

Parakrama Chandrasoma and Juan Guo

Introduction

The entire esophagus is lined by stratified squamous epithelium from its proximal cricopharyngeal end to its distal limit at the gastroesophageal junction. In the normal person, the squamous epithelium is protected from exposure to gastric contents by the lower esophageal sphincter.

The cellular changes of reflux occur when the lower esophageal sphincter fails to protect the esophageal squamous epithelium and allows it to become exposed to gastric contents. Reflux is like a battle to attack a target (the esophageal squamous epithelium) with the lower esophageal sphincter being the defense and gastric juices the offense.

Exposure of esophageal squamous epithelium occurs when there is free reflux of gastric contents into the esophagus as a result of temporary sphincter relaxation or permanent sphincter destruction. The latter is the primary cause and sine qua non of chronic gastroesophageal reflux disease. When the barrier of adequately high sphincter pressure is removed, reflux tends to occur because there is a pressure gradient from positive in the gastric lumen to negative in the intra-thoracic esophagus. Such free reflux can be measured by an abnormal 24-h pH test where a pH sensitive electrode placed in the distal esophagus detects acid exposure, which is a marker of exposure of the esophagus to gastric contents.

Exposure of the squamous epithelium to gastric juice may occur during the post-prandial period if the stomach becomes over-distended without there being free reflux into the esophagus. Gastric over-distension and increased intra-gastric pressure put pressure on the sphincter, causing it to shorten. As the sphincter is effaced, there is an effective downward

movement of the squamo-columnar junction, causing the squamous epithelium to be progressively exposed to the environment of the stomach and thus the gastric juice. This mechanism of the descent of the squamo-columnar junction into the stomach can be simulated and observed when the stomach is insufflated with air during endoscopy.

The changes caused by reflux in the esophageal mucosa must initially be limited to changes in the squamous epithelium because there is no other epithelium in the normal esophagus. However, one of the consequences of chronic reflux disease is columnar metaplasia of the squamous epithelium. This appears to occur early in the course of reflux disease and is seen at a microscopic level in the vast majority if not all patients with chronic reflux disease [1, 2]. Once columnar metaplasia has occurred in the esophagus the gastric contents cause a range of pathologic changes in this metaplastic columnar epithelium that is very different than in the native squamous epithelium.

Present management algorithms of reflux disease are directed towards control of symptoms and of erosive esophagitis. Symptoms and erosive esophagitis are largely the result of acute damage to the squamous epithelium caused by acid exposure. These acute squamous epithelial changes are reversible and largely curable with acid suppressive drug therapy. The metaplastic columnar epithelium of patients with reflux disease is more resistant to acid and less sensitive than squamous epithelium. Acid suppressive drug therapy is, however, not aimed at addressing the pathologic changes in metaplastic columnar epithelium.

Management guidelines that single-mindedly emphasize acid neutralization and acid suppressive drug therapy to treat patients with reflux disease have been in place for five decades. The increasing effectiveness of acid suppression in this time frame has resulted in better control of symptoms, improved healing of erosive esophagitis, and prevention of chronic squamous epithelial complications such as deep intractable ulcers and strictures. Alkalinization of gastric contents is powerful in protecting and healing the esophageal squamous epithelium in a patient with reflux [3].

P. Chandrasoma, MD, MