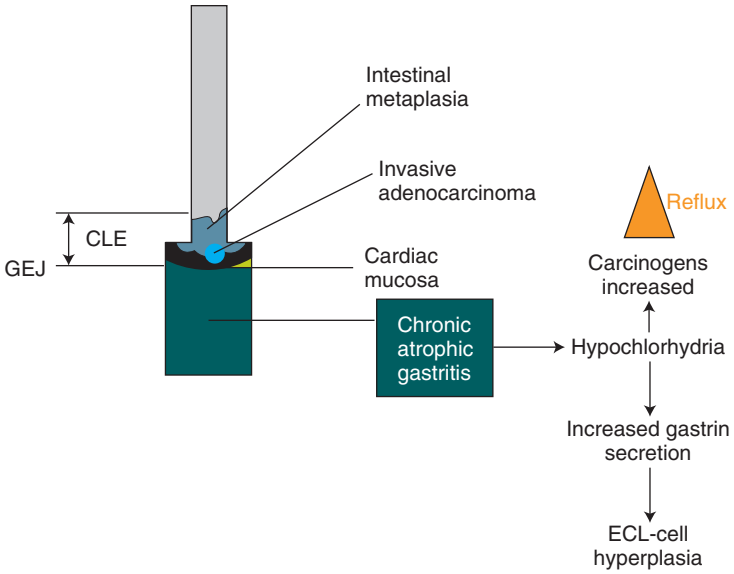


Figure 6–10 Diagrammatic representation of the patient's findings, showing the columnar-lined segment with cardiac and intestinal metaplasia and an invasive adenocarcinoma in the dilated end-stage esophagus. The stomach shows diffuse atrophic gastritis with extensive intestinal metaplasia *(green areas).* The combined effect of the atrophic gastritis and reflux *(orange triangle)* is shown. *CLE,* Columnar-lined esophagus; *ECL,* enterochromaffin-like; *GEJ,* gastroesophageal junction. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *gray,* squamous epithelium.

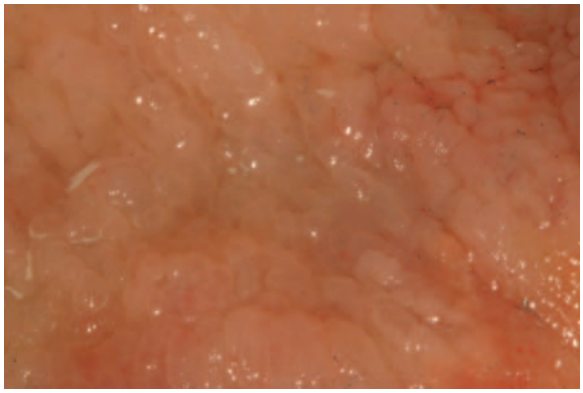


Figure 6–11 Mucosal surface of the stomach, showing flattening with absence of well-formed rugal folds. There is a cobblestone-like appearance in some areas.

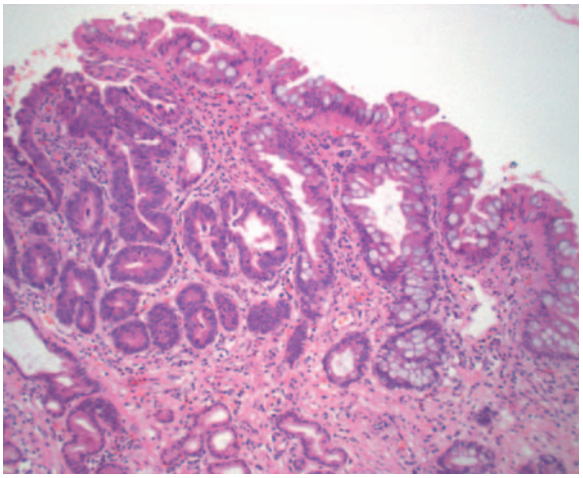


Figure 6–12 Biopsy from the visible columnar-lined esophagus above the tumor nodule showing cardiac mucosa with intestinal metaplasia and evidence of low-grade dysplasia (left half).

arising in chronic autoimmune gastritis or an adenocarcinoma arising in Barrett esophagus. He and the gastroenterologist favored a gastric adenocarcinoma because the lesion was distal to the end of the tubular esophagus (the absence of rugal folds made the end of the tubular esophagus the only available criterion for the junction).

The following things about this case are true:

1. There can be no argument that this patient had intestinal metaplasia of Barrett type in the esophagus and intestinal metaplasia in chronic atrophic

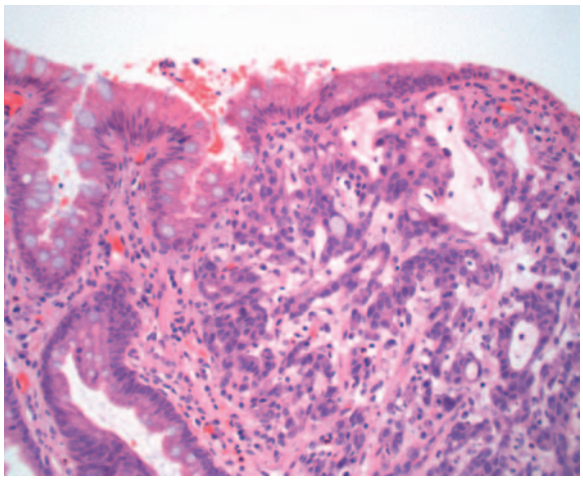


Figure 6–13 Biopsy from the tumor showing an invasive, poorly differentiated adenocarcinoma. Residual goblet cells are present.

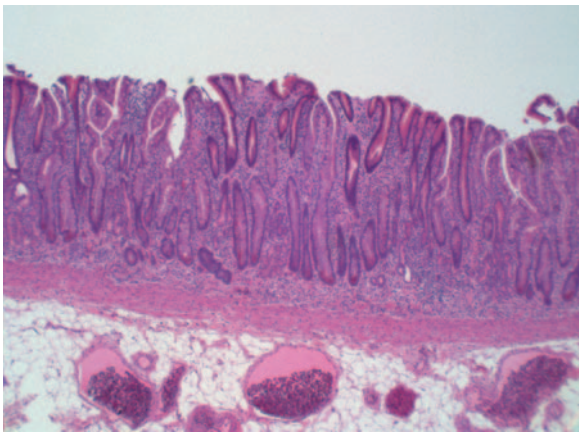


Figure 6–14 Biopsy from the gastric body showing chronic atrophic gastritis with extensive intestinal metaplasia.

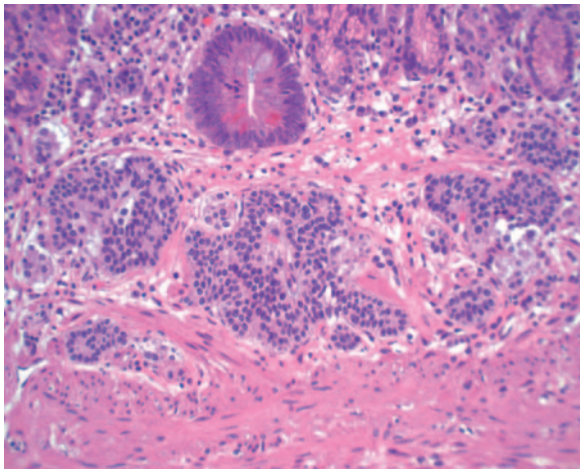


Figure 6–15 Biopsy of the gastric body showing micronodular neuroendocrine (ECL-cell) hyperplasia in the deep mucosa.

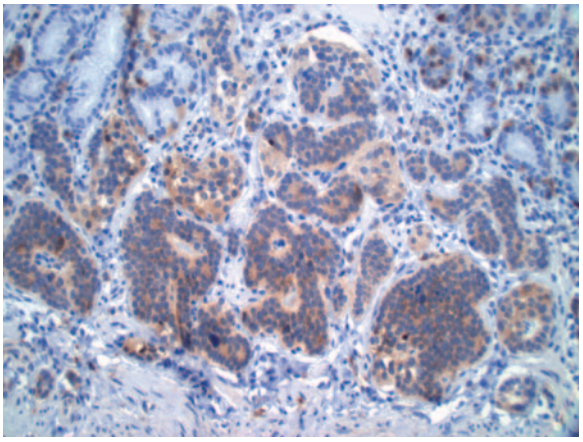


Figure 6–16 Biopsy of the gastric body, stained by immunoperoxidase technique for chromogranin, showing positive staining of the micronodules of neuroendocrine cells.

gastritis. The fact that there was a visible columnar-lined segment with intestinal metaplasia indicates Barrett esophagus.

2. There is a clear histologic difference between the appearance of the intestinal metaplasia in the esophageal segment (see Figure 6–12), which shows disorganized glands with lamina propria fibrosis and mild inflammation with non-intestinalized cardiac type glands in the deeper region, and in the gastric segment (see Figure 6–14), which shows a flat mucosa with straight glands that demonstrate intestinal metaplasia and Paneth cells with marked chronic inflammation. The neuroendocrine hyperplasia is restricted to the gastric intestinal metaplasia (see Figure 6–15). It appears that the adenocarcinoma arises in epithelium that has features of cardiac mucosa with and without intestinal metaplasia rather than the chronic atrophic gastritis.
3. The adenocarcinoma appears in the expected location for an adenocarcinoma arising in Barrett esophagus, which is known to favor the most distal region of the intestinal metaplastic segment. This is related to the fact that the carcinogen dose is greatest most distally in the esophagus.

4. It is possible for adenocarcinoma arising in chronic atrophic gastritis to involve the most proximal stomach, but this would not be the typical location. There is no reason why a gastric adenocarcinoma should arise in this region instead of the rest of the gastric body.
5. The risk of adenocarcinoma is greater in Barrett esophagus than in chronic atrophic gastritis. At the present time, this is statistically more likely to be a reflux-induced adenocarcinoma than one arising in chronic atrophic gastritis.
6. If the non-intestinalized cardiac mucosa seen at the edge of the cancer in one of the biopsies is at the distal edge, by our criteria, it would indicate that the metaplastic esophageal segment extends to a point distal to the tumor, which makes it entirely esophageal.
7. Based on these factors, I concluded that this was an adenocarcinoma arising in the dilated end-stage esophagus at the distal region of the segment of Barrett esophagus. This conclusion can only be reached by using our definition of the gastroesophageal junction as a point distal to the end of the tubular esophagus and marked by the distal limit of esophageal columnar metaplastic epithelium.

In one respect, the gastroenterologist was happy with this conclusion because it removed any issues of liability about the failure to monitor a patient with known chronic atrophic gastritis. However, he also objected to this conclusion by saying that it was not possible that adenocarcinoma could arise in Barrett esophagus in a patient known to be hypochlorhydric for the past 5 years. There was proof of severe hypochlorhydria in the presence of enterochromaffin cell hyperplasia seen in the gastric biopsy. This is a trophic effect of elevated serum gastrin.

In fact, the reverse is more likely to be true. The absence of acid is not a reason to rule out reflux-induced cancer; it is likely to have promoted carcinogenesis. This patient probably had asymptomatic reflux with intestinal metaplasia in the esophagus for an unknown period. The target cells in the intestinal metaplasia were continually exposed to gastric refluxate, which included potential carcinogens. The increasing alkalinity of the gastric juice induced by the hypochlorhydria of chronic atrophic gastritis is likely to have caused a progressive increase of carcinogenicity in the refluxate. The fact that this adenocarcinoma arose 5 years after known hypochlorhydria provides excellent evidence that acid is not the carcinogen in reflux-induced adenocarcinoma of the esophagus.

Bile

There is significant evidence that bile acid metabolites are implicated in the genesis of esophageal adenocarcinoma.[9,10] The entry of bile into the stomach by duodenogastric reflux is a very common phenomenon in humans. In a patient with normal gastric acidity in the 1 to 3 pH range, bile acids precipitate into harmless insoluble molecules. At a pH above 6, the bile acids remain in an ionized form, which precludes their entry into cells. Between a pH of 3 and 6, the bile acids and their metabolites are converted to unionized soluble molecules that can penetrate cell membranes and enter esophageal epithelial cells (Figure 6–17). Acid suppression, particularly when it is uncontrolled (as in the vast majority of patients who take these medications—both over the counter and prescribed), has the effect of increasing gastric pH into the critical 3 to 6 range. Carcinogens responsible for reflux-induced esophageal cancer are likely activated from bile acids in the weak acid gastric milieu of the patient taking acid-suppressive medication on a long-term basis.

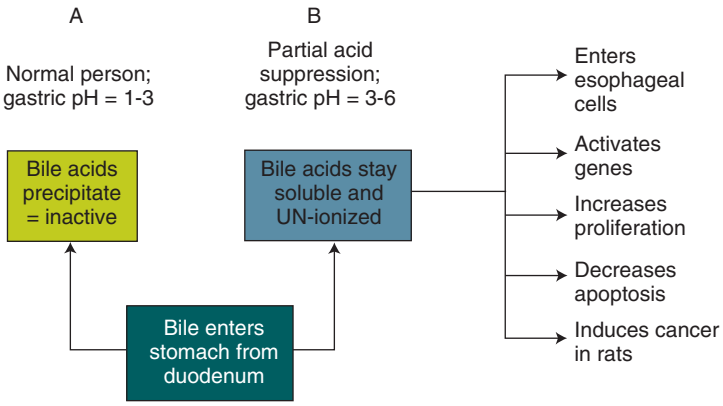


Figure 6–17 The effect of gastric pH on bile acids that enter the stomach via duodenogastric reflux. In normal cases, the high acidity inactivates bile acids. At an intermediate pH (3 to 6), the bile acids become converted to soluble and unionized metabolites that enter the esophageal cells and induce genetic changes that promote proliferation, inhibit apoptosis, and cause cancer.

Bile components, notably the bile acids cholic, taurocholic, and glycocholic, and their deoxygenated metabolites, have been considered to be instrumental in potentiating the early stage of reflux disease, acting synergistically with acid to contribute to severe erosive esophagitis, strictures, and Barrett esophagus.[11] More importantly, they act in the carcinogenic phase of Barrett esophagus in a manner that is probably opposite to the action of acid.

Jaiswal et al[12] showed that the conjugated bile salt glycochenodeoxycholic acid was highly effective in activating the P13 kinase/Akt signaling pathway in a Barrett adenocarcinoma cell line. This pathway is known to promote cell proliferation and inhibit apoptosis (see Figure 6–17). In a more recent paper, Jaiswal et al[13] studied the effect of bile salts on normal esophageal squamous cells and non-neoplastic Barrett cells. Normal esophageal squamous cells exposed to 5 minutes of bile salts did not increase cell numbers. In Barrett epithelial cells, bile salt exposure increased cell numbers by 31%, increased phosphorylated p38 and ERK levels by twofold to threefold, increased BrdU incorporation by 30%, and decreased UV-induced apoptosis by 15% to 20%. The authors concluded that bile salt exposure induces a non-neoplastic Barrett cell line to proliferate by activation of both the ERK and p38 MAPK pathways and suggested that this could be a potential mechanism whereby bile reflux may facilitate the neoplastic progression of Barrett esophagus.

Stamp[14] showed that rats who were gastrectomized and jejunostomized to allow bile acids to reflux into the esophagus developed many carcinomas in 50 weeks, while other modifications that kept bile out of the esophagus did not produce any cancers (see Figure 6–17). The authors concluded that bile acids refluxing into the esophagus of humans should also cause cancers, especially in Westernized societies with their high-fat diets, which provide an abundant supply of bile. They showed that bile acids can enter the model OE33 cells and activate the oncogene c-myc at pH 4, the gene complex NF-kappaB at pH 6.5, and induce cellular proliferation. In their discussion, the authors suggest that acid-suppression therapy used to treat patients with Barrett esophagus will solubilize free bile acids and some of the glycine conjugates, allowing them to enter the epithelial cells. These intracellular bile acids have the ability to produce cellular changes that induce carcinogenesis. The authors conclude that acid-suppression therapy should be restricted, not promoted.

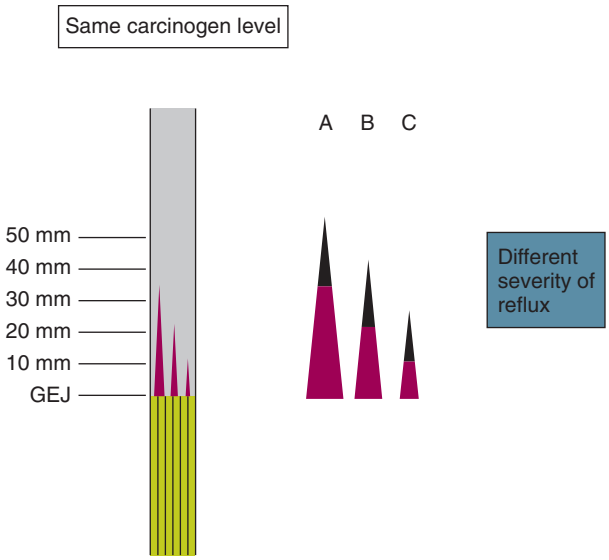


Figure 6–18 Three patients with the same carcinogen concentration in the gastric juice. They have varying severity of reflux (shwon by triangle size; **A** is highest, **C** is lowest). The carcinogen concentration progressively decreases from the gastroesophageal junction *(GEJ)* upward. Delivery of an effective carcinogen dose *(red areas)* in these three patients will therefore vary from most proximal in patient **A** to limited to the most distal esophagus in patient **C.**

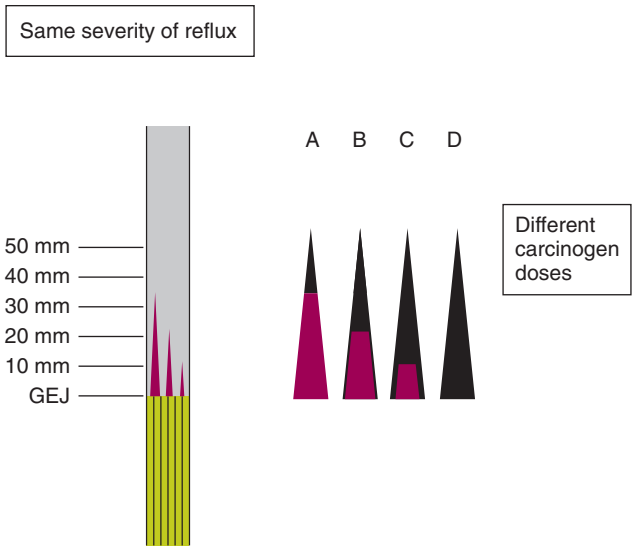


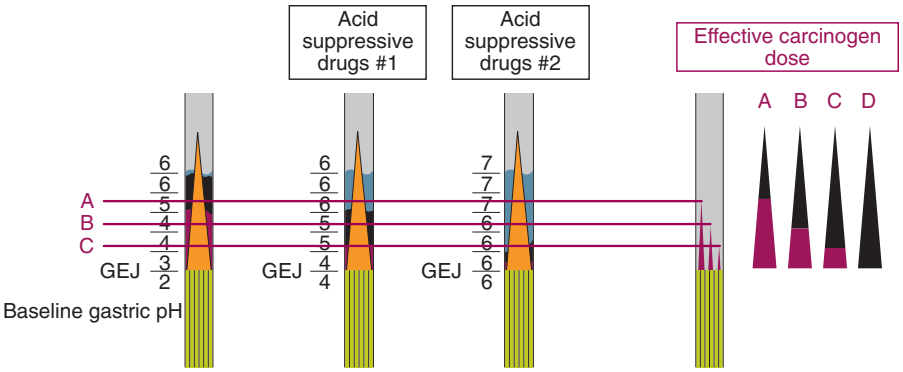
Figure 6–19 Four patients with the same severity of reflux (shown by triangle size). They have four different levels of carcinogen in their gastric juice *(red areas)*. The height in the esophagus to which an effective carcinogen is delivered is greatest in patient **A,** who has the highest carcinogen concentration. Patient **D** does not have any carcinogens in the gastric juice and therefore has no cancer risk. Unfortunately, there is no method of assessing the carcinogen activity of gastric juice. *GEJ,* Gastroesophageal junction.

Interaction Between Carcinogens and Target Cells

Whatever the carcinogenic molecules, it can be reasonably assumed they exist at highest concentration in the stomach, reach the esophagus by reflux, and decrease in concentration from the gastroesophageal junction to the more proximal esophagus (Figures 6–18 and 6–19). The effective carcinogen concentration is always greatest in the most distal esophagus and reaches a variable height in the esophagus (see Figures 6–18 and 6–19). The exact height to which an effective carcinogen dose is delivered by reflux will depend on the severity of the reflux (see Figure 6–18) and the concentration of the carcinogen (see Figure 6–19).

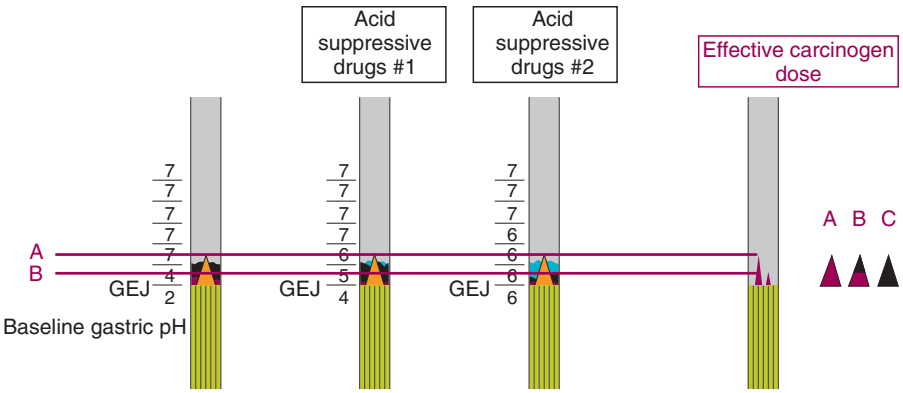
It is extremely interesting that the maximum carcinogenic tendency operates in the lowest regions of the esophagus. This is almost exactly opposite of the tendency to intestinal metaplasia. Patients with intestinal metaplasia limited to the most proximal region of the columnar-lined esophagus are more protected because it is unlikely that the carcinogen will reach an effective dose level so high in the esophagus (Figures 6–20 and 6–21). This is true whether the segment of columnar-lined esophagus is long and has been induced by severe, high volume reflux (see Figure 6–20) or whether the segment of columnar-lined esophagus is short and has been induced by less severe, low-volume reflux (see Figure 6–21). The only difference between the different lengths of columnar-lined esophagus is that the prevalence of intestinal metaplasia is lower in patients with the shorter lengths.

The risk of cancer, however, increases as the intestinal metaplasia moves distally in such a patient. The patient who develops intestinal metaplasia in very short segments of columnar-lined esophagus has the highest theoretical exposure to the carcinogen because of the proximity to gastric juice (see Figure 6–10). This is counterbalanced by the fact that the number of target cells in longer segments is greater, resulting in a complex interplay of factors.



Volume of reflux	High	Remains high	Remains high
Time of exposure	Long	Remains high	Remains high
Amount of IM	Small	Increased	More increased
Amount of OCM	Moderate	Less	Still less
Cancer risk	Zero	Low	High

Figure 6–20 Influence of acid-suppressive drug therapy and the mechanism by which it promotes reflux-induced adenocarcinoma. The patient (shown at the left) has severe reflux disease with a long segment of columnar-lined esophagus that has intestinal metaplasia *(IM)* limited to the proximal region. This patient is not at risk for cancer at any of the four carcinogen concentrations (**A, B, C,** and **D**) that are shown because the effective carcinogen dose *(red lines)* is below the area of intestinal metaplasia *(blue areas).* Carcinogen has no effect on cardiac *(black areas)* and oxyntocardiac *(red areas)* mucosa. With minor acid suppression (e.g., with H2-receptor blockers, #1), the change in the pH gradient in the esophagus causes the intestinal metaplasia to extend more distally. This patient will be at risk for cancer only at the carcinogen dose **A,** where an effective carcinogen dose is delivered to the target cell in intestinal metaplasia. With more effective acid suppression (#2), the intestinal metaplasia extends farther down, and the patient is at risk at increasingly lower concentrations of carcinogen in the refluxate. *GEJ,* Gastroesophageal junction; *OCM,* oxyntocardiac mucosa.



Volume of reflux	Low	Unchanged	Unchanged
Time of exposure	Short	Unchanged	Unchanged
Amount of IM	Zero	Low	Increased
Amount of OCM	Moderate	Less	Still less
Cancer risk	Zero	Low	High

Figure 6–21 The same mechanism of increased cancer risk with acid-suppressive drug use is seen in a patient with mild reflux disease and a shorter segment of columnar-lined esophagus. Though the exposure to carcinogen is small because reflux is mild, the proximity of the target cell to carcinogen makes this situation dangerous. *GEJ,* Gastroesophageal junction; *IM,* intestinal metaplasia; *OCM,* oxyntocardiac mucosa. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

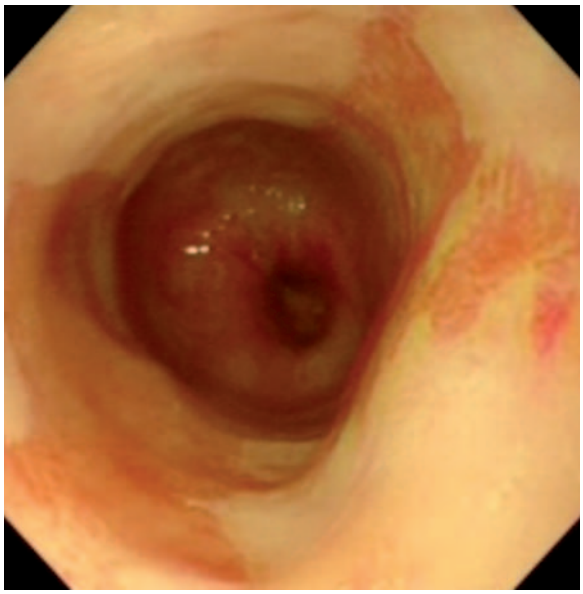


Figure 6–22 Case study: endoscopy shows a long segment of columnar-lined esophagus.

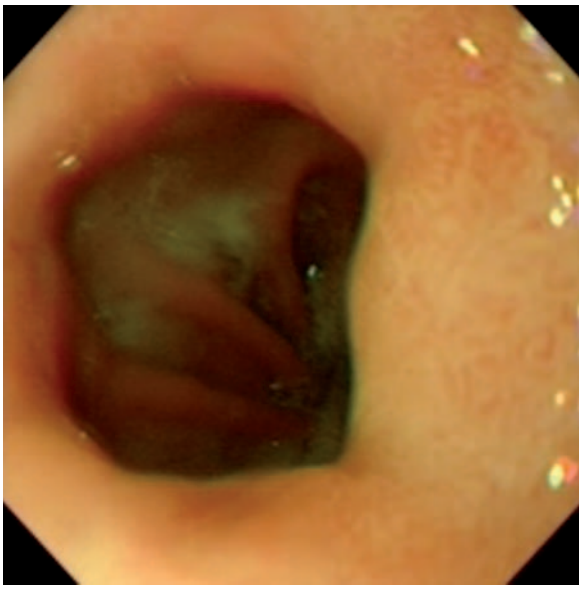


Figure 6–23 Distal area showing the rugal folds. There is no visible nodular or ulcerated lesion.

Carcinogen concentrations of gastric refluxate most likely vary among patients. Patients with high carcinogen concentration in the refluxate (see Figures 6–20*A* and 6–21) will tend to have the highest cancer risk. However, even the patient with the highest carcinogen dose will not be at risk for cancer if there is no intestinal metaplasia at the maximum height of effectiveness of carcinogenesis (see Figures 6–20 and 6–21). In contrast, patients with no carcinogenicity in their refluxate (see Figures 6–20*D* and 6–21*C*) will not be at risk for cancer, regardless of the extent of intestinal metaplasia in the esophagus. Unfortunately, there is no test to assess the level of carcinogenicity in a given patient. Without this information, the only risk factor that can be assessed is the extent of intestinal metaplasia.

There is clinical evidence to support this hypothesis. Adenocarcinomas in Barrett esophagus are distributed throughout the esophagus but tend to occur more commonly in the distal part of the esophagus than in the proximal esophagus, even when long segments of Barrett esophagus are present. Thiesen et al[15] reported that adenocarcinoma occurred maximally at the distal end of the intestinal metaplasia within a columnar-lined segment. In our study of 74 adenocarcinomas of the esophagus and "gastric cardia," intestinal metaplasia was found at the proximal edge of the tumor in 25 cases and at the distal edge in 16 cases, again suggesting that malignant transformation favored the more distal part of the segment of intestinal metaplasia.[5]

CASE STUDY

This case was graciously referred to me by Dr. Franz Martin Riegler in Vienna, Austria. A 70-year-old male (the age has been changed to hide the patient's identity) was treated in Vienna. During surveillance biopsy of long-segment Barrett esophagus (Figure 6–22), there was high-grade dysplasia detected in the distal third of the columnar-lined segment within the tubular esophagus (Figures 6–23 and 6–24). The high-grade dysplasia occurred in flat mucosa without ulceration or nodularity (see Figure 6–23). The more proximal region showed cardiac mucosa with intestinal metaplasia (Figure 6–25). The patient underwent esophagectomy with two field lymphadenectomy and had a gastric

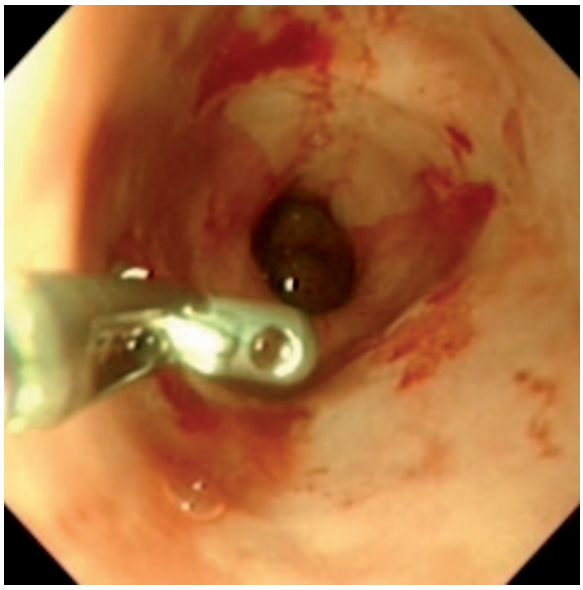


Figure 6–24 Biopsy of the distal part of the visible columnar-lined segment.

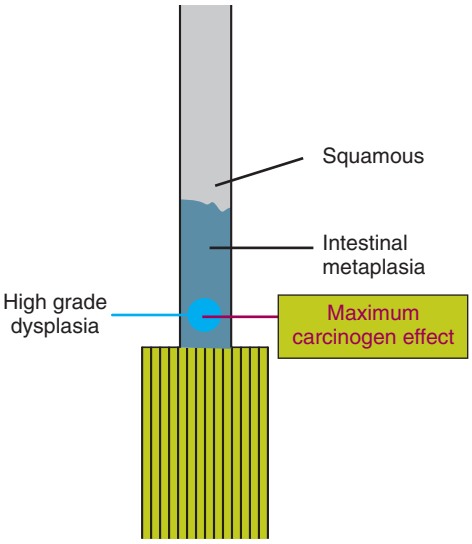


Figure 6–25 Biopsy showed a long columnar-lined segment composed predominantly of intestinal metaplasia *(blue area).* An area of high-grade dysplasia *(blue circle)* was present in the distal region of this segment. This is the maximum point of carcinogen effectiveness, which is related to the number of target cells present and the concentration of carcinogen.

pull-up. In the resected specimen, the tumor was T1a stage with negative lymph nodes. He recovered uneventfully after surgery, and a recent follow-up endoscopy 1 year after the surgery showed a normal anastomotic line with no evidence of columnar-lined esophagus.

This patient demonstrates the typical features of carcinogenesis within a columnar-lined esophagus. There is a long segment of intestinal metaplasia; this certainly indicates severe, long-duration reflux disease of high volume. Although the entire segment is at risk, if there is a quantitation of target cells, the highest density of target cells (defined by the number of goblet cells within cardiac mucosa) is likely at the proximal end and decreases more distally. In contrast, the carcinogen dose, which is delivered by gastroesophageal reflux, is maximal in the most distal region of the columnar-lined esophagus immediately above the gastroesophageal junction (the rugal folds are visible in Figure 6–23, but the position of the proximal limit of gastric oxyntic mucosa is not known). The maximum carcinogen effect is determined by the optimum combination of the number of target cells and carcinogen dose. In this patient, it was in the distal third of the esophagus close to the end of the segment with intestinal metaplasia.

If we hypothesize about this patient's life history (Figure 6–26), he was born without any columnar-lined esophagus and developed reflux disease that progressively increased, resulting in a long segment of columnar-lined esophagus. This was likely complete by the time he was 30 years old. As long as the columnar-lined esophagus did not contain intestinal metaplasia, he was not at risk for cancer, regardless of the carcinogen dose in his refluxate, because no target cells were present. At some stage, most likely around 40 years of age, intestinal metaplasia developed in the most proximal region of the columnar-lined segment. The risk for cancer now surfaced, but it was still low because his target cells were far removed from the maximum carcinogen dose. In a patient with a relatively low carcinogen dose (as shown in Figure 6–26), carcinogenesis only begins when the intestinal metaplasia extends dis-

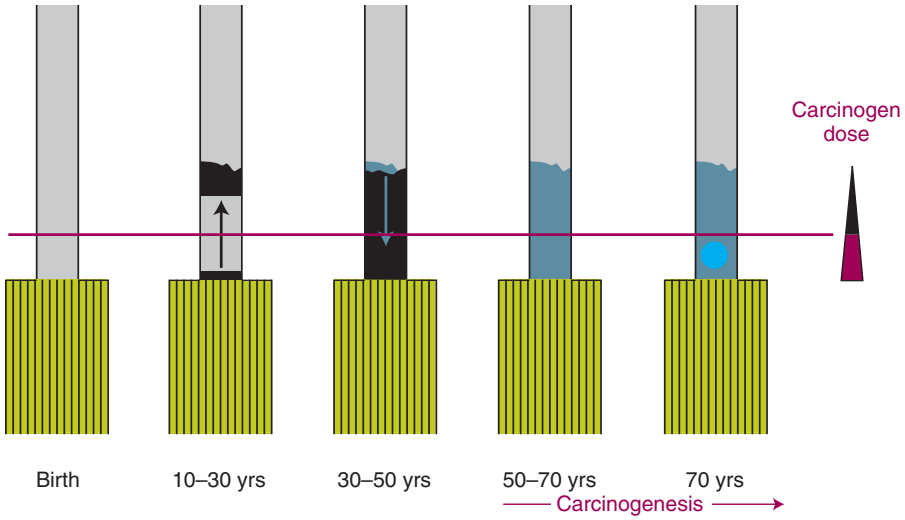


Figure 6–26 Hypothetical construct of the events in the esophagus during this patient's lifetime. At birth, there was no cardiac mucosa. Reflux likely began early in life, resulting in a progressive increase in the length of columnar-lined esophagus up to about age 30. Intestinal metaplasia develops in the most proximal part of this columnar-lined segment at this time. Over the next 20 years, the intestinal metaplasia gradually extends downward to involve the more distal esophagus. This process is accelerated if acid-suppressive drugs are used. When the intestinal metaplasia reaches a point in the distal esophagus where there is delivery (by reflux) of an adequate carcinogen dose, the mutations of cancer begin and progress to the point where the epithelium shows high-grade dysplasia at age 70.

tally to the point where there is an effective carcinogen dose. Within the area of the distal esophagus that is exposed to this effective carcinogen dose, the maximum dose is most distal (see Figure 6–26). The actual neoplasm occurs at the site of maximum carcinogenicity, which is a function of the number of target cells and carcinogen dose.

Two things should be noted here:

1. There is a long period of recognizable abnormality in this patient extending from the time he first develops cardiac mucosa to the time at which carcinogenesis begins. In this hypothetical construct, cardiac mucosa was first detectable at 10 years and intestinal metaplasia at 30 years, while carcinogenesis began at 50 years. There was 40 years of recognizable abnormality during which there was no intervention to prevent the induction of change that exposed this patient to cancer risk. This failure is based on the present practice guidelines for reflux disease. Surely, this is a missed opportunity. We would do better if we attacked the disease in this patient before age 50. A successful anti-reflux procedure any time during that period would have prevented any possibility of cancer. This would have been a superior alternative to simply waiting for high-grade dysplasia to develop and then precipitating an esophagectomy. This, however, is the present standard of care.
2. What were the factors that resulted in this patient developing intestinal metaplasia, which extended down to the distal region of the esophagus, where there was carcinogenic potential? This could have happened naturally. However, if this patient was on acid-suppressive drug treatment, the resulting alkalinity would have induced the downward extension of intestinal metaplasia in cardiac mucosa (see Figure 5–16). Although this patient could have developed high-grade dysplasia without acid-suppressive drugs, the use of such drugs would promote carcinogenesis by this mechanism.

Factors Associated with an Increased Cancer Risk in Gastroesophageal Reflux Disease

All patients who develop esophageal adenocarcinoma have progressed through the reflux-to-adenocarcinoma sequence. This means that at some stage before the development of cancer, the patient must have passed through a phase of Barrett esophagus (and a phase of cardiac metaplasia of the esophagus before that). Both these phases usually extend over many decades (see Figure 6–26). It is a travesty that we do nothing to identify and treat these patients effectively during this recognizable premalignant phase. Instead, the basic management plan is to simply allow these patients to progress to advanced disease and present with symptoms of cancer. At this stage, they have an expected survival rate of about 15%. If a patient is lucky, a physician will perform an endoscopy, detect Barrett esophagus, place the patient on surveillance, and find the cancer in the noninvasive stage. Even then, the patient may require an esophagectomy (see Figure 6–26). These lucky patients are those who "fail" to control initial symptoms with acid-suppressive drug therapy.

In this section, I will describe the current methods used to assess cancer risk and will show why this is extremely ineffective. In Chapter 1, I made a plea for a change in the approach to managing this disease with a new aggressive method of detecting the premalignant phase. In Chapter 7, I will outline how correctly performed endoscopy and biopsy can assess cancer risk at a cellular level far more accurately than presently used methods.

Symptomatic Reflux Disease

Lagergren et al[4] reported that 60% of patients who develop adenocarcinoma of the esophagus gave a history of reflux symptoms (heartburn and/or regurgitation at least once a week) 5 years before the diagnosis of cancer. The association between symptomatic reflux and adenocarcinoma of the "cardia" is less (only 29% of patients gave a positive history of reflux symptoms in the study by Lagergren et al[4]).

The reality of these data is that although the presence of symptoms indicates risk of esophageal adenocarcinoma, the absence of such symptoms does not indicate an absence of risk. If Lagergren et al's[4] definition of symptomatic reflux is used, 40% of patients who develop esophageal adenocarcinoma and 71% of patients who develop adenocarcinoma of the "cardia" would not be detected by a screening test that was dependent on the presence of symptoms. If a more sensitive definition of symptomatic reflux (e.g., any heartburn) had been used, a greater number of people who develop adenocarcinoma would have been symptomatic. However, these data are not available.

Demographic Factors

Reflux-induced adenocarcinoma of the esophagus tends to occur in Caucasian males over the age of 40 years, with the incidence increasing with age to about 80 years. African-Americans, Asians, and Hispanic-Americans have a lower incidence.

The male-female ratio is highest for adenocarcinoma arising in the distal esophagus, where it is 6–8:1. The male predominance decreases as the cancer migrates distally. Adenocarcinoma of the "gastric cardia" has an almost equal incidence among the sexes. This most likely reflects the sex distribution of the segment length of Barrett esophagus. Long-segment Barrett esophagus is a strongly male-predominant disease, with the sex distribution becoming progressively more equal as the length of the Barrett segment decreases.

There is an association between obesity and esophageal adenocarcinoma. Bu et al,[16] from our group, showed that there was a relationship between the presence of cardiac mucosa and Barrett esophagus, suggesting that obesity acted at an early stage in the reflux-to-adenocarcinoma sequence.

Clinical Evidence of Severity of Reflux Disease

There is a strong association between the severity of reflux, however measured, and the risk of reflux-induced adenocarcinoma. In the study by Lagergren et al,[4] the odds ratio for adenocarcinoma of the esophagus increased from 7.7 (95% confidence interval, 5.3 to 11.4) in patients with and without symptoms to 43.5 (95% confidence interval, 18.3 to 103.5) in patients with the most severe symptoms for the longest duration. There was a similar increase for adenocarcinoma of the "cardia," in which the odds ratio increased from 2.0 (95% confidence interval, 1.4 to 2.9) to 4.4 (95% confidence interval, 1.7 to 11.0) for the same two comparative groups.

There is also a strong association between the presence of a hiatal hernia, which is a manifestation of severe reflux disease, and the risk of adenocarcinoma. Similarly, there is a strong association between the degree of abnormality of the 24-hour pH test and adenocarcinoma.

All these associations (symptom severity, hiatal hernia, and an abnormal 24-hour pH test) also exist for the presence of cardiac mucosa and Barrett esophagus. Many studies show a step-wise increase in these associations from cardiac mucosa, Barrett esophagus, to adenocarcinoma.

Unfortunately, the absence of even all these features cannot predict an absence of risk. Adenocarcinoma can arise in patients without symptoms, hiatal hernia, or an abnormal 24-hour pH test.

Evidence of Duodenogastroesophageal Reflux

There is a strong association between the presence of duodenal elements in the gastroesophageal refluxate (as shown by the presence of a positive Bilitec test) and esophageal adenocarcinoma.[17] There is also evidence for an association of a positive Bilitect test with the occurrence of Barrett esophagus.

Barrett Esophagus

The diagnosis of Barrett esophagus is the strongest risk indicator for esophageal adenocarcinoma. At the time the patient is diagnosed, the duration for which intestinal metaplasia has been present is unknown. The risk of cancer for patients with Barrett esophagus is 0.5% per year.[18] This is not an insignificant risk; it means that one in every five patients who is diagnosed with Barrett esophagus at age 40 will develop adenocarcinoma by age 80. The risk increases in patients who have evidence of progression in the carcinogenic pathway at the index biopsy (e.g., low-grade dysplasia,[19] aneuploidy,[20] or high-grade dysplasia).[20–22]

There are factors within the diagnosis of Barrett esophagus that may be useful in delineating the risk of cancer.

The Length of Barrett Esophagus

The length of the Barrett segment (i.e., long-segment versus short-segment disease) as a risk indicator is controversial. At present, the classification of Barrett esophagus into long-segment and short-segment disease is based entirely on the length of the endoscopically measured columnar-lined esophagus in a

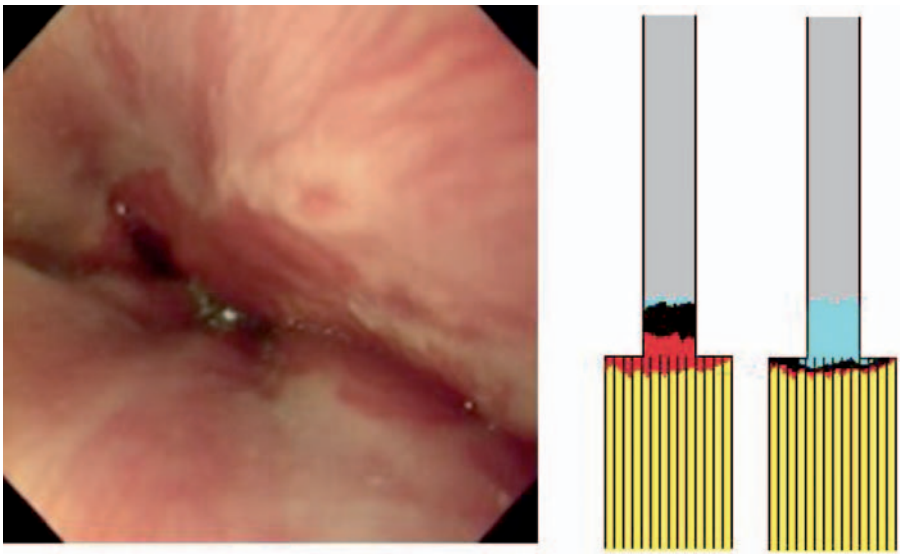


Figure 6–27 Endoscopy showing a short segment of columnar-lined esophagus with intestinal metaplasia on biopsy (Barrett esophagus). Histologic mapping is required to determine the amount of intestinal metaplasia, which could vary between a very small area in the most proximal part of the segment or almost the entire segment. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

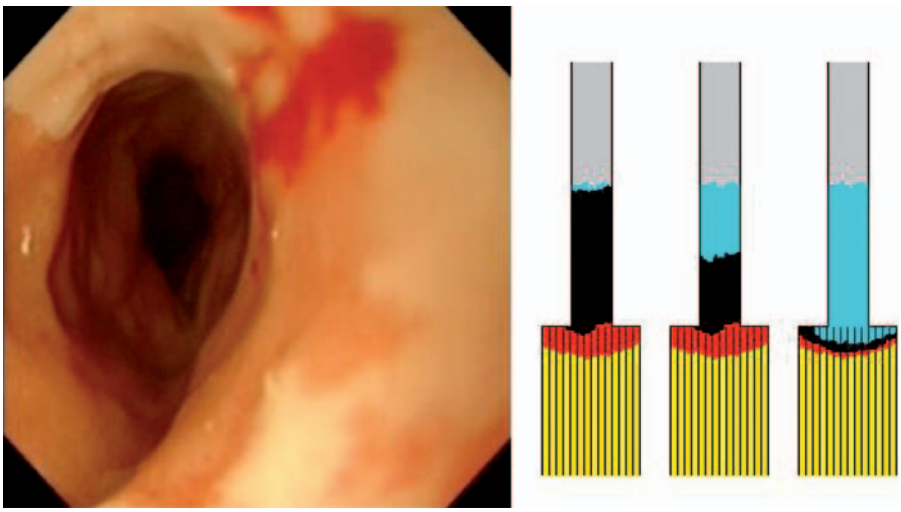


Figure 6–28 Endoscopy showing a long segment of columnar-lined esophagus with intestinal metaplasia on biopsy (Barrett esophagus). Histologic mapping is required to determine the amount of intestinal metaplasia, which could vary considerably, involving a small, intermediate, or large part of the columnar-lined segment, always beginning in the proximal region and extending downward into the distal esophagus. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

patient with intestinal metaplasia. This basically assumes that the entire segment of columnar-lined esophagus consists of intestinal metaplasia, which is clearly a false assumption. In a patient who has intestinal metaplasia, the columnar-lined segment seen at endoscopy almost always contains cardiac and oxyntocardiac mucosa admixed with and usually distal to the intestinal metaplasia. The amount of intestinal metaplasia is highly variable. It is very feasible that a patient with short-segment Barrett esophagus (Figure 6–27) may have more intestinal metaplasia than one with long-segment disease (Figure 6–28).

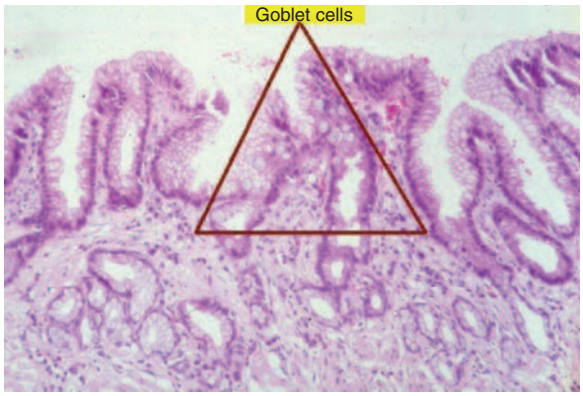


Figure 6–29 The amount of intestinal metaplasia within cardiac mucosa varies considerably. This shows a very small area with goblet cells (limited to the area within the triangle) in cardiac mucosa.

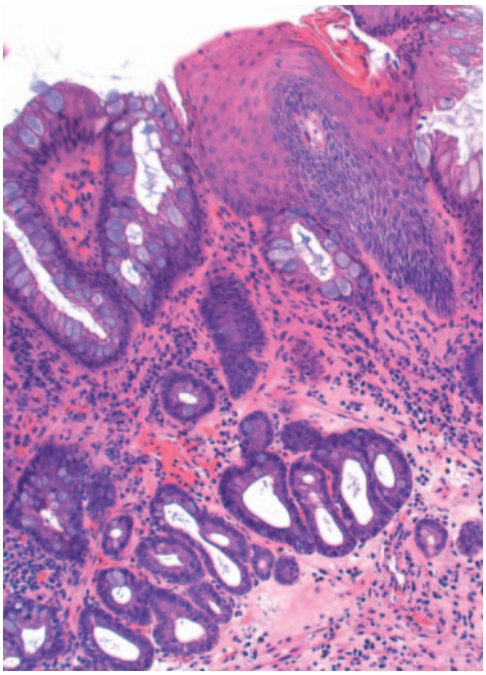


Figure 6–30 Cardiac mucosa with intestinal metaplasia showing a higher density of goblet cells than what is seen in Figure 6–29. The number of target cells receptive to carcinogens is likely to be greater in this area than in Figure 6–29.

Evidence is mixed about the risk of cancer in long- and short-segment Barrett esophagus. Although many studies find a correlation between Barrett segment length and cancer risk, one of the most authoritative studies found that there was no significant difference.[23] This view is generally adhered to in patient management; patients with both long- and short-segment Barrett esophagus are placed under an equivalent surveillance protocol.

The Amount of Intestinal Metaplasia

This is an unevaluated risk, but it is logical to believe that the cancer risk will be directly proportional to the number of target cells present, because the likelihood of a mutational event will be proportional to the number of target cells. Reclassification of Barrett esophagus by some measure of the number of target cells is likely to provide better risk delineation than the present classification into long- and short-segment Barrett esophagus (Figures 6–29 and 6–30). Quantitation of intestinal metaplasia is difficult; it requires a standardized biopsy protocol with adequate sampling within the entire columnar-lined segment and some system of histologic quantitation of goblet cells.

The Proximity of the Intestinal Metaplasia to the Gastroesophageal Junction

Because the concentration of the carcinogen is highest at the gastroesophageal junction, the risk of cancer increases when the intestinal metaplasia involves the distal part of the columnar-lined segment. In a patient with a long segment of columnar-lined esophagus, the more proximal region may not receive an adequate carcinogen dose during reflux. If the patient with long-segment Barrett esophagus has intestinal metaplasia restricted to the proximal region, there may be no cancer risk for a given carcinogen dose. If, however, intes-

tinal metaplasia is present more distally, the patient develops a risk of cancer at the same carcinogen dose.

This is supported by two pieces of evidence:

1. The location of cancer in a Barrett esophagus segment tends to be in the more distal rather than proximal region (see Figure 6–25).[15] This is despite the fact that the density of intestinal metaplasia is usually greatest in the more proximal region.
2. A large number of adenocarcinomas arise in the end-stage dilated esophagus, where they occur in very short segments of intestinal metaplasia. The total number of adenocarcinomas of the "gastric cardia" is only slightly less than that of adenocarcinomas of the tubular esophagus.

The Proliferative Rate of the Target Cells

Intestinal epithelium has the highest proliferative rate among the different epithelial types in columnar-lined esophagus.[24] It is logical that cancer risk will correlate with proliferative rate, because the probability of mutations increases with increasing proliferative rate. Any factor that decreases the proliferative rate of intestinal metaplastic epithelium can be expected to cause a slight decrease in the cancer risk. This is likely to be a minor factor.

Acid-suppressive drugs are used in the treatment of patients with Barrett esophagus based on the belief that acid increases proliferation rates in the target cells. Feagins et al[25] showed that the reverse is true. In a study that used a non-neoplastic Barrett's epithelial cell line, they showed that acid exposure had an antiprolifeartive effect on these cells. They concluded that the use of acid suppressive drugs in Barrett esophagus could therefore be detrimental.

Acid-Suppressive Drug Therapy

Coincidental with the development of increasingly effective acid-suppressive drugs—from simple antacids to H2-receptor antagonists to proton pump inhibitors—the incidence of adenocarcinoma of the esophagus has increased sixfold in the United States from 1975 to 2000.[26] If we credit the decline in uncontrolled symptoms, ulcers, and strictures to the efficacy of acid suppression, we should consider whether the increase in adenocarcinoma is due to a cancer-promoting effect of these drugs. We may be treating the symptoms of a disease with an agent that promotes cancer. Although we are benefiting millions of people who suffer from heartburn, we may also be contributing to the death of 22,000 Americans every year from reflux-induced adenocarcinoma. This is not a good trade-off.

This question must be seriously addressed along two lines.

Statistical Evidence of Increased Risk with Acid-Suppressive Drugs

There is evidence that the use of acid-suppressive drugs promotes esophageal adenocarcinoma. In the landmark study that established the association between symptomatic reflux and adenocarcinoma of the esophagus and gastric cardia, Lagergren et al[4] reported (see Figure 1–9):

> We compared the risk of esophageal adenocarcinoma among persons who used medication for symptoms of reflux at least five years before the interview with that among symptomatic persons who did not use such medication. The odds ratio was

3.0 (95% confidence interval, 2.0 to 4.6) without adjustment for the severity of symptom and 2.9 (95% confidence interval, 1.9 to 4.6) with this adjustment.

For some reason, they do not provide the data on which this conclusion is based. This is powerful evidence that acid-suppressive drugs play a primary role in promoting reflux-induced adenocarcinoma. Because the increased risk persisted when the severity of symptoms were taken into account, the data suggest that acid-suppressive drug use has an equal or greater association with adenocarcinoma as does symptomatic reflux.

In a more recent study by the same group,[27] the use of acid-suppressive drugs was again shown to increase the risk of esophageal adenocarcinoma. This was a population-based, nested case-control study that looked at persons 40 to 84 years of age registered in the General Practitioners Research Database in the United Kingdom between 1994 and 2001. In 4,340,207 person-years of follow-up, 287 patients with esophageal adenocarcinoma, 195 with gastric cardia adenocarcinoma, and 327 with gastric non-cardia adenocarcinoma were identified. An "esophageal" indication for long-term acid suppression (reflux symptoms, esophagitis, Barrett esophagus, or hiatal hernia) rendered a fivefold increased risk of esophageal adenocarcinoma (odds ratio 5.42, 95% confidence interval, 3.13 to 9.39). No association was observed among users within a group of other indications, including peptic ulcer and "gastroduodenal symptoms" (e.g., gastritis, dyspepsia, indigestion, and epigastric pain). The latter suggests that the presence of reflux-induced pathology must be present in the esophagus for these drugs to act as promoters of reflux-induced adenocarcinoma. However, these data are not conclusive enough to establish a cancer-promoting role of acid-suppressive drugs. As the authors suggest, the association is most likely explained by the underlying treatment indication (i.e., symptomatic reflux) as a risk factor.

There is no contrary data that prove that acid-suppressive drug use either decreases or does not increase the risk of cancer. Most studies show a trend that suggests that acid-suppressive drugs may promote cancer, but these studies do not have the statistical power to prove this.

Theoretical Considerations

Understanding why acid-suppressive drugs can theoretically promote carcinogenesis (see Figures 6–20 and 6–21) is not difficult. Acid suppression does not prevent reflux; it simply removes the acid from the refluxate. Reflux continues unabated; the esophageal epithelium is exposed to all the molecules in the refluxate except acid.[28]

From a theoretical standpoint, there are only two ways by which acid-suppressive drugs would *decrease* the risk of cancer in a patient with reflux disease:

1. If acid was responsible for critical steps in the reflux-to-adenocarcinoma sequence: there is evidence that acid is responsible for the early stages of reflux disease wherein the squamous epithelium is damaged, resulting in cardiac transformation. However, this phase occurs early in the course of reflux disease, and cardiac metaplasia already exists at the time of presentation in the vast majority of patients. It is possible that acid-suppressive drugs, when used early enough, will decrease the length of columnar-lined esophagus. There is no evidence that acid is responsible for the conversion of cardiac mucosa to intestinal (Barrett) metaplasia or Barrett esophagus to adenocarcinoma.
2. If acid increases the proliferation rate in cardiac mucosa and intestinal (Barrett) epithelium: there is little evidence that this is true. Acid suppressive

drugs may decrease the proliferative rate of cardiac mucosa in the esophagus and thereby decrease the overall likelihood of the genetic switch that results in intestinal metaplasia. On the other hand, acid suppression likely increases the proliferative rate in intestinal (Barrett) epithelium, thereby increasing the risk of genetic mutations. The overall effect of acid suppression in Barrett esophagus is likely to be detrimental rather than protective.[25]

On the other hand, acid-suppressive drug therapy is theoretically highly likely to *increase* the risk of cancer. I have shown that the mechanism of action of acid-suppressive drugs (decreasing gastric acidity) has a strong theoretical likelihood of promoting the development of intestinal metaplasia in cardiac mucosa as well as increasing the amount of intestinal metaplasia within the columnar-lined segment (see Figures 5–16 and 5–17). This fact is critically important; as the acid-suppressed patient develops intestinal metaplasia in the more distal esophagus, the target cell for carcinogenesis is brought closer to the highest concentration of carcinogen, which is at the gastroesophageal junction (see Figures 6–20 and 6–21).

The other damning evidence that acid-suppressive drugs may promote cancer is the effect of alkalinization on the metabolism of bile acids often present in the gastric lumen because of duodenogastric reflux. Studies of bile salt metabolism show that there is a critical pH range, between 3 and 6, in which bile acids exist in their soluble, unionized form; can penetrate cell membranes; and accumulate within esophageal mucosal cells[9] (see Figure 6–17). At a lower pH, bile acids are precipitated, and at a higher pH, bile acids exist in their non-injurious ionized form.[10] Penetration of bile salt metabolites into epithelial cells of the esophagus is a critical factor in carcinogenesis, because this activates a variety of metabolic pathways that lead to increased proliferation of the cells.

Acid-suppressive drugs are probably not the primary reason patients with reflux disease develop adenocarcinoma. Many patients who present with reflux-induced adenocarcinoma give no history of acid-suppressive medication use. There is some other basic reason for the dramatic increase in the adenocarcinoma incidence in the past three decades. This basic reason is unknown but is probably related to an increase in the concentration of the yet unknown carcinogens in the gastric refluxate.

However, whatever carcinogenic tendency exists in any given patient, acid-suppressive drug therapy will cause a tilt in the equilibrium that promotes and increases the risk of carcinogenesis. First, the increased alkalinization of the refluxate will bring the target cell closer to the gastroesophageal junction and carcinogen (see Figures 5–16 and 5–17). Second, the alkalinization of gastric juice will boost the generation of carcinogens from bile acids (see Figure 6–17), increasing the dose of carcinogen in gastric juice and driving the point of effective carcinogenesis in the esophagus more proximally. The combination of the two factors brings the target cell and carcinogen into increasingly greater contact in the patient using acid-suppressive drugs (see Figures 6–20 and 6–21). Acid-suppressive agents have *promoted* reflux-induced adenocarcinoma. They have caused adenocarcinoma in some patients, who otherwise would have been below the threshold for carcinogenesis, and accelerated the development of cancer in others.

Factors that Are Protective Against Development of Cancer in Barrett Esophagus

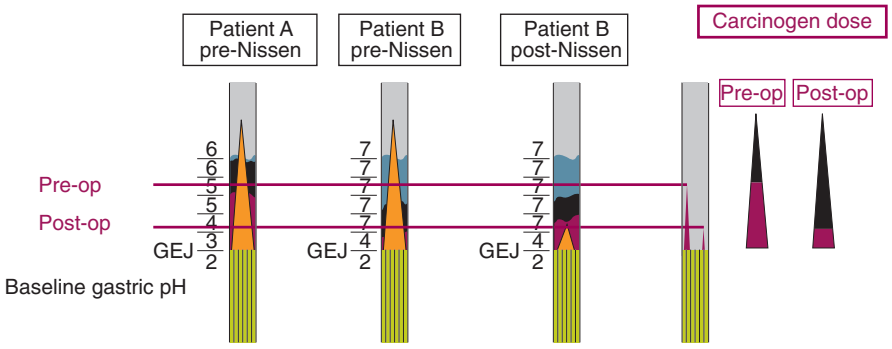
The following section discusses the only effective methods of decreasing the risk of cancer.

Decreasing Gastroesophageal Reflux

Reducing reflux to an extent that the changes in the reflux-to-adenocarcinoma sequence are prevented will decrease cancer risk, both theoretically and practically. Because the cause of gastroesophageal reflux is usually an abnormality of the lower esophageal sphincter, decreasing reflux usually entails some method of improving sphincter function. There are no drugs at present that effectively improve sphincter function over the long term. Many endoscopic techniques have been attempted to improve sphincter function, all without significant success.

The only effective method of creating a permanent valve is some form of surgical fundoplication, in which the fundus of the stomach is wrapped around the distal esophagus and sutured in place. The most common technique is a Nissen fundoplication, which can be performed laparoscopically. A successful anti-reflux surgical procedure, defined as one that normalizes the 24-hour pH test, has been shown to prevent the occurrence of intestinal metaplasia in non-intestinalized columnar-lined esophagus.[29] Although not yet proven, there is an increasingly convincing body of literature that strongly suggests that a successful fundoplication decreases the incidence of high-grade dysplasia and cancer in patients with Barrett esophagus, even when done in the presence of low-grade dysplasia.[30]

Theoretically, a successful anti-reflux operation, by reducing the amount of reflux, will lower the point in the esophagus at which the carcinogen is delivered at an effective dose (Figure 6–31). This will have a preventive effect in the induction of cancer in Barrett esophagus by separating the target cell in the proximal esophagus from the carcinogen. Anti-reflux surgery may also reverse or decrease intestinal metaplasia, converting it into cardiac or squamous epithelium. Another potential benefit of anti-reflux surgery is that it is



Volume of reflux	High	High	Decreased
Time of exposure	Long	Long	Decreased
Amount of IM	Small	Large	Same or less
Amount of OCM	Moderate	Small	Increased
Cancer risk	Zero	Present	Zero

Figure 6–31 Effect of anti-reflux surgery on the risk of cancer. Two patients with long-segment, columnar-lined esophagus are shown with a high carcinogen concentration in the refluxate *(black triangles on right)*. Patient **A** has a very short area of intestinal metaplasia *(IM)* in the most proximal region. The reflux fails to deliver an effective carcinogen dose to this area; this patient is not at risk despite a very long segment of Barrett esophagus and a significant carcinogen concentration. Patient **B** is similar except for the fact that intestinal metaplasia extends lower into the distal esophagus and is present in the region of effective carcinogen dose. This patient is at risk for cancer. When an anti-reflux operation is performed, the reflux volume decreases, and the delivery of carcinogen to the esophagus decreases. The intestinal metaplasia is no longer exposed to an effective carcinogen dose; the patient has no cancer risk. *GEJ,* Gastroesophageal junction; *OCM,* oxyntocardiac mucosa.

highly effective in controlling symptoms of reflux; most patients do not require any acid-suppressive drug treatment after the surgery. As a result, the conversion of bile acids to carcinogens in the stomach is prevented because baseline gastric pH is restored to the normal 1 to 3 level, at which level bile acids are inactivated (see Figure 6–17).

Ablation of Barrett Epithelium

Removing the target epithelium at risk by some ablative technique or surgical resection can theoretically decrease the cancer risk. However, in these cases, there remain the same conditions that prevailed before the ablation was undertaken, and the risk of recurrence of Barrett esophagus is very high. When ablation of the epithelium is accompanied by a method to decrease gastroesophageal reflux (such as a Nissen fundoplication) the recurrence of Barrett esophagus can be prevented. This begs the question as to whether the ablation is necessary at all. An effective fundoplication renders the Barrett epithelium harmless by removing the carcinogens in the refluxate; if this is true, ablating the epithelium is only worthwhile if there is evidence that it is the site of a prevalent cancer (e.g., in high-grade dysplasia).

When Barrett epithelium is ablated, the esophagus can be induced to heal by regeneration of squamous epithelium if acid is removed from the refluxate with well-controlled acid-suppressive drug therapy. Once squamous epithelium has developed, there is the possibility that effective acid suppression can prevent cardiac metaplasia in squamous epithelium. This is the earliest change in reflux disease and is acid-induced. Ablation has given us the opportunity to prevent the first step in the reflux-to-adenocarcinoma sequence. Practically, this is difficult because it requires excellent acid suppression. If there is any failure of acid suppression that results in cardiac metaplasia, the acid-suppressed alkaline refluxate will promote intestinal metaplasia rapidly in the cardiac metaplastic segment because the milieu was correct for this before the ablation was performed.

The other problem with ablation is the uncertainty about the structure of the lamina propria under the regenerated squamous epithelial surface. If a residual glandular component of the Barrett epithelium remains under the squamous epithelium (Figure 6–32), this may progress to adenocarcinoma under the seemingly normal squamous epithelium (Figure 6–33). To remove this risk, the ablation must remove the entire thickness of the mucosa up to the muscularis mucosae. This is difficult because of the great variability of thickness of the glandular mucosa in different areas of columnar-lined esophagus (Figures 6–34 and 6–35) and the fact that the muscularis mucosae frequently undergoes irregular hyperplasia, often splitting into two distinct layers (Figure 6–36). When intramucosal adenocarcinoma is present, the epithelial thickness can be much greater than usual and extremely variable (Figure 6–37). Ablation that extends deeper than the muscularis mucosae has a high risk of stricture formation.

Exclusion of Bile from the Refluxate

Csendes et al[31] have recently suggested a new operation for Barrett esophagus that adds to a fundoplication a step to exclude the duodenum and prevent the entry of bile into the stomach. If bile acids are important in carcinogenesis, as is strongly suggested by the evidence, this will protect against cancer better than a fundoplication alone. This surgery requires separation of the stomach from the duodenum and creation of a Roux-en-Y loop for gastric outflow. Although it sounds radical, the surgery is not much more radical than the

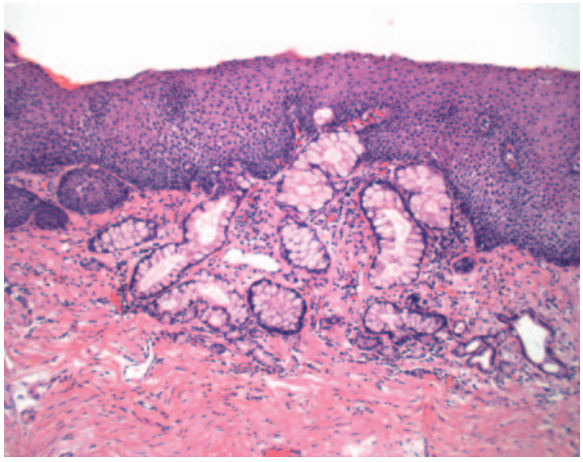


Figure 6–32 Residual intestinal metaplasia in glands in the lamina propria after the surface has reverted to squamous epithelium.

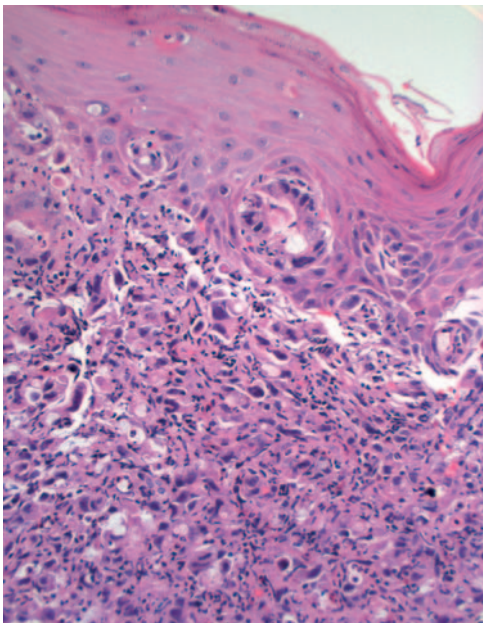


Figure 6–33 Poorly differentiated adenocarcinoma under a surface lined by squamous epithelium.

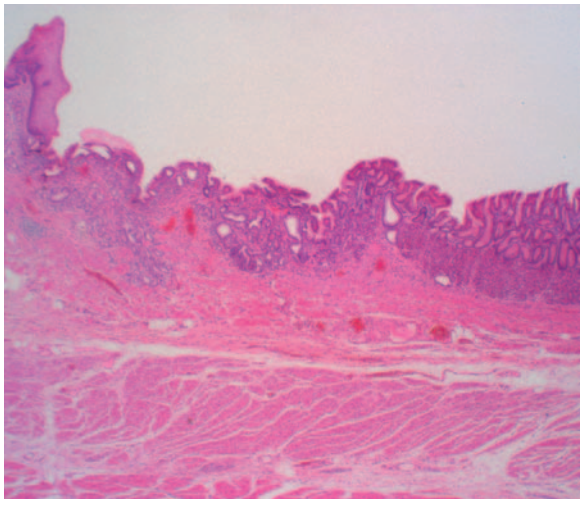


Figure 6–34 Segment of columnar-lined esophagus showing a relatively thin epithelium, which varies considerably in thickness from place to place.

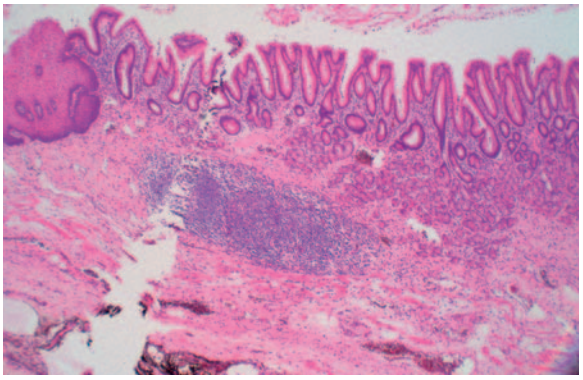


Figure 6–35 Segment of columnar-lined esophagus showing variation in thickness of the epithelial element and lymphoid infiltration and fibrosis in the deep mucosa.

very commonly performed bariatric procedures for obesity. It is certainly worthy of consideration because its purpose is to prevent esophageal adenocarcinoma.

Assessment of Cancer Risk in Barrett Esophagus

As mentioned earlier, the baseline risk of cancer in a patient with Barrett esophagus is estimated at 0.5% per year.[18] This is not currently considered an adequate risk to precipitate any cancer-preventing maneuver. The only management recommended for such patients is surveillance and acid-suppressive drug therapy in the naïve and false belief that acid suppression will magically prevent cancer in Barrett esophagus. There is some movement toward ablation and anti-reflux surgery to prevent cancer, but this is still miniscule.

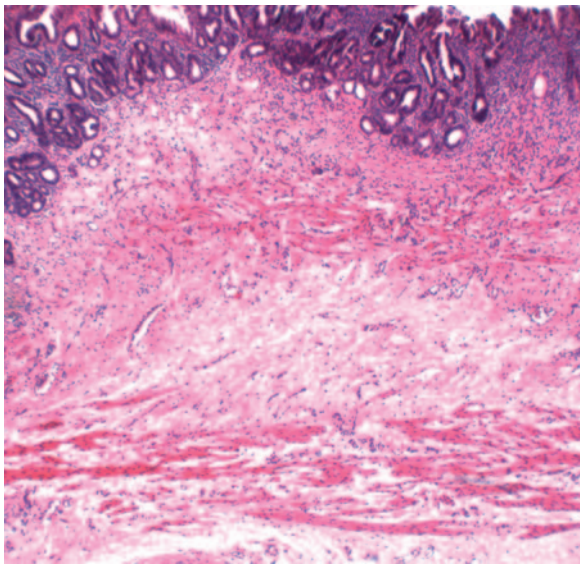


Figure 6–36 Segment of columnar-lined esophagus showing marked hyperplasia of the muscularis mucosae. This has split to form two distinct layers, separated by a considerable thickness. It is impossible to determine the actual thickness of the mucosa in each area because of the tremendous variation from point to point over even a short distance.

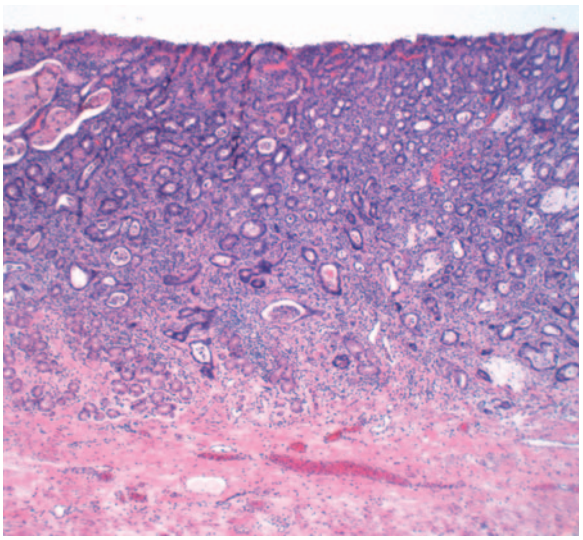


Figure 6–37 Intramucosal adenocarcinoma showing extreme thickness of the mucosa. The mucosal thickness is approximately eight times of that shown in Figure 6–35.

I have suggested that the mere presence of Barrett esophagus is a sufficient risk factor for cancer that it should precipitate an aggressive cancer prevention operation (anti-reflux surgery; see Chapter 1). This only requires a change in attitude. The current belief is that a patient with Barrett esophagus only rarely develops cancer. The reality is that 1 of 10 people with Barrett esophagus will develop a lethal cancer in the next 20 years. In contrast, when one considers breast cancer, the fact that 1 in 8 or 9 women will develop the disease (which is less often lethal than esophageal adenocarcinoma) has precipitated mass screenings for mammographic lesions that are far less specific cancer indicators than Barrett esophagus.

The only recognized criterion to assess progression in the adenocarcinoma sequence in Barrett esophagus is dysplasia, which indicates a risk increase proportional to its grade. The ability to detect and grade dysplasia is flawed for the following reasons:

1. Dysplasia is often invisible, and we depend on random biopsies to procure specimens to detect it. The efficacy of random biopsies to provide an adequate sample is determined by the extent of Barrett esophagus (which is uncertain because endoscopy cannot differentiate intestinal from non-intestinalized columnar epithelium), the extent of the area of dysplasia (which can be small), and the number and size of biopsies. If a patient has a 4-cm length of Barrett esophagus (assuming a circumference of esophagus as 5 cm), this means that the surface area of Barrett esophagus is potentially 20 square cm. The most compulsive biopsy protocol recommended (four-quadrant biopsies at 1-cm intervals; Figure 6–38) will take 24 biopsies from this area at six 1-cm levels. If each biopsy samples a surface area of 0.4 × 0.4 cm (the average biopsy size, 0.16 sq cm), the total surface area sampled is 3.2 square cm or less than 20% of the total surface area. With less compulsive biopsy sampling, this percentage decreases. It should not be surprising that there is a significant potential for missing a small focus of dysplasia in any random biopsy protocol.

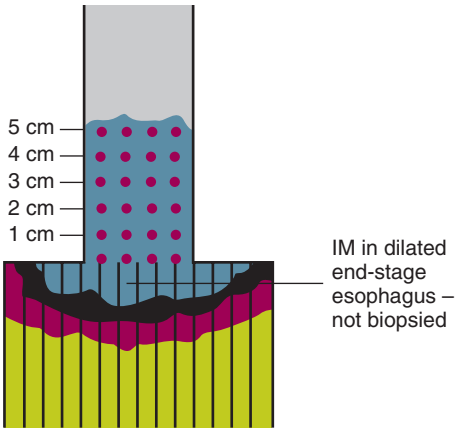


Figure 6–38 The most thorough biopsy protocol in a patient with columnar-lined esophagus is a four-quadrant biopsy. By calculation, this samples approximately 20% of the mucosal surface area, assuming a biopsy size of 4 mm and an esophageal circumference of 5 cm. *Blue,* intestinal metaplasia; *black,* cardiac mucosa; *red,* oxyntocardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

2. Even if the area of maximum dysplasia is sampled, the pathologic diagnosis of dysplasia and its grade has significant error and interobserver variation (see page 213).
3. The rate of progression from Barrett esophagus to cancer is very variable. In patients with a high carcinogen milieu, the rate of passing through dysplasia to cancer may be more rapid than any surveillance interval. This would mean that cancer can develop between two surveillance endoscopies. This is particularly true because the commitment to regular surveillance for Barrett esophagus is not high, and many patients have gaps of more than 1 year between surveillance endoscopies. It is not even commonly accepted in the medical community that annual surveillance endoscopy is indicated for Barrett esophagus.
4. There is a lag phase between a genetic change and its phenotypic expression. Patients who have no dysplasia may actually have all the genetic mutations required for cancer. These are prevalent cancers and are recognized when patients develop cancer within 1 to 2 years after an index endoscopy or after anti-reflux surgery.

All these problems relating to defining increased risk in Barrett esophagus should motivate everyone treating this disease to become more aggressive in preventing cancer as soon as Barrett esophagus is detected. This has not yet happened. We still wait until high-grade dysplasia is detected before there is active intervention. At this point, there is a 40% risk of a prevalent cancer that is not detected because of the limitations of random biopsies. Does this make any sense?

Molecular Abnormalities

Carcinogenesis in intestinal metaplastic epithelium probably progresses through a series of irreversible genetic mutations comparable to the development of adenocarcinoma in the colon. The molecular pathway of carcinogenesis in Barrett esophagus is much less understood than that of colonic adenocarcinoma, and it can be accurately stated that it is largely unknown.

The only molecular marker for cancer risk that has some support in the literature is the detection of aneuploidy and 4N fraction increase in a biopsy of Barrett esophagus by flow cytometry.[20] Reid et al[20] showed that the flow cytometrically defined abnormalities of aneuploidy and increased 4N fraction are valuable in identifying a subset of patients with low-grade dysplasia who are at increased risk for cancer. The data are not so convincing for patients

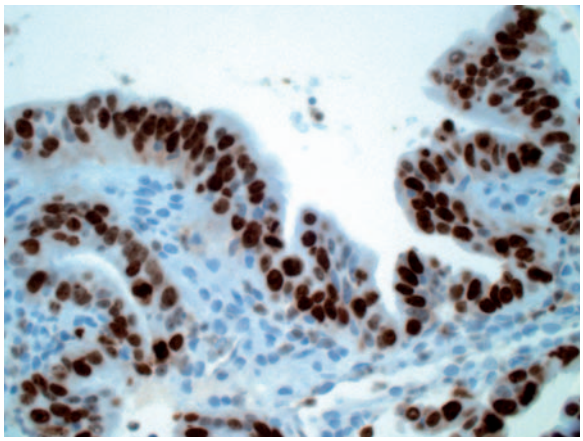


Figure 6–39 Immunoperoxidase staining for Ki67 in high-grade dysplasia showing positive staining in a high percentage of cells in the surface and superficial foveolar region. This is an aberrant Ki67 staining pattern that is typical of high-grade dysplasia. It is seen infrequently in low-grade dysplasia.

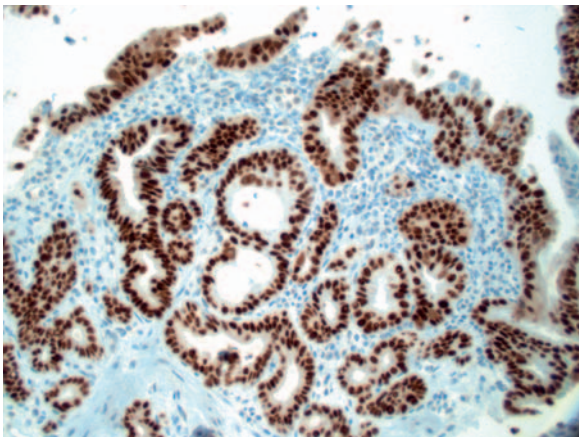


Figure 6–40 Immunoperoxidase stain for p53 in high-grade dysplasia showing strong expression in the dysplastic cells in both the foveolar region and on the surface.

who are negative or indefinite for dysplasia. In a patient with low-grade dysplasia, the absence of both aneuploidy and increased 4N fraction strongly suggests that cancer is much less likely. Flow cytometry requires special handling of specimens at the time of biopsy and considerable extra expense. This precludes its use in every patient with Barrett esophagus in standard practice outside the academic environment. However, in a patient with known low-grade dysplasia, its value justifies the extra effort and cost.

Many other genetic mutations have been described in Barrett esophagus, dysplasia, and adenocarcinoma. Although these genetic changes are more frequent in these epithelia, none has been identified as reliable molecular markers that define the stage of carcinogenesis. There is some evidence for a value of Ki67 expression patterns (Figure 6–39) and p53 expression (Figure 6–40) as risk indicators, but they are not yet considered reliable diagnostic tests with predictive value. P53, in particular, is often expressed at a low level in reactive epithelia and is sometimes completely negative in high-grade dysplasia.

In the absence of accurate molecular markers, reliance for clinical management of patients with Barrett esophagus must still be placed on the phenotypic expression of these changes (i.e., grade of dysplasia).

Dysplasia

Irreversible carcinogenic mutations may not be expressed phenotypically; when expressed, the phenotypic change may follow the genetic mutation after a significant lag phase. In Barrett esophagus, the phenotypic expression of genetic changes of carcinogenesis is believed to progress through low-grade dysplasia, high-grade dysplasia, and invasive adenocarcinoma (Figure 6–41). There is evidence for such a progression from longitudinal studies in patients under long-term surveillance for Barrett esophagus. The changes of dysplasia are the cytologic abnormalities of neoplasia; in other sites in the body, the term *intraepithelial neoplasia* has replaced the term *dysplasia*.

Dysplasia progresses seamlessly within the spectrum from normal to the highest grade of dysplasia, which is the presence of all the cytologic features of malignancy without invasion (i.e., carcinoma in situ). The histologic criteria

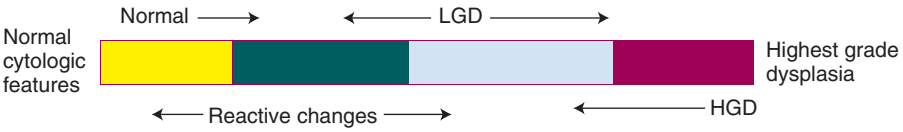


Figure 6–41 The spectrum of change from normal to the highest grade of dysplasia *(HGD)*. The diagnosis and grading of dysplasia depend on drawing lines within this continuous spectrum of change. These lines may overlap. Not every pathologist draws lines at the same point, resulting in significant interobserver variation in the diagnosis of both low-grade *(LGD)* and high-grade dysplasia.

TABLE 6–1 Summary of Selected Studies Relating to the Incidence of Adenocarcinoma in Patients with Non-Dysplastic, Low-Grade Dysplastic, and High-Grade Dysplastic Barrett Esophagus

Study	Number of patients	Follow-up (mean years)	No dysplasia	LGD	HGD
Miros et al, 1991[32]	124	3.6	0/111	1/10 (10%)	2/3 (67%)
Hameetman et al, 1989[33]	50	5.2	2/43 (5%)	3/6 (50%)	0/1
O'Connor et al, 1999[34]	136	4.2	1/125 (1%)	1/10 (10%)	0/1
Weston et al, 1999[19]	108	3.3	2/80 (2.5%)	1/20 (5%)*	2/8 (25%)†
Reid et al, 2000[20]	327	5	6/208 (3%)*	3/43 (7%)	45/76 (59%)
Montgomery et al, 2001[35]	125	—	4/66 (6%)*	4/26 (15%)	20/33 (61%)
Schnell et al, 2001[21]	1057	7.3	0/230	10/748 (1.3%)	12/75 (16%)†

*Includes "indefinite for dysplasia."
†Excludes prevalent cancers.
LGD, Low-grade dysplasia; *HGD*, high-grade dysplasia.

used to define and grade dysplasia are numerous and exist in an infinite combination of changes. They are evaluated by the pathologist who, when dysplasia is present, makes the diagnosis and then assigns its grade. This is done by drawing lines within a continuous spectrum (see Figure 6–41).

Dysplasia is presently the most reliable practical test for assessing increased cancer risk in a patient with Barrett esophagus. The incidence of adenocarcinoma on long-term follow-up increases progressively from non-dysplastic to low-grade dysplastic to high-grade dysplastic Barrett esophagus (Table 6–1).

Although dysplasia is recognized and universally used as the only cancer risk indicator in a patient with Barrett esophagus, its diagnosis is difficult and fraught with interobserver variation and error. The error is greatest at the low end of the spectrum. In high-grade dysplasia, errors are not as prevalent, although significant interobserver variation still remains. Errors occur because the lines drawn by pathologists to differentiate grades of dysplasia may vary slightly, and the criteria used for defining dysplasia are multiple, complex, and subjectively interpreted.

The diagnosis and grading of dysplasia are based on the evaluation of changes in the epithelial cells in routine hematoxylin- and eosin-stained sections. At present, dysplasia is categorized as low grade and high grade. Some authorities have an "indefinite for dysplasia" category. I do not use this term. I make a diagnosis of low-grade dysplasia only when definite criteria exist. If criteria are not definite, I do not make a diagnosis of dysplasia. The older classification of dysplasia into mild, moderate, and severe is no longer used. The term *carcinoma in situ* is equivalent to high-grade dysplasia. The diagnosis of intramucosal adenocarcinoma is made when there is lamina propria invasion; in most cases, the presence of intramucosal carcinoma requires

formal treatment for esophageal adenocarcinoma because the presence of invasion below the mucosa cannot be excluded in a mucosal biopsy. Intramucosal carcinoma is beyond "high-grade dysplasia" even when it is only suggested, or the statement is made in the microscopic diagnosis that it cannot be excluded (i.e., the diagnosis reads "high-grade dysplasia; intramucosal carcinoma cannot be excluded").

The diagnostic criteria used for dysplasia grading are multiple and complex.[36,37] They have such a high rate of interobserver variation that the data in studies using dysplasia as a diagnosis are unreliable. The diagnosis of dysplasia is observer-dependent; the published criteria are so numerous and have so many different combinations that their application in any individual case is highly subjective. The criteria I use may be different than those used by any other pathologist. I receive many requests for my expert opinion regarding dysplasia in Barrett esophagus. Disagreements are very common in these cases.

The variance in the diagnosis of dysplasia between even expert pathologists is shown in the consensus study of Montgomery et al.[37] In this study of 42 cases of low-grade dysplasia and 52 cases of high-grade dysplasia (these were the diagnoses of the submitting institutions), only 27 of 42 cases of low-grade dysplasia and 27 of 52 cases of high-grade dysplasia reached a majority agreement. High-grade dysplasia diagnosis is not identical in different institutions, even when they are considered to be the best in the country.

In this milieu of uncertainty and lack of diagnostic standardization, it is important to recognize that accuracy (i.e., how predictive a positive or negative test is) and not precision (i.e., interobserver concordance) is the primary goal. Each pathologist must strive to ensure that his or her diagnosis of dysplasia is accurate. If a pathologist makes a diagnosis of low-grade dysplasia that frequently disappears on a subsequent sample, the possibility of overdiagnosis of low-grade dysplasia must be considered. If many patients with non-dysplastic or low-grade dysplastic Barrett esophagus develop cancer rapidly, it is possible that the pathologist failed to accurately recognize high-grade dysplasia. If many esophagectomies performed for a diagnosis of high-grade dysplasia have no dysplasia in the resected specimen, a flag should be raised about the accuracy of the high-grade dysplasia diagnosis. Retrospective analysis of biopsy results, particularly at a subsequent surveillance biopsy or esophagectomy, can improve accuracy of diagnosis. This can be the basis for an excellent quality improvement indicator in the laboratory.

My record of accuracy of the diagnosis of dysplasia in Barrett esophagus, established by formal retrospective study, is as follows:

1. Hofstetter et al[38] reported the findings of 85 patients with a diagnosis of non-dysplastic and low-grade dysplastic Barrett esophagus who underwent anti-reflux surgery at our institution based on my preoperative diagnoses. After 408 patient-years of follow-up (mean follow-up per patient of 4.8 years after surgery), there were no patients with high-grade dysplasia or cancer. This indicates that I am not classifying patients with high-grade dysplasia as low grade or no dysplasia with any significant frequency (i.e., my specificity of diagnosis of high-grade dysplasia is very high). In this study, 7 of 16 patients who had Barrett esophagus with low-grade dysplasia regressed to non-dysplastic intestinal epithelium. This suggests that I may be overcalling low-grade dysplasia in patients who have no true dysplasia. From a theoretical standpoint, true dysplasia should be irreversible.
2. In two separate studies of patients who underwent esophagectomy based on my diagnosis of high-grade dysplasia, there was prevalent cancer in the resected specimen in a significant number of cases. Peters et al[3] in a 1994 study showed that five of nine had foci of invasive carcinoma in the

resected specimen; Tharavej et al[39] found prevalent cancer in the resected specimen in 14 of 31 patients taken to esophagectomy with a diagnosis of high-grade dysplasia. All patients without invasive cancer had residual high-grade dysplasia in their resected specimens. This indicates a high sensitivity (no false-positives) of my diagnosis of high-grade dysplasia.

Based on these studies, it appears that I have a record of considerable accuracy in the diagnosis and grading of dysplasia in Barrett esophagus. With this level of accuracy, it is a safe to perform anti-reflux surgery in patients with Barrett esophagus who do not have a diagnosis of high-grade dysplasia. It is also reasonable to perform a limited esophagectomy in patients who have a diagnosis of high-grade dysplasia. It is rare for individual pathologists to provide outcome data on their diagnoses of dysplasia in Barrett esophagus such as I have done.

Criteria for Diagnosis of Dysplasia

These criteria were originally reported in 1988 by Reid et al[36] and are shown in Table 6–2.

These criteria for recognizing dysplasia represented a great advance from the totally random pathologic diagnosis of dysplasia that existed at the time. However, the criteria are extremely complex and so vague that it is not likely that they would achieve significant reproducibility.

Over the years, the criteria have evolved, more by general usage than by any definitional studies.

The Diagnosis of High-Grade Dysplasia

High-grade dysplasia in Barrett esophagus is the only presently available criterion that indicates a high and imminent risk of adenocarcinoma in a patient with gastroesophageal reflux disease. It is the last point in the process before

TABLE 6–2 Criteria for Diagnosis and Grading of Dysplasia in Barrett Esophagus, Reproduced Exactly from Reid et al[35]

Grade	Criteria
Negative	The architecture is within normal limits. The nuclei do not vary greatly in size or shape and are located basally. The nuclear:cytoplasmic ratio is not increased. The nuclear envelope is generally smooth. Nucleoli are not markedly enlarged. Focal nuclear stratification is acceptable, as are small numbers of "dystrophic" goblet cells whose apical aspect does not communicate with the luminal surface. Greater nuclear alterations are acceptable when associated with evidence of inflammation, erosion, or ulceration. Numbers of abnormal-appearing mitoses are variable. Apical cytoplasmic mucin is usually present but may be reduced or absent in inflammation.
Indefinite	The architecture may be moderately distorted. Nuclear abnormalities are less marked than those seen in dysplasia. Other features include more numerous dystrophic goblet cells, more extensive nuclear stratification, diminished or absent mucus production, increased cytoplasmic basophilia, and increased mitoses. The diagnosis of indefinite for dysplasia should be limited to cases in which the changes are too marked for negative but not sufficient for the diagnosis of dysplasia.
Positive (LGD and HGD)	The diagnosis of low-grade dysplasia (LGD) or high-grade dysplasia (HGD) is based on the severity of both architectural and cytologic criteria that suggest neoplastic transformation of the columnar epithelium. Although either architectural or cytologic abnormalities may predominate, high-grade dysplasia is diagnosed if either one is sufficiently prominent. Architectural abnormalities may include budded, branched, crowded, or irregularly shaped glands; papillary extensions into gland lumina; and villiform configuration of the mucosal surface. Nuclear features may include marked variation in size and shape, nuclear and/or nucleolar enlargement, increased nuclear:cytoplasmic ratio, hyperchromatism, and increased numbers of abnormal mitoses. Nuclear alterations are especially noteworthy if they involve the mucosal surface. Diagnostic features easily recognizable at lower power are cytoplasmic basophilia with loss of mucus and excessive nuclear stratification, often extending from the epithelial basement membrane to the luminal surface.
Intramucosal carcinoma	Intramucosal carcinoma is defined as carcinoma that has penetrated through the basement membrane of the glands into the lamina propria but has not yet invaded through the muscularis mucosae into the submucosa.

invasion occurs and the patient develops a risk for metastatic disease. From a practical standpoint, the diagnosis of high-grade dysplasia is significant because its presence in a biopsy indicates two things:

1. There is a significant risk that the patient may already have invasive carcinoma in an unsampled area of the esophagus.
2. It is a recognized indication for removing the area of dysplasia by either surgery or ablation.

In our series, approximately 40% of patients with high-grade dysplasia have prevalent invasive adenocarcinoma in the esophagectomy specimen. The risk of prevalent invasive cancer increases if the high-grade dysplasia is present in multiple biopsy levels and if there is a visible lesion associated with the high-grade dysplasia. Recent studies have shown that the natural history and progression to cancer are greater in patients who have multiple foci of high-grade dysplasia rather than a single focus.[22]

The line drawn to separate high-grade from low-grade dysplasia varies among pathologists (see Figure 6–41). Studies of "high-grade dysplasia" are therefore not necessarily equivalent, making it very difficult to evaluate data and compare different studies on the natural history of high-grade dysplasia. The high risk of prevalent cancer, however, and the high incidence of progression to adenocarcinoma are strong reasons for immediate aggressive resection in patients with high-grade dysplasia. Management with multiple biopsies waiting for invasive cancer to occur seems irrational for a disease with a reported 40% prevalent cancer rate in our esophagectomy specimens and a nearly 60% incidence of adenocarcinoma within 5 years.[20]

Criteria for Diagnosis of High-Grade Dysplasia

The criteria for a diagnosis of high-grade dysplasia in Barrett esophagus are the presence of a severe cytologic abnormality and one of the two following features: complete loss of nuclear polarity and gland complexity. Loss of nuclear polarity consists of a rounding up of the nuclei, which cease to have their long axis perpendicular to the basement membrane (Figures 6–42 to 6–46). Severe cytologic abnormality and loss of nuclear polarity usually occur simultaneously and represent the most important diagnostic criteria. Mitotic figures and individually necrotic cells are common (see Figures 6–45 and 6–46), but they are not necessary criteria for the diagnosis or exclusion of high-grade dysplasia. Gland complexity is characterized by luminal bridges and cribriform architecture, which usually signifies high-grade dysplasia (see Figure 6–46; Figures 6–47 to 6–49). However, cribriform architecture can rarely occur in low-grade dysplasia; in these cases, the absence of the required cytologic abnormality and retention of nuclear polarity are what negate the diagnosis of high-grade dysplasia (Figure 6–50).

Diagnosing high-grade dysplasia is problematic because several of the criteria are subjective:

1. What exactly is "severe cytologic abnormality," and does its determination vary among pathologists? (Figures 6–51 to 6–54)
2. What exactly is "complete" loss of polarity, and does its determination vary among pathologists? (Figures 6–53 and 6–54)
3. When faced with a biopsy, do all pathologists evaluate all criteria separately, or do they form an opinion based on a combination of the criteria? (Figure 6–55)

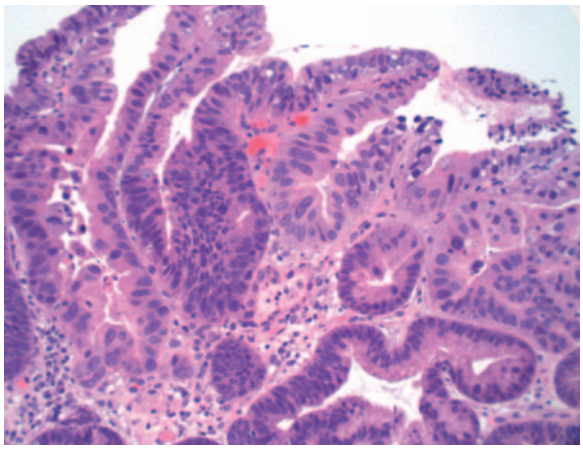


Figure 6–42 Dysplastic Barrett epithelium; no goblet cells are seen. There is both low-grade and high-grade dysplasia. The low-grade dysplasia shows retained nuclear polarity. The high-grade dysplasia is characterized by cells that have rounded nuclei with their long axis more parallel rather than perpendicular to the basement membrane.

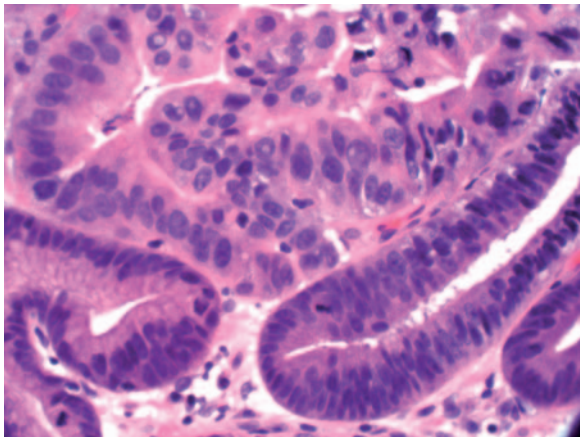


Figure 6–44 Comparison of high-grade *(upper half)* and low-grade *(lower half)* dysplasia. The loss of nuclear polarity is easily seen in the high-grade dysplasia, and the cytologic abnormality is more severe.

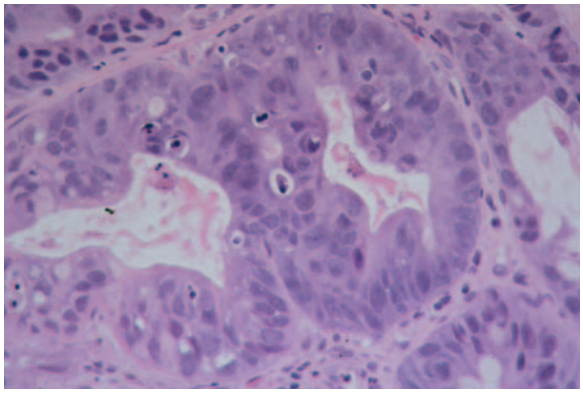


Figure 6–46 High-grade dysplasia, showing severe cytologic abnormality, complete loss of nuclear polarity, and gland complexity with luminal bridges resulting in early cribriform change.

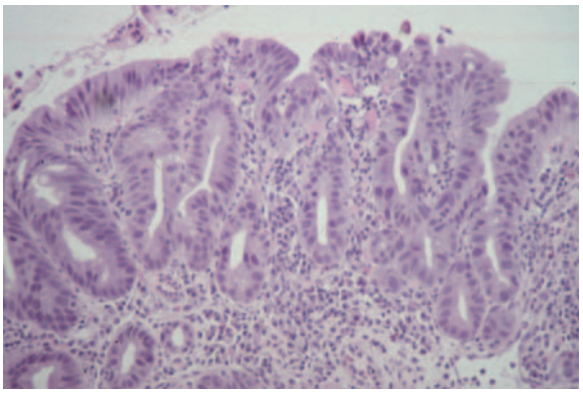


Figure 6–43 Dysplasia without much architectural distortion or crowding showing cytologic features of high-grade dysplasia. A small area of low-grade dysplasia is seen at the left edge.

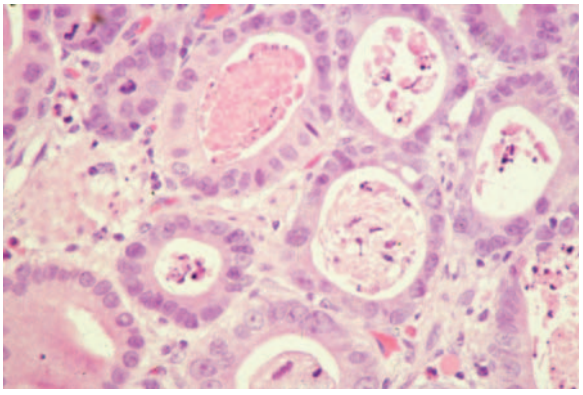


Figure 6–45 High-grade dysplasia, microcystic type, showing dilated glands lined by cuboidal cells with complete loss of nuclear polarity. The lumen contains necrotic debris.

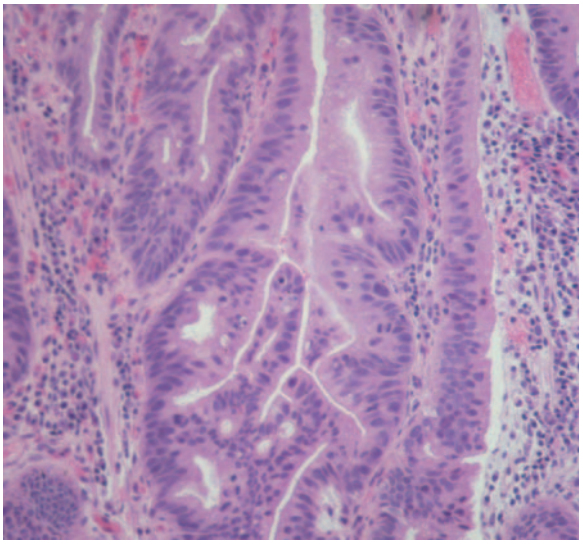


Figure 6–47 High-grade dysplasia with gland crowding, disordered architecture, cytologic abnormality that is interpreted as severe (although it is less severe than in Figure 6–46), and gland complexity with cribriform change.

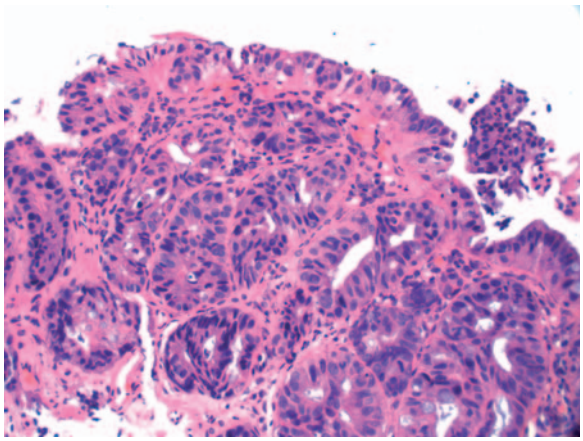


Figure 6–48 High-grade dysplasia with gland crowding, severe cytologic abnormality, loss of nuclear polarity, and cribriform change.

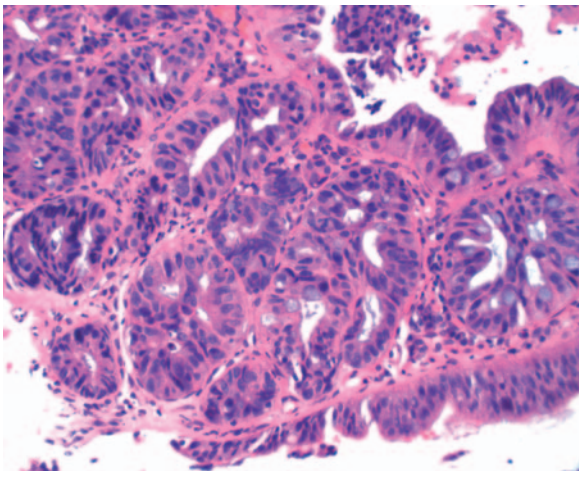


Figure 6–49 Higher magnification of Figure 6–48 showing well-developed cribriform change.

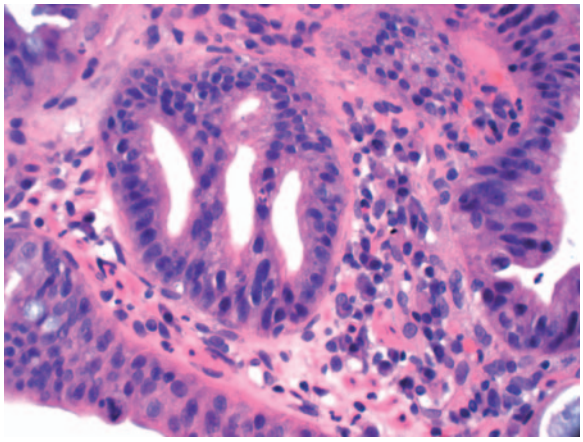


Figure 6–50 Complex cribriform architecture in a gland showing less than necessary cytologic abnormality for a diagnosis of high-grade dysplasia. Nuclear polarity is also not completely lost. This was classified as low-grade dysplasia.

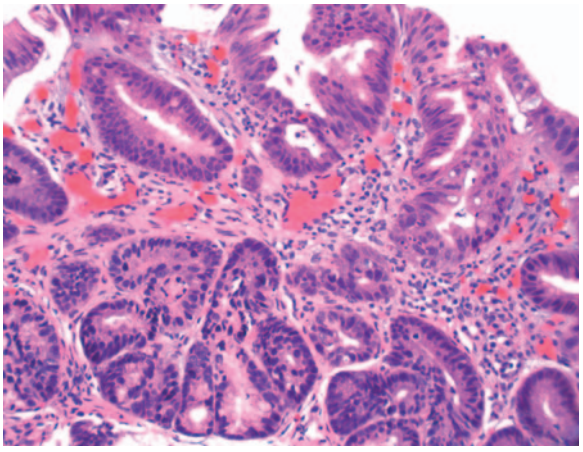


Figure 6–51 High-grade dysplasia with severe cytologic abnormality present in some of the glands. There is room for interobserver variation in this case. This was not a problem because it was part of a more extensive high-grade dysplasia.

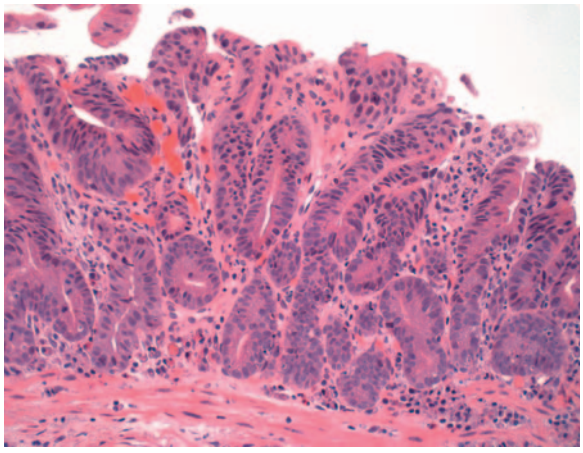


Figure 6–52 High-grade dysplasia. The cytologic abnormality is severe, and there are foci where the nuclear polarity appears lost. However, this is close to borderline and may be associated with interobserver variation.

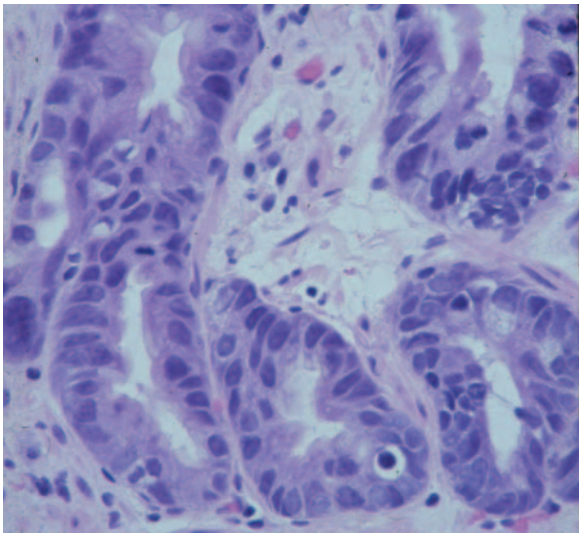


Figure 6–53 High-grade dysplasia, showing severe cytologic abnormality and loss of nuclear polarity.

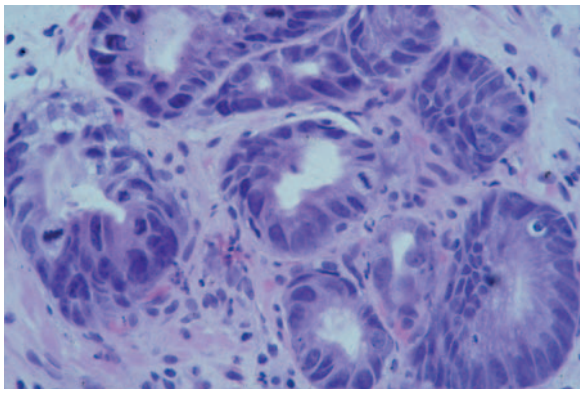


Figure 6–54 Another area of the case illustrated in Figure 6–53. This area shows borderline changes. However, the presence of many such areas of borderline change favors a diagnosis of high-grade dysplasia compared to a case in which there is only one small area of abnormality.

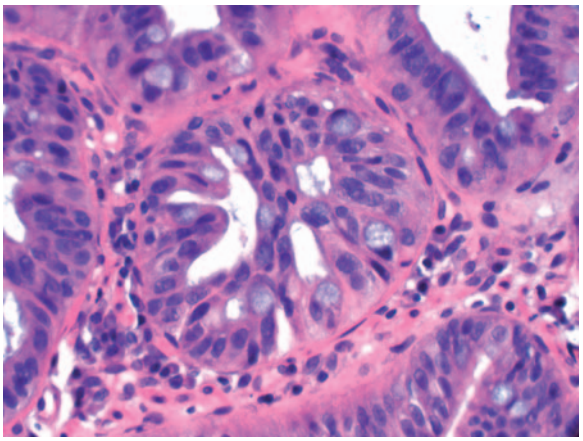


Figure 6–55 Low-grade dysplasia with borderline features that were considered insufficient for a diagnosis of high-grade dysplasia. There is cribriform architecture, but the cytologic abnormality is not sufficiently severe, and nuclear polarity is not completely lost. Residual goblet cells are present. Other areas in this biopsy showed high-grade dysplasia.

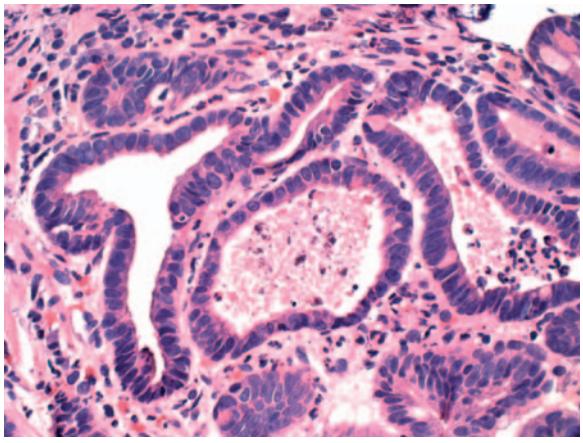


Figure 6–56 Cystically dilated irregular glands lined by flattened dysplastic epithelium should be regarded with great suspicion in Barrett esophagus. This was diagnosed as high-grade dysplasia; the presence of intramucosal carcinoma cannot be excluded. The presence of such cystically dilated dysplastic glands are predictive of invasive carcinoma.

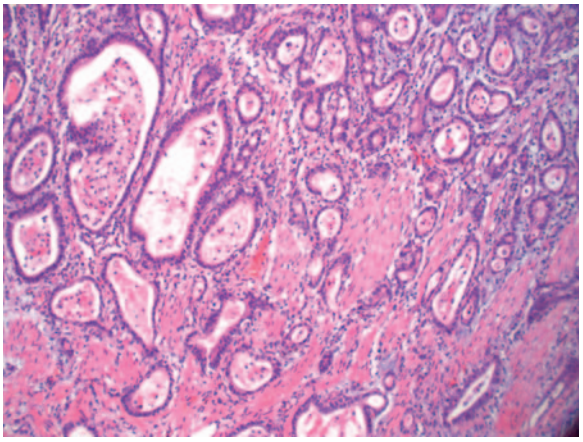


Figure 6–57 Invasive adenocarcinoma, microcystic type.

4. What is the effect of the amount of high-grade dysplasia? Do pathologists hesitate to make a diagnosis of high-grade dysplasia when only one focus is affected (compared to extensive high-grade dysplasia, when multiple biopsies are positive)?
5. Does the coexistence of extensive versus no low-grade dysplasia influence the facility of diagnosing high-grade dysplasia?

All these questions are difficult to answer. One misleading variant of high-grade dysplasia is characterized by microcystic glands lined by a relatively flat epithelium with complete loss of polarity but a relatively low level of cytologic abnormality (Figure 6–56). Such microcystic glands are a frequent indicator of invasive carcinoma (Figures 6–57 and 6–58).

Gland crowding and disorganization are frequently used criteria in the grading of dysplasia (Figure 6–59). The less the epithelium recapitulates the normal epithelial structure, the more likely is the diagnosis of high-grade

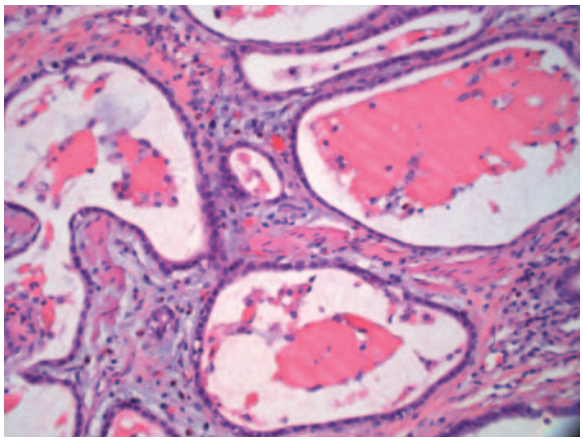


Figure 6–58 Invasive adenocarcinoma, microcystic type. The glands are dilated, lined by a flattened epithelium, and infiltrate into the muscularis mucosae. The cytologic features of the cells lining the microcysts are deceptively bland.

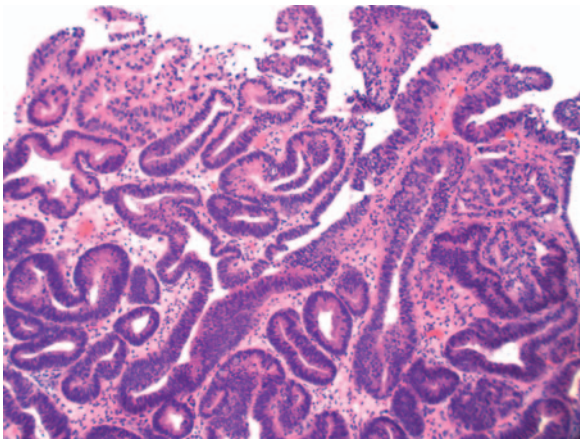


Figure 6–59 High-grade dysplasia showing crowding and disorganization. The majority of this field shows the cytology of low-grade dysplasia with foci of high-grade dysplasia. In this setting, crowding and disorganization of glands rate as secondary diagnostic criteria to push the diagnosis to high-grade dysplasia.

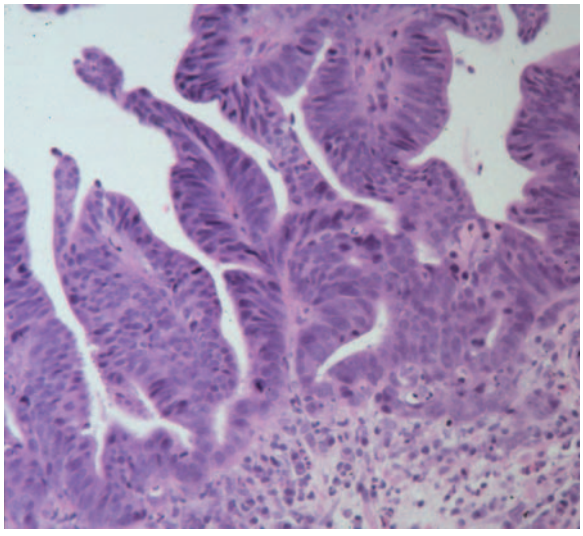


Figure 6–60 High-grade dysplasia with severe cytologic abnormality, loss of nuclear polarity, and a villiform surface architecture.

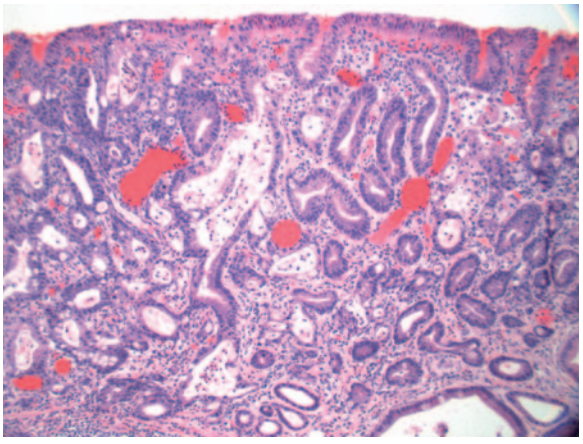


Figure 6–61 Intramucosal adenocarcinoma showing high-grade dysplastic glands and irregularity associated with lamina propria invasion.

dysplasia. However, gland crowding varies considerably and is difficult to define. Another criterion is a villiform surface architecture that is commonly seen in high-grade dysplasia but can also be seen in low-grade dysplasia (Figure 6–60).

The presence of invasion in high-grade dysplasia is recognized by the penetration of the basement membrane of the dysplastic glands and extension of malignant cells into the lamina propria (Figures 6–61 to 6–64). When limited to the lamina propria without extension into the submucosa, this represents intramucosal adenocarcinoma. In a mucosal biopsy, the depth of invasion below the mucosa is difficult to assess accurately. However, mucosal biopsies of deeply invasive tumors show obvious invasive features, frequently with desmoplasia around the invasive glands.

The presence of glands under intact squamous epithelium is a common finding in columnar-lined esophagus. All types of columnar metaplastic

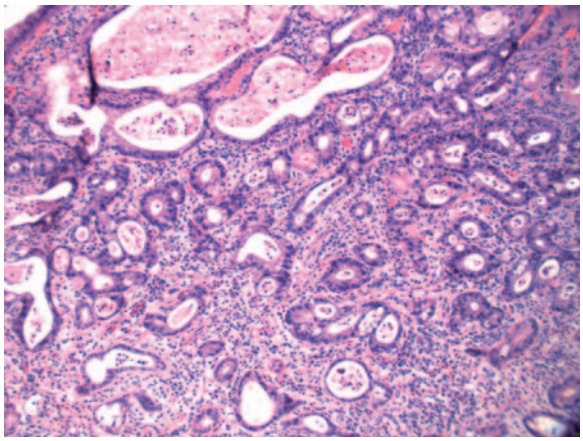


Figure 6–62 Intramucosal adenocarcinoma, showing irregular dysplastic glands with lamina propria invasion.

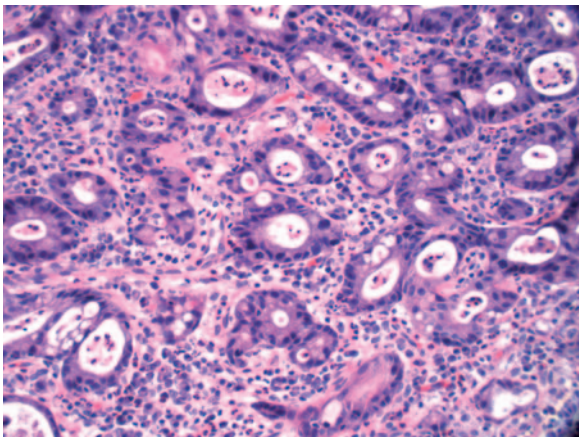


Figure 6–63 Intramucosal adenocarcinoma, showing irregular lamina propria invasion.

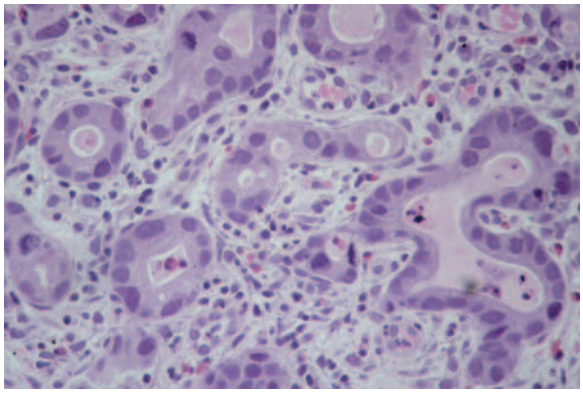


Figure 6–64 Intramucosal adenocarcinoma showing infiltration of the high-grade dysplastic cells across the basement membrane of the gland into the lamina propria.

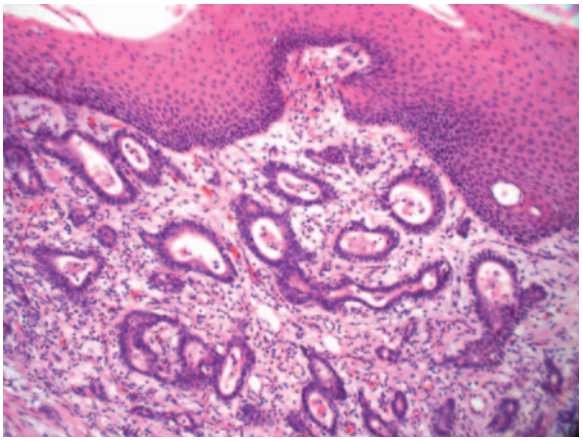


Figure 6–65 Intramucosal adenocarcinoma undermining a normal squamous epithelial surface. The malignant glands are irregular with an infiltrative pattern, but there are relatively bland cytologic features.

epithelia, dysplastic and otherwise, can be found under squamous epithelium. As such, glands under squamous epithelium must be evaluated for dysplasia just like glands in columnar-lined epithelia (Figure 6–65). The mere presence of a gland under the squamous epithelium is inconsequential.

Similarly, the muscularis mucosae tend to become hyperplastic, split, and extend irregularly into the lamina propria in columnar-lined esophagus. Muscle fibers extend vertically into the lamina propria, often reaching near the surface. When prominent, the hyperplastic smooth muscle may surround benign epithelial elements in the mucosa. This phenomenon must not be interpreted as a manifestation of invasion. The presence of muscle around gland is never a criterion of malignancy or invasion in Barrett esophagus. Malignancy is determined by cytologic criteria of malignancy in the glands (see Figures 6–57 and 6–58).

Criteria for Diagnosis of Low-Grade Dysplasia

The problems with criteria and lack of interobserver agreement relating to the reliable diagnosis of low-grade dysplasia are infinitely greater than those associated with high-grade dysplasia. True low-grade dysplasia occurs as a

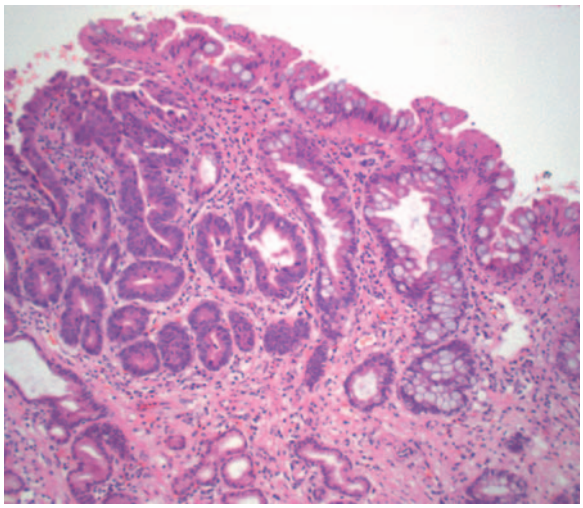


Figure 6–66 Low-grade dysplasia *(left half)* arising in non-dysplastic intestinal metaplasia *(right half).* The dysplastic glands have lost the goblet cell appearance, showing moderate cytologic abnormality involving the foveolar region all the way to the surface. Nuclear polarity is maintained, and there is no gland complexity.

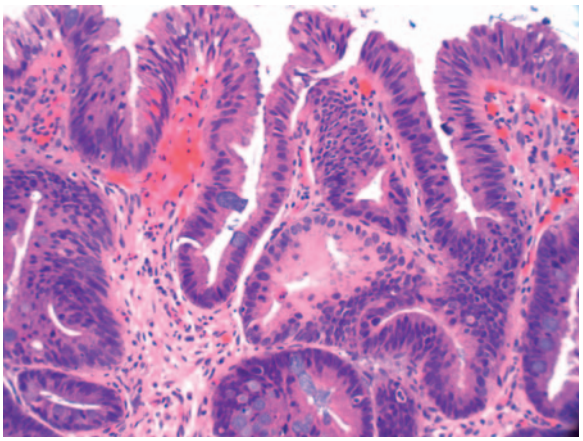


Figure 6–67 Low-grade dysplasia with residual goblet cells. The cytologic abnormality is moderate, and nuclear polarity is maintained. The change is similar throughout the foveolar region all the way to the surface.

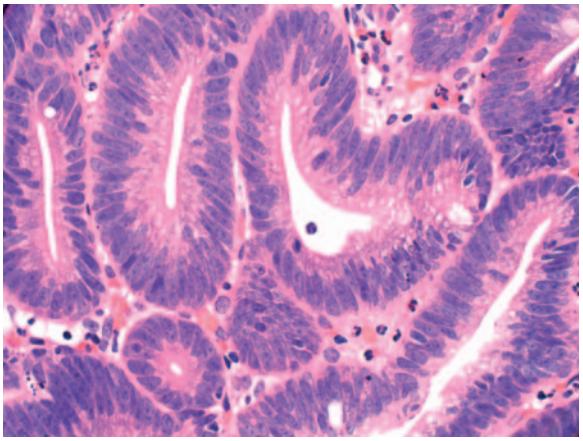


Figure 6–68 Low-grade dysplasia. The cells have enlarged, cigar-shaped nuclei with retained nuclear polarity, with the long axis of the nuclei being perpendicular to the basement membrane of the gland.

result of an irreversible genetic change that is an early step in the sequence necessary to produce adenocarcinoma. The change occurs in intact epithelium; typical low-grade dysplastic epithelium is therefore un-eroded, without active inflammation and shows the dysplastic cytologic change extending from the base of the foveolar pit (where the proliferating progenitor cell pool resides) to involve the surface (Figure 6–66). The cytologic change includes nuclear enlargement, stratification, and hyperchromasia with absence of cytoplasmic goblet-type mucin (Figure 6–67). Nuclear polarity is maintained (Figure 6–68). The degree of change is less than that required to satisfy criteria for high-grade dysplasia.

The genetic change of dysplasia occurs in the proliferating stem cell in the deep foveolar region of the epithelium. It does not occur in the terminally differentiated goblet cells. The genetically altered dysplastic cell may show the nuclear abnormality while differentiating into a goblet cell. In such cases, the low-grade dysplastic epithelium can be recognized as arising in intestinal metaplasia (Figures 6–69 and 6–70). In many cases, however, the dysplastic stem cell does not mature sufficiently as it moves to the surface to produce

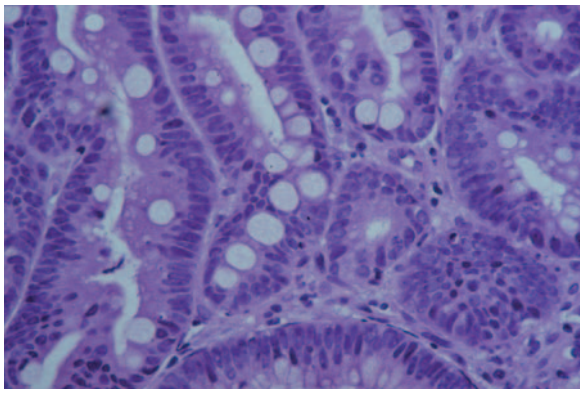


Figure 6–69 Low-grade dysplasia with residual goblet cells.

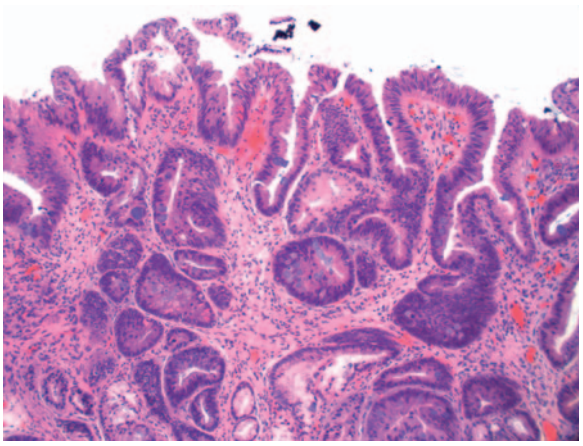


Figure 6–70 Low-grade dysplasia with residual goblet cells.

a goblet cell. In these cases, low-grade dysplasia may occur seemingly without intestinal metaplasia. The presence of low-grade dysplasia in the esophagus is as diagnostic for Barrett esophagus as intestinal metaplasia because dysplasia does not occur in the absence of intestinal metaplasia. Dysplasia must have arisen from intestinal metaplasia, even when goblet cells are not present in the dysplastic epithelium.

The cytologic abnormality of low-grade dysplasia is mimicked exactly by changes that are not associated with genetic abnormalities of the carcinogenetic pathway. These are known as reactive atypias; they are commonly seen in association with regenerative epithelial activity in areas of erosion and active inflammation. Because of this, the diagnosis of low-grade dysplasia should not be made in these areas. Most reactive atypias are associated with increased proliferation, but maturation of the cells remains normal; as such, the cytologic abnormality is greatest in the deep part of the foveolar pit with normal cytologic features at the surface. It is for this reason that surface epithelial abnormality is usually necessary for a diagnosis of low-grade dysplasia (see Figures 6–66, 6–67, and 6–70). In cases in which the cytologic change is limited to or maximal in the foveolar region with normal maturation at the surface, a greater degree of cytologic change is necessary than when there is surface involvement.

At present, the difference between the diagnoses of intestinal metaplasia with low-grade dysplasia and reactive atypia is merely a matter of surveillance interval. The rate of transformation of low-grade dysplasia to adenocarcinoma is, with very rare exceptions, slow. Routine surveillance is probably adequate. I therefore restrict diagnosis of low-grade dysplasia to cases in which the criteria of low-grade dysplasia are definite and well developed. In such cases, shortening the surveillance interval is probably justified. If there is any doubt about the criteria, I generally diagnose reactive change without dysplasia. I do not make a diagnosis of indefinite for dysplasia; because I diagnose only dysplasia when it is definite, "indefinite for dysplasia" is equivalent to "negative for dysplasia."

Although the literature does not address the issue of extent of dysplasia, most pathologists will agree with a diagnosis of low-grade dysplasia when this is present extensively in the epithelium. A similar change affecting a single area is more likely to have considerable interobserver variation.

True borderline cases exist between low-grade and high-grade dysplasia (Figures 6–71 and 6–72). Some have associated erosion and active inflammation; in such cases, the possibility should be considered that reactive changes

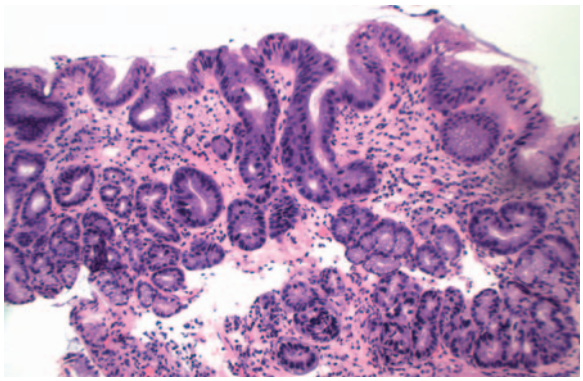


Figure 6–71 Borderline case that was diagnosed as low-grade dysplasia. The cytologic abnormality is close to severe focally, but there is no gland crowding, and the abnormality is largely restricted to the deeper region of the mucosa with only focal involvement of the surface. Cases such as this receive a cautionary comment after the diagnosis of low-grade dysplasia, recommending increased care in surveillance (i.e., a shorter surveillance interval). Note the absence of erosion or active inflammation.

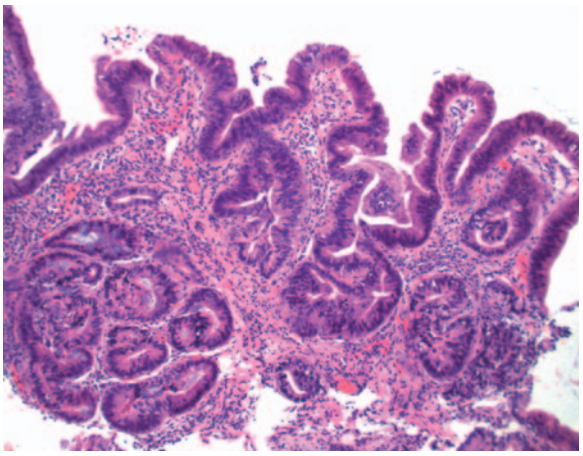


Figure 6–72 Low-grade dysplasia, with the worrisome potential for the presence of foci of high-grade dysplasia. Again, a cautionary comment recommends short interval surveillance.

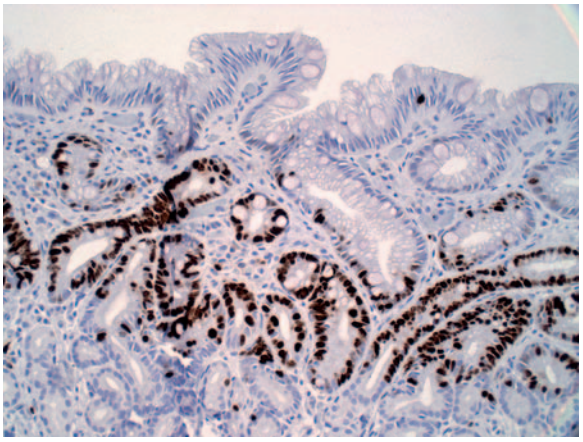


Figure 6–73 Immunoperoxidase staining for Ki67 in a case of low-grade dysplasia, showing the Ki67 positive proliferative cell pool limited to the base and middle of the foveolar region. The surface and superficial foveolar region are negative. This recapitulates the normal staining distribution with Ki67 and is a strong argument against a diagnosis of high-grade dysplasia.

have become superimposed on low-grade dysplasia, producing an additive change that mimics high-grade dysplasia. In these cases, a recommendation for follow-up biopsy after the inflammation has been controlled is a reasonable course of action. In borderline cases without active inflammation, the diagnosis of low-grade dysplasia with a cautionary comment regarding the borderline nature of the dysplasia is appropriate; this will alert the patient to careful follow-up. I use immunoperoxidase staining for Ki67 and p53 in borderline cases. The most valuable use of these stains is the negative finding. In borderline cases, a normal Ki67 staining pattern, with the proliferative zone limited to the deep foveolar region with sparing of the surface and superficial foveolar region, is a strong argument against a diagnosis of high-grade dysplasia[24] (Figure 6–73). Similarly, negative staining for p53 supports low-grade dysplasia over high-grade dysplasia.

Prevalent Cancer in Barrett Esophagus

One thing rarely addressed is that at no point can we guarantee that the patient with Barrett esophagus does not already have cancer within the epithelium. When the patient is subject to a regular surveillance endoscopy, has

no visible lesion, has the most compulsive series of biopsies as recommended by protocol, and the pathologist reports the absence of high-grade dysplasia or cancer in the biopsies, we assume that all is well.

In real life, this ideal scenario is uncommon; surveillance of Barrett esophagus is not believed to be effective and therefore not done with enthusiasm, and biopsies are rarely taken as recommended. The medical community belittles the disease from its outset, minimizing the fact that 10% of sufferers are destined to develop cancer within the next 20 years (a risk of 0.5% per year).

All is not well—even after the ideal negative surveillance examination. Every researcher who has studied the patient with Barrett esophagus who has been declared cancer free at an index endoscopy, indicates that a small percentage of these patients have cancer at the time they are declared cancer free. This is called a "prevalent cancer." Prevalent cancer is defined as a cancer that occurs within a short time (usually 1 year) of a negative examination. It is the result of one of the following:

1. The cancer was present but missed by the sampling biopsies.
2. The genetic changes for the cancer were present without phenotypic changes, and the cancer expressed itself within that period.
3. The cancer developed rapidly after the negative examination.

Prevalent cancer is regarded as a nuisance that makes studies difficult to evaluate; it is not recognized for its true horror. The truth is that when we send patients out of the office after doing the best we can for them, *we cannot guarantee that they do not have cancer at that point in time.*

In studies evaluating the long-term probability of cancer in Barrett esophagus during follow-up after an index endoscopy, patients with prevalent cancers drop out of the study because they are declared irrelevant. In the study by Weston et al,[19] patients who developed adenocarcinoma, multifocal high-grade dysplasia, or a dysplasia-associated lesion or mass at or within 6 months of initial diagnosis were excluded. The number of such patients is not mentioned, although this would be one of the most important factors of whether follow-up was appropriate for a patient with Barrett esophagus.

In studies evaluating the results of anti-reflux surgery, prevalent cancers give the impression that surgery is not successful in preventing cancer. The true test of surgery as a cancer prevention method must exclude prevalent cancers. The data are powerful in this regard. It is difficult to identify any patients with Barrett esophagus who have developed cancer more than 5 years after an anti-reflux operation that has been shown to be successful by a normal postoperative 24-hour pH test. The incidence of cancer after anti-reflux surgery is at its highest in the first year; it drops to zero after 5 years. This is consistent with a lag phase of 5 years between the occurrence of the genetic changes required for cancer and their phenotypic expression as cancer.

It is essential to identify the probability of prevalent cancer in patients who are under surveillance for Barrett esophagus because treating it with anything other than resection guarantees that prevalent cancer will progress to more advanced stages. Cancer prevention is not effective when cancer already exists, even when we cannot detect it. Endoscopic mucosal resection or esophagectomy is necessary to eradicate prevalent cancer; otherwise, these patients are at serious risk for advanced cancer and death. Ablation is less appropriate because it does not permit histologic evaluation of the resected specimen; we will never know whether the patient had an invasive cancer or not.

The following sections deseribe indicators of risk for prevalent cancer.

High-Grade Dysplasia

The risk of prevalent cancer is greatest when high-grade dysplasia is present in a biopsy. In our hands, the rate of prevalent cancer is approximately 50%. In two USC studies in which esophagectomy was performed based on a diagnosis of high-grade dysplasia, invasive cancer was present in five of nine patients[3] and in 14 of 31 patients in the study by Tharavej et al.[39] This high incidence of prevalent cancer suggests that esophagectomy is strongly indicated when high-grade dysplasia is diagnosed in a biopsy. Hameetman et al[33] reported the finding of invasive cancer in five of eight patients within 1 year of an initial diagnosis of high-grade dysplasia, indicating an incidence of prevalent cancer similar to our data.

There is a contrary viewpoint. Schnell et al[21] reported the detailed findings of 79 patients with high-grade dysplasia; only four (5.1%) had prevalent cancer manifesting within 1 year of the initial diagnosis of high-grade dysplasia. The most likely explanation for the difference is that the criteria for diagnosis of low- and high-grade dysplasia are different. This is suggested by several facts in the study:

1. In their study, the authors state that the diagnosis of dysplasia was based on "previously established definitions." The reference they cite is for criteria for dysplasia in inflammatory bowel disease from 1983,[40] not those for Barrett esophagus detailed by Reid et al in 1988.[36]
2. An amazing 738 of their 1099 patients with Barrett esophagus had low-grade dysplasia at some point in the follow-up. A 67% incidence of low-grade dysplasia in Barrett esophagus is higher than in any other study, suggesting their criteria for dysplasia are less stringent than usual.
3. The serial biopsies of patients with high-grade dysplasia who remained without cancer show that high-grade dysplasia was an ephemeral phenomenon, being found only once or twice during the course of the disease. This suggests a problem; the higher grades of dysplasia are likely to be a progressive field effect rather than the focal and transient change that these authors report.
4. Only 12 (16%) of the 75 patients diagnosed with high-grade dysplasia progressed to invasive cancer during a mean follow-up period of 7.3 years. This contrasts with the study by Reid et al[20] in which 59% of patients with high-grade dysplasia developed invasive cancer within 5 years. All these factors point toward a diagnosis of high-grade dysplasia being less predictive of prevalent and imminent cancer in Schnell et al[21] than in the other studies mentioned, including Reid et al,[20] where the very reliable Rodger Haggitt would have been the pathologist who made the diagnosis of high-grade dysplasia. The data in this study should not be interpreted to mean that the patients with high-grade dysplasia who seek treatment at the Hines VA Hospital in Illinois have a different disease than patients with the same diagnosis in other centers. Patients do not vary in their behavior; it is pathologists who frequently vary in their diagnosis of high-grade dysplasia!

High-Grade Dysplasia in a Lesion that Is Visible at Endoscopy

Our data suggest that the presence of high-grade dysplasia in a lesion that is visible at endoscopy (Figure 6–74) has a very high risk of prevalent invasive cancer, which will be detected only if the lesion is resected. The presence of high-grade dysplasia in a visible lesion must be an indication for resection.

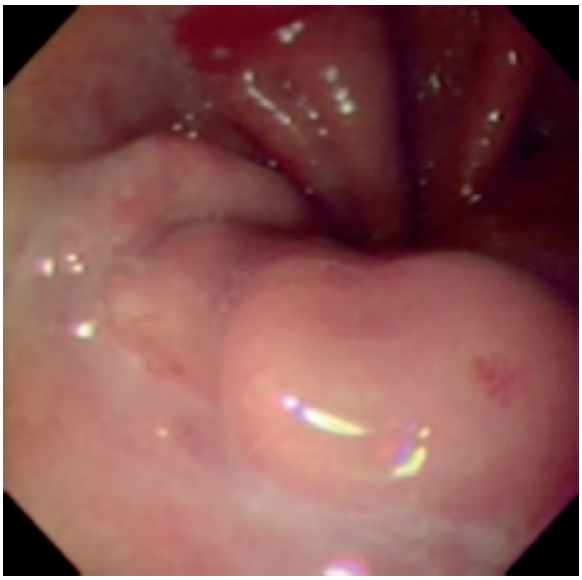


Figure 6–74 Nodular lesion in a patient with columnar-lined esophagus. If a biopsy shows high-grade dysplasia, an invasive carcinoma is likely when the resected lesion is examined.

Weston et al[19] used dysplasia in a visible lesion as the end-point for Barrett surveillance in their study.

Multifocal Versus Unifocal High-Grade Dysplasia

The presence of high-grade dysplasia at multiple biopsy levels is similarly associated with a high risk of prevalent cancer and is a powerful indication for resection.[40] Weston et al[19] used multifocal dysplasia as an end-point for Barrett surveillance in their study.

In our data,[40] the presence of unifocal high-grade dysplasia has an approximately 10% risk of prevalent cancer in the resected specimen but an almost invariable prevalence of residual high-grade dysplasia. Buttar et al[22] showed a difference in both prevalent and rapidly incident cancer in focal versus diffuse high-grade dysplasia. Their criterion for focal high-grade dysplasia was the presence of high-grade dysplasia in less than five crypts limited to one biopsy piece. Patients with focal high-grade dysplasia had a 93% and 86% cancer-free survival rate at 1 and 3 years, respectively, compared with 62% and 44% for diffuse high-grade dysplasia.

Some authorities regard a 10% incidence of prevalent cancer as an acceptable risk and recommend careful follow-up for high-grade dysplasia. Such an attitude is very unusual with any other cancer in the body. It is like saying that we will simply watch a patient with ductal carcinoma in situ in a breast biopsy without surgical intervention until invasive cancer develops. We spend billions of dollars to find preinvasive breast cancer and ignore preinvasive esophageal cancer, even when we find it. High-grade dysplasia is carcinoma in situ of the esophagus.

Extensive (Multifocal and Multilevel) Low-Grade Dysplasia

The presence of extensive, multilevel low-grade dysplasia is a worrisome finding, particularly when the changes in some foci approach (but do not

reach) the criteria for a diagnosis of high-grade dysplasia. There is no information on immediately prevalent cancers in this population because low-grade dysplasia is not an indication for resection. Srivastava et al[41] showed that the presence of extensive low-grade dysplasia in biopsies was predictive of progression to adenocarcinoma in 77 patients with dysplastic Barrett esophagus; 44 (57%) of these 77 patients developed adenocarcinoma after a mean follow-up period of 25 months.

The data suggest that an anti-reflux operation performed in patients with low-grade dysplasia prevents cancer in most cases.[37] However, these patients have the greatest likelihood of prevalent cancers after surgery and have the highest risk of quickly progressing to high-grade dysplasia. If it is shown that multifocal low-grade dysplasia has a high risk of prevalent cancer on follow-up or anti-reflux surgery, it may become an indication for resection in the future. This would follow the history of ulcerative colitis, in which the indication for prophylactic colectomy has recently moved from high-grade dysplasia to include more patients with low-grade dysplasia.

Non-Dysplastic Barrett Esophagus

Patients with non-dysplastic Barrett esophagus or those with focal low-grade dysplasia have an extremely low risk of prevalent cancer. They can be reasonably managed without resecting the lesion by methods designed to prevent the progression of change toward cancer. However, this assumes that ideal biopsy sampling has been done. A negative surveillance endoscopy that has been biopsied suboptimally always has an unknown risk of prevalent cancer.

Conclusion

All patients who develop reflux-induced adenocarcinoma must pass through a non-dysplastic stage of Barrett esophagus. Barrett esophagus is a highly reliable and significant cancer risk indicator. If we recognize the risk of cancer in non-dysplastic Barrett esophagus (1 in 10 persons will get cancer within 20 years) and agree that this significant risk demands an aggressive cancer-prevention treatment, a flawed diagnostic test (the detection of dysplasia) becomes less important. Our aim should be to prevent the occurrence of dysplasia in Barrett esophagus, not to find it. By the time we find dysplasia with our flawed methods, it may actually be too late for some patients who we declare as having "prevalent cancer." Prevalent cancer is a disaster that we can prevent by aggressive cancer-preventive treatment of non-dysplastic Barrett esophagus.

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CHAPTER 7

New Histology-Based Definitions and Method of Diagnosis of Reflux Disease

At present, the definition of gastroesophageal reflux disease is clinically based and full of contradiction. It is defined by the presence of classical symptoms, but we recognize that asymptomatic patients can manifest serious complications of reflux disease such as Barrett esophagus and adenocarcinoma. It is defined by the presence of erosive esophagitis, but we recognize "non-erosive reflux disease." It is defined by an abnormal 24-hour pH test or impedance study that quantitates reflux, but we recognize that the correlation between the amount of reflux and reflux disease is imperfect. There is no accepted histologic definition of reflux disease; the only current criteria are changes in squamous epithelium, and these lack sensitivity and specificity to an extent that they are useless as a diagnostic test[1] (Table 7–1).

Without a standard definition, the diagnosis of reflux disease is haphazard, illogical, and at the whim of whatever a physician wants to use at any given moment. As a result, the management of patients with reflux is confusing. It is based on the false belief that every facet of the patient's reflux disease is effectively controlled by acid-suppressive therapy. As new drugs have improved our ability to suppress acid secretion, two things have happened:

1. Patients have had the ability to control their reflux symptoms very effectively and improve the quality of their lives.
2. There has been an explosion in the incidence of reflux-induced adenocarcinoma (see Chapter 1).

A New Histologic Definition of Gastroesophageal Reflux Disease

The current major threat to life for patients with gastroesophageal reflux disease is Barrett esophagus and adenocarcinoma. It therefore seems appropriate to make adenocarcinoma the end-point in the diagnosis of reflux disease and seek to find a criterion in the reflux-to-adenocarcinoma sequence to define the disease (Figure 7–1). At present, the only accepted criterion is Barrett esophagus (defined by the presence of intestinal metaplasia in an endoscopically visualized columnar-lined segment of the esophagus). Barrett esophagus is 100% specific for reflux disease; no etiology other than gastroesophageal reflux results in Barrett esophagus. However, Barrett esophagus cannot be used to define reflux disease because of its very low sensitivity;

TABLE 7–1 Diagnostic Criteria for Gastroesophageal Reflux Disease*

Criterion	Specificity	Sensitivity
Presently used diagnostic methods		
Classical symptoms	High	Intermediate
Erosive esophagitis	High	Low
24-hour ambulatory pH test	High	Intermediate
Multichannel impedance test	High	Intermediate
Histologic changes in squamous epithelium	Intermediate	Low
Barrett esophagus	100%	Low
Suggested new criteria		
Cardiac mucosal metaplasia (reflux carditis)	100%	High
Oxyntocardiac mucosal metaplasia	100%	Nearly 100%

*The present criteria, used either singly or in any combination, do not provide a means of accurately diagnosing whether a patient has reflux disease.

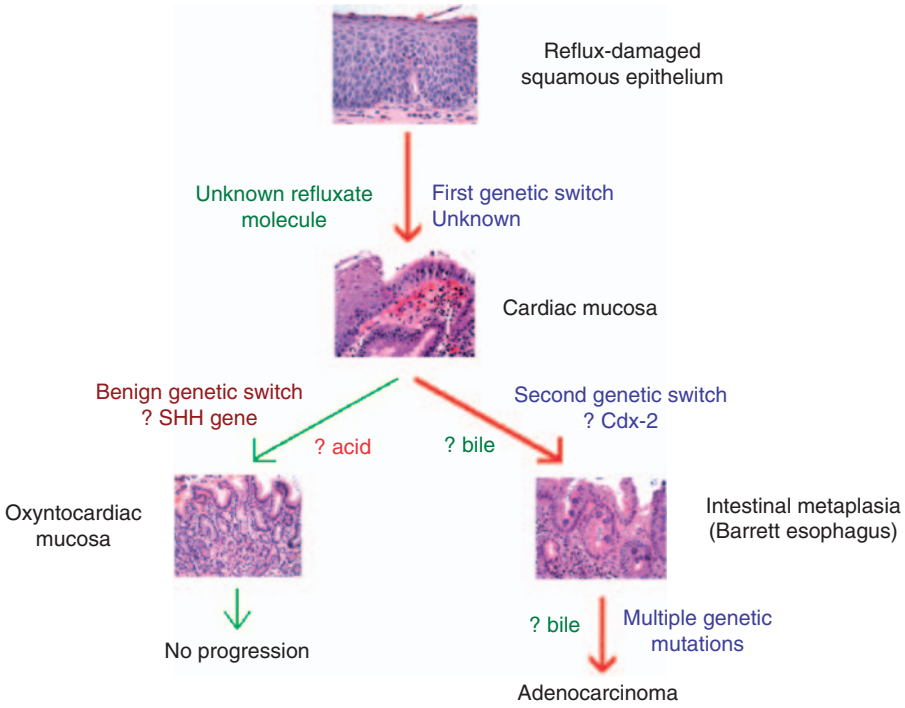


Figure 7–1 The reflux-to-adenocarcinoma sequence *(red arrows).* Carcinogenesis begins only when intestinal metaplasia is present in the esophagus. Intestinal metaplasia is preceded by cardiac mucosa, which is derived from columnar metaplasia of acid-damaged squamous epithelium. Cardiac mucosa can also convert to oxyntocardiac mucosa, which is a stable, benign epithelium that is out of the reflux-to-adenocarcinoma sequence *(green arrows). SHH,* Sonic hedgehog gene.

the vast majority of patients with reflux disease do not have Barrett esophagus. The main value of Barrett esophagus is that it is a highly specific and sensitive marker for future risk of adenocarcinoma.

The transformation of normal squamous epithelium to Barrett esophagus occurs through a series of changes, often taking many years. The earliest changes that involve the squamous epithelium are relatively nonspecific, representing injury changes that are caused by many esophageal diseases.[1] These include dilated intercellular spaces,[2,3] intraepithelial eosinophils, basal cell hyperplasia, papillary elongation, erosions, and ulceration[4] (see Figures 2–20 to 2–32). Recognizable changes in squamous epithelium also lack sensitivity; up to 50% of patients with abnormal reflux proven by 24-hour pH studies

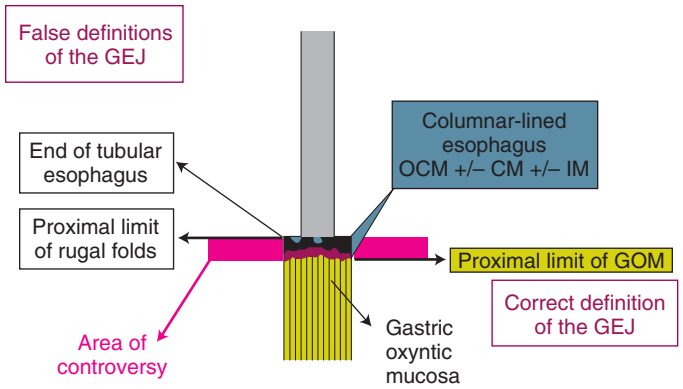


Figure 7–2 The resolution of the present controversy regarding cardiac mucosa *(CM)* distal to the end of the tubular esophagus and proximal limit of rugal folds (the present endoscopic definition of the gastroesophageal junction). When it is recognized that the true gastroesophageal junction *(GEJ)* is defined histologically as the proximal limit of gastric oxyntic mucosa, the area of controversy is seen to be the dilated end-stage esophagus. *IM,* Intestinal metaplasia; *OCM,* oxyntocardiac mucosa; *GOM,* gastric oxyntic mucosa.

and the presence of symptoms have no specific changes in the squamous epithelium.

In contrast, columnar metaplasia of esophageal reflux disease is absolutely specific; no other disease causes it. The presence of any of the three types of columnar epithelium in the esophagus is therefore 100% specific for reflux disease (see Table 7–1). Columnar metaplasia is also extremely sensitive for the presence of reflux. Although squamous epithelial criteria are absent in many patients with symptomatic reflux, columnar metaplastic epithelia (defined as cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa) can be found in virtually all patients with symptomatic reflux and many patients without symptoms of reflux.

The occurrence of intestinal metaplasia in cardiac mucosa is preceded by many decades during which the esophagus is lined by columnar epithelium consisting of cardiac and oxyntocardiac mucosa. In the past, the problem with using these non-intestinalized columnar epithelia as a diagnostic criterion for gastroesophageal reflux disease has been that they have been regarded as normal epithelia in the distal esophagus, proximal stomach, or both.[5] Based on the evidence in many autopsy studies, this concept of normalcy has changed. It is now accepted that these epithelial types are never found in the distal esophagus.[6] I have suggested in Chapter 2 that it is inexplicable that the presence of an endoscopically visible columnar-lined esophagus is not used as a diagnostic criterion for gastroesophageal reflux disease.

The present controversy relates entirely to the significance of cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa found distal to the endoscopic gastroesophageal junction.[6] In Chapter 4, I provided strong evidence that the controversy is easily resolved when we recognize that the present endoscopic definition of the gastroesophageal junction is incorrect[7] (Figure 7–2).

When the true gastroesophageal junction is recognized as the proximal limit of gastric oxyntic mucosa, the area that is presently controversial resolves into the dilated end-stage esophagus[7] (see Figure 7–2). A microscopic phase of gastroesophageal reflux disease that we ignore by present criteria now emerges as the most common manifestation of reflux disease.

If cardiac and oxyntocardiac mucosae are not normal, as suggested by the evidence (Table 7–2), its presence is 100% specific and nearly 100% sensi-

TABLE 7–2 Studies that Indicate that Cardiac Mucosa is not a Normal Epithelial Structure, but Rather an Abnormal Reflux-Induced Metaplastic Epithelium of the Esophagus

Sources	Evidence
Allison and Johnstone, 1953[14]	The epithelial type at the peritoneal reflection (GEJ) in patients with CLE is gastric oxyntic mucosa.
De Hertogh et al, 2003[15]	The epithelial type at the angle of His (GEJ) in fetal autopsies is gastric oxyntic mucosa.
Chandrasoma et al, 2000[16]; Zhou et al, 2001[17]	Cardiac mucosa is not universally found at the SCJ in autopsies of fully developed humans (over 1 year old).
Chandrasoma et al, 2000[16]; Kilgore et al, 2000[18]	When present at autopsy, cardiac mucosal length is less than 5 mm in the majority of patients, and often less than 1 mm.
Chandrasoma et al, 2000[16]; Kilgore et al, 2000[18]	The prevalence and length of cardiac mucosa tend to increase with age.
Jain et al, 1998[19]	The lowest reported prevalence of cardiac mucosa at the SCJ is 35%, in a population of patients with a bias toward having a normal GEJ at endoscopy.
Marsman et al, 2004[20]	The prevalence of cardiac mucosa is higher (61%) in patients with symptomatic reflux, even when endoscopy is normal.
Chandrasoma et al, 2003[21]	When endoscopically visible columnar epithelium is present, the prevalence of cardiac mucosa approaches 100%.
Csendes, 1993[22]	The length of cardiac mucosa (= length of CLE = proximal migration of the SCJ) correlates with severity of reflux.
Oberg et al, 1997[23]	The presence of cardiac and/or oxyntocardiac mucosa at the GEJ is associated with more reflux and a higher incidence of LES abnormality than absence of these epithelia.
Glickman et al, 2002[24]	The presence of >1 mm of cardiac mucosa at the GEJ is associated with more reflux than when it is <1 mm.
Chandrasoma et al, 2000[25]	The presence of CLE >2 cm is associated with more reflux than <2 cm of CLE.
Hamilton et al, 1977[26]; Oberg et al, 2002[27]; Dresner, 2003[28]; Lord et al, 2004[29]	Cardiac mucosa develops above the anastomotic line in patients who have had an esophagogastrectomy with gastric pull-up.

CLE, Columnar-lined esophagus; *GEJ,* gastroesophageal junction.

tive for reflux disease, potentially making it a perfect definition of gastroesophageal reflux.[8–12] Although all metaplastic columnar epithelia are 100% specific for reflux disease, only two (cardiac mucosa with and without intestinal metaplasia) are in the reflux-to-adenocarcinoma sequence (see Figure 7–1). Oxyntocardiac mucosa is a benign epithelium that does not progress to intestinal metaplasia and adenocarcinoma.[11–13] As such, the definition of reflux disease is more meaningful if the defining criterion is restricted to cardiac mucosa, with and without intestinal metaplasia. The presence of oxyntocardiac mucosa, although caused by and diagnostic of reflux disease, is irrelevant in terms of the adenocarcinoma that we have suggested is the appropriate end-point of our definition. I have suggested the term *compensated reflux* for oxyntocardiac mucosa to indicate its association with reflux and the fact that it is not an epithelium that places the patient at risk for reflux-induced adenocarcinoma.[11]

There are two other practical advantages for excluding oxyntocardiac mucosa from the definition of reflux disease:

1. Oxyntocardiac mucosa is almost universally present if the entire circumference of the gastroesophageal junction is examined,[16] reflecting the almost universal presence of gastroesophageal reflux in humans. As such, it will be too sensitive as a definitive criterion to have practical meaning. In contrast, cardiac mucosa is present in 50% or less of the general population. This is based on our autopsy study in which 44% of patients with complete sampling of the junction had cardiac mucosa[16] and another study, which showed cardiac mucosal presence at the esophagogastric junction in 35% of patients in endoscopic biopsies.[19]
2. Oxyntocardiac mucosa can be difficult to differentiate from normal gastric oxyntic mucosa when it contains large numbers of parietal cells. As such, diagnostic error is possible. This is not the case with cardiac mucosa,

TABLE 7–3 Definitional Value of Different Types of Metaplastic Columnar Epithelial in Gastroesophageal Reflux Disease*

Criterion	Sensitivity for reflux	Specificity for reflux	In the adenocarcinoma sequence?
Cardiac mucosa (reflux carditis)†	High	100%	Yes–early‡
Intestinal metaplasia (Barrett esophagus)	Low (5%–15%)	100%	Yes–late
Oxyntocardiac mucosa	Nearly 100%	100%	No

*Although oxyntocardiac mucosa is 100% specific and 100% sensitive, it is not an epithelium that is in the reflux-to-adenocarcinoma sequence. Cardiac mucosa, although less sensitive as an indicator of reflux, is highly specific as an indicator for cancer because all Barrett esophagus and cancer must be preceded by cardiac mucosa.

†The terms *cardiac mucosa* and *reflux carditis* are synonymous because cardiac mucosa is always inflamed.[4,30]

‡Cardiac mucosa is not transformed to cancer directly by carcinogens. Its presence indicates that the patient is at risk of developing intestinal metaplasia and progressing in the reflux-to-adenocarcinoma sequence.

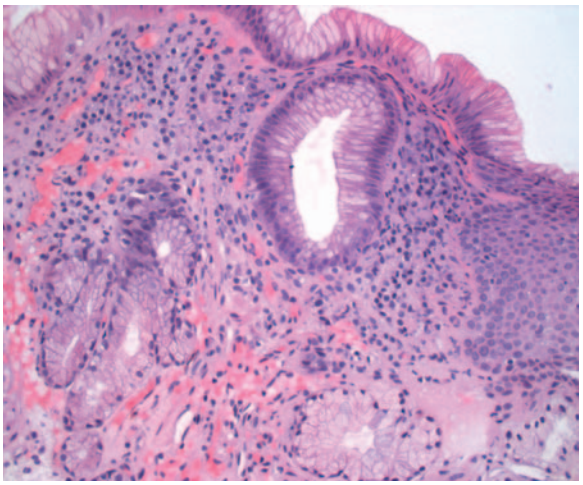


Figure 7–3 Cardiac mucosa at the squamocolumnar junction. This is always inflamed and always represents reflux-induced squamous metaplasia of the esophagus. It is never gastric and never normal. This is reflux carditis, the perfect definition of gastroesophageal reflux disease, which we have always erroneously called a *normal gastric epithelium.*

because its definition as an epithelium lacking any parietal cells makes its recognition highly reproducible and accurate.

We therefore propose that the presence of cardiac mucosa (reflux carditis) should define gastroesophageal reflux disease (Table 7–3, Figure 7–3). Its presence is 100% specific for reflux (i.e., all patients with cardiac mucosa have gastroesophageal reflux). A patient who has only metaplastic oxyntocardiac mucosa without any cardiac mucosa is a patient with reflux who is out of the reflux-to-adenocarcinoma sequence and is not at risk for cancer. The use of cardiac mucosa to define reflux disease therefore limits the definition to those patients who are in the reflux-to-adenocarcinoma sequence. A patient who does not have cardiac mucosa (with and without intestinal metaplasia) is not at risk for reflux-induced adenocarcinoma with 100% predictability. Cardiac mucosa is as close to a perfect definition of gastroesophageal reflux disease as possible if one's end-point is reflux-induced adenocarcinoma.

Reflux Carditis: The Perfect Definition of Gastroesophageal Reflux Disease

When cardiac mucosa is found, it is always histologically abnormal (see Figure 7–3). The earliest researchers noted this. Allison and Johnstone[14] describe it

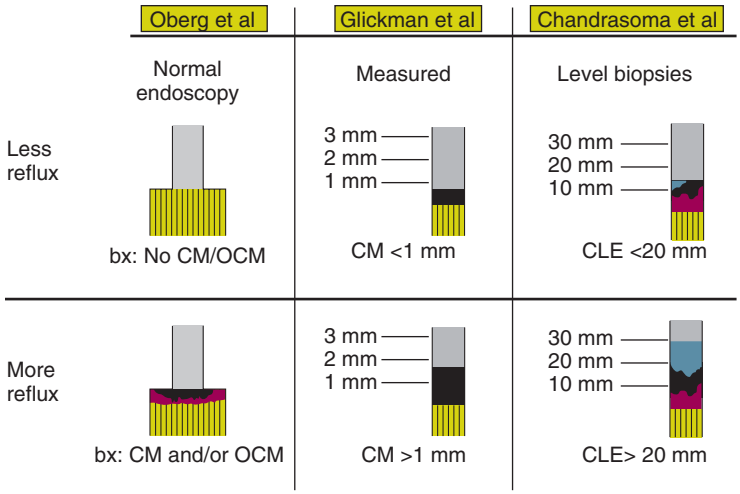


Figure 7–4 Three studies that have evaluated the significance of cardiac mucosa. In Oberg et al,[23] patients with any cardiac mucosa *(CM)* have more reflux than those without cardiac mucosa. In Glickman et al,[24] patients with greater than 1 mm of cardiac mucosa have a higher likelihood of reflux than those with less than 1 mm. In Chandrasoma et al,[25] patients with greater than 2 mm of cardiac mucosa have more reflux than those with less than 2 mm. *CLE,* Columnar-lined esophagus; *OCM,* oxyntocardiac mucosa.

as follows: "the rather villous type of cardiac mucosa, its lack of depth, and a diffuse fibrosis of the submucosa. . . suggest healing of previous shallow ulcerations."

Der et al[30] reported that cardiac mucosa always showed chronic inflammation and that the degree of chronic inflammation in cardiac mucosa correlated with the severity of gastroesophageal reflux as assessed by a 24-hour pH test. The presence of cardiac mucosa is therefore equivalent to carditis because cardiac mucosa is always inflamed. There is no "histologically normal" cardiac mucosa.

When defined by histologic criteria, the presence of cardiac mucosa (i.e., carditis) is associated with gastroesophageal reflux (Figure 7–4). Oberg et al[23] showed that the presence of cardiac mucosa in biopsies taken from an endoscopically normal junction predicted the presence of reflux compared to patients who did not have cardiac mucosa (see Table 7–2). Glickman et al,[24] comparing children with greater than and less than 1 mm of cardiac mucosa in biopsies across the gastroesophageal junction, showed that reflux was significantly more common in patients with greater than 1 mm of cardiac mucosa. The adjective "reflux" can therefore be appended to all "carditis," making "reflux carditis" an appropriate equivalent to "cardiac mucosa." Reflux carditis results from columnar metaplasia of the squamous epithelium of the esophagus followed by continued damage of the metaplastic columnar epithelium by the refluxate.

Definition of Reflux Carditis

Reflux carditis is defined as the finding of cardiac mucosa between the squamocolumnar junction and gastric oxyntic mucosa (true gastroesophageal junction) (Figure 7–5). These biopsies may come to the pathologist labeled as "distal esophagus," "gastroesophageal junction," "gastric cardia," "proximal stomach," or "1–3 cm distal to the gastroesophageal junction." The histologic finding of cardiac mucosa supersedes the endoscopic landmarks.

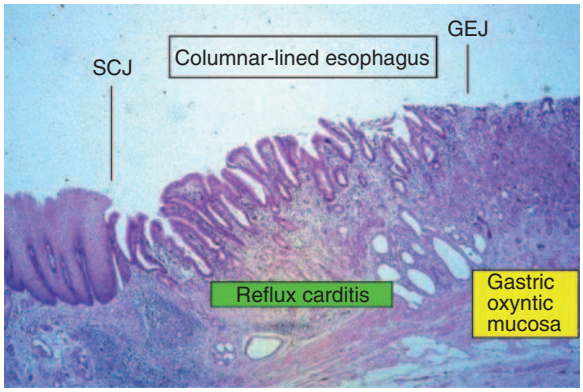


Figure 7–5 Reflux carditis is the presence of cardiac mucosa between the squamocolumnar junction *(SCJ)* (Z-line, visible endoscopically) and the true gastroesophageal junction *(GEJ)* (not visible endoscopically and definable only by histology). It is an error to regard the squamocolumnar junction as the true gastroesophageal junction at endoscopy when no columnar-lined esophagus is visualized. There must be a microscopic stage of columnar-lined esophagus before it reaches the limit of optical resolution of the endoscope.

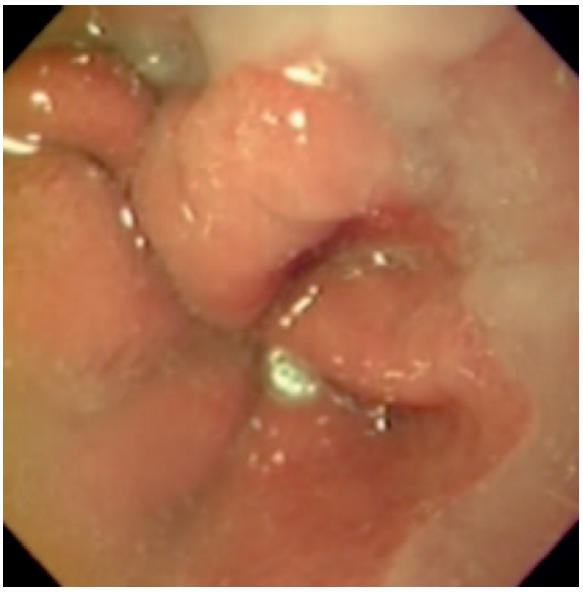


Figure 7–6 Endoscopic appearance of the squamocolumnar junction. The Z-line is horizontal, and the rugal folds appear to reach the Z-line. However, there is significant interobserver variability regarding the presence or absence of small amounts (less than 5 mm) of columnar-lined esophagus, particularly when the Z-line is not serrated. The proximal limit of the rugal folds, although universally recognized as the endoscopic junction, is not so precisely defined that it can detect the smallest amounts of columnar-lined esophagus.

Histologic Features of Reflux Carditis

The histologic features of reflux carditis are those of cardiac mucosa (see Figure 7–3; also see Figures 3–67 to 3–74). It is an epithelium in the distal esophagus (including dilated end-stage esophagus) consisting of mucous cells without parietal or goblet cells. It ranges from a flat epithelium to a complex glandular epithelium (see Chapter 3); invariably shows chronic inflammation with plasma cells, lymphocytes, and eosinophils; and frequently shows reactive features such as foveolar elongation and serration and smooth muscle proliferation in the lamina propria. The severity of the chronic inflammation and foveolar hyperplasia correlates with the severity of reflux. Erosion of the surface with granulation tissue may be seen.

Gross Pathologic and Endoscopic Features of Reflux Carditis

Grossly and endoscopically, reflux carditis is commonly invisible. In such patients, it is present in rugated mucosa distal to the squamocolumnar junction in dilated end-stage esophagus. In these patients, endoscopy is normal, and microscopic reflux carditis represents the histologic criterion that is diagnostic of "non-erosive reflux disease." When reflux carditis is recognized as the definition of reflux disease, the entity of "non-erosive reflux disease" will disappear.

Depending on the observer, it is likely that up to 5 mm of flat columnar epithelium between the squamocolumnar junction and the proximal limit of the rugal folds may be interpreted as "normal" (Figure 7–6). Part of this "invisible" cardiac mucosa may therefore represent epithelium that may be recognized endoscopically as endoscopic resolution and technique improves.

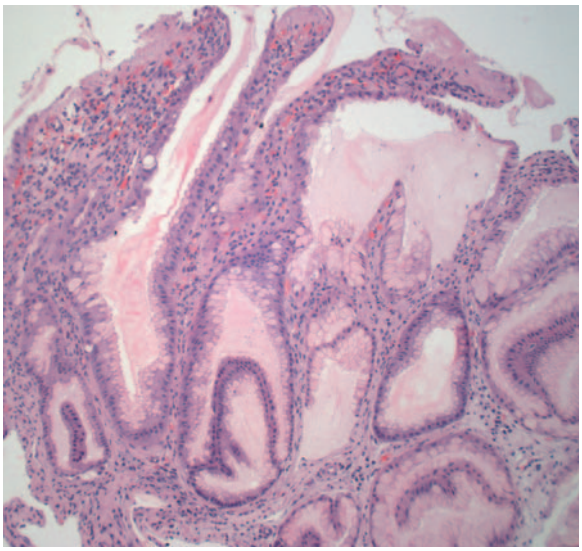


Figure 7–7 Reflux carditis with marked hyperplasia of the foveolar region, presenting an appearance similar to hyperplastic polyps of the stomach. This biopsy was taken from a polypoid lesion at the "gastroesophageal junction." Reflux carditis is the most common pathology in non-neoplastic polyps in the distal esophagus, including the dilated end-stage esophagus.

Part of it, however, is always likely to be invisible to endoscopy and detectable only by histology.

When visible, reflux carditis is seen as a flat epithelium between the proximal limit of the rugal folds and the squamocolumnar junction. It may form tongues extending into the squamous epithelium or be circumferential in the tubular esophagus (see Figures 2–8 to 2–19). It may be interposed between the Z-line at the end of the tubular esophagus and the proximal limit of the rugal folds, occupying the most proximal part of the saccular region distal to the tubular esophagus, which is the dilated end-stage esophagus. In rare cases, the reactive cardiac mucosa forms small, inflamed, polypoid lesions (Figure 7–7).

Visible reflux carditis is equivalent to endoscopic columnar-lined esophagus. Therefore, the presence of an endoscopically visible columnar-lined esophagus is diagnostic of reflux disease, and its length is an accurate assessment of the severity of reflux disease. The only requirements of biopsy are the following:

1. To identify the small number of patients with only oxyntocardiac mucosa in their columnar-lined esophagus (this is rare when there is a visible columnar-lined esophagus).
2. To diagnose Barrett esophagus, which is the presence of intestinal metaplasia in the columnar-lined segment.

Many gastroenterologists make the mistake of equating columnar-lined esophagus with Barrett esophagus at endoscopy. Endoscopy is not capable of differentiating the three epithelia—intestinal, cardiac, and oxyntocardiac—that comprise the histologic spectrum of columnar-lined esophagus. Only when biopsies show intestinal metaplasia in any part of the columnar-lined esophagus can the diagnosis of Barrett esophagus be made.

To make a diagnosis of reflux carditis, biopsies must be taken (Figure 7–8); cardiac mucosa cannot be distinguished from other columnar epithelia

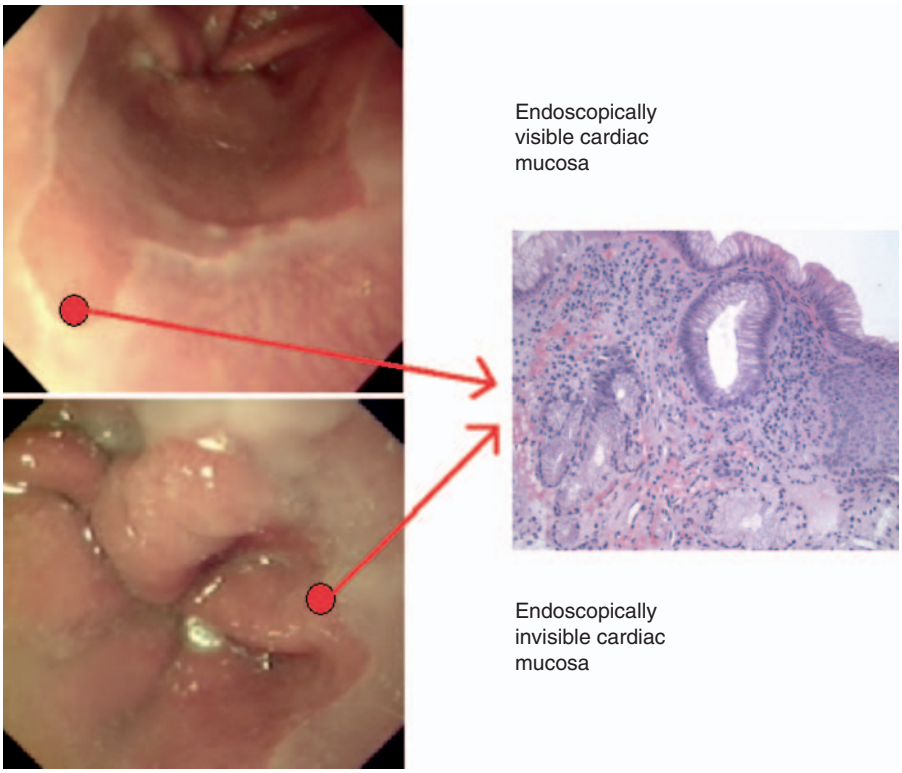


Figure 7–8 Reflux carditis requires biopsy of the region immediately distal to the squamocolumnar junction. It may be endoscopically visible *(top)* or may occur in endoscopically normal patients *(bottom)*. It is defined by histology, not by the location of the biopsy. When there is an endoscopically visible columnar-lined epithelium, the probability of finding cardiac mucosa is nearly 100%; when the endoscopy is normal, the probability depends on whether the patient has reflux symptoms. When reflux symptoms are present, approximately 70% of patients will have cardiac mucosa; when the patient is asymptomatic, approximately 35% to 50% will have cardiac mucosa.

by anything other than histology. When there is any visible deviation from normal at endoscopy, the probability of finding reflux carditis in a biopsy is close to 100%.

Clinical Features of Reflux Carditis

Patients with reflux carditis may or may not have symptoms of reflux. When biopsies are taken in patients with symptomatic reflux, the prevalence of cardiac mucosa is very high. When endoscopy shows a visible columnar-lined esophagus, reflux carditis is almost invariably found in the symptomatic patient. Even when the symptomatic patient has a normal endoscopy, reflux carditis is present in approximately 70% of patients. In such patients, the presence of reflux carditis confirms the clinical suspicion of reflux. The diagnosis of "non-erosive reflux disease" disappears because the sensitivity of reflux carditis in the diagnosis of reflux disease is extremely high; this is the pathologic change of "non-erosive reflux disease."

A significant number of patients who are endoscopically normal and asymptomatic (or do not have classical symptoms of reflux) will have cardiac mucosa in their biopsies. In our autopsy study, the prevalence of cardiac mucosa was 44%.[16] Despite their absence of symptoms, these patients can progress in the reflux-to-adenocarcinoma sequence, presenting for the first time with dysphagia caused by advanced adenocarcinoma or significant extra-

esophageal manifestations such as laryngitis, asthma, chronic cough, and idiopathic pulmonary fibrosis.[31]

Reflux carditis is valuable in the diagnosis of atypically symptomatic reflux disease because of its high sensitivity as a criterion for reflux disease. If an atypically symptomatic patient does not have reflux carditis in an appropriate biopsy sample, it is highly unlikely that the atypical symptoms are caused by reflux. However, the presence of reflux carditis does not prove whether the atypical symptoms are caused by or simply coincident with reflux disease.

The presence of reflux carditis is not associated with any known risk of carcinoma; however, it is the earliest specific step in the reflux-to-adenocarcinoma sequence. Patients with cardiac mucosa have an epithelium that is at risk for developing intestinal metaplasia and progressing in the reflux-to-adenocarcinoma sequence. The greater value of this diagnostic criterion is that the absence of both cardiac mucosa and intestinal metaplasia can be used to reassure the patient that there is minimal risk of adenocarcinoma. This is a significant population (approximately 50% of people in the United States). If a 50-year-old patient has no reflux carditis in an adequately sampled junction at endoscopy, it is highly unlikely that cardiac mucosa will develop and progress through intestinal metaplasia to cancer during his or her lifetime.

Reflux Carditis and the 24-Hour pH Test

Most patients with reflux carditis have an abnormal 24-hour pH study. In Oberg et al,[23] the presence of cardiac and/or oxyntocardiac mucosa in endoscopically normal patients was predictive of a greater likelihood of an abnormal 24-hour pH test compared with patients who did not have these mucosal types.

However, the presence of reflux carditis is a more sensitive criterion for reflux disease than an abnormal 24-hour pH study. The reason for this is that the level of acid exposure in the 24-hour pH test that was used to define abnormal reflux was calibrated to the presence of symptoms.[32] Therefore, it should not be surprising that patients with asymptomatic reflux disease can have reflux carditis but have a normal 24-hour pH test.

In the study by Der et al,[30] 41 of 105 (39%) of patients with reflux carditis had a pH study within the normal range. Among these patients, the lowest percentage time the pH was less than 4 was 2.1%. This means that the 31 patients who had normal 24-hour pH studies had a daily acid exposure of between 30 and 60 minutes in the lower esophagus. Although this may not cause symptoms, it should not be surprising that it causes cellular damage to the squamous epithelium leading to cardiac metaplasia.

The pH electrode is located in the esophageal body 5 cm above the upper limit of the lower esophageal sphincter. This is approximately 8 to 9 cm above the gastroesophageal junction, given a sphincter length of 3 to 4 cm. Not surprisingly, there can be reflux-induced changes in the most distal few millimeters of the esophagus when the pH study is normal. We have suggested that the most distal few millimeters of the esophageal squamous can be damaged in the absence of free reflux when it becomes exposed to gastric luminal contents during periods of gastric overdistension and in patients who have short segments of dilated end-stage esophagus resulting from sphincter damage. These are the bases for patients who have reflux carditis with a normal 24-hour pH test.

Significance of Reflux Carditis

Reflux carditis is a 100% specific histologic marker for gastroesophageal reflux. No other etiologic agent is known to produce this change. Reflux carditis is

infinitely more specific than present squamous epithelial criteria for the diagnosis of gastroesophageal reflux.

The sensitivity of reflux carditis for the diagnosis of reflux disease is less than 100%. Reflux carditis is much more sensitive than Barrett esophagus for the diagnosis of gastroesophageal reflux. It is less sensitive than the presence of oxyntocardiac mucosa.

Reflux carditis may be absent in a patient with evidence of reflux for the following reasons:

1. True false-negative, type 1: Metaplastic columnar epithelia may be absent in the very early stage of reflux disease when reflux has caused changes in squamous epithelium without causing columnar metaplasia. This is rare and is most likely restricted to young children at the very onset of lifelong reflux disease. Most adult patients with evidence of reflux disease will have reflux carditis.
2. True false-negative, type 2: These patients with reflux disease have only oxyntocardiac mucosa as a columnar metaplastic type. This occurs when all the cardiac mucosa resulting from columnar metaplasia converts to oxyntocardiac mucosa. This is a very common occurrence in the asymptomatic population. In our autopsy study,[16] small amounts of oxyntocardiac mucosa were present in some part of the circumference of the squamocolumnar junction in the 56% of patients who did not have cardiac mucosa. Patients who have only oxyntocardiac mucosa are likely to be asymptomatic and endoscopically normal. When the columnar epithelial length reaches 1 cm, there is almost always some cardiac mucosa in the columnar-lined esophagus.[21]
3. Sampling error (false negative): Biopsy sampling of the junction is limited, with the possibility that cardiac mucosa that is present may be missed, causing a false negative result. Increasing the sampling boosts the level of confidence that absence of cardiac mucosa is a true negative result. If each biopsy is 4 mm, and the circumference of the esophagus is 5 cm, a four-quadrant biopsy will sample 32% of the epithelium at the junction; this standard is likely to be an adequate sample.

Differential Diagnosis of Reflux Carditis

There is very little confusion or difficulty with the diagnosis of reflux carditis. The diagnosis is accurate, precise, and reproducible. It is the presence of a columnar epithelium in the esophagus, including the dilated end-stage esophagus, which is composed only of mucous cells; there are no parietal cells or goblet cells. The only condition that may theoretically cause confusion with reflux carditis is atrophic gastritis with pseudo-pyloric metaplasia that complicates *Helicobacter pylori* gastritis and autoimmune gastritis (see Chapter 3).

A New Definition of Barrett Esophagus

The present definition of Barrett esophagus is the presence of intestinal metaplasia in a biopsy taken from an endoscopically visible columnar-lined esophagus.[33] This definition is patently incorrect. One cannot define a disease by a visible change; a visible change must be preceded by a microscopic change, because the magnification power of the endoscope does not allow it to be seen at a microscopic level. By defining Barrett esophagus in this manner, we ignore the microscopic phase of Barrett esophagus. Physicians must recognize that they cannot make diseases disappear by the edict of definition.

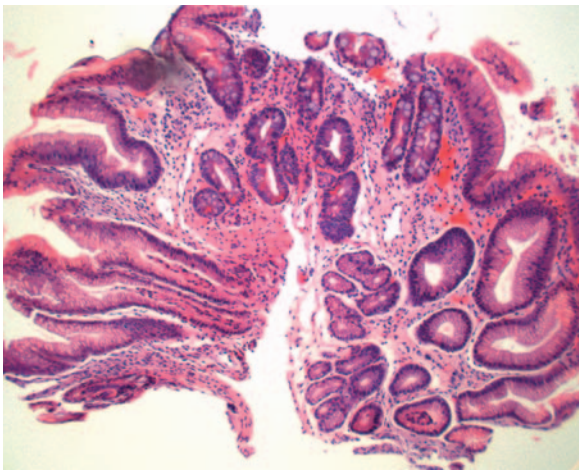


Figure 7–9 The newly proposed definition of Barrett esophagus is that it is defined histologically as the presence of intestinal metaplasia in cardiac mucosa, regardless of endoscopic appearance or perceived location. This is equivalent to intestinal metaplasia of the esophagus, because cardiac mucosa is always a metaplastic esophageal epithelium resulting from reflux-induced damage.

The correct definition of Barrett esophagus is the presence of intestinal metaplasia in cardiac mucosa (Figure 7–9), regardless of endoscopic findings. Cardiac mucosa is always a metaplastic reflux-induced esophageal columnar epithelium and is the only precursor epithelium in which esophageal intestinal metaplasia occurs. Esophageal intestinal metaplasia (Barrett esophagus) does not occur in squamous or oxyntocardiac epithelia of the esophagus. When intestinal metaplasia occurs in gastric oxyntic mucosa, it represents chronic atrophic gastritis, a disease that has nothing to do with reflux disease. There may, on occasion, be difficulty in differentiating chronic atrophic gastritis from microscopic Barrett esophagus in a single biopsy from the squamocolumnar junction. I have addressed this differential diagnosis in Chapter 3 (see Figures 3–112 to 3–122).

Barrett esophagus is clinically and endoscopically indistinguishable from reflux carditis. The two are separable only by the presence of intestinal metaplasia (Figure 7–10). When intestinal metaplasia occurs in an endoscopically visible columnar-lined segment of the esophagus, this is visible Barrett esophagus. When intestinal metaplasia is found in cardiac mucosa in an endoscopically normal patient, this is microscopic Barrett esophagus occurring in the dilated end-stage esophagus.[7,11] The prevalence of microscopic Barrett esophagus is not known with certainty. In our population of patients with a strong bias of having reflux disease, we reported that 15.8% of patients with less than 1 cm of histologically defined columnar-lined esophagus had intestinal metaplasia.[21] Rex et al[34] reported that 12.9% of patients who presented for screening colonoscopy who were offered an upper endoscopy had intestinal metaplasia in a biopsy taken at "the proximal edge of the gastric folds, just distal to the end of the tubular esophagus." It is unknown how many of these patients had intestinal metaplasia in cardiac or gastric oxyntic mucosa, because the histologic features were not reported apart from the presence of intestinal metaplasia. Considering the evidence available, it is reasonable to suggest that 7% to 15% of the U.S. population over the age of 40 years have microscopic Barrett esophagus.

Barrett esophagus is the only pathogenetic pathway to reflux-induced adenocarcinoma. Although Barrett esophagus is undoubtedly the pathway

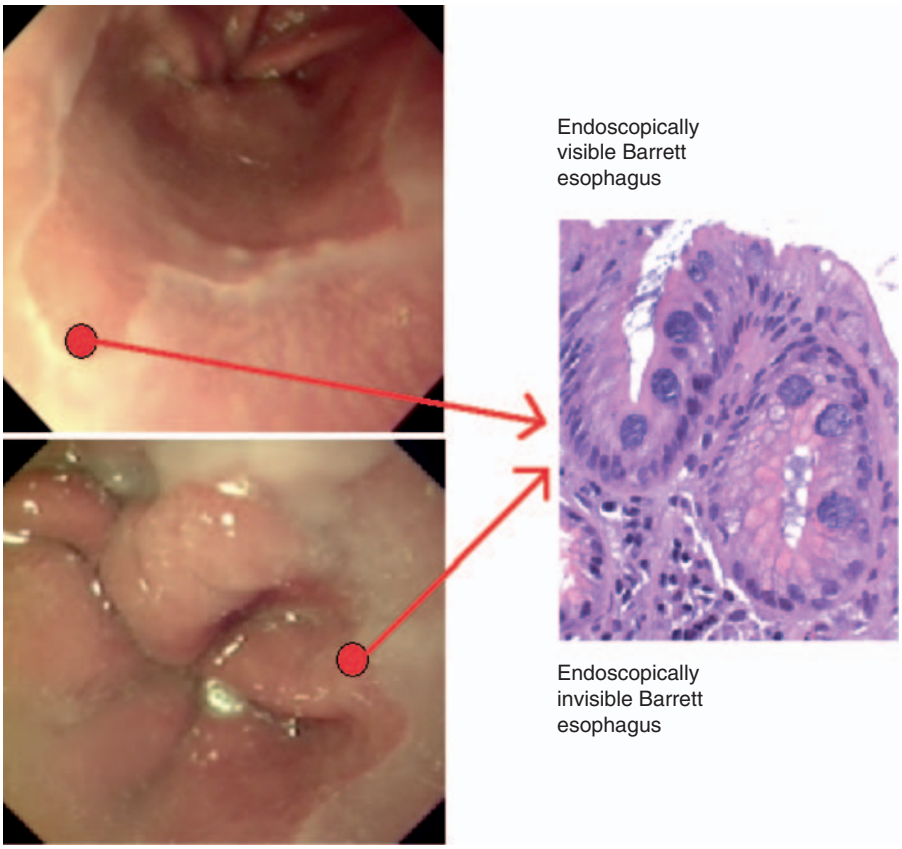


Figure 7–10 Barrett esophagus and reflux carditis are endoscopically indistinguishable. Biopsies from the patients shown in Figure 7–8, who were diagnosed with reflux carditis if they had cardiac mucosa without intestinal metaplasia, would be diagnosed as Barrett esophagus if they had intestinal metaplasia in the cardiac mucosa. Barrett esophagus can therefore be endoscopically visible or can occur in the endoscopically normal patient as a purely microscopic finding.

resulting in adenocarcinoma of the distal tubular esophagus, the etiology of what is presently called *adenocarcinoma of the gastric cardia* is considered to be less certainly associated with reflux. I have produced evidence that most adenocarcinomas presently classified as *gastric cardiac* are adenocarcinomas arising in the dilated end-stage esophagus. This would mean these tumors are reflux-induced and must have a pathway through microscopic Barrett esophagus in the dilated end-stage esophagus (Figures 7–11 and 7–12); there is no other mechanism whereby reflux results in adenocarcinoma.

Proving the association between reflux disease and adenocarcinoma arising in microscopic Barrett esophagus limited to the dilated end-stage esophagus is difficult. These patients, by virtue of the very short segment of columnar-lined esophagus, are those with the least severity of reflux. However, when it occurs in short segments, microscopic Barrett esophagus is exposed to the highest concentration of carcinogen in the gastric refluxate. The low risk resulting from the very small number of target cells (i.e., intestinal metaplasia) is counterbalanced by the exposure to the highest carcinogen dose. From a practical standpoint, the combination of the two factors leads to approximately 12,000 patients per year in the United States developing adenocarcinoma in microscopic Barrett esophagus in the end-dilated stage esophagus. This is only slightly less than the total number who develop adenocarcinoma of the tubular esophagus. These patients are completely ignored by the

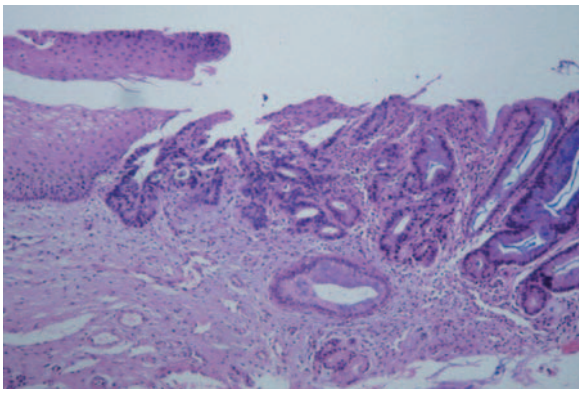


Figure 7–11 High-grade dysplasia in a microscopic segment of Barrett esophagus in an endoscopically normal patient. Intestinal metaplasia in the lowest regions of the esophagus is exposed to the highest carcinogen dose and is theoretically highly susceptible to malignant transformation.

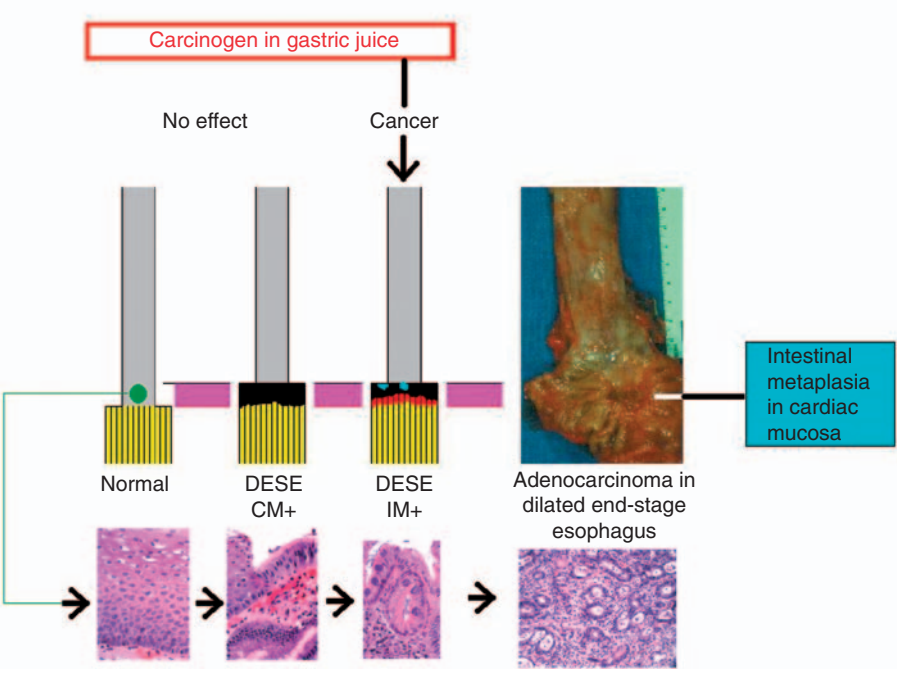


Figure 7–12 The pathogenesis of adenocarcinoma in columnar-lined esophagus limited to the dilated end-stage esophagus *(DESE, pink area)* distal to the end of the tubular esophagus is identical to the pathogenesis of reflux-induced adenocarcinoma of the distal esophagus. It traverses the reflux-to-adenocarcinoma sequence, passing through cardiac mucosa *(CM),* intestinal metaplasia *(IM),* and then from increasing dysplasia to adenocarcinoma. Until a tumor or ulcer results from cancer, the premalignant stages are endoscopically invisible and can be detected only if biopsies are taken distal to the Z-line in the endoscopically normal patient. Note that the epithelium at the epicenter of the tumor is shown to contain cardiac mucosa with intestinal metaplasia, indicating the precursor lesion of Barrett esophagus in the dilated end-stage esophagus.

present criteria of definition and practice guideliness until they develop advanced cancer.

CASE STUDY

The patient is an 83-year-old male with a long history of occasional heartburn associated with intermittent episodes of difficulty in swallowing for the past 20 years. He has treated this himself with over-the-counter medications. Approximately 1 month ago, he noted that he was having increasing difficulty in swallowing both solid and liquid food. When this progressed, he was referred to a gastroenterologist by his primary care physician.

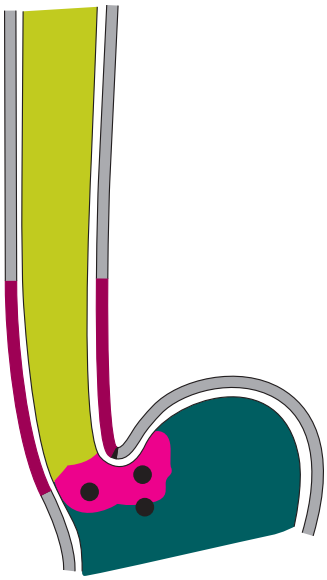


Figure 7–13 Diagrammatic representation of this patient's presentation. The tumor is largely in the proximal region of the pouch involving the dilated end-stage esophagus (mistaken for gastric cardia) and forms a large mass. It has extended to involve and obstruct the end of the tubular esophagus, causing dysphagia, which is the presenting symptom.

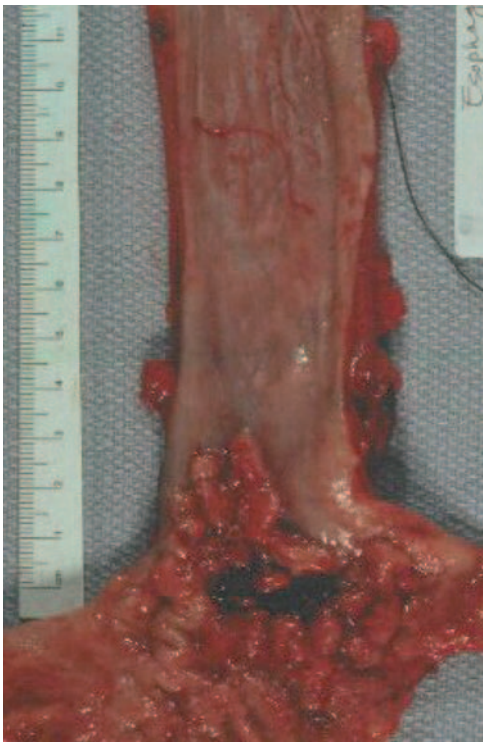


Figure 7–14 Esophagectomy. The tumor is ulcerated and involves the dilated end-stage esophagus, extending into the distal tubular esophagus. The squamous epithelium extends to the proximal edge of the tumor.

At endoscopy, there was an obstructing, ulcerated, circumferential mass lesion at the gastroesophageal junction. The upper edge of the tumor was composed of squamous epithelium; there was no visible columnar-lined esophagus above the tumor (Figures 7–13 and 7–14). This involved the lesser curvature of the proximal stomach to a distance of 2 to 3 cm and extended toward the fundus for 3 to 4 cm. Biopsies were taken from the tumor and the interface of the tumor with the adjacent epithelium and submitted in one container.

Biopsies showed the presence of an invasive, moderately differentiated adenocarcinoma arising in high-grade dysplasia (Figures 7–15 and 7–16). The tumor invaded the muscle fibers of the muscularis mucosae (Figure 7–17). There was residual intestinal metaplasia at the edge of the tumor, characterized by goblet cells (Figure 7–18). One of the biopsies showed gastric oxyntic mucosa with adenocarcinoma in the deep mucosa, including the muscularis mucosae (Figure 7–19). The gastric oxyntic mucosa showed no significant inflammation in the superficial region away from the tumor and no intestinal metaplasia (i.e., there was no evidence of chronic atrophic gastritis).

This is an adenocarcinoma of the end-stage dilated esophagus presenting at an advanced stage. The major part of the tumor is in the saccular region distal to the end of the tubular esophagus. The tumor extended to involve the end of the tubular esophagus, causing dysphagia only when it obstructed the tube. The tumor extended distally to involve the stomach (as shown by a tumor undermining gastric oxyntic mucosa).

Despite the fact that this biopsy series was not complete, there is sufficient evidence to indicate that this is a reflux-induced adenocarcinoma arising in dilated end-stage esophagus: (a) The patient has a long history of symptomatic

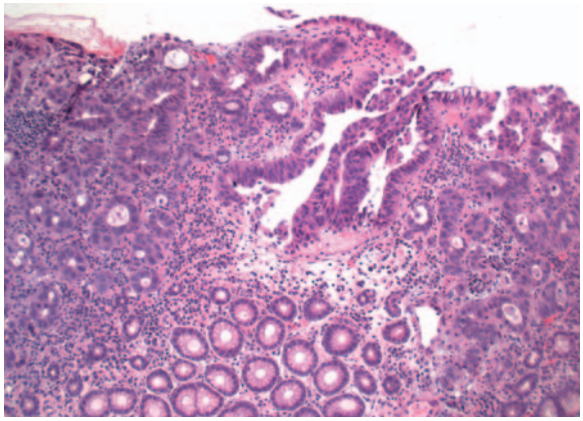


Figure 7–15 Low magnification of the interphase between tumor and adjacent epithelium showing high-grade dysplasia and early lamina propria invasion. The non-neoplastic epithelium is cardiac with residual intestinal metaplasia.

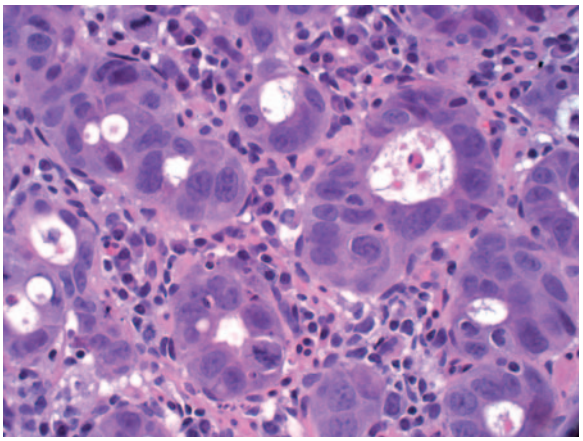


Figure 7–16 Higher magnification of Figure 7–15, showing high-grade dysplasia with early lamina propria invasion.

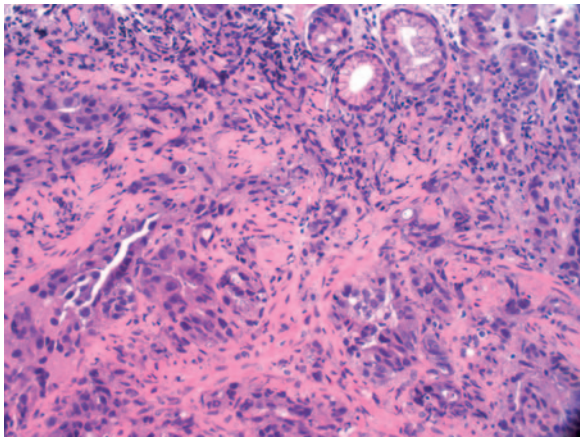


Figure 7–17 Invasive adenocarcinoma, showing irregular nests of malignant cells invading the muscle fibers of the muscularis mucosae. This appearance usually signifies a deeply invasive tumor, although the biopsy is still limited to the mucosa. The epithelium above the muscularis mucosae is oxyntocardiac, with rare parietal cells present in the predominantly mucous glands.

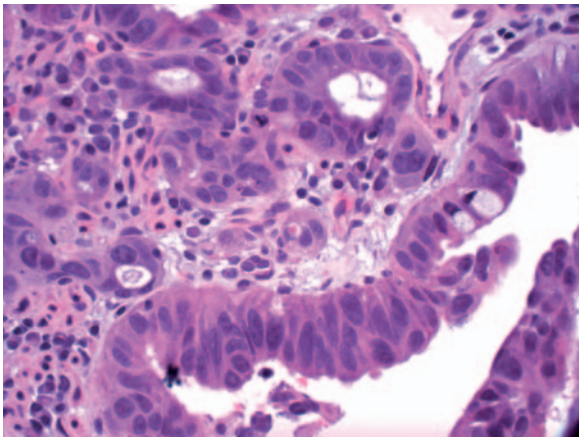


Figure 7–18 Higher magnification of Figure 7–15, showing residual intestinal metaplasia in the high-grade dysplasia, characterized by the presence of goblet cells.

reflux; (b) the gastric oxyntic mucosa is normal without atrophic gastritis; and (c) there is residual intestinal metaplasia around the tumor. The presence of intestinal metaplasia in this region with a normal gastric oxyntic mucosa is essentially diagnostic of microscopic Barrett esophagus (see Chapter 3).

This is the classical clinical presentation of a patient with reflux-induced adenocarcinoma involving the dilated end-stage esophagus. The tumor grows silently until it impinges on the distal tubular esophagus and causes obstruction and dysphagia. The 20-year history of heartburn and what appears to be reflux-induced motility disturbance causing intermittent dysphagia is the opportunity that was missed. The use of over-the-counter, acid-suppressive drugs also may have had a role in promoting this patient's Barrett esophagus and adenocarcinoma.

It is interesting to try to reconstruct this patient's life in terms of how his reflux-induced disease progressed (Figure 7–20). At birth, there is no columnar-lined esophagus. At some point in his life, he developed mild

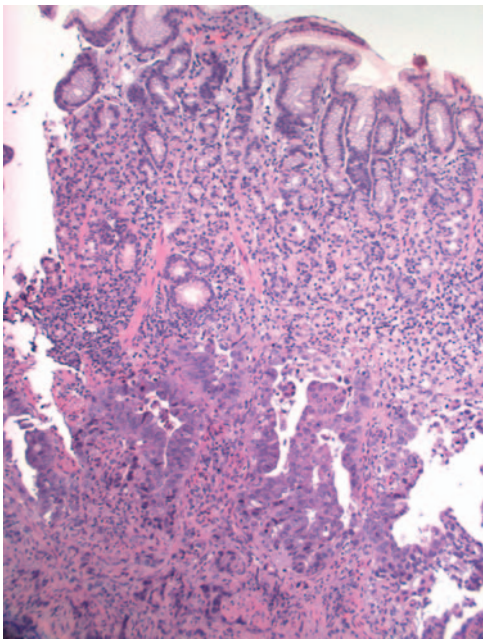


Figure 7–19 Biopsy showing undermining of gastric oxyntic mucosa by the invasive adenocarcinoma, a typical feature of advanced carcinoma. The oxyntic mucosa shows only minimal inflammation in the superficial region away from the tumor.

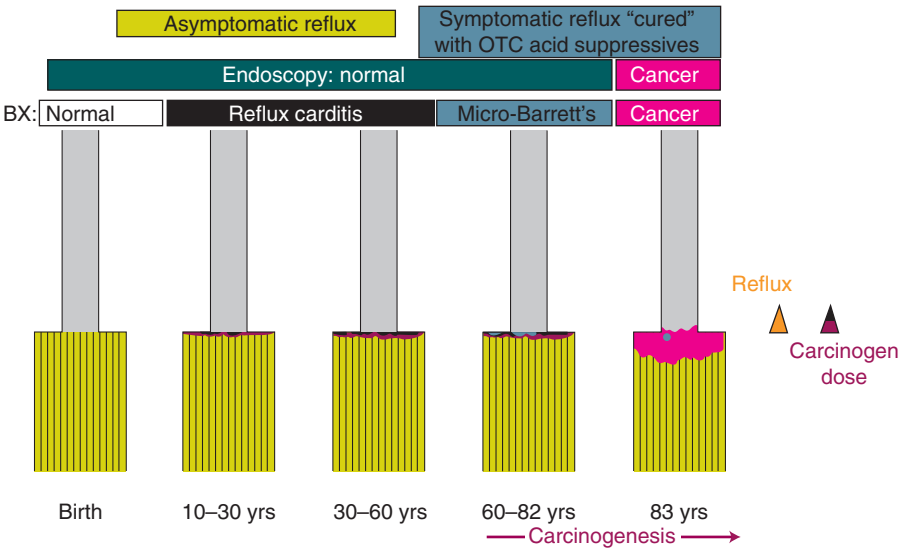


Figure 7–20 The hypothetical life history of this patient's disease. It is likely that he had mild, asymptomatic reflux for the first 60 years of his life, beginning at an unknown point in time, although it probably first occurred early in life. Reflux produced small amounts of cardiac and oxyntocardiac mucosa in dilated end-stage esophagus; he would have been endoscopically normal. Around the age of 60, he became symptomatic and started taking over-the-counter, acid-suppressive drugs, which relieved his symptoms. The change in the pH milieu caused the cardiac mucosa to develop into microscopic intestinal metaplasia. The carcinogens in gastric juice now had a target cell to act upon, resulting in genetic mutations leading to carcinoma. When the carcinoma developed, it progressed to form a large tumor that caused obstruction, shown here to have occurred within 1 year. This is the first point at which the disease was endoscopically visible. Note that this patient had mild reflux *(orange triangle)* and the effective carcinogen dose *(red part of triangle)* was limited to the most distal esophagus.

reflux, which produced a very short segment of columnar-lined esophagus consisting of cardiac and oxyntocardiac mucosa. This was limited to the dilated end-stage esophagus and increased minimally in length until he was 60 years old. At this point, reflux was sufficiently severe to cause symptoms, leading him to use over-the-counter, acid suppressive drugs, which "cured" him. For the next 20 years, his cardiac mucosa underwent intestinal metaplasia and increasing dysplasia until cancer developed in his dilated end-stage esophagus when he was 83 years old. This rapidly progressed to produce a large, obstructive mass lesion. By present criteria, the patient would have been endoscopically normal until he showed evidence of a mass lesion caused by the cancer. No biopsies would have been indicated by present practice guidelines. By the biopsy protocol suggested here, the patient would have been diagnosed with reflux carditis 50 years before his cancer, and microscopic Barrett esophagus would have been diagnosed 20 years before his cancer. Withdrawal of acid-suppressive drugs and anti-reflux surgery would have theoretically prevented his cancer. If this was done before he was 60 years old, it would have likely prevented intestinal metaplasia developing in reflux carditis. If it was done after he was 60 years old, it would have prevented adenocarcinoma arising in Barrett esophagus and possibly reversed intestinal metaplasia to cardiac mucosa. Opportunities like these for cancer prevention in reflux disease are being ignored at this time.

A New Diagnostic Method for Reflux Disease

The availability and recognition of a reliable and accurate histologic diagnostic criterion for reflux disease permit the development of a new method of assessing patients for gastroesophageal reflux.[8–12] This can provide scientifically validated information regarding the presence of reflux disease at a cellular level, the severity of reflux disease at a cellular level, and the risk of adenocarcinoma.

Protocols for Histologic Assessment

At endoscopy, the following are true (Table 7–4):

TABLE 7–4 Endoscopic Landmarks and Their Meaning

Landmark	Precision	Normal	Abnormal	Significance
Squamocolumnar junction (= Z-line)	High	Horizontal; at end of tubular esophagus	Serrated; migrated proximally into tubular esophagus	Defines the proximal limit of columnar-lined esophagus
End of tubular esophagus	Moderate	Sharp; 2–3 cm below diaphragm	Ill-defined; flared; closer to diaphragm	Best endoscopic estimate of GEJ when rugal folds are not clear; 0–3 cm proximal to true GEJ
Diaphragm	Low	Pinch-cock appearance	Not detectable	Of value only in detecting hiatal hernia
Distal limit of lower esophageal sphincter	Very low	At end of tubular esophagus	At end of tubular esophagus	Shortened in reflux disease; does not mark end of esophagus
Proximal limit of rugal folds	Moderate	Coincident with SCJ at end of tubular esophagus	Separated from SCJ by flat columnar epithelium	Best endoscopic estimate of GEJ; 0–3 cm proximal to true GEJ
Rugated mucosa	Moderate	Lines entire stomach	Lines entire stomach and end-stage dilated esophagus	Composed of oxyntic mucosa (stomach) or metaplastic esophageal columnar mucosa (proximal 0–3 cm)
Flat columnar mucosa	Moderate	Normally absent	Seen between SCJ and proximal limit of rugal folds	Composed of metaplastic esophageal columnar mucosa or atrophic gastric mucosa

GEJ, Gastroesophageal junction; *SCJ,* squamocolumnar junction.

TABLE 7–5 An Ideal Biopsy Protocol that Permits Accurate Assessment of the Histologic Features of Columnar-Lined Esophagus

Biopsy location	Circumstance	Purpose
A: At SCJ, attempting to straddle the junction	Always	Define the proximal limit of CLE; define epithelium at proximal limit of CLE; diagnose Barrett esophagus
B: 1–3 cm distal to end of tubular esophagus (in retroflexed position)	Always	Find CLE in dilated end-stage esophagus; find oxyntic mucosa to define distal limit of CLE and true GEJ
C: 1 cm distal to end of tubular esophagus	Always	Define reflux disease in the dilated end-stage esophagus; diagnose microscopic Barrett esophagus
D, E, F: Measured biopsies at 1–2 cm intervals between A and C	When CLE is seen endoscopically	Define length of CLE; map epithelial composition of CLE
X: Gastric antrum and body	Always	Define coexisting gastric pathology

CLE, Columnar-linded esophagus; *SCJ,* squamocolumnar junction.

1. The determination of the Z-line is a reliable marker of the proximal limit of any columnar-lined esophageal segment.
2. The end of the tubular esophagus and the proximal limit of the rugal folds are endoscopic markers that are assessed with moderate precision, but they do not define the true gastroesophageal junction.
3 There is no method other than histology to reliably differentiate columnar-lined esophagus from gastric mucosa.
4. The true gastroesophageal junction can only be defined histologically by the proximal limit of gastric oxyntic mucosa. This is a reliable marker of the distal limit of the columnar-lined esophageal segment.
5. The true gastroesophageal junction is 0 to 3 cm distal to the point of the end of the tubular esophagus or the proximal limit of the rugal folds, depending on the severity of reflux damage to the distal esophagus (0 = normal; increasing lengths are correlated with increasing reflux damage and end-stage dilated esophagus).

Once these facts are recognized, the diagnostic aim is to histologically define the extent of the columnar-lined esophagus that may be present between the true gastroesophageal junction (the proximal limit of gastric oxyntic mucosa) and the squamocolumnar junction. This is achieved by a systematic biopsy protocol (Table 7–5). An adequate biopsy series will have squamous epithelium in the most proximal biopsy and gastric oxyntic mucosa in the retrograde biopsy, thereby sampling the entire region between these two normal epithelia (Figure 7–21).

Biopsy Protocol for Patients Who Are Endoscopically Normal

In the endoscopically normal patient, all pathologic changes of reflux disease are microscopic. These can affect the distal squamous epithelium, which can show features of reflux esophagitis even when endoscopically normal. However, changes in the columnar epithelium distal to the squamous epithelium are far more sensitive, specific, and meaningful. Attention is therefore focused on this region at biopsy, and the intention is to characterize the presence and histologic features of the dilated end-stage esophagus (see Figure 7–11).

The following biopsies are recommended in the endoscopically normal patient (Figure 7–22):

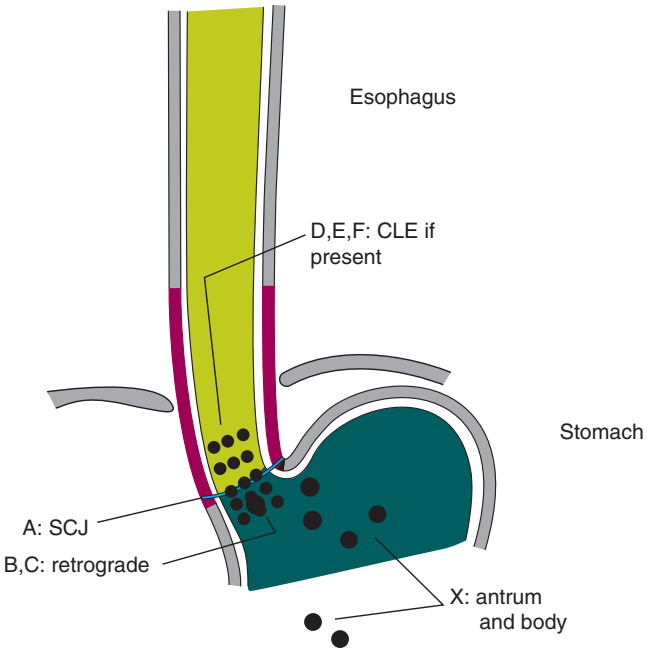


Figure 7–21 The ideal biopsy protocol samples the entire region between the squamocolumnar junction and the true gastroesophageal junction. The squamocolumnar junction *(SCJ)* biopsy *(A)* attempts to straddle the junction. Biopsies are taken retrograde from 1 cm distal *(B)* and 2 to 3 cm distal *(C)* to the proximal limit of the rugal folds. These biopsies attempt to delineate the true gastroesophageal junction (proximal limit of gastric oxyntic mucosa) and define the presence, extent, and composition of the dilated end-stage esophagus. When the Z-line is displaced proximally, four-quadrant biopsies *(D,E,F)* are taken at 1- to 2-cm intervals within the columnar-lined segment. Biopsies of the distal body and antrum of the stomach *(X)* are always taken. *CLE,* Columnar-lined esophagus.

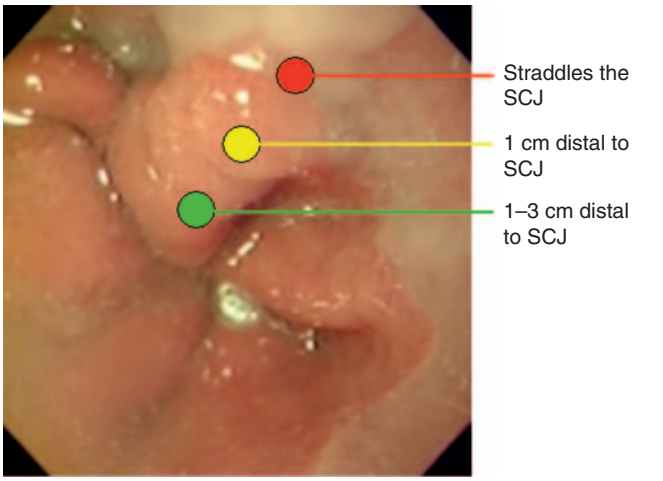


Figure 7–22 Biopsy protocol for the endoscopically normal patient. The squamocolumnar junction *(SCJ)* biopsy *(red circle)* attempts to straddle the junction. Biopsies are taken retrograde from 1 cm distal *(yellow circle)* and 2 to 3 cm distal *(green circle)* to the proximal limit of the rugal folds. The distal stomach is also biopsied.

1. A measured (from the incisor teeth) antegrade four-quadrant biopsy from the squamocolumnar junction, attempting to straddle the junction and procure mucosa that shows the transition of squamous to columnar epithelium (specimen *A*).
2. Biopsies taken with the endoscope in the retroflexed position from the area immediately distal to the location of the antegrade biopsies, sampling the area 0 to 3 cm distal to the end of the tubular esophagus. Ideally, a set of biopsies is taken 1 cm distal to the squamocolumnar junction (specimen *B*), and another set is taken from the mucosa between this and 3 cm of the squamocolumnar junction (specimen *C*).
3. The distal stomach; three biopsies are taken from the antrum and two biopsies from the gastric body or fundus at a point greater than 3 cm from the end of the tubular esophagus (specimen *X*).

Biopsy Protocol for Patients with a Visible Columnar-Lined Esophagus

In patients with a visible columnar-lined esophagus, the following protocol is recommended (Figure 7–23):

1. Biopsy the distal stomach (three antral and two body samples–specimen *X*).

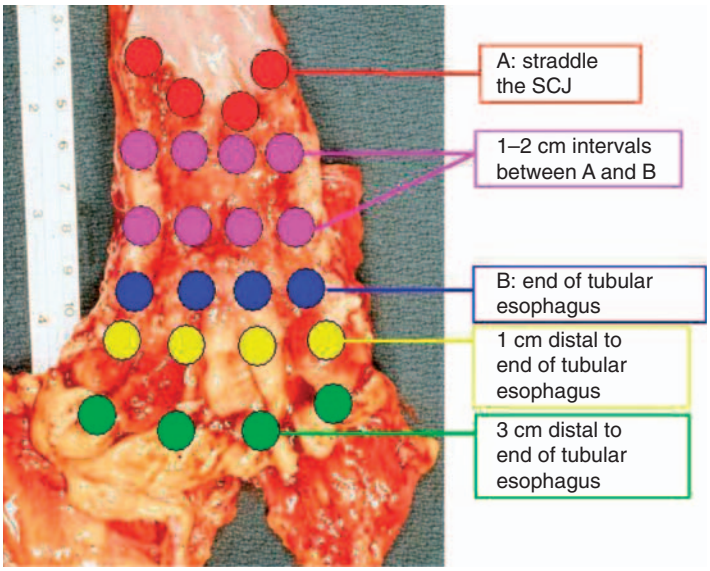


Figure 7–23 Biopsy protocol for a patient with a visible columnar-lined segment in the tubular esophagus. The biopsy from the squamocolumnar junction *(SCJ) (red circles)* is now separated from the retrograde biopsies *(yellow and green circles)* by the distance of the columnar-lined esophagus. Four-quadrant biopsies from this segment *(purple circles)* are taken at 1- to 2-cm intervals. Distal gastric biopsies in Table 7–5 are also taken. When the proximal limit of the rugal folds is at a point distal to the end of the tubular esophagus, the tubular esophagus *(blue circles)* replaces the proximal limit of the rugal folds as the point that defines landmarks.

2. With the endoscope in the retroflexed position, biopsy the line of the proximal limit of the rugal folds and/or the end of the tubular esophagus, whichever is best defined (specimen *B*).
3. Take another one or two sets of biopsies within 3 cm distal to biopsy "*B*" with the endoscope still in the retroflexed position (specimen *C*).
4. Take four-quadrant biopsies at 1- to 2-cm intervals from the columnar-lined esophagus visualized in the tubular esophagus (specimens *D, E, F,* and so on). Whether the interval is 1 or 2 cm depends on the length of the segment.
5. Take four-quadrant biopsies at the squamocolumnar junction, attempting to straddle the junction (specimen *A*).

Quick Biopsy Protocol for the Busy Gastroenterologist

The most significant findings in all biopsy protocols will be present at the squamocolumnar junction. If intestinal metaplasia is present, it will be found there; in the patient without intestinal metaplasia, reflux carditis is most likely to be found there. Because these epithelial types take priority in diagnosis, the information provided in the other biopsies is less relevant. For the busy gastroenterologist, a reasonable biopsy protocol at the index endoscopy in all patients will be as follows:

1. Take a four-quadrant biopsy straddling the squamocolumnar junction, regardless of its level (specimen *A*).
2. Take biopsies of the distal stomach, at least one of the antrum and one of the body. This is the quickest and most efficient biopsy protocol that will provide the maximum information with the least number of biopsies.

Biopsy Protocol for Barrett Surveillance

The objective in a patient under surveillance for Barrett esophagus is to detect the presence of dysplasia and/or adenocarcinoma. The need for surveillance is dictated by the generally accepted 0.5% per year risk of adenocarcinoma for patients with Barrett esophagus. The surveillance interval is determined by the rate of progression from non-dysplastic Barrett esophagus to adenocarcinoma. Although this is usually slow, it is unpredictable. Surveillance is successful if the patient is recognized as showing progression to adenocarcinoma at a treatable stage (high-grade dysplasia or stage I adenocarcinoma). If the adenocarcinoma is detected at a more advanced stage, surveillance has failed, either because biopsy sampling during surveillance endoscopy was inadequate or because the surveillance interval was too long for that patient. Because the rate of progression is not predictable, failure to find cancer at an early stage may be impossible to avoid in patients who progress to cancer rapidly.

The biopsy protocol at endoscopy depends on whether a mass lesion is identified (discussed in the following section). If there is no visible lesion, one is attempting to find high-grade dysplasia (or worse) with a random sample. Even the most compulsive biopsy sampling (four-quadrant biopsies at 1-cm intervals in the columnar-lined segment) will sample approximately 20% of the surface area (see Figure 6–38).

If the segment of columnar-lined esophagus is flat without visible lesions, four-quadrant biopsies must be taken at intervals of at least at 2-cm intervals throughout the columnar-lined segment from the squamocolumnar junction down to the proximal limit of gastric oxyntic mucosa (see Figure 7–23). In patients with a prior biopsy diagnosis, the extent of the dilated end-stage esophagus should have been determined by the previous biopsy series; if not, this needs to be defined.

When a prior biopsy has shown low-grade dysplasia, it represents evidence of progression and an increased risk of prevalent cancer and risk of future cancer. When it shows high-grade dysplasia, these risks are extremely high. If surveillance is selected as the method of treatment, the surveillance interval must decrease, and intensity of biopsy sampling must increase. Some authorities use 3-month intervals for surveillance endoscopy when high-grade dysplasia is present. Biopsy sampling is increased to four-quadrant biopsies every 1 cm of the columnar-lined segment. If there is no commitment to intense surveillance on the part of either the patient or the physician, it is not appropriate to manage patients with dysplastic Barrett esophagus with follow-up. The risk of prevalent cancer as well as progression to advanced cancer is too high.

Failure to recognize the dilated end-stage esophagus is common when present definitions and practice guidelines are used; biopsies stop at the end of the tubular esophagus or proximal limit of the rugal folds. Any intestinal metaplasia present in the dilated end-stage esophagus is exposed to the highest carcinogen dose and is at greatest risk. These patients will fail during surveillance by developing adenocarcinoma in the end-stage dilated esophagus below the lower limit of surveillance biopsies. This can only be prevented by carrying the biopsies all the way to the end of the columnar-lined segment (i.e., until gastric oxyntic mucosa is reached by histology, 0 to 3 cm distal to the presently defined endoscopic gastroesophageal junction).

Biopsy Protocol for the Patient with a Mass Lesion

When a mass lesion is encountered, the primary objective is a histologic diagnosis. For this purpose, generously sampling different areas of the mass is essential.

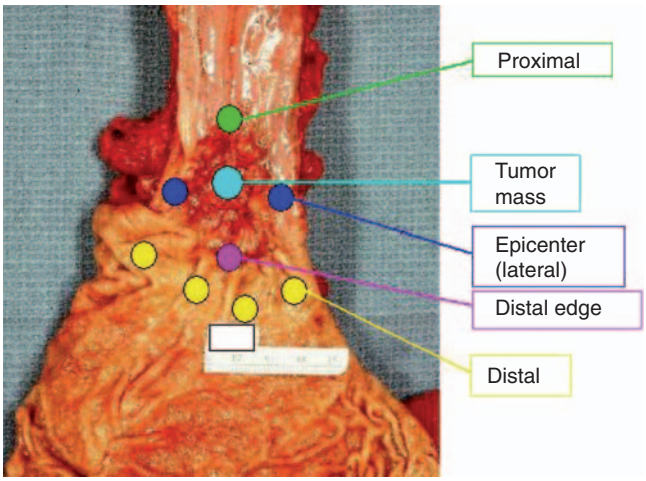


Figure 7–24 Biopsy protocol for a patient with a mass lesion. This biopsy attempts to delineate the tumor within the epithelial types. Biopsies are taken from the tumor *(light blue circle),* proximal edge *(green circle),* lateral edge (the epicenter, *dark blue circles*), and the distal edge *(purple circle).* Biopsies are also taken proximal and distal *(yellow circles)* to the tumor to define the extent of the columnar-lined segment within which the tumor arises.

Once this primary objective has been met, the following secondary objectives are valuable (Figure 7–24):

1. Determine whether the tumor is esophageal (reflux-induced) or gastric. This is only a question in distally located tumors; tumors located entirely in the tubular esophagus are esophageal. Many of these distally located tumors are currently designated as "gastroesophageal" or "gastric cardiac" in origin, based on the relationship to the endoscopic gastroesophageal junction (end of the tubular esophagus or proximal limit of rugal folds). In a recent study of tumors in this region, we established that many of these tumors are actually located in the dilated end-stage esophagus, proximal to the true gastroesophageal junction (proximal to gastric oxyntic mucosa). These distal esophageal tumors can be recognized as such by the type of epithelium surrounding the tumor. Two sets of biopsies should be taken: (a) Biopsy from the distal edge of the tumor. If metaplastic columnar epithelia (cardiac mucosa with and without intestinal metaplasia or oxyntocardiac mucosa) are found in this specimen, the tumor is located entirely in the esophagus and is unquestionably esophageal. If, however, the distal edge of the tumor is lined by gastric oxyntic mucosa, the tumor involves both esophagus and stomach and can be derived from either organ; (b) Biopsy from the lateral edge of the tumor at its epicenter. This is possible only in tumors that do not involve the entire circumference. The type of mucosa encountered in this biopsy indicates where the majority of the tumor is located. If this is metaplastic columnar epithelium, it indicates that the majority of the tumor is esophageal and suggests an esophageal origin. This assumes equivalent growth of the tumor.
2. Determine the location of the tumor within the segment of columnar-lined esophagus. This involves taking additional biopsies at the proximal edge of the tumor and from the esophagus above and below the tumor at 1- to 2-cm intervals. These biopsies will map the epithelium around the tumor and localize the tumor within the segment of columnar-lined esophagus. They also will show residual intestinal metaplasia, if it is present. The data provided by these biopsies are of academic value. It has been shown that

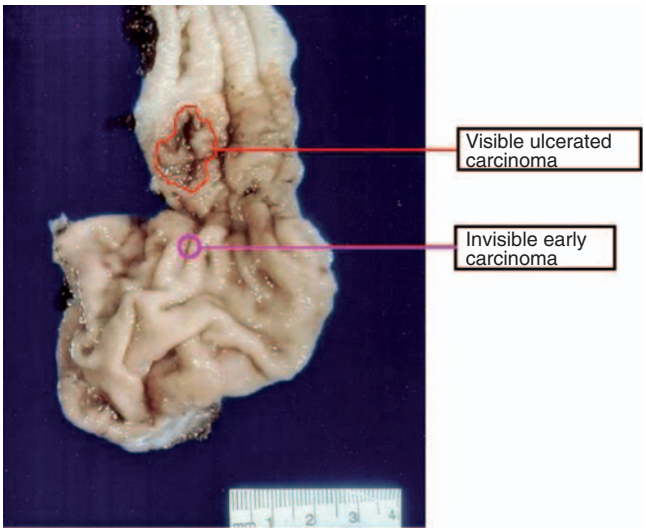


Figure 7–25 Esophagectomy specimen in a patient with a large adenocarcinoma of the distal esophagus *(area outlined in red).* A second early intramucosal adenocarcinoma was found in the dilated end-stage esophagus by sectioning of the area distal to the end of the tubular esophagus and in an area that showed rugal folds *(circled purple area).* This second cancer was surrounded by cardiac mucosa with intestinal metaplasia and had submucosal glands, proving an esophageal location.

residual intestinal metaplasia is present in approximately 65% to 70% of esophageal adenocarcinomas and that cancers tend to arise at the distal limit of intestinal metaplasia within the columnar-lined segment. The biopsies are also of practical value because they identify foci of high-grade dysplasia and intramucosal adenocarcinoma (Figure 7–25).

Protocol for Dissecting an Esophagectomy Specimen

The dissection of an esophagectomy specimen has the same objectives as the biopsy protocols, except that the examination can largely remove the problem of sampling error, and measurements can be made directly without using the less precise endoscopic measurements. Three potential artifacts are created in the esophagectomy specimen:

1. When the specimen is removed, there is an inevitable contraction of the muscular wall, which distorts the length of the total specimen.
2. The mucosa moves freely in a longitudinal direction in relation to the muscle wall, making it difficult to precisely correlate points on the external surface of the specimen (e.g., the peritoneal reflection) with the mucosa.
3. Formalin fixation and tissue processing cause a slight shrinkage, which may distort measurements made on the slides.

When there is no distortion of the most distal esophagus by a tumor or ulcer, the following information should be accurately recorded:

1. The position and appearance of the squamocolumnar junction (Z-line).
2. The relationships of the end of the tubular esophagus, Z-line, and the proximal limit of the rugal folds. If these are not clearly defined, this should be recorded.

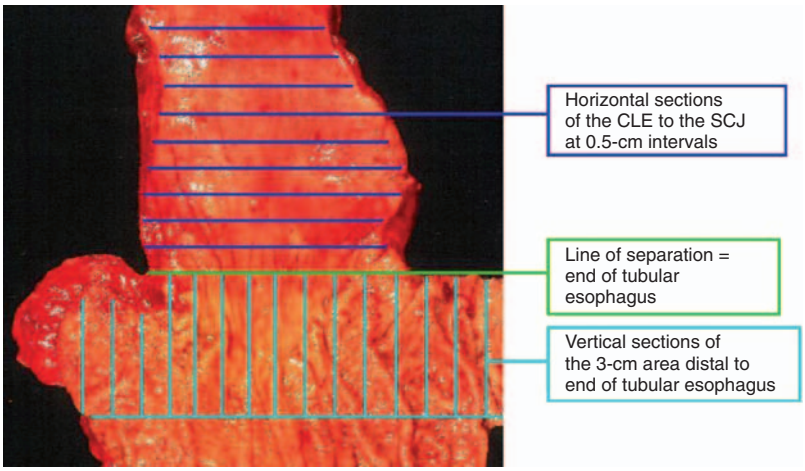


Figure 7–26 Method of sectioning the esophagectomy specimen, designed to map the epithelium. The specimen is divided horizontally at the end of the tubular esophagus. The area 3 cm distal to this is entirely submitted as vertical sections. The entire columnar-lined segment in the tubular esophagus is submitted as horizontal sections taken at 5-mm intervals. Random sections are taken from the distal stomach and proximal squamous-lined esophagus.

3. The distance between the highest point of the Z-line and the proximal limit of the rugal folds and the appearance of the columnar epithelium that separates them. After this is recorded, the specimen should be divided along a horizontal line at the end of the tubular esophagus into the tubular esophagus and the saccular region distal to the end of the tubular esophagus (Figure 7–26). The proximal 3 cm of the saccular structure should be entirely submitted using vertical sections. The tubular esophagus can be examined either by vertical sections or by horizontal sections taken at 5-mm intervals. Vertical sections are appropriate when there is no visible columnar-lined esophagus or the segment is short (less than 3 cm); sampling by horizontal sections is preferable when there is a long columnar-lined segment (see Figure 7–26). Sections should be taken from the gastric mucosa in the specimen near its distal margin.

Histologic examination of the resulting sections permits exact mapping of the areas of carcinoma, dysplasia, and the different epithelial types (Figure 7–27). The proximal limit of gastric oxyntic mucosa defines the distal end of the esophagus. It is possible to determine the extent of intestinal metaplasia, the relationship of the intestinal metaplasia to carcinoma and high-grade dysplasia, and the extent of non-intestinalized columnar metaplastic epithelia (cardiac and oxyntocardiac mucosa).

When a mass lesion is present in the junctional region, sections should be taken to examine the lesion completely and determine the location of the tumor in relation to the gastroesophageal junction (proximal limit of gastric oxyntic mucosa) (see Figure 7–24). When the tumor or ulcer is non-circumferential, a section should be taken at the lateral edge of the tumor at its mid-point to determine the type of epithelium present at the epicenter of the tumor. Additional sections from the proximal margin to the Z-line (when there is a columnar-lined esophagus) will accurately localize the tumor within the segment of columnar-lined esophagus as well as define the relationship of the tumor to the different epithelial types in the columnar-lined segment.

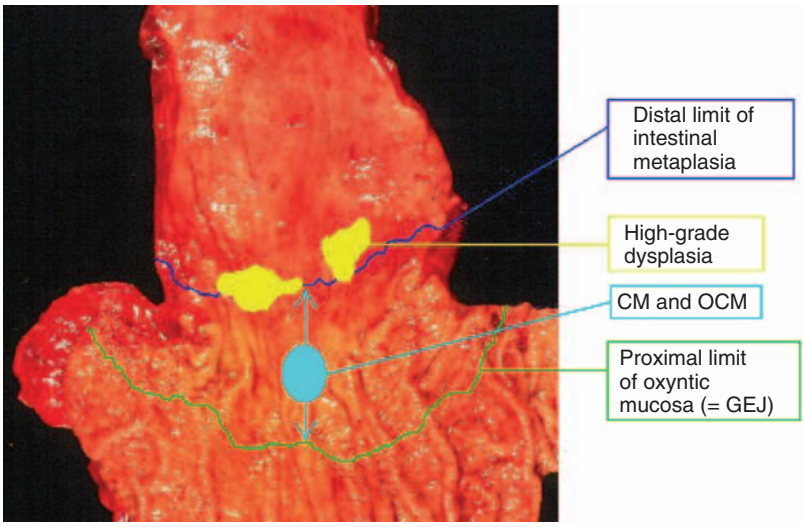


Figure 7–27 Mapping of the epithelium by histologic examination and measurement will delineate the true gastroesophageal junction *(GEJ)* (proximal limit of gastric oxyntic mucosa; *green line*), the dilated end-stage esophagus *(light blue area),* the lowest limit of intestinal metaplasia within the columnar-lined segment *(dark blue line),* and any dysplasia or cancer that may be present *(yellow areas).* The length of columnar-lined esophagus is the maximum distance from the proximal limit of gastric oxyntic mucosa to the Z-line (not seen in this specimen). *CM,* Cardiac mucosa; *OCM,* oxyntocardiac mucosa.

Data Generated by Histologic Assessment

The biopsies (or sections taken from the esophagectomy specimen) are evaluated by routine histology using hematoxylin- and eosin-stained sections. With biopsies, each specimen level is processed as a separate specimen. The biopsies of the distal stomach are routinely stained for *H. pylori* (Giemsa stain is recommended).

The histologic examination records the following information:

1. The presence of gastric pathology in the distal gastric biopsy.
2. The types of columnar mucosa present in each biopsy piece (Figure 7–28*A*). Priority is given to the highest grade of abnormality in terms of cancer risk (see Chapter 3). Therefore, when cardiac mucosa with intestinal metaplasia is present, coexisting cardiac and oxyntocardiac mucosa need not be mentioned. When cardiac and oxyntocardiac mucosa are present, only the former need be mentioned. Squamous epithelium and gastric oxyntic mucosa are normal epithelia of the esophagus and stomach, and their presence equates to "no pathologic abnormality" if they are normal.

   The changes in each biopsy can be converted to a diagnosis based on the highest grade of epithelium (intestinal > cardiac > oxyntocardiac) for each level based on the examination of all biopsies from that level (Figure 7–28*B*). This is usually the diagnosis recorded in the pathology report for the level.

   In esophagectomy specimens, it is possible to map the exact distribution of the three epithelial types within the columnar-lined segment of the esophagus (Figure 7–28*C*). This type of accurate mapping is not possible for biopsies, because all biopsies at one level are placed in one container. It is impossible to localize the biopsies into the four quadrants. Theoretically, marking each biopsy with a different color of ink before placement

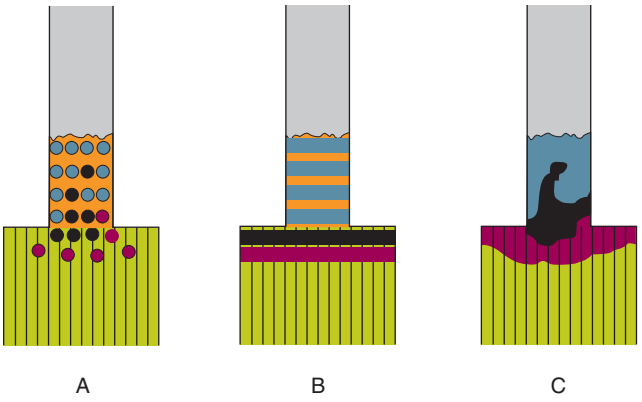


Figure 7–28 Methods of assessing and reporting biopsy results. **A,** Each biopsy is diagnosed by the most abnormal metaplastic epithelium found (*light blue,* intestinal > *black,* cardiac > *red,* oxyntocardiac). **B,** The level is diagnosed by the most abnormal epithelium found in all the biopsies at that level. This is what appears in the diagnosis line of the pathology report; a more detailed description can be provided in the microscopic description. The data in the mapping biopsies can be used to construct a diagrammatic map of the epithelial types **(C).** This is more accurate in esophagectomy specimens than in biopsy samples.

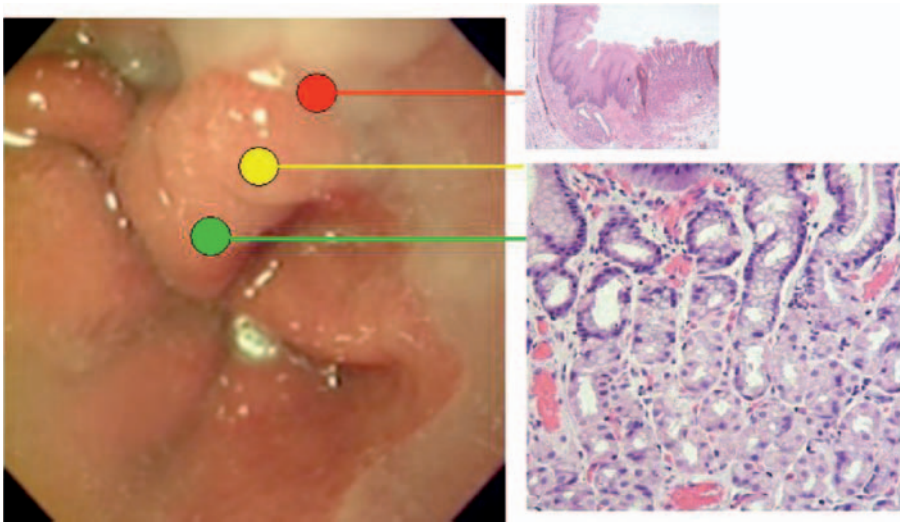


Figure 7–29 A patient (endoscopically normal) with a direct transition from squamous epithelium to gastric oxyntic mucosa in the biopsy straddling the junction *(red circle)* with gastric oxyntic mucosa in the retrograde biopsies *(yellow and green circles)* has no columnar-lined esophagus.

into the container can provide better mapping, but there is no practical value to this, and such techniques are extremely time-consuming.

3. The length of the columnar-lined esophagus is presently measured by the distance between the squamocolumnar junction and the endoscopic gastroesophageal junction. This excludes the dilated end-stage esophagus, which is misinterpreted as stomach and ignored at endoscopy.

   In the new diagnostic method, the measurement is made by histology, as follows:

   a. The length of columnar-lined esophagus is zero if only squamous epithelium and gastric oxyntic mucosa are found (Figure 7–29).

   b. In an endoscopically normal patient, in whom metaplastic columnar epithelium is present only in one biopsy sample, it is not possible to

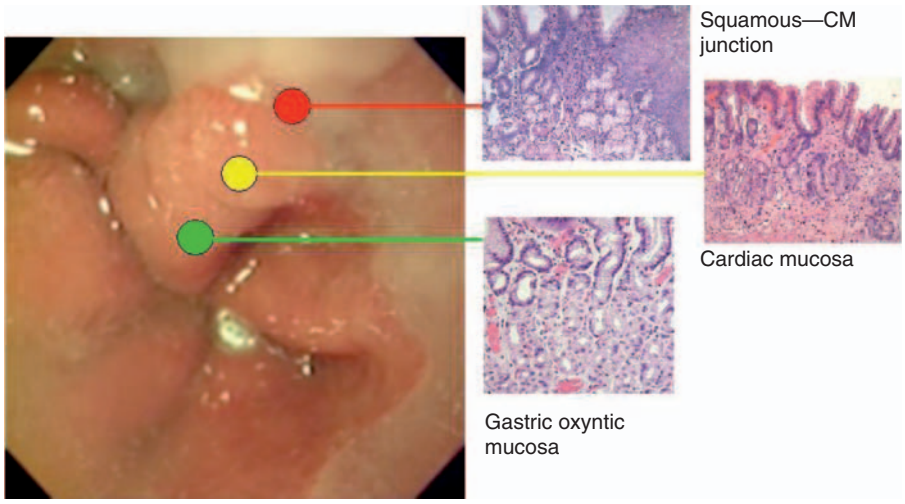


Figure 7–30 A patient (endoscopically normal) who has cardiac mucosa at the squamocolumnar junction *(red circle)* and 1 cm distal to the junction *(yellow circle)* with gastric oxyntic mucosa 2 to 3 cm distal to the junction *(green circle)* has a 1-cm length of columnar-lined esophagus composed of cardiac mucosa.

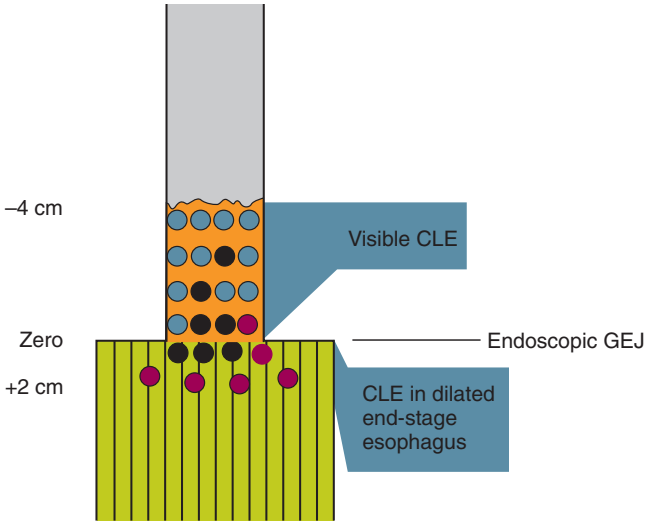


Figure 7–31 In a patient with a visible columnar-lined esophagus, the columnar-lined esophagus *(CLE)* does not end at the distal limit of measurement at endoscopy. The extent of the microscopic columnar-lined esophagus in the dilated end-stage esophagus must be added by assessment of the retrograde biopsies to derive its full length. *GEJ,* Gastroesophageal junction.

determine length accurately. The presence of metaplastic columnar epithelia in this situation is generally considered as "microscopic" in extent and grouped in the less-than-1-cm category.

c. When more than one measured biopsy shows metaplastic columnar epithelia, the length is the distance between the biopsies (Figures 7–30 and 7–31). With the histologic technique of measurement, the total length of columnar-lined esophagus is always greater than the endoscopically measured columnar-lined segment because of the invariable presence of the dilated end-stage esophagus, which is missed completely by the present endoscopic definition of the gastroesophageal junction.

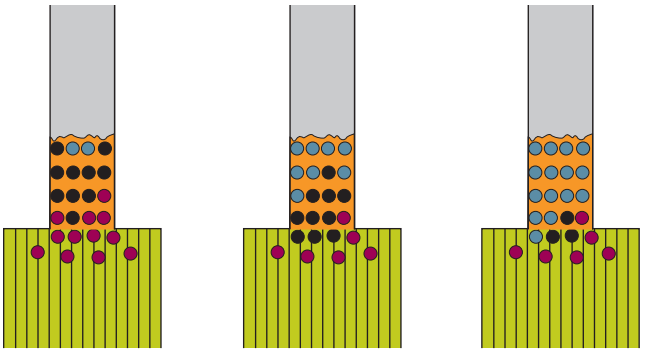


Figure 7–32 Three patients with an identical 4-cm length of endoscopically visible columnar-lined esophagus have a total histologic length of columnar-lined esophagus of 6 cm. These patients have varying lengths of intestinal metaplasia within the columnar-lined esophagus; the patient in **A** has <1 cm, the patient in **B** has 3 cm, and the patient in **C** has 5 cm of intestinal metaplasia. Note that the level of intestinal metaplasia is lowest in the patient in **C,** who therefore has the highest exposure to carcinogen located in the gastric juice.

TABLE 7–6 Interpretation of Histologic Findings of Biopsies at the Squamocolumnar Junction

Finding	Interpretation
Gastric oxyntic mucosa and squamous epithelium only	No evidence of gastroesophageal reflux
Oxyntocardiac mucosa +/– squamous epithelium and gastric oxyntic mucosa	Evidence of mild gastroesophageal reflux (compensated reflux)
Cardiac mucosa +/– oxyntocardiac mucosa +/– squamous epithelium and gastric oxyntic mucosa	Gastroesophageal reflux disease
Intestinal metaplasia in cardiac mucosa +/– cardiac mucosa +/– oxyntocardiac mucosa +/– squamous epithelium and gastric oxyntic mucosa	Barrett esophagus, non-dysplastic
Dysplasia and adenocarcinoma	Barrett esophagus, neoplastic phase

4. The length of intestinal metaplasia within the columnar-lined segment can also be assessed in an identical manner to measuring the columnar-lined esophagus. In Figure 7–32, three patients with the identical length of columnar-lined esophagus are shown to have three widely different lengths of intestinal metaplasia.
5. Each biopsy is assessed for the presence and grade of dysplasia and the presence of adenocarcinoma. Any dysplasia found can be localized to a specific level but not to any specific part of the circumference, unless the dysplastic lesion was visible at endoscopy.

Interpretation of the Data

The data recorded in this series of biopsies can now be analyzed (Table 7–6). If the patient is endoscopically normal, biopsy of the squamocolumnar junction may show the squamous epithelium transitioning into gastric oxyntic mucosa (normal), oxyntocardiac mucosa (compensated reflux), cardiac mucosa (reflux disease), or cardiac mucosa with intestinal metaplasia (Barrett esophagus) (Figure 7–33). If the patient has a visible columnar-lined esophagus, this indicates cellular damage caused by gastroesophageal reflux. Biopsy of the squamocolumnar junction may rarely show oxyntocardiac mucosa (compensated reflux) but usually shows either cardiac mucosa (reflux carditis) or cardiac mucosa with intestinal metaplasia (Barrett esophagus) (Figure 7–34).

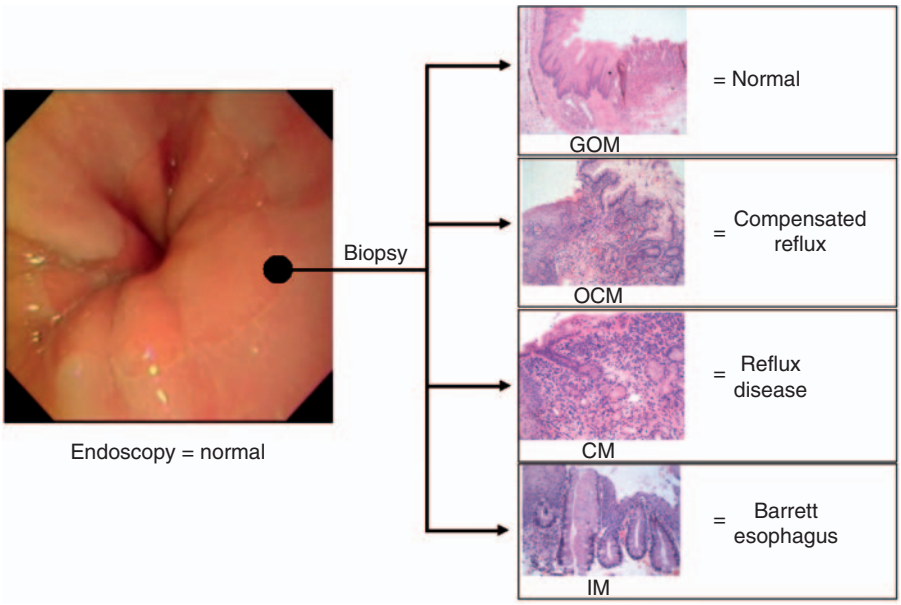


Figure 7–33 Biopsy of the squamocolumnar junction (in an endoscopically normal patient) permits identification of the columnar epithelial type immediately adjacent to the distal limit of squamous epithelium. This can vary in different points in the circumference of the Z-line. If gastric oxyntic mucosa *(GOM)* is found, the patient is normal. If oxyntocardiac mucosa *(OCM)* is found, the patient has compensated reflux. If cardiac mucosa *(CM)* is found, the patient falls within the definition of reflux disease (reflux carditis). If cardiac mucosa with intestinal metaplasia *(IM)* is found, the patient has Barrett esophagus.

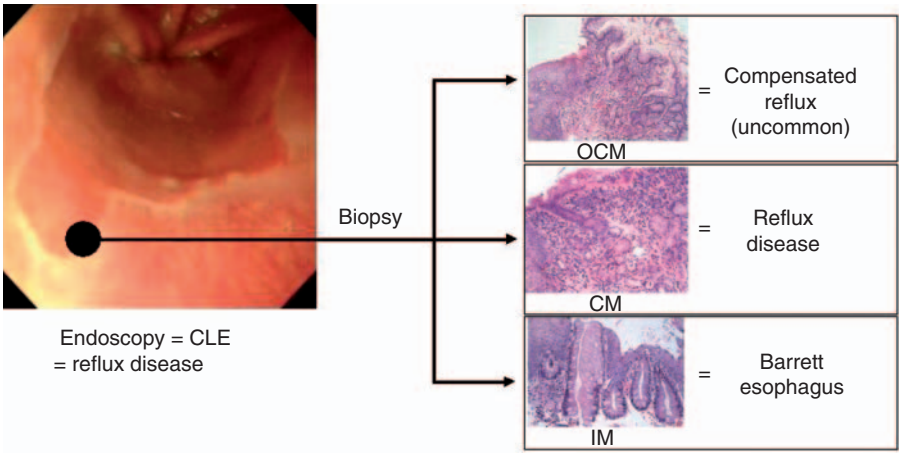


Figure 7–34 When there is a visible columnar-lined esophagus *(CLE),* the patient always has metaplastic columnar epithelium. If this is solely oxyntocardiac *(OCM),* the patient has compensated reflux; when cardiac mucosa *(CM)* is found, it is reflux disease (reflux carditis); when cardiac mucosa with intestinal metaplasia *(IM)* is found, the patient has Barrett esophagus.

Based on the results of the biopsies, the following questions can be answered:

Does the Patient Have Evidence of Reflux-Induced Cellular Change?

In the normal person without any reflux damage, there will be no columnar-lined esophagus (i.e., cardiac mucosa with and without intestinal metaplasia or oxyntocardiac mucosa). The squamous epithelium of the esophagus

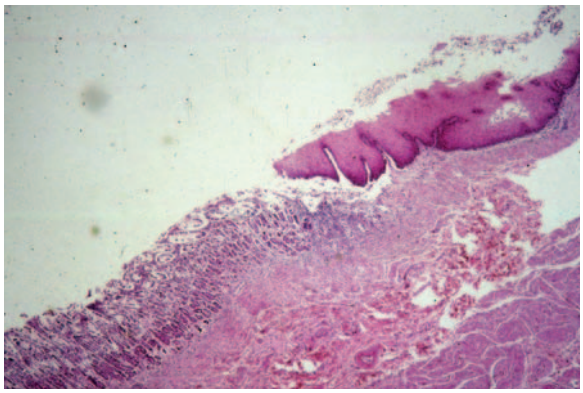


Figure 7–35 Autopsy of a young child who died in a traffic accident. The squamous epithelium transitions directly to gastric oxyntic mucosa. There is no columnar-lined esophagus. This patient has no evidence of reflux-induced cellular change.

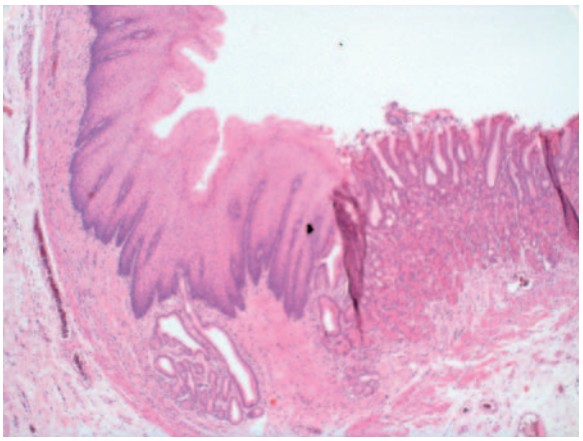


Figure 7–36 Squamocolumnar junction in an esophagectomy specimen of a 67-year-old patient with squamous carcinoma of the mid-esophagus. The squamous epithelium transitions directly to gastric oxyntic mucosa. There is no evidence of reflux-induced change (no columnar-lined esophagus at microscopic level).

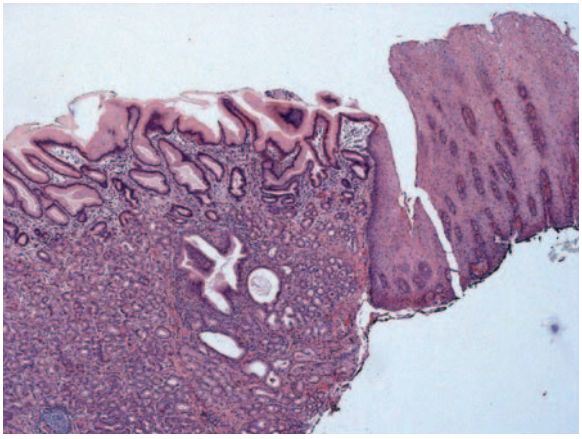


Figure 7–37 Squamocolumnar junction in an esophagectomy specimen of an adult male patient with a large squamous papilloma of the distal esophagus. The squamous epithelium transitions directly to gastric oxyntic mucosa. There is no evidence of reflux-induced change (no-columnar lined esophagus at microscopic level).

transitions directly to gastric oxyntic mucosa (see Figure 7–29). This is designated as a person without any evidence of cellular change caused by reflux. Such patients are very rarely encountered in clinical practice. They are asymptomatic; have no visible endoscopic abnormality; do not present to physicians; and can be seen only in autopsy studies that include young children[16,35] (Figure 7–35), esophagectomies performed for other reasons such as squamous carcinoma and other neoplasms not caused by reflux (Figures 7–36 and 7–37), and in clinical studies that include biopsy of large numbers of volunteers or asymptomatic patients with no endoscopic abnormality.[23]

In most "normal" adults, chronic subclinical gastroesophageal reflux at a level below the threshold for abnormality in a 24-hour pH test will have produced very small amounts of columnar-lined esophagus. When the high frequency of heartburn is considered, it should not be surprising that minimal cellular changes produced by gastroesophageal reflux are present in almost all people. The situation is analogous to the incidence of atherosclerosis in American adults.

The distinction between reflux and reflux-induced cellular change and reflux disease is emphasized. Reflux is defined by a 24-hour pH test or impedance test and classified as normal or abnormal by quantitative criteria. Reflux-

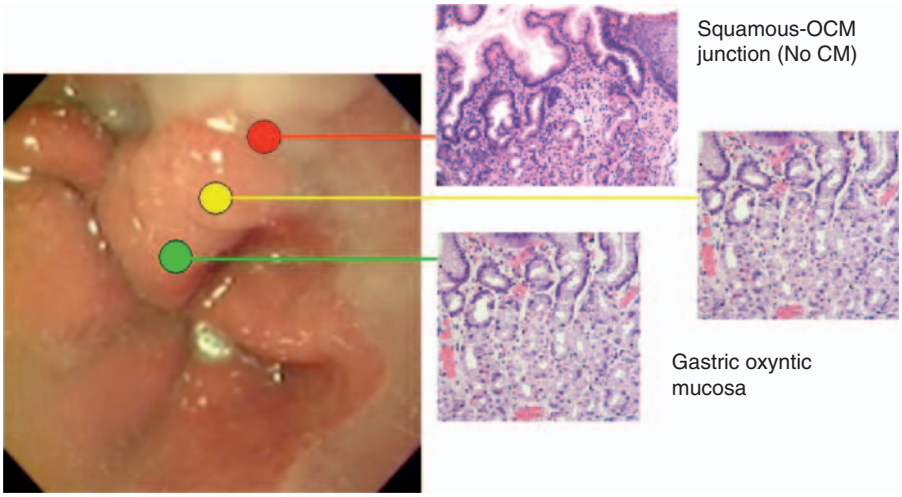


Figure 7–38 Biopsy series from an endoscopically normal patient showing features of compensated reflux. The squamous epithelium transitions to oxyntocardiac mucosa *(OCM)* without any cardiac mucosa *(CM)* intervening *(red circle)*. The more distal retrograde biopsies *(yellow and green circles)* show gastric oxyntic mucosa, indicating that this patient has a very short segment of columnar-lined esophagus composed entirely of oxyntocardiac mucosa.

induced cellular change represents alterations in the squamous epithelium and the presence of any metaplastic columnar epithelium. Reflux disease requires the presence of cardiac mucosa, with or without intestinal metaplasia. Although an excellent correlation exists between the amount of abnormal reflux in the 24-hour pH and impedance tests and the presence of cellular changes, these are independent characteristics.

Does the Patient Have Reflux Disease?

By our definition, patients with cardiac mucosa (reflux carditis) have reflux disease (see Figures 7–3 and 7–30). Patients without cardiac mucosa do not have reflux disease. Cardiac mucosa may become intestinalized in a small number of patients; this defines Barrett esophagus and indicates progression in the reflux-to-adenocarcinoma sequence.

Because we have defined reflux disease as the presence of reflux carditis, patients who only have oxyntocardiac mucosa without cardiac or intestinal epithelium will be designated as not having reflux disease (Figures 7–38 and 7–39). We use the term "compensated reflux" for patients who have only oxyntocardiac mucosa in addition to squamous and oxyntic mucosa because, although they have evidence of reflux-induced cellular damage, they have no epithelia that are at risk to progress to intestinal metaplasia or adenocarcinoma. Patients with only oxyntocardiac mucosa are rarely symptomatic, have a normal endoscopy, and have a histologically defined columnar metaplastic segment less than 1 cm in length. When the columnar metaplastic segment reaches 1 cm in length or when it is endoscopically visible, cardiac mucosa is almost always present.[21]

Biopsies only give information at the point in time the biopsy is performed. Patients with no evidence of reflux disease (i.e., reflux carditis) can develop cardiac mucosa in the future; patients with no intestinal metaplasia can develop intestinal metaplasia in the future. The significance of absence of reflux carditis and intestinal metaplasia depends on the patient's age. If the patient is 60 years old and has no cardiac or intestinal mucosa, it is likely that the existing gastroesophageal reflux is so minimal that the patient will not develop cardiac and intestinal mucosa. The situation is much different for a

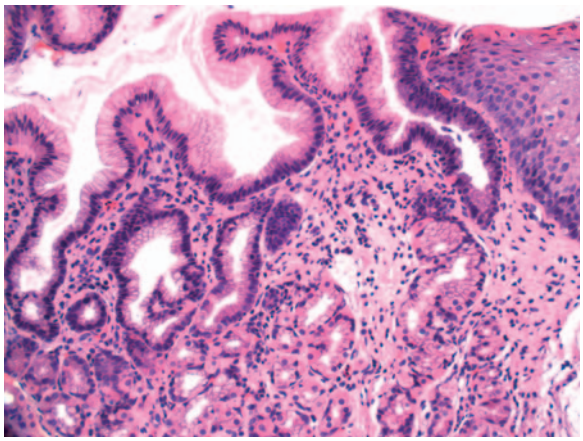


Figure 7–39 Compensated reflux, showing transition of squamous epithelium to oxyntocardiac mucosa without intervening cardiac mucosa. This is the most common histologic finding at the junction if one examines the entire population (as at autopsy). In clinical populations, the incidence of carditis increases because of the prevalence of reflux in patients who undergo endoscopy. Compensated reflux is almost never seen in patients who have an endoscopically visible columnar-lined esophagus.

Figure 7–40 Esophagectomy specimen showing a large squamous carcinoma in the mid-esophagus. The squamous epithelium extends to the end of the tubular esophagus where it transitions to rugated columnar epithelium. The Z-line appears convex but is regular.

10-year-old child; the risk of future cardiac and intestinal mucosa is much higher because the cellular changes may be evolving.

Reflux carditis establishes a cellular basis for the diagnosis of reflux disease. Patients who have reflux disease histologically can now be classified into various subgroups: patients who are classically symptomatic, atypically symptomatic, mildly symptomatic, and asymptomatic; patients with or without an abnormal 24-hour pH test; and patients with or without erosive esophagitis.

As with any other common pathologic finding, careful clinical correlation is necessary before reflux carditis is ascribed as a cause of the patient's disease. For example, patients who present with squamous carcinoma of the esophagus, asthma, laryngitis, or interstitial lung disease frequently have small amounts of cardiac mucosa at the junction. This may represent an incidental finding; it does not mean that reflux disease is the cause of these conditions in this particular patients, although this possibility cannot be excluded.

CASE STUDY

A 78-year-old male presented with a history of progressive dysphagia for solid foods over the past 3 weeks. There was no history suggestive of reflux disease. Endoscopy showed a large, exophytic mass lesion with surface ulceration in the mid-esophagus (28 to 35 cm). This was surrounded by unremarkable squamous epithelium that extended all the way down to the end of the tubular esophagus (40 cm) where it transitioned with columnar epithelium characterized by rugal folds. The rugal folds reached the squamocolumnar junction at the end of the tubular esophagus (Figure 7–40).

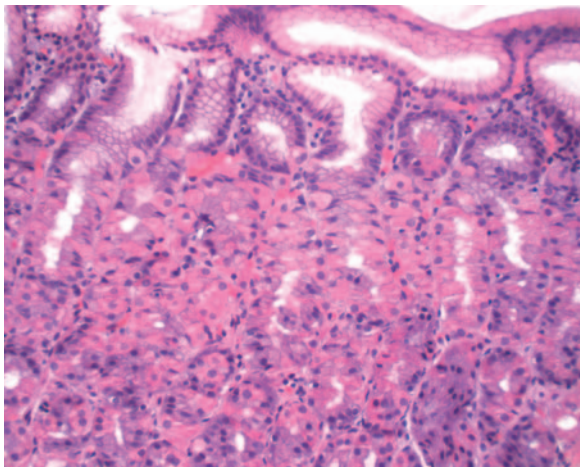


Figure 7–41 Distal gastric biopsy showing normal gastric oxyntic mucosa. There is no significant inflammation. *H. pylori* was absent.

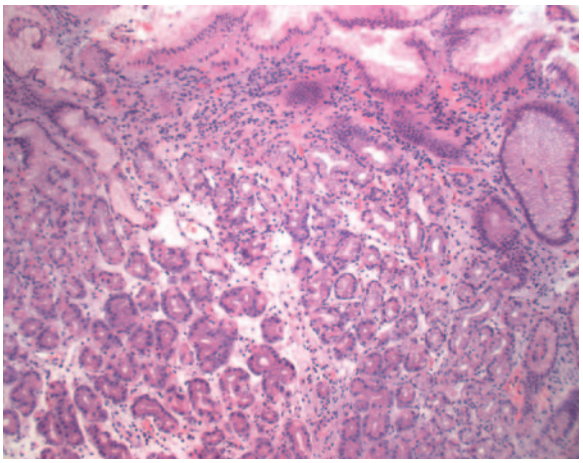


Figure 7–42 Section from the retrograde biopsy showing the true gastroesophageal junction, which is the junction between gastric oxyntic mucosa *(left)* and oxyntocardiac mucosa *(right).* There is mild chronic inflammation. This junction is not well defined. There is no cardiac mucosa.

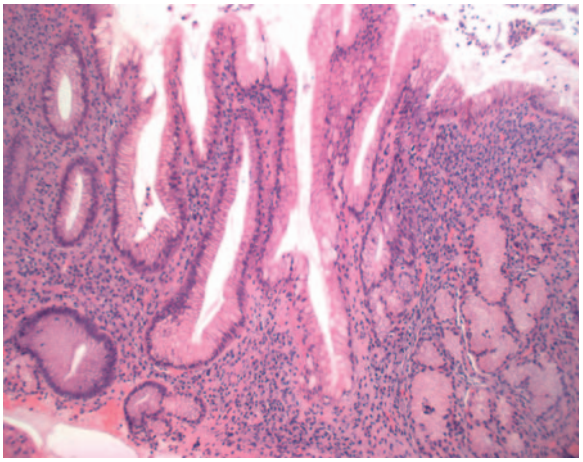


Figure 7–43 Section from another piece of the retrograde biopsy showing cardiac mucosa with marked chronic inflammation and foveolar hyperplasia, which is typical of reflux carditis. Note that this is slightly separated in location from the biopsy shown in Figure 7–42, but it is likely to be more proximal. There are pseudo-goblet cells but no true intestinal metaplasia.

Biopsies were taken as follows:

A: Antrum and body of stomach.

B: Retrograde biopsy from the proximal limit of the rugal folds within 1 cm distal to the squamocolumnar junction (unmeasured).

C: Antegrade biopsy from the squamocolumnar junction at 40 cm.

D: Biopsy of squamous epithelium at 38 cm between the distal edge of the tumor and the squamocolumnar junction.

E: Biopsy of the tumor.

The distal gastric biopsies showed antral and oxyntic mucosa without significant inflammation (Figure 7–41). Giemsa stain for *H. pylori* was negative. Sections from the retrograde biopsy showed one piece of tissue consisting of oxyntic and oxyntocardiac mucosa (the latter with chronic inflammation, Figure 7–42) and one piece of tissue with cardiac mucosa that showed marked chronic inflammation and reactive foveolar hyperplasia (Figure 7–43). The biopsy of the squamocolumnar junction showed squamous epithelium transitioning to cardiac mucosa with chronic inflammation and foveolar hyper-

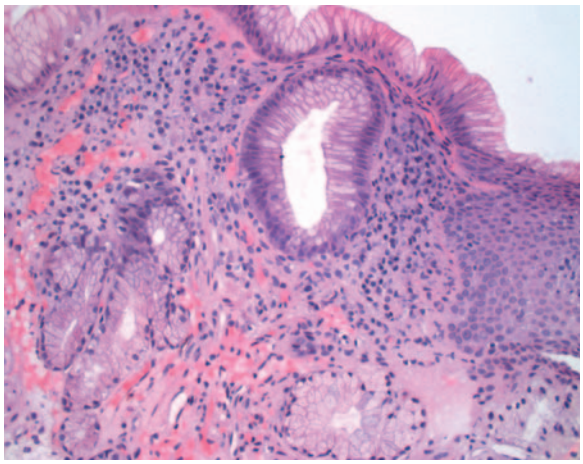


Figure 7–44 Sections across the squamocolumnar junction showing the transition from squamous epithelium to cardiac mucosa.

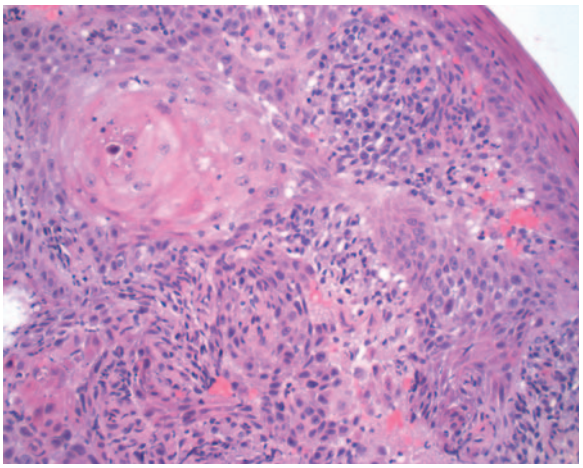


Figure 7–45 Biopsy from the tumor, showing an invasive, moderately differentiated squamous carcinoma.

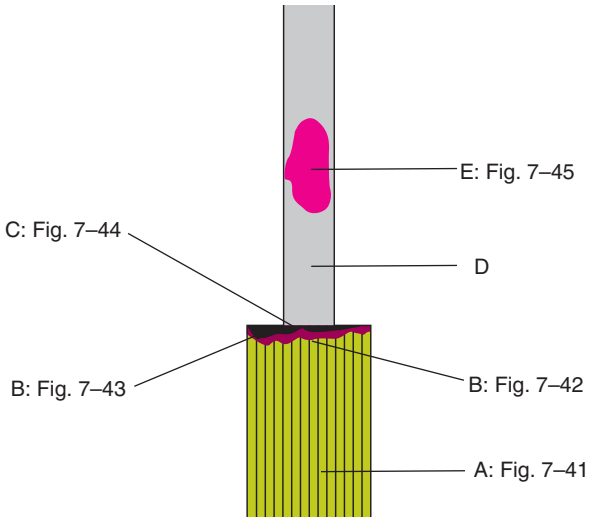


Figure 7–46 Diagrammatic representation of the specimen shown in Figure 7–40. The patient shows the typical features of the earliest stage of reflux disease, manifested as a microscopic segment of cardiac and oxyntocardiac mucosa involving the dilated end-stage esophagus. The patient has a normal endoscopic and gross gastroesophageal junction and is likely to not have had symptoms of reflux. The points of biopsy and the histologic appearances are referred to Figures 7–41 through 7–45.

plasia (Figure 7–44). There was no intestinal (Barrett) metaplasia. Sections from the squamous epithelium of the distal esophagus showed papillary elongation and scattered intraepithelial lymphocytes, but there was no significant basal cell hyperplasia and no eosinophils or neutrophils in the epithelium. Sections from the tumor showed an invasive, moderately differentiated squamous carcinoma (Figure 7–45). The diagnosis section of the pathology report read as follows:

Microscopic diagnosis:

A: Antrum and body, biopsy: no significant pathologic abnormality.

B: Retrograde biopsy: reflux carditis.

C: Antegrade biopsy at 40 cm: reflux carditis.

D: Esophagus, 38 cm, biopsy: no specific pathologic abnormality.

E: Esophageal mass, 34 cm, biopsy: invasive, moderately differentiated squamous carcinoma.

This patient showed the typical features of microscopic reflux disease characterized by the presence of cardiac and oxyntocardiac mucosa in the area distal to the endoscopic gastroesophageal junction (end of tubular esophagus and proximal limit of rugal folds, Figure 7–46). The junction between gastric

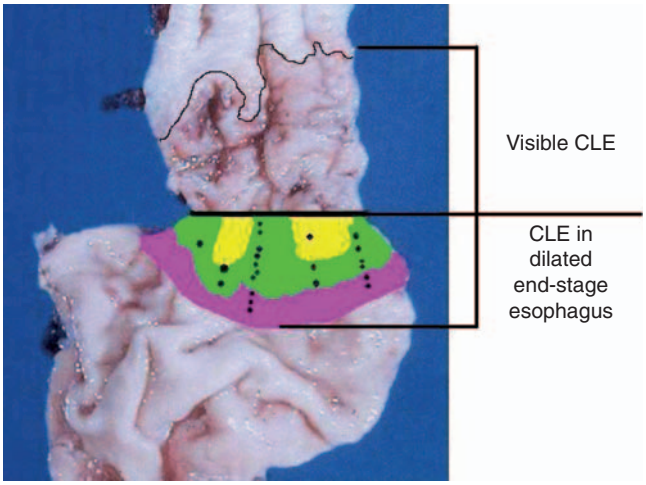


Figure 7–47 An accurate determination of the total length of columnar-lined esophagus *(CLE)* requires adding the microscopically defined extent of the dilated end-stage esophagus to the endoscopically visible columnar-lined segment. Present criteria for endoscopic measurement underestimate the total length by the extent of the dilated end-stage esophagus.

oxyntic mucosa and oxyntocardiac mucosa in the retrograde biopsy sample represents the true histologic gastroesophageal junction (see Figure 7–42). The presence of cardiac mucosa at the squamocolumnar junction in the antegrade biopsy (see Figure 7–44) and in some of the pieces of the retrograde biopsy (see Figure 7–43) indicates that the patient has reflux disease. The total columnar epithelial length cannot be measured, because only one measured biopsy level (40 cm) has metaplastic columnar epithelium. However, the fact that there is gastric oxyntic mucosa in the retrograde biopsy makes it likely that the approximate overall length of columnar-lined esophagus is 1 cm.

This patient has two diseases: squamous cell carcinoma of the mid-esophagus and reflux carditis. They are most likely independent diseases; the presence of minimal reflux disease limited to the dilated end-stage esophagus represents an incidental finding caused by asymptomatic and mild reflux disease (see Figure 7–46).

What Is the Severity of Reflux Disease in the Patient?

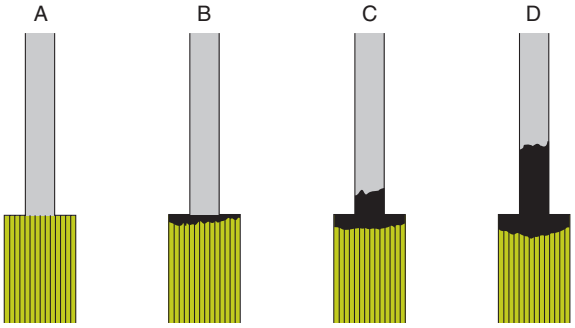
The severity of reflux disease is related to the amount (length) of squamous epithelium that has undergone columnar metaplasia.[22,25] At present, the length of the columnar-lined segment of esophagus is measured at endoscopy as the distance between the highest point in the squamocolumnar junction and the endoscopic gastroesophageal junction. This underestimates the true length by the extent of the dilated end-stage esophagus distal to the proximal limit of rugal folds (see Figure 7–31).

In the recommended biopsy series, the length of columnar-lined esophagus is determined by the maximum separation of measured biopsies that show cardiac mucosa with or without intestinal metaplasia and oxyntocardiac mucosa (see Figure 7–31). In patients with intestinal metaplasia, this is the IM + CM + OCM length. In patients without intestinal metaplasia, this will be the CM + OCM length. In resection specimens and at autopsy, this length is determined by direct measurement in a vertical section taken from the squamocolumnar junction to gastric oxyntic mucosa (Figure 7–47).

TABLE 7–7 Assessment of Reflux Disease Severity by Measurement of the Length of Columnar-Lined Esophagus Determined by Histologic Mapping According to a Strict Biopsy Protocol

Criterion	Histologic length†	Interpretation
CLE* absent	0	No evidence of reflux
CLE* not visible endoscopically	<1 cm	Mild reflux disease
CLE* visible, short	1–2 cm	Moderate reflux disease
CLE* visible, long	>2 cm	Severe reflux disease

*Columnar-lined esophagus; this is defined histologically by the presence of oxyntocardiac and cardiac mucosa, the latter with and without intestinal metaplasia.
†Histologic length is defined by mapping biopsies taken at measured levels as the separation between squamous epithelium and gastric oxyntic mucosa; endoscopic correlations are secondary.



	A	B	C	D
Visible CLE	Zero	Zero	<2 cm	>2 cm
Endoscopy	Normal	Normal	Abnormal	Abnormal
CLE in dilated end-stage esophagus	Zero	Present	Present	Present
Reflux severity	Zero	Mild	Moderate	Severe

Figure 7–48 The linear relationship between the length of columnar-lined esophagus *(CLE) (black areas),* regardless of histologic type, and the severity of reflux.

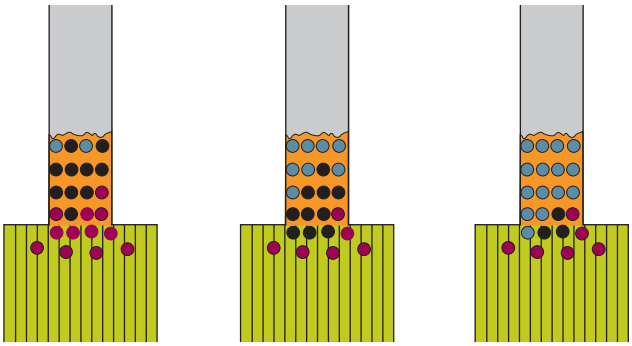
The true length of columnar-lined esophagus determined by histology provides the best correlation with the severity of reflux disease (Table 7–7, Figure 7–48).

What Is the Risk of Cancer in These Patients?

Cancer arises only in intestinal metaplastic epithelium; the risk of cancer begins if and when intestinal metaplasia occurs.[36] A patient with reflux disease who does not have intestinal metaplasia does not have any risk. However, if the patient has cardiac mucosa, this represents an epithelium that has the potential to undergo intestinal metaplasia in the future. Although cardiac mucosa has no cancer risk, there is the possibility that the patient will develop a risk if intestinal metaplasia develops. This risk of transformation decreases with age, because the more time that elapses without the development of intestinal metaplasia, the more likely it is that the milieu of the refluxate will have a low risk of intestinal metaplasia.

The assessment of cancer risk is currently based on the following factors:

1. The presence of Barrett esophagus, defined by the presence of intestinal metaplasia in an endoscopically visible columnar-lined esophagus. If the



Length of CLE	6 cm	6 cm	6 cm
Length of IM	1 cm	3 cm	5 cm
Cancer risk	Low	Moderate	High

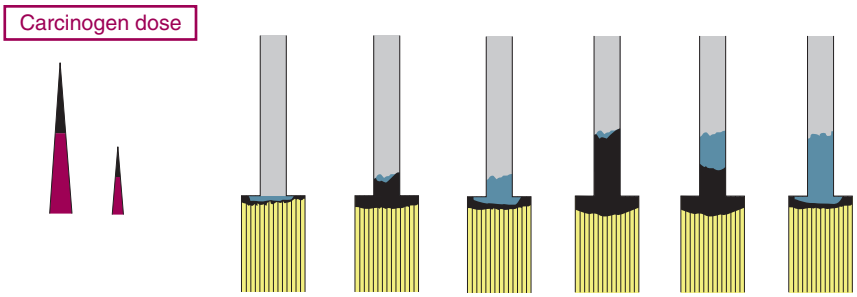
Figure 7–49 The cancer risk in three patients with identical endoscopic appearance is likely to be different based on the amount of intestinal metaplasia *(IM)* present. Intestinal epithelium represents the only target epithelium for carcinogenesis. Carcinogen dose is maximal at the gastroesophageal junction. *CLE,* Columnar-lined esophagus.

patient has no visible columnar-lined esophagus, biopsy is not performed. If biopsy is performed and intestinal metaplasia is found distal to the normal endoscopic gastroesophageal junction, "intestinal metaplasia of the gastric cardia" is diagnosed. Although this is not within the definition of Barrett esophagus, many gastroenterologists will place these patients under a surveillance protocol similar to that for Barrett esophagus.

2. The length of columnar-lined esophagus associated with the presence of intestinal metaplasia in the biopsy. Patients are divided into short-segment and long-segment Barrett esophagus based on whether the endoscopically defined columnar-lined segment is less than or greater than 2 cm. Although most physicians believe long-segment Barrett esophagus has a greater risk than short-segment disease, there is controversy about this. Practically, patients with short-segment and long-segment Barrett esophagus are placed on similar surveillance protocols.
3. The presence of dysplasia in Barrett esophagus, classified as no dysplasia, indefinite for dysplasia, low-grade dysplasia, and high-grade dysplasia. As the grade of dysplasia increases, another concern that emerges is the potential presence of prevalent cancer, which may be missed because of inadequate sampling. This risk exists for all patients, but it is significant only in patients diagnosed with high-grade dysplasia (see Chapter 6).

These current cancer risk assessment methods can be refined in the following ways, based on the recommended biopsy protocols:

1. The intestinal metaplasia within the columnar-lined segment can be quantitated by evaluating the measured biopsy levels that show intestinal metaplasia (Figure 7–49). Defining short-segment and long-segment Barrett esophagus by the measured length of intestinal metaplasia rather than the length of columnar-lined esophagus is likely to provide a more meaningful cancer risk assessment.
2. The number of goblet cells within each level varies considerably and can be assessed by a grading system that quantitates the number of goblet cells. I have used such a grading system in research projects but do not consider it necessary in clinical practice. The mere presence of intestinal metaplasia is more significant than the number of goblet cells.



Proximity of IM to GEJ	Close	Intermediate	Close	Far	Intermediate	Close
Exposure to carcinogen	High	Moderate	High	Low	Moderate	High
Cancer risk	High	Moderate	High	Low	Moderate	High

Figure 7–50 In any given patient, the carcinogen dose (*red area in triangles,* representing two different levels of carcinogen activity, which cannot be assessed clinically) is always maximal in the stomach. Reflux delivers an effective carcinogen dose to a different level in the esophagus, but the carcinogen level always decreases in the more proximal esophagus. The cancer risk is therefore greatest in patients who have intestinal metaplasia *(IM)* closest to the gastroesophageal junction *(GEJ),* regardless of the total length of columnar-lined esophagus. This also explains why cancer tends to occur in the most distal part of intestinal metaplasia within a columnar-lined esophagus. *Blue,* Intestinal metaplasia; *black,* cardiac mucosa; *gray,* squamous epithelium; *yellow,* gastric oxyntic mucosa.

3. The lowest level at which intestinal metaplasia is found is measured by its distance from the proximal limit of gastric oxyntic mucosa (Figure 7–50). The likelihood of cancer increases as the intestinal metaplasia extends distally in the esophagus, because the target cell is exposed to the higher carcinogen environment of the distal region. This is the site of maximum carcinogenesis; most esophageal adenocarcinomas occur at the distal limit of the intestinal metaplasia within the columnar-lined segment.
4. Dysplasia within a segment of intestinal metaplasia will be assessed in a manner not unlike the present method of surveillance biopsies for patients with Barrett esophagus.

The use of non-histologic tests has limited value in the assessment of cancer risk for patients with Barrett esophagus. There is no practical molecular diagnostic test at the present time. Although it is hoped that accurate molecular definition of progression within the reflux-to-adenocarcinoma sequence will emerge in the future, there is no strong reason for optimism. In the meantime, the use of dysplasia and its grades (with all their inaccuracy) is the only current method for assessing progression toward adenocarcinoma.

Reid et al[37] showed that in Barrett esophagus patients with low-grade dysplasia, flow cytometric study to evaluate aneuploidy and increased 4N fraction is valuable. In particular, the absence of aneuploidy or increased 4N fraction predicted a low risk of progression. Flow cytometry presents technical difficulties in specimen collection and adds significant cost. Its limited use in a surveillance biopsy of patients whose prior biopsy has shown low-grade dysplasia is valuable and should be advocated. Flow cytometry has not shown to be of value in patients with high-grade dysplasia.

In patients with dysplasia, the use of immunoperoxidase stain for Ki67 has shown promise in separating reactive atypia and low-grade dysplasia from high-grade dysplasia. Olvera et al[38] showed that benign epithelia, including those with reactive cytologic changes and low-grade dysplasia, demonstrated expanded proliferative activity with a normal pattern that spared the superficial

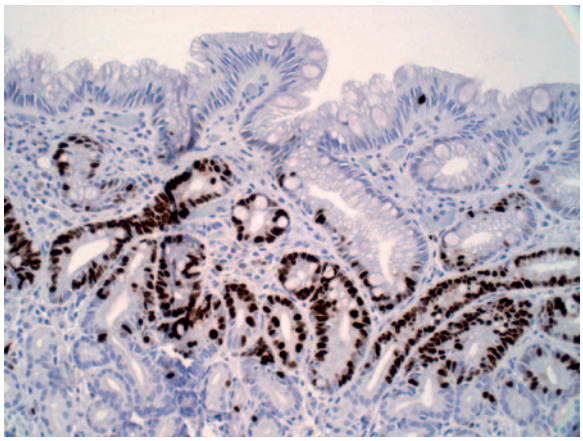


Figure 7–51 Immunoperoxidase-stained section for Ki67 in a patient with Barrett esophagus, showing reactive change without dysplasia. Ki67 expression is increased, but the distribution is normal with the surface epithelium and superficial part of the foveolar region being negative, indicating normal maturation into terminally differentiated non-proliferative cells.

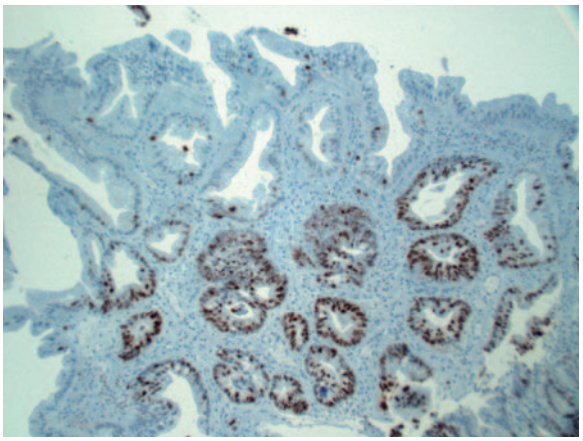


Figure 7–52 Immunoperoxidase-stained section for Ki67 in a patient with Barrett esophagus with low-grade dysplasia, showing an expanded Ki67 expression with a normal pattern of staining similar to the reactive epithelium in Figure 7–51.

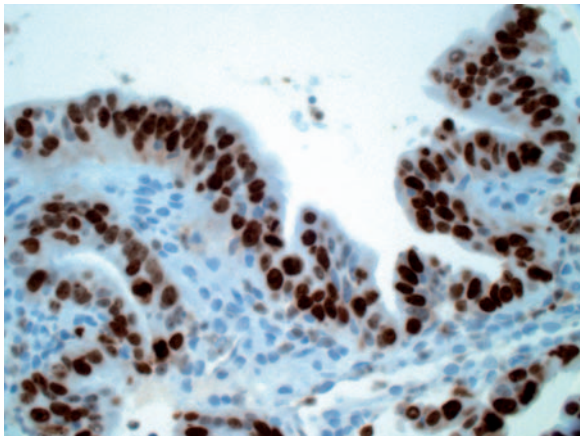


Figure 7–53 Immunoperoxidase-stained section for Ki67 in a patient with Barrett esophagus with high-grade dysplasia, showing intense Ki67 positivity in the surface epithelium and superficial foveolar region. This represents an aberrant pattern of Ki67 expression that indicates abnormal maturation. This pattern is seen more frequently in high-grade dysplasia but is not yet sufficiently defined to override morphologic criteria of dysplasia grading.

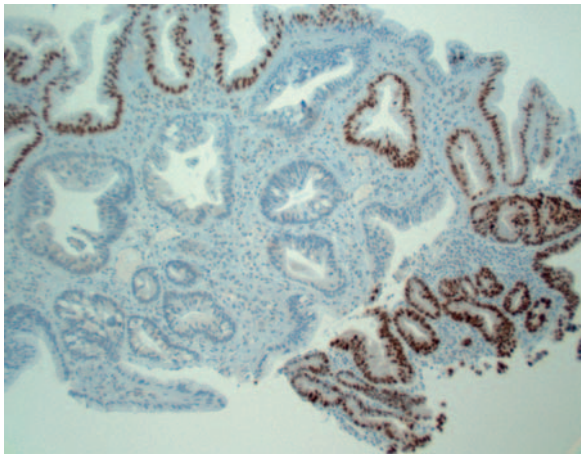


Figure 7–54 Immunoperoxidase-stained section for p53 in a patient with Barrett esophagus with a focus of high-grade dysplasia (on right) that shows strong and specific staining for p53. This type of staining is seen more frequently in high-grade dysplasia but is not yet sufficiently defined to override morphologic criteria of dysplasia grading.

foveolar region and surface epithelium (Figures 7–51 and 7–52). In contrast, most cases of high-grade dysplasia demonstrated an aberrant pattern of proliferation defined by the expression of Ki67 positivity in the surface and superficial foveolar region (Figure 7–53). Although this is useful, the fact that some cases of low-grade dysplasia express an aberrant Ki67 pattern makes it unreliable as a means of distinguishing low-grade and high-grade dysplasia.

Staining for p53 and p504 (racemase) have also been suggested in borderline cases. Strong expression of p53 and p504 are a worrisome feature but not sufficient to upgrade morphologic low-grade dysplasia to high-grade dysplasia (Figure 7–54). Weak p53 expression can often be expressed in reactive processes and low-grade dysplasia; many cases of high-grade dysplasia are p53-negative.

TABLE 7–8 Classification Based on Risk of Adenocarcinoma of the Esophagus*

Grade zero: No risk of adenocarcinoma (55%–65%)
Definition: No cardiac mucosa or intestinal metaplasia in any biopsy
Subgroups:
Group 0a: Normal: Only squamous epithelium and gastric oxyntic mucosa
Group 0b: Compensated reflux: Oxyntocardiac mucosa as the only epithelium in the metaplastic columnar esophagus
Grade 1: Reflux disease (30%–45%): no risk of adenocarcinoma but risk of Barrett esophagus present
Definition: Cardiac mucosa (reflux carditis) present; oxyntocardiac mucosa also present in most cases
Subgroups:
Group 1a: Mild reflux disease: CM + OCM length <1 cm
Group 1b: Moderate reflux disease: CM + OCM length = 1–2 cm
Group 1c: Severe reflux disease: CM + OCM length >2 cm
Grade 2: Barrett esophagus (5%–15%): imminent risk of neoplastic transformation
Definition: Intestinal metaplasia (goblet cells) present in cardiac mucosa; non-intestinalized cardiac mucosa and oxyntocardiac mucosa also present in most cases
Subgroups:
Group 2a: Barrett esophagus in reflux disease limited to dilated end-stage esophagus (microscopic Barrett esophagus): Endoscopy normal
Group 2b: Short-segment Barrett esophagus: Measured length of intestinal metaplasia <2 cm long (regardless of endoscopic length of columnar-lined esophagus)
Group 2c: Long-segment Barrett esophagus: Measured length of intestinal metaplasia >2 cm long (regardless of endoscopic length of columnar-lined esophagus)
Grade 3: Neoplastic Barrett esophagus (1%–2%)
Definition: Dysplasia or adenocarcinoma present
Subgroups:
Group 3a: Low-grade dysplasia
Group 3b: High-grade dysplasia
Group 3c: Adenocarcinoma

*The approximate percentage of the population within each group is in parentheses.

A Classification Based on the Cellular Status as it Relates to Gastroesophageal Reflux

The combination of the previously mentioned items permits the classification of the entire population into histologically defined groups or grades based on the presence of cellular changes of reflux, the severity of the cellular changes of reflux, and the cancer risk.[11] The primary division is based on the risk of cancer, which must be the focus of any system. Placement of an individual within groups 0, 1, 2, and 3 provides a cumulative, lifelong assessment of that person's cellular response to gastroesophageal reflux within the broad groups defined by the risk of adenocarcinoma at the time of the biopsy (Table 7–8; Figures 7–55 to 7–58).

This diagnostic method is recommended as the primary method for evaluating patients for reflux disease. It is the basis for all correlations with symptoms, endoscopic abnormalities, 24-hour pH testing, and impedance testing. For example, asymptomatic patients can belong to grade 0, 1a, 2a, and all subgroups of grade 3, but they are unlikely to belong to grades 1b and 2b, and only very rarely belong to grades 1c and 2c. This type of classification is critical because it provides the only method of stratifying asymptomatic patients with regard to cancer risk. As many as 95% of patients with adenocarcinoma present for the first time with symptoms related to the cancer. For this reason, the ability to recognize risk before cancer develops is extremely valuable.

This method identifies patients who are not at risk for cancer. By present criteria, there is no way that the medical community can guarantee that any patient is not at risk for reflux-induced cancer. Patients with no symptoms and no endoscopic abnormality are at lower risk than patients with severe reflux of long duration and those with long-segment Barrett esophagus, but they

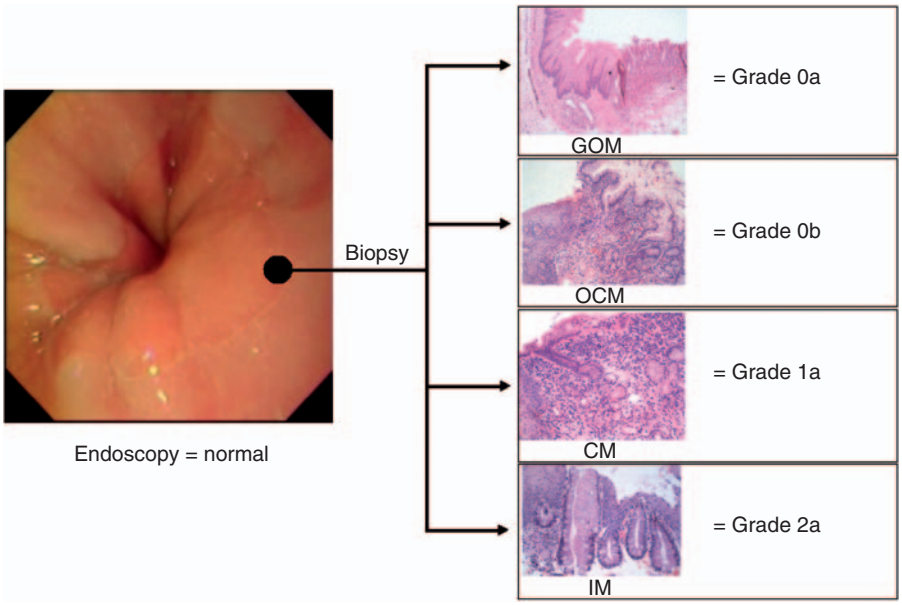


Figure 7–55 Proposed histologic grading system applied to patients who are endoscopically normal. This is defined by the epithelium found adjacent to the squamous epithelium. *Grade 0a,* Gastric oxyntic mucosa; *Grade 0b,* oxyntocardiac mucosa; *Grade 1a,* cardiac mucosa (microscopic reflux carditis); *Grade 2a,* cardiac mucosa with intestinal metaplasia (microscopic Barrett esophagus). *CM,* Cardiac mucosa; *GOM,* gastric oxyntic mucosa; *IM,* intestinal metaplasia; *OCM,* oxyntocardiac mucosa.

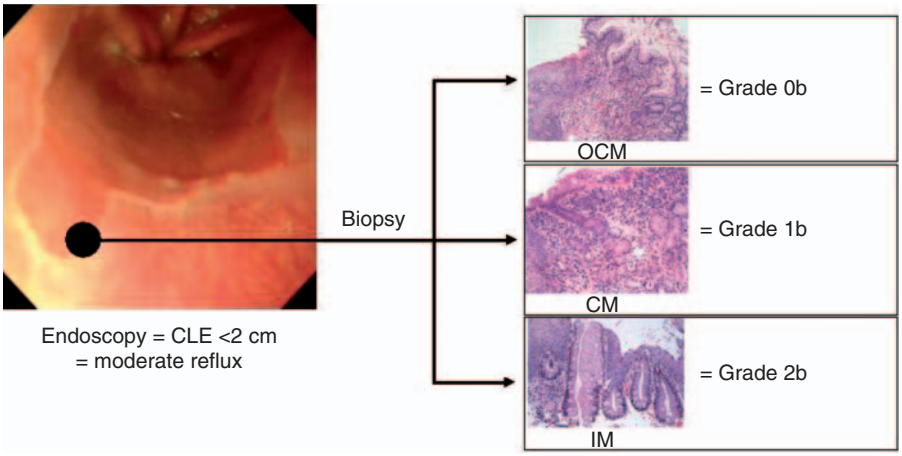


Figure 7–56 Proposed histologic grading system applied to patients who have an endoscopically visible columnar-lined segment measuring less than 2 cm at endoscopy. This is defined by the epithelium found adjacent to the squamous epithelium. There will be no grade 0a patients. *Grade 0b,* Oxyntocardiac mucosa *(OCM)* (rare); *Grade 1b,* cardiac mucosa (reflux carditis); *Grade 2b,* cardiac mucosa with intestinal metaplasia (microscopic Barrett esophagus). *CM,* Cardiac mucosa; *IM,* intestinal metaplasia; *OCM,* oxyntocardiac mucosa.

cannot be declared risk free. In the study by Lagergren et al,[39] 40% of patients with esophageal adenocarcinoma and 71% of patients with adenocarcinoma of the gastric cardia did not have symptomatic reflux by their definition.

In this diagnostic method, the 55% to 65% of the population without cardiac mucosa and intestinal metaplasia can be declared free of risk at the point of the biopsy (see Figure 7–55). If a patient is over 40 years old, the likelihood of developing cardiac mucosa, which progresses to intestinal metaplasia and cancer during his or her natural lifetime, is probably close to zero. This is because the failure of the reflux condition to produce at-risk columnar

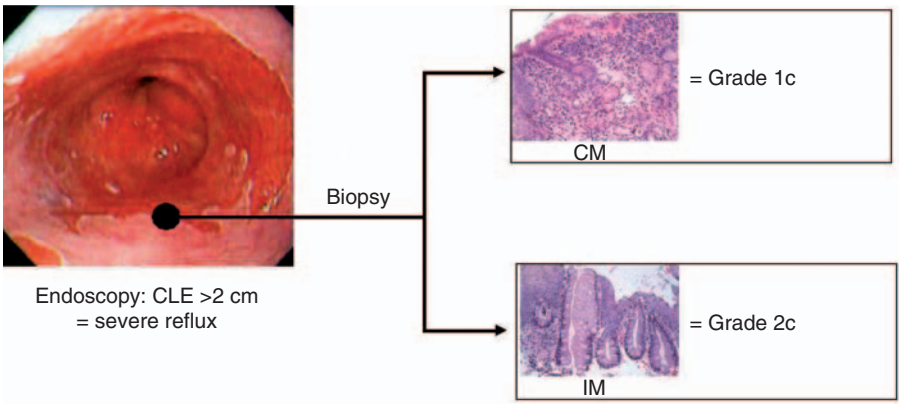


Figure 7–57 Proposed histologic grading system applied to patients who have an endoscopically visible columnar-lined segment *(CLE)* measuring greater than 2 cm at endoscopy. This is defined by the epithelium found adjacent to the squamous epithelium. There will be no grade 0a or 0b patients. *Grade 1c,* Cardiac mucosa (reflux carditis); *Grade 2c,* cardiac mucosa with intestinal metaplasia (microscopic Barrett esophagus). *CM,* Cardiac mucosa; *IM,* intestinal metaplasia.

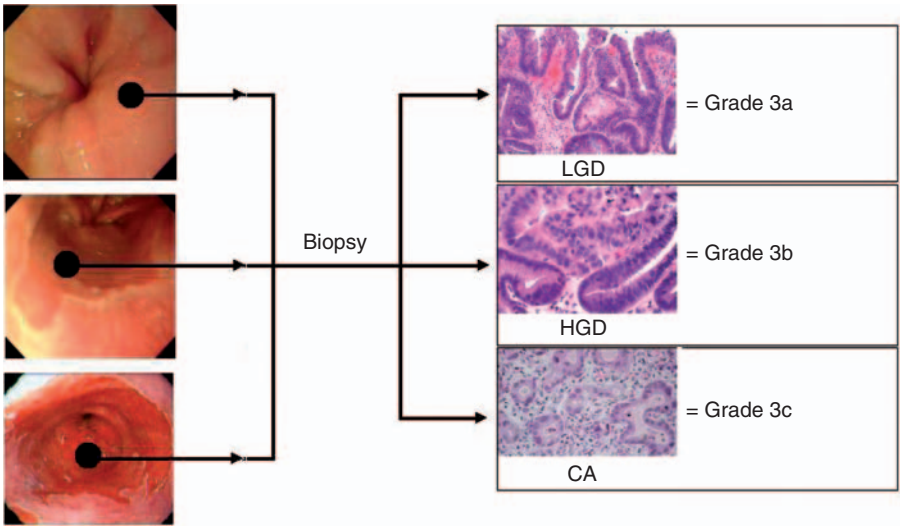


Figure 7–58 Grading of neoplastic (grade 3) Barrett esophagus is based on the degree of dysplasia. *Grade 3a,* Low-grade dysplasia *(LGD)*; *Grade 3b,* high-grade dysplasia *(HGD)*; *Grade 3c,* adenocarcinoma *(CA)*. All grades of dysplasia and adenocarcinoma can occur in all patients who have intestinal metaplasia. The precursor Barrett lesion in these patients may be microscopic (grade 2a), associated with a short segment of columnar-lined esophagus (grade 2b), or with a long segment (grade 2c).

epithelia indicates a low risk; unless the milieu changes for some reason, it is unlikely to cause new changes. Patients like this do not need to ever have another endoscopy for reflux; they can be managed symptomatically without worry about cancer.

Assessment of Treatment of Gastroesophageal Reflux Disease

Currently, the treatment of a patient with reflux disease is assessed clinically by the reversal of symptoms. When "cure" of reflux disease is defined in this manner, acid-suppressive drug therapy has a success rate in excess of 95%, particularly if higher-dose protocols are used. If these patients are studied by

impedance technology, this symptomatic "cure" is not a cure of reflux; reflux continues, because the patient's basic problem (a defective lower esophageal sphincter) has not been addressed. The decrease in the acidity of the refluxate relieves symptoms relatively easily; even slight acid suppression is effective. Patients who are "cured" at a symptomatic level have their target cells exposed to non-acid carcinogens in the refluxate and progress in their reflux-to-adenocarcinoma sequence. Evidence suggests that acid-suppressive drugs actually promote the rate of progression to adenocarcinoma.[39]

Some patients do not respond to acid-suppressive therapy for a variety of reasons. These include nocturnal breakthrough of acid secretion, symptoms produced by weak acid reflux, and non-reflux causes for the symptoms. Patients who do not respond to medical therapy, even high-dosage proton pump inhibitors supplemented by an evening dose of an H2-receptor antagonist, undergo endoscopy and are sometimes treated with anti-reflux surgery. These patients are the lucky ones. Their reflux is stopped by an anti-reflux procedure.

The only assessments of treatment are the endoscopic reversal of erosive esophagitis and a decrease in the endoscopic length of Barrett esophagus. There is no current attempt to define either progression or regression of reflux disease at a histologic level.

Both acid-suppressive drug therapy and anti-reflux surgery are effective in reversing erosive reflux disease in approximately 95% of patients. When there is an endoscopically visible columnar-lined esophagus with intestinal metaplasia, the present criteria for treatment success are as follows:

1. Reversal of intestinal metaplasia: because of the potential sampling error, assessing the reversal of intestinal metaplasia must be done carefully. In general, true reversal is increasingly likely when the volume of intestinal metaplasia was high in the pretreatment biopsies and intestinal metaplasia is absent in multiple post-treatment biopsies, either at one endoscopy or in serial endoscopies.
2. Decrease in the length of the columnar-lined segment in a patient with Barrett esophagus: this can occur as a result of a change in the surface epithelium from columnar to squamous, causing either a decreased total length of the columnar segment as measured endoscopically, or a decrease in the surface area of the columnar lining. The latter determination will include an assessment of squamous islands within the columnar-lined segment. Surface squamous transformation is not recognized as a true reversal, because columnar epithelium can be present in the lamina propria under the squamous surface[40] (Figure 7–59). However, many studies expend much effort to document surface area or length reduction in columnar-lined esophagus in patients treated with acid-suppressive drugs. The data suggest that such reduction is uncommon.[41,42]

   The significance of finding intestinal metaplastic epithelium under a squamous surface is uncertain. Hornick et al[40] reported that the epithelium under the squamous surface had a lower Ki67 proliferative rate than adjacent surface intestinal metaplasia. They suggested that this may be due to decreased exposure of the intestinal epithelium under the squamous surface to luminal molecules. Despite this, there is concern about the presence of intestinal epithelium under a squamous surface for three reasons:

   a. The glandular epithelium is hidden from the endoscope during surveillance.

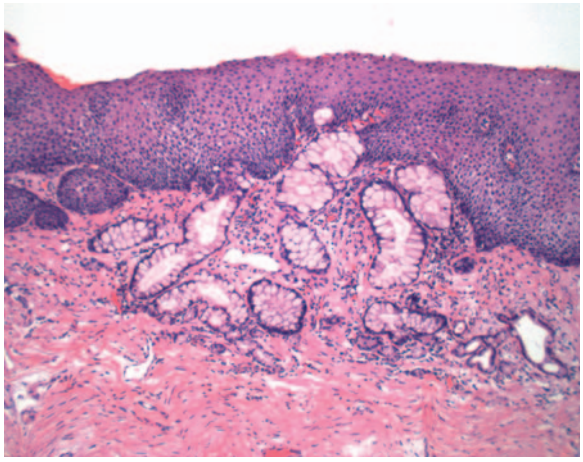


Figure 7–59 Patient with squamous re-epithelialization of the surface who has intestinal metaplasia in the lamina propria under the squamous epithelium. This represents endoscopic regression but not true regression of Barrett esophagus.

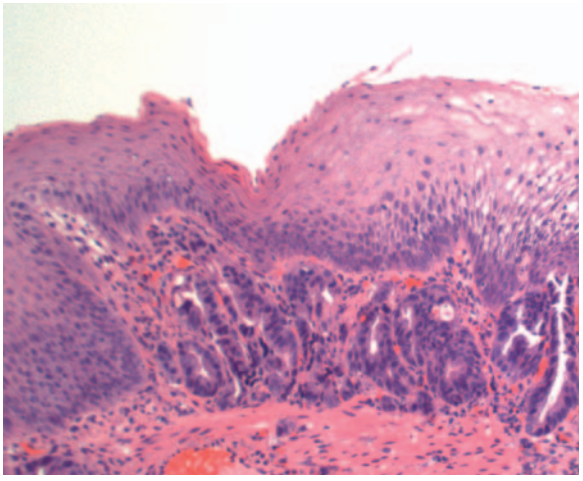


Figure 7–60 High-grade dysplasia in intestinal (Barrett) epithelium under surface squamous epithelium, showing progression of intestinal metaplasia in the reflux-to-adenocarcinoma sequence. This will appear normal endoscopically.

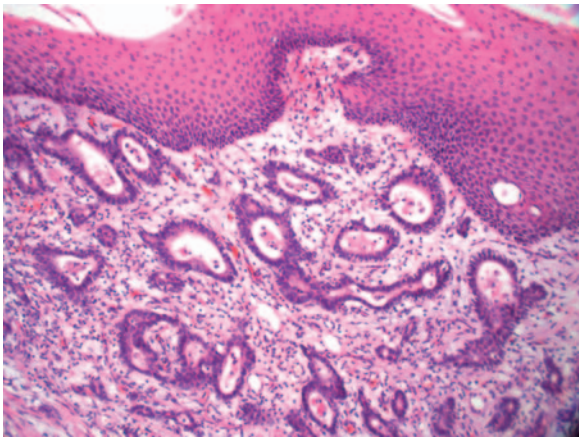


Figure 7–61 Invasive adenocarcinoma in the lamina propria under a squamous surface. This will be invisible at endoscopy until a nodular mass lesion or ulcer appears in squamous-lined esophagus.

b. If genetic changes exist in the intestinal epithelium, they can progress to dysplasia and cancer (Figures 7–60 and 7–61) without being visible at endoscopy.

3. Reversal of dysplasia in Barrett esophagus (grade 3b to 3a to 2): true dysplasia is a manifestation of neoplastic transformation within a cell and is inexorably progressive. One important and fundamental element of a neoplastic transformation is that it does not reverse when the etiology that produced the change is removed. Cessation of smoking does not reverse dysplasia and cancer in the lung. Any study that claims to show that dysplasia has reversed with treatment should be viewed skeptically, because the only way that dysplasia can reverse is if the entire area of dysplasia is removed. When the diagnosis of dysplasia has been made by biopsy, it is highly unlikely that the biopsy has removed all dysplasia in the patient. Reversal of dysplasia in sequential biopsy studies is most commonly an expression of an inaccurate diagnosis. If a reactive change is mischaracterized as true dysplasia, this change will reverse with healing of erosions and inflammation, giving a spurious result of "reversal of dysplasia." This criticism includes studies in which the author has been the pathologist who diagnosed the dysplasia.[43] Although this is usually a problem with low-grade

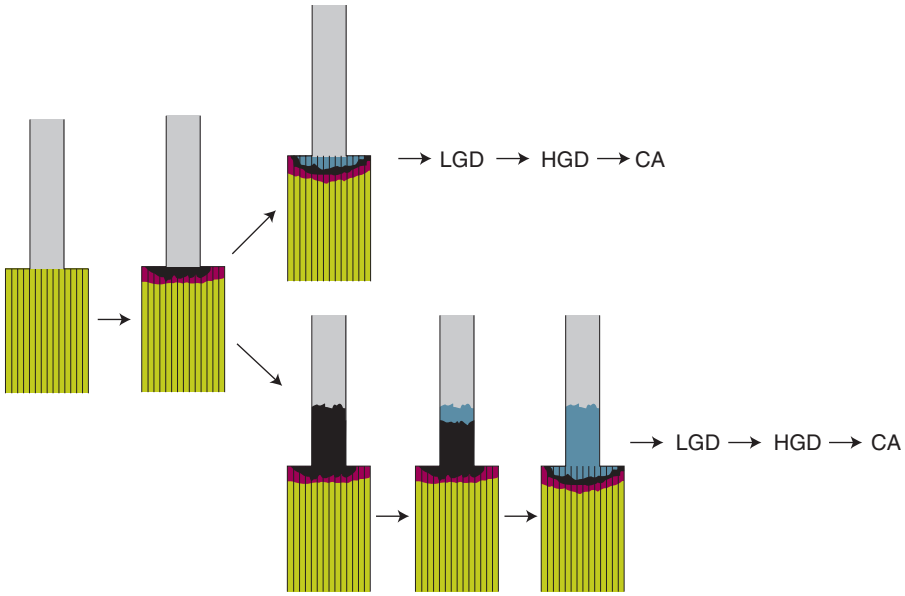


Figure 7–62 Histologic criteria for progression of reflux disease include any increase in the amount of columnar-lined esophagus, any increase in the amount of intestinal metaplasia within a columnar-lined segment, and any increase in the amount or grade of dysplasia in intestinal metaplasia. *CA,* Adenocarcinoma; *HGD,* high-grade dysplasia; *LGD,* low-grade dysplasia.

dysplasia only, some studies have suggested that high-grade dysplasia is an ephemeral and reversible phenomenon.[44] True high-grade dysplasia is highly unlikely to reverse. Reversal of high-grade dysplasia is more likely to be a problem with diagnosis of high-grade dysplasia than true reversal.

When gastroesophageal reflux disease is defined by histologic examination of the biopsies produced by the recommended protocol, new histologic criteria of progression and regression of reflux disease can be developed. These criteria are based on the recognition that a columnar-lined segment of esophagus is an infinitely variable mixture of cardiac mucosa with intestinal metaplasia (grade 2) and without intestinal metaplasia (grade 1) and oxyntocardiac mucosa (grade 0), and that changes in the amounts of these epithelial types signify widely varying cancer risks. Such histologic assessment is likely to be a much more meaningful assessment of progression and regression in the early non-dysplastic phase of reflux disease than present methods (Figures 7–62 and 7–63).

Progression can be defined in the following ways:

1. An increase in the amount of squamous epithelium that transforms into cardiac mucosa (grade 0 to grade 1). This will be seen as the presence of cardiac mucosa at a level that is higher than the previous biopsy series as well as an increase in the overall length of metaplastic columnar epithelium by histology (see Figure 7–62).
2. Development of and increase in the amount of intestinal metaplasia (grade 1 to 2), which represent progression in the reflux-to-adenocarcinoma sequence. Any increase in the amount of intestinal metaplasia will also increase the proximity of the intestinal metaplasia to the high carcinogen region near the gastroesophageal junction (see Figure 7–63).
3. Quantitation of intestinal metaplasia, expressed as the number of biopsy levels that show goblet cells, is possible in the standard biopsy protocol. Of lesser significance is an assessment of the number of goblet cells within

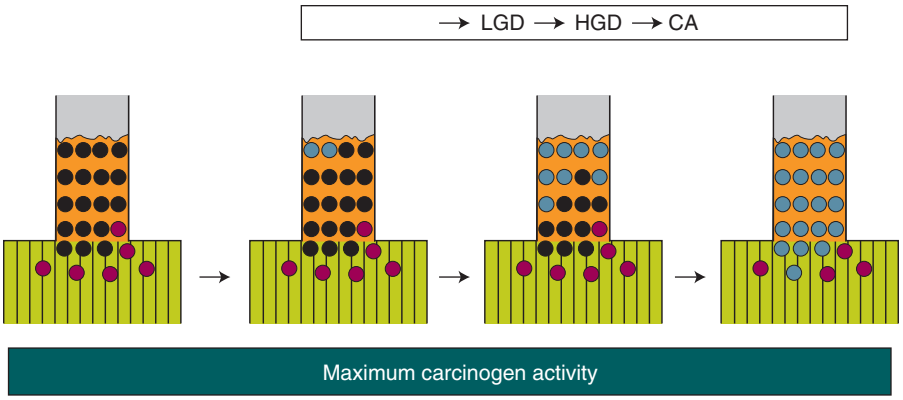


Figure 7–63 An example of histologic progression in a patient who stays constant in terms of endoscopy. On the left, the columnar-lined esophagus does not have intestinal metaplasia. In succeeding frames, the amount of intestinal metaplasia progressively increases, starting at the top and extending down the columnar-lined segment. Protocol biopsies are necessary to separate the three patients with intestinal metaplasia, who all fall within the diagnosis of long-segment Barrett esophagus (according to the current definition). The risk of cancer increases progressively to the right as the proximity of the target cell in intestinal metaplasia approaches the gastroesophageal junction. An increase in dysplasia in the intestinal epithelium also represents disease progression. *CA,* Adenocarcinoma; *HGD,* high-grade dysplasia; *LGD,* low-grade dysplasia.

each biopsy level; an increase in this number represents a potential increase in the number of target cells available for carcinogenesis. This determination is usually limited to research studies, because it is time-consuming and not very useful.

4. Increasing grades of dysplasia in intestinal metaplasia (grade 2 to 3a to 3b to 3c) indicates progressively increasing genetic transformation toward adenocarcinoma. Any true dysplasia must be considered a serious manifestation of neoplasia because there is a significant potential lag phase (usually 1 to 2 years, but up to 5 years) before a carcinogenic genetic mutation produces a phenotypic abnormality in a cell that we recognize as dysplasia. The expression of true dysplasia, even low-grade dysplasia, should be regarded as an ominous signal that carcinogenetic events are taking place and that there is the possibility that all the irreversible genetic changes of prevalent cancer may be present in an unexpressed form in the affected cell.

Regression can be defined in the following ways:

1. An increase in the amount of squamous epithelium, by reversal of cardiac or intestinal mucosa to squamous epithelium (i.e., grades 1 and 2 to grade 0). This is seen in the biopsies as an absence of glandular epithelium at a level where it previously existed. Only full-thickness biopsies can differentiate squamous metaplasia occurring on the surface with metaplastic glandular epithelium in the lamina propria (squamous overgrowth or false regression) (Figure 7–64) from the situation where the full thickness of the mucosa is squamous without underlying glands (true regression) (Figure 7–65). This is superior to endoscopic assessment of surface area decrease, because endoscopy cannot detect glands under the squamous surface.
2. Reversal of intestinal metaplasia, by conversion to cardiac mucosa (i.e., grade 2 to grade 1). This is endoscopically undetectable, because these two epithelial types cannot be distinguished. Histology can show both a complete absence as well as a decrease in the amount of intestinal meta-

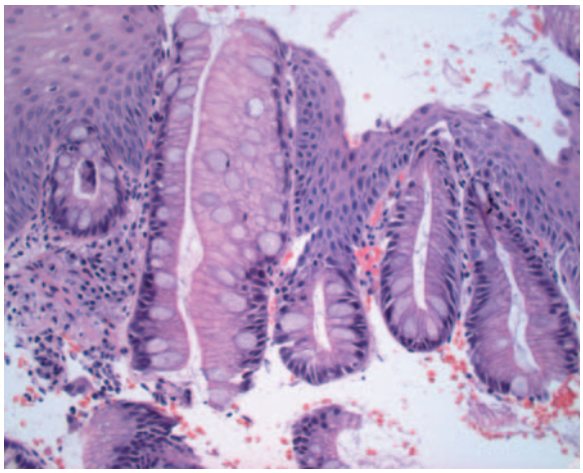


Figure 7–64 Squamous epithelial growth on the surface, partially covering intestinal metaplasia remaining in the lamina propria. Although this will appear as endoscopic regression by decreasing the surface area of the columnar-lined esophagus, the regression is not real.

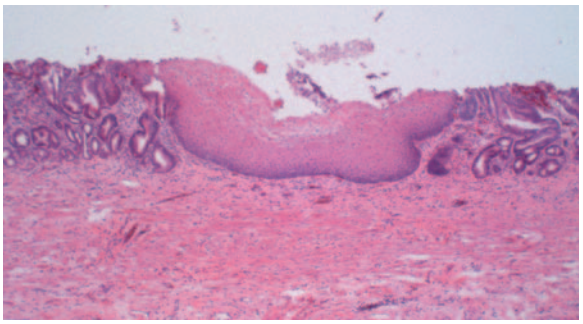


Figure 7–65 True regression, resulting from replacement of the entire thickness of columnar-lined epithelium by squamous epithelium. There is no residual metaplastic epithelium under the squamous epithelium.

plasia by demonstrating a reduction in the number of levels with intestinal metaplasia, the number of biopsies with intestinal metaplasia, and the number of goblet cells within the overall biopsy series. Assessment of the reduction of intestinal metaplasia in a standard biopsy protocol is likely to be far more sensitive than the all-or-none reversal of intestinal metaplasia, which is all that is assessed by present criteria.

3. An increase in the amount of oxyntocardiac mucosa, by conversion of cardiac mucosa to oxyntocardiac mucosa (grade 1 to 0). This is a critically important step because it converts an epithelium, which is in the reflux-to-adenocarcinoma sequence, to a stable benign epithelium that is not at risk. If the columnar epithelium in a patient with Barrett esophagus can be converted entirely into a columnar epithelium of identical length composed only of oxyntocardiac mucosa, the patient is no longer at any risk for adenocarcinoma. Within the context of our definition of reflux disease, such a patient does not have reflux disease (despite the presence of a visible segment of columnar-lined esophagus) because there is no adenocarcinoma risk.

In a patient with microscopic reflux disease limited to the end-stage esophagus, these criteria of regression cannot be demonstrated by any means other than the standard biopsy protocol (Figure 7–66). In a patient with visible columnar-lined esophagus, the only features of regression that can be detected without the standard biopsy protocol are a decrease in the length of the columnar-lined segment and the presence of squamous islands. Neither of these criteria are guaranteed to be evidence of regression, because it is unknown whether glands are present under the squamous epithelial surface (see Figures 7–64 and 7–65). The findings in the standard biopsy protocol permit microscopic determination of the three columnar epithelial types and provide a sensitive means of assessing regression. Using the findings in the standard biopsy protocol, the three different epithelial types that constitute columnar-lined esophagus can be accurately mapped. This will provide highly sensitive information regarding regression (Figure 7–67). *Not all columnar-lined esophagus is dangerous; one composed only of oxyntocardiac mucosa is actually the best result for a patient with reflux disease, because not only*

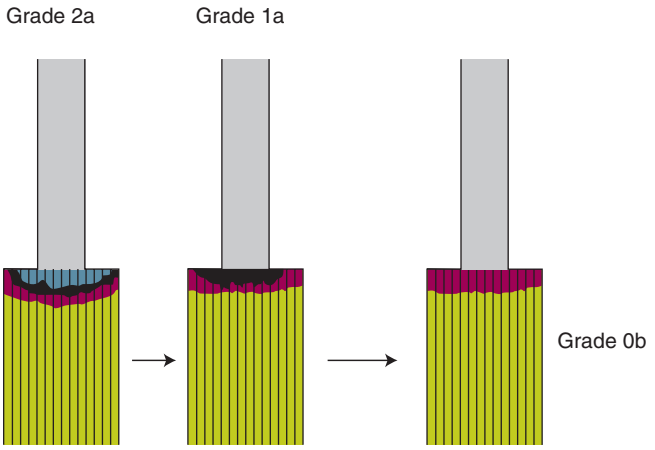


Figure 7–66 Histologic definition of regression of reflux disease in dilated end-stage esophagus is any decrease in the amount of intestinal metaplasia within the columnar-lined segment and conversion of cardiac mucosa to oxyntocardiac mucosa.

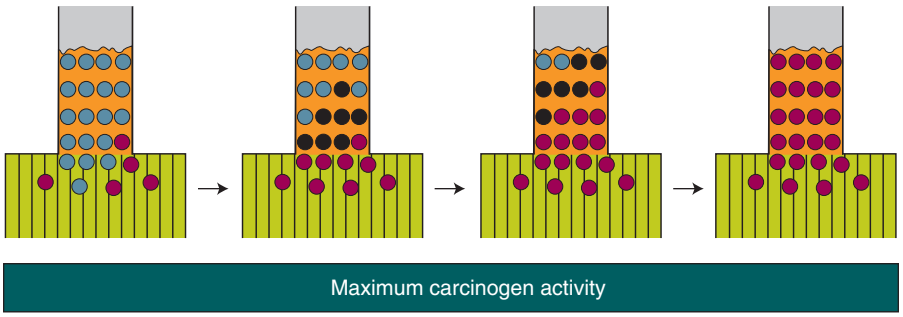


Figure 7–67 Histologic regression in a patient with a long segment of columnar-lined esophagus can occur without any change in endoscopic appearance (i.e., length of columnar-lined esophagus does not change). Progressing toward the right, the amount of intestinal metaplasia progressively decreases, and the amount of oxyntocardiac mucosa progressively increases. In the extreme right, the entire columnar-lined segment is composed of oxyntocardiac mucosa (stage 0b), and the patient is out of the reflux-to-adenocarcinoma sequence. This almost never happens with presently available treatments, except after anti-reflux surgery in patients with very short segments of columnar-lined esophagus.

does it not have any risk of cancer, but it is also the esophageal epithelial type that is least damaged by acid and least likely to be symptomatic.

Effect of Acid-Suppressive Drug Therapy

Most patients who undergo endoscopy and biopsy have been on long-term acid-suppressive drug therapy. Endoscopy is presently indicated when treatment has been ineffective has not been effective in relieving symptoms, or when non-cancerous complications of reflux disease arise, such as motility disturbances and strictures. Patients in this group show a high prevalence of reflux carditis and intestinal metaplasia.[21] This suggests that acid-suppressive drug therapy is ineffective in reversing these two types of columnar-lined esophagus. I have suggested that they may actually promote the occurrence of intestinal metaplasia in cardiac mucosa (see Figures 5–17

and 5–18). There is weak evidence in the literature that when the dosages of acid-suppressive drug therapy are controlled to produce a normalization of the 24-hour pH test rather than relief of symptoms, there may be some reduction in the surface area of columnar-lined esophagus due to squamous overgrowth.[42]

Similarly, the exponential increase in the incidence of reflux-induced adenocarcinoma suggests that acid-suppressive drug therapy is incapable of preventing progression in the reflux-to-adenocarcinoma sequence through increasing dysplasia to adenocarcinoma. I have suggested that it may actually promote cancer in the patient with Barrett esophagus (see Figure 6–20).

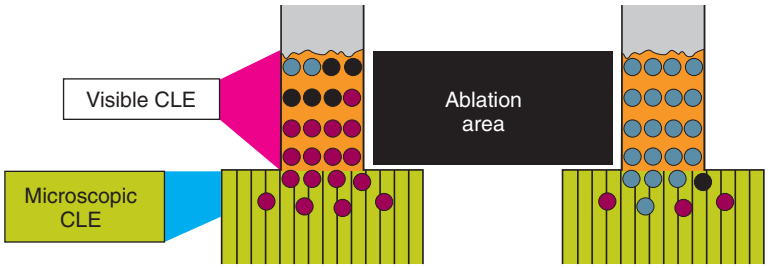
Effect of Mucosal Ablation

Ablation is used to remove the entire area of endoscopically visible columnar-lined esophagus, using either endoscopic mucosal resection or a variety of physical modalities. The purpose of both techniques is to remove the entire thickness of the mucosa up to the muscularis mucosae. When endoscopic mucosal resection is undertaken for a visible dysplastic lesion in Barrett esophagus, the objective may be to simply remove the lesion rather than ablate the entire visible columnar-lined segment. After mucosal ablation, the epithelium is induced to regenerate as squamous rather than columnar epithelium by post-ablation acid suppression. Acid suppression is achieved either medically, with effective doses of proton pump inhibitors, or with anti-reflux surgery.

In the absence of acid, the denuded epithelium regenerates as stratified squamous epithelium by movement of stem cells from the edges of the denuded area and squamous-lined ducts within the ablated area. Failure of acid suppression, either inadequate dosage of proton pump inhibitors or failed anti-reflux surgery, is associated with a recurrence of columnar metaplasia, including intestinal metaplasia. Recurrence rates of intestinal metaplasia after ablation are variable.

The lack of understanding of the variable nature and true extent of the columnar-lined esophagus results in two significant errors when ablation is performed (Figure 7–68).

1. Ablation is often excessive because of the lack of recognition that the columnar-lined esophagus is not entirely composed of intestinal metaplastic epithelium (patient *A* in Figure 7–68). It is only necessary to ablate intestinal metaplasia and possibly cardiac mucosa. It is certainly not necessary to ablate the stable and benign oxyntocardiac epithelium within the columnar-lined segment. Intestinal metaplasia has a constant distribution within the columnar-lined segment; it almost always begins at the squamocolumnar junction and extends distally in a contiguous manner. Mapping biopsies by protocol will delineate the distal limit of the intestinal metaplasia within the columnar-lined segment. Ablation can be limited to this area with a potential decrease in the amount of ablation needed.
2. At present, ablation generally stops at the endoscopic gastroesophageal junction; the columnar-lined esophagus in the dilated end-stage esophagus ("gastric cardia") is ignored. In patients with intestinal metaplasia extending into this dilated end-stage esophageal segment, at-risk epithelium remains after successful ablation (patient *B* in Figure 7–68). This is the area of highest carcinogen concentration because it is the area closest to the true gastroesophageal junction. High-grade dysplasia and adenocarcinoma



Ablated area	Visible CLE; 4 cm	Visible CLE; 4 cm
Length of CM+IM	2 cm	6 cm
Ablation extent	2–3 cm too much	2 cm too little
Risk	↑ Complications	CA in residual IM

Figure 7–68 Errors can occur during ablation therapy if it is not recognized that the endoscopically defined columnar-lined segment can have a variable histology and if the ablation is limited to the visible columnar-lined segment. On the left, the ablation area is too great because it extends into the region with oxyntocardiac mucosa, which is a benign epithelium that does not need to be ablated. A more limited ablation to remove only intestinal metaplasia or intestinal metaplasia *(IM)* and cardiac mucosa *(CM)* is adequate and is likely to produce fewer complications. On the right, the ablation of the entire visible area of columnar-lined esophagus *(CLE)* leaves intestinal metaplasia in the dilated end-stage esophagus. This remains an at-risk epithelium that can progress to cancer. *CA,* Adenocarcinoma.

occur in these patients because of this error. This has been reported to be true.[45]

Effect of Anti-Reflux Surgery

Anti-reflux surgery is most commonly achieved by a Nissen fundoplication, usually performed laparoscopically. In more complicated cases involving shortening of the esophagus or motility disorders, other types of anti-reflux surgeries are performed. In general, anti-reflux surgery wraps the fundus of the stomach around the distal esophagus, creating a valve that decreases the amount of reflux. The aim of the surgery is to adjust the tightness and length of the wrap to achieve the maximum reduction of reflux, without causing dysphagia. The surgery is highly effective in eliminating reflux symptoms and healing erosive esophagitis. To be considered successful in terms of its effectiveness in preventing cancer, the surgery must normalize the 24-hour pH test. Anti-reflux surgery that does not achieve this result has been shown to be ineffective in preventing cancer, even when it effectively decreases symptoms.

The following results have been reported in patients who have successful anti-reflux surgery, defined as a normalization of the 24-hour pH study after the surgery:

Decrease in the Incidence of High-Grade Dysplasia and Adenocarcinoma

In the only randomized clinical trial with significant follow-up, Parrilla et al[46] reported on 101 patients with Barrett esophagus with and without low-grade

dysplasia treated with acid-suppressive drugs (43 patients) or anti-reflux surgery (58 patients) since 1982. In the medical group, three patients had low-grade dysplasia at the index biopsy. During treatment, low-grade dysplasia persisted in one of these patients; 8 of 40 patients without dysplasia pretreatment developed low-grade dysplasia. Two patients developed high-grade dysplasia and went on to have esophagectomy in which an adenocarcinoma was present. The surgery group had nine failures (there was no normalization of the 24-hour pH study after surgery); two of these patients developed adenocarcinoma and required esophagectomy. Among the 49 patients who had a successful anti-reflux operation, five had low-grade dysplasia preoperatively. All these reversed after surgery. De novo low-grade dysplasia developed in 1 patient, and none of the patients developed high-grade dysplasia or adenocarcinoma. The malignancy rate was 1 in 129 patient-years (0.8% per year) for the medical treatment group, and 1 in 203 patient-years (0.5% per year) for the surgical treatment group. When surgery was successful, the rate was zero and significantly less than the medical group.

This study shows the difficulties in demonstrating a significant reduction in cancer rates following anti-reflux surgery compared with medical treatment. The risk of cancer is so low that the study required large numbers of patients followed over many years. The statistical data in this study are still not sufficient to show a significant difference. However, with a median follow-up of 6 years, the expectation is that over half the patients in the anti-reflux surgery group have eliminated their cancer risk, because cancer very rarely develops more than 5 years after successful anti-reflux surgery.[47] In contrast, the medical group will continue to show the approximately 0.5%-per-year cancer risk, which is a lifetime phenomenon. If these assumptions are true, over time this study will likely show a statistically significant divergence of cancer incidence in the medical and total (including unsuccessful) surgery groups.

Reversal of Intestinal Metaplasia

The only studies available are those that have looked for a complete disappearance of intestinal metaplasia after anti-reflux surgery. Hofstetter et al[43] reported on 85 patients with Barrett esophagus treated with anti-reflux surgery in whom follow-up was complete at a median of 5 years. Barrett esophagus was defined as the presence of intestinal metaplasia in a biopsy taken from an endoscopically visualized columnar-lined segment. Patients with intestinal metaplasia of the cardia were excluded. At a median follow-up of 5 years, 9 of 63 (14%) patients with non-dysplastic Barrett esophagus regressed to cardiac mucosa; 7 of 16 patients who had Barrett esophagus with low-grade dysplasia regressed to non-dysplastic intestinal epithelium. No patient developed high-grade dysplasia or cancer in 410 patient-years of follow-up.

This study shows that in conventional Barrett esophagus, both long- and short-segment, anti-reflux surgery is relatively ineffective in reversing intestinal metaplasia. However, a 14% complete disappearance of Barrett esophagus indicates that reduction of the amount of intestinal metaplasia, short of complete disappearance, is likely in this group if tested for by complete mapping biopsy protocols after surgery. Such studies are not available.

DeMeester et al[48] reported on 60 patients with intestinal metaplasia of the esophagus or cardia treated with anti-reflux surgery. Patients in the group with intestinal metaplasia of the cardia (CIM) (n = 15) had no endoscopically visible segment of columnar epithelium. Patients in the Barrett's group (n = 45) had columnar epithelium visible within the esophagus with intestinal metaplasia present in a biopsy. Median follow-up was 25 months in each group. Postoperative biopsies showed complete loss of intestinal metaplasia

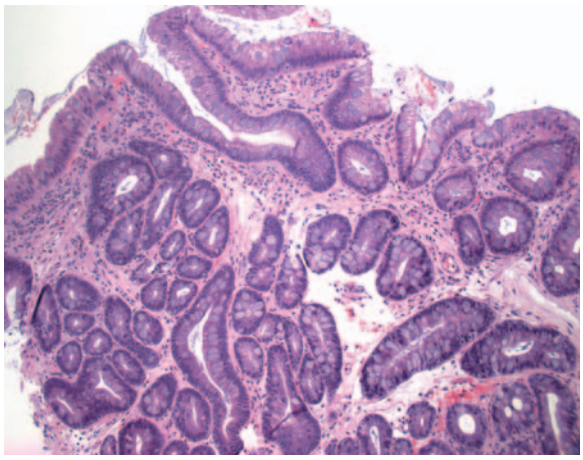


Figure 7–69 Preoperative biopsy at 36 cm, showing cardiac mucosa with intestinal metaplasia. The density of goblet cells is high.

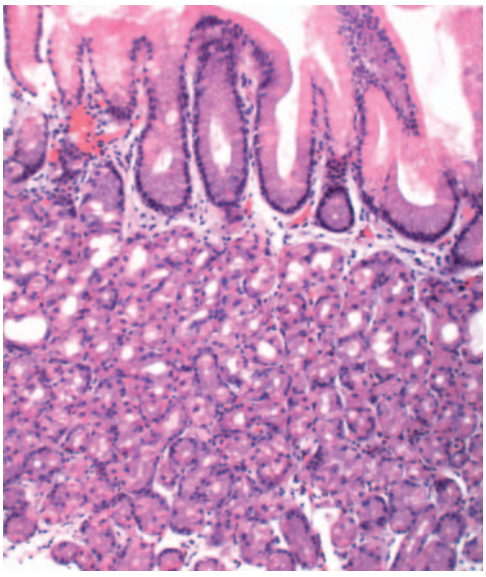


Figure 7–70 Preoperative biopsy of the distal stomach, showing unremarkable gastric oxyntic mucosa. There is no significant inflammation. *H. pylori* is absent.

in 73% of the patients with CIM compared with 4.4% of the patients in the Barrett's group. Low-grade dysplasia, present in 10 patients preoperatively, regressed in seven patients (70%). No patient progressed to high-grade dysplasia or cancer. The authors concluded that small microscopic areas of intestinal metaplasia are able to regress much more frequently than longer, visible segments of intestinal metaplasia.

CASE STUDY

A 56-year-old male with long-segment Barrett esophagus underwent a Nissen fundoplication. He gave a history of heartburn and regurgitation of 8 years' duration that had been controlled with proton pump inhibitors (omeprazole, 20 mg twice a day) until 3 months ago. He had his first endoscopy 1 month before being referred to the University of Southern California's Foregut Surgery Department; the endoscopy showed long-segment Barrett esophagus. The preoperative endoscopy showed the irregular squamocolumnar junction's upper limit at 34 cm; the proximal limit of the rugal folds was 39 cm. Biopsies showed intestinal metaplasia at all levels, including the retrograde biopsy taken from the region of the proximal limit of the rugal folds. Every biopsy at 34, 36, and 38 cm contained intestinal metaplasia with a high density of goblet cells (Figure 7–69). The biopsies taken at and distal to the proximal limit of the rugal folds showed intestinal metaplasia, cardiac mucosa, and oxyntocardiac mucosa. The distal gastric biopsies were normal (Figure 7–70). No dysplasia was present. Surgery was successful as determined by cessation of symptoms, elimination of acid-suppressive drug use, and a normal 24-hour pH test.

Biopsies were repeated 1 year later and showed the squamocolumnar junction at 36 cm. Biopsies at that level showed intestinal metaplasia with squamous overgrowth (Figure 7–71). Two of four biopsies at 38 cm showed intestinal metaplasia, although the density of goblet cells at this level appeared to be somewhat less than in the preoperative biopsies (Figure 7–72). The other two biopsies showed a mixture of cardiac and oxyntocardiac mucosa. There was also evidence of squamous islands (Figure 7–73). The retrograde

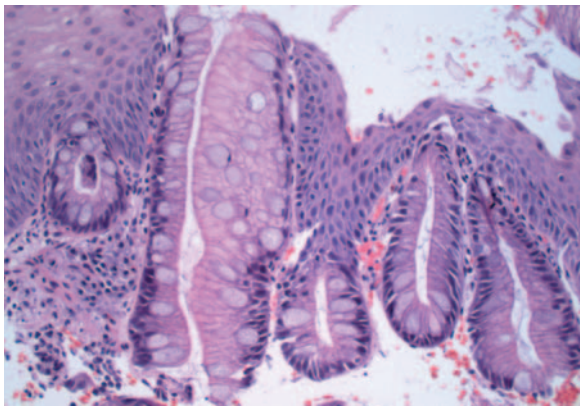


Figure 7–71 Post-fundoplication biopsy at 36 cm, showing partial squamous overgrowth over intestinal metaplastic epithelium.

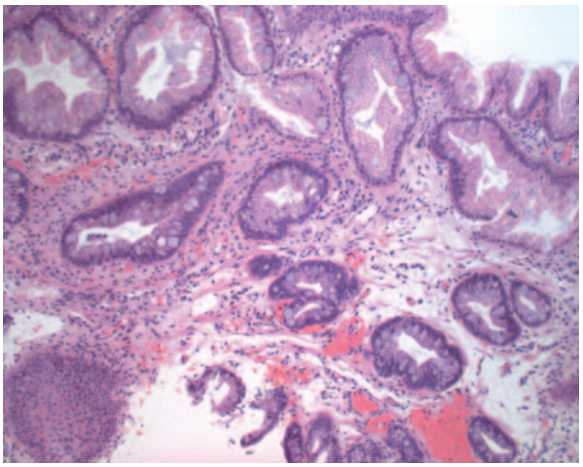


Figure 7–72 Post-fundoplication biopsy at 38 cm, showing cardiac mucosa with intestinal metaplasia. The density of goblet cells is lower than in the preoperative biopsy shown in Figure 7–69. Note the squamous-lined duct near the left lower edge.

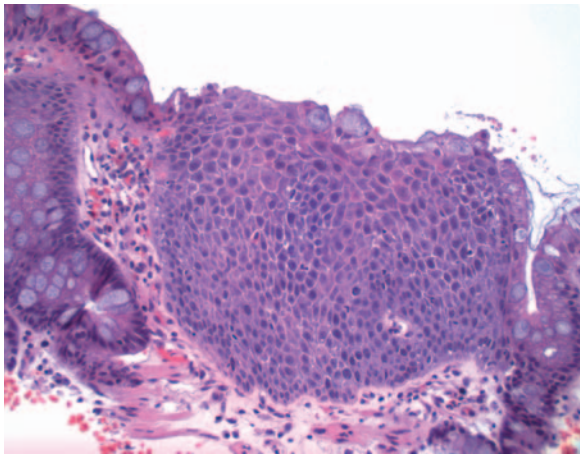


Figure 7–73 Post-fundoplication biopsy at 38 cm, showing a squamous island with features of reflux esophagitis surrounded by intestinal metaplasia with a high density of goblet cells.

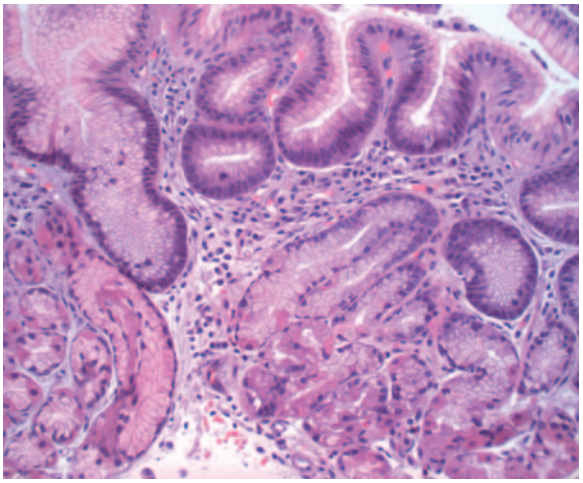
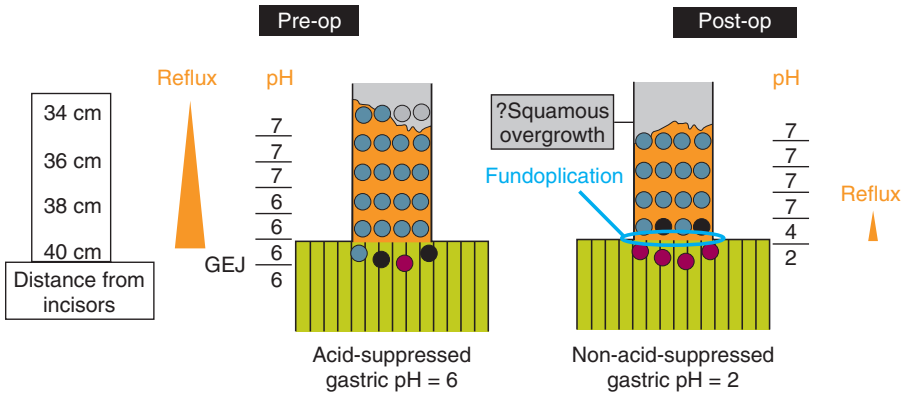


Figure 7–74 Post-fundoplication retrograde biopsy showing oxyntocardiac mucosa with mild chronic inflammation.

biopsies taken from the region of the proximal limit of the rugal folds showed only oxyntocardiac mucosa (Figure 7–74); there was no intestinal metaplasia or cardiac mucosa in this region.

The changes before and after fundoplication are shown in Figure 7–75. The fundoplication is usually performed around the end of the tubular esophagus. It is very likely that the point of effective prevention of reflux lies above the dilated end-stage esophagus. Because the patient is no longer on acid-suppressive drugs, the baseline gastric pH has returned to normal. The amount of reflux after surgery is greatly reduced. This means that the more proximal part of the esophagus is no longer exposed to refluxate and that the exposure of the most distal esophagus to refluxate is of lower volume and is generally more acidic with a shorter pH gradient. Neutral pH is reached much more distally in the esophagus than before surgery.

The detected histologic changes post-fundoplication can be explained as follows:



Length of CLE	7 cm	5 cm (?)
Length of IM	6 cm	4 cm (?)
IM → CM		In distal esophagus
IM and CM → OCM		Below wrap

Figure 7–75 Difference between pre-fundoplication and post-fundoplication findings in this patient. The site of the valve-like effect produced by the fundoplication is identified with a dark blue ring at the end of the tubular esophagus. The amount of reflux *(orange triangles)* has decreased after surgery, and the pH gradient has changed dramatically as reflux has lessened and gastric pH has become more acidic upon withdrawal of acid-suppressive drugs. The epithelium above the wrap in the tubular esophagus is no longer exposed to refluxate and remains stable. The epithelium below the wrap, which is exposed to the acidic gastric juice, has changed to oxyntocardiac mucosa *(OCM),* representing reversal of intestinal metaplasia and conversion of cardiac mucosa *(CM)* to oxyntocardiac mucosa. The cancer risk has dramatically decreased in this patient because the exposure of target cells (intestinal metaplasia *[IM]*) to carcinogen has been greatly reduced. *CLE,* Columnar-lined esophagus.

1. There is an apparent reduction in the total length of columnar-lined esophagus because the upper limit of the Z-line is at 36 cm, compared to the 34 cm before surgery. This is questionable because of the presence of squamous overgrowth over intestinal metaplastic epithelium in the lamina propria (see Figure 7–71).
2. The upper limit of intestinal metaplasia seems to be lower, but this is uncertain because of squamous overgrowth. This area has now been rendered irrelevant because it is no longer exposed to refluxate. This intestinal metaplasia will only progress to cancer if the genetic change to prevalent cancer has already taken place. There is no risk of progression in the reflux-to-adenocarcinoma sequence.
3. In the distal esophagus above the wrap, the intestinal metaplasia is relatively stable, with no reduction in length (see Figure 7–75). There is a detectable decrease in the density of goblet cells in the postsurgical biopsies (see Figures 7–69 and 7–72), and there is a slight tendency of conversion of intestinal metaplasia to cardiac mucosa in the most distal level (38 cm).
4. There are dramatic histologic changes below the wrap in the dilated end-stage esophagus. This area continues to be exposed to gastric juice. However, the gastric juice has become much more acidic because of the withdrawal of acid-suppressive drugs. The highly acidic milieu created has resulted in a conversion of all the metaplastic epithelia, including the intestinal metaplasia, into oxyntocardiac mucosa (see Figure 7–74). Although it continues to be exposed to carcinogens in the gastric juice, this area no longer has any target cells. Theoretically, these changes in the post-

fundoplication state reduce progression in the reflux-to-adenocarcinoma sequence and therefore prevent cancer.

Prevention of Conversion of Cardiac Mucosa to Intestinal Metaplasia

Oberg et al[49] reported on 177 patients enrolled in a surveillance program for columnar-lined esophagus. This study is unique because the indication for surveillance was simply the presence of an endoscopic columnar-lined esophagus without the requirement of intestinal metaplasia. To be included in the study, the patients needed to have had three or more surveillance endoscopies over a minimum of 2 years. Intestinal metaplasia was present in 108 of 177 patients in the first two endoscopies; 69 patients did not have intestinal metaplasia. Intestinal metaplasia was more prevalent in those patients with a longer columnar-lined segment; 88.9% of patients with long (greater than 3 cm) segments had intestinal metaplasia, compared with 30.5% with segments shorter than 3 cm.

Patients who did not have intestinal metaplasia on the first two biopsies who continued medical treatment were compared to those who had anti-reflux surgery for development of intestinal metaplasia in a later biopsy. The authors point out that a sampling error may account for the absence of intestinal metaplasia and attempted to decrease this possibility by requiring two successive biopsies that were negative for intestinal metaplasia.

Patients with surgically treated reflux disease were 10.3 times less likely to develop intestinal metaplasia compared with a group receiving standard medical therapy in surveillance biopsies (after the first two biopsies were negative for intestinal metaplasia). In the medically treated group of 49 patients, there was a progressive increase in intestinal metaplasia, with 80% of the patients progressing to intestinal metaplasia at 8 years. In the anti-reflux surgery group of 20 patients, 12 (60%) remained without intestinal metaplasia at 16 years.

The fact that anti-reflux surgery was able to prevent intestinal metaplasia in 60% of patients again supports the hypothesis that anti-reflux surgery creates a milieu around the target cell (the progenitor cell in cardiac mucosa) that decreases the likelihood of conversion to intestinal metaplasia. Intestinal metaplasia is not completely prevented, which is explained easily by the fact that surgery does not completely abolish reflux; normalization of the 24-hour pH test is not equivalent to abolition of reflux. At the upper limit of what is considered normal in the 24-hour pH test, there is exposure of the target cell to refluxate for 4% of the 24-hour period (more than 1 hour per day).

Conversion of Cardiac Mucosa to Oxyntocardiac Mucosa

In a recent study in our department, Tharavej et al (unpublished data) reported on 61 consecutive patients who underwent anti-reflux surgery with preoperative and postoperative biopsies from the gastroesophageal junction. Patients with intestinal metaplasia were excluded; all patients had cardiac mucosa in these biopsies. Matched preoperative and postoperative biopsies were evaluated for the type of columnar epithelium present at the gastroesophageal junction. Regression of cardiac mucosa was defined when conversion from cardiac mucosa to oxyntocardiac or oxyntic mucosa occurred (i.e., when parietal cells were present). Non-regression was defined as the persistence of cardiac mucosa. Progression was defined as the occurrence of intestinal metaplasia (i.e., when goblet cells were present).

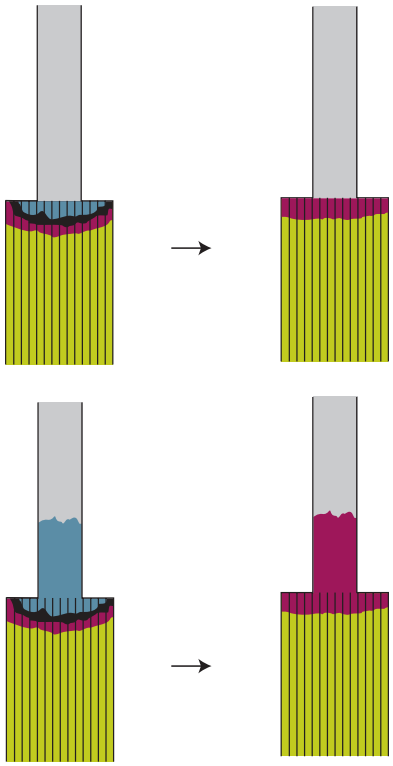


Figure 7–76 Histologic cure in gastroesophageal reflux is the conversion of all columnar metaplasia to oxyntocardiac mucosa, which is a stable and benign columnar epithelium that is out of the reflux-to-adenocarcinoma sequence.

At a median follow-up of 2 years after surgery, complete regression of cardiac mucosa was demonstrated in 18 (29%) patients; 17 had regression to oxyntocardiac mucosa, and 1 had regression to oxyntic mucosa. Cardiac mucosa was unchanged in 39 (64%) and progressed to intestinal metaplasia in 4 (6%). The decrease in prevalence of cardiac mucosa before and after anti-reflux surgery was significant ($p = 0.001$).

A total of 36 of these patients had postoperative pH studies. Of these, 28 had a normal 24-hour pH test; 12 of the 28 (43%) had regression to oxyntocardiac mucosa, 16 (57%) had unchanged cardiac mucosa, and none progressed to intestinal metaplasia. Of the eight patients who had an abnormal 24-hour pH test, cardiac mucosa was unchanged in six and progressed to intestinal metaplasia in two. The frequency of regression of cardiac mucosa was significantly higher when the 24-hour pH test was normalized (12/28 versus 0/8, $p = 0.02$).

Regression of cardiac mucosa to oxyntocardiac mucosa allows the removal of the patient from the reflux-to-adenocarcinoma sequence. Oxyntocardiac mucosa is a stable epithelium that does not undergo intestinal metaplasia. It represents a cure of reflux disease if the end-point is defined as removing the patient's risk of reflux-induced adenocarcinoma (Figure 7–76). In the future, I expect that the optimal treatment method for reflux disease will be a drug that converts all cardiac and intestinal epithelia in columnar-lined esophagus to oxyntocardiac mucosa. This occurred in the case study involving the distal region of the columnar-lined segment that was below the wrap, probably as a result of acid. Is acid, which is the cause of columnar-lined esophagus, also its cure?

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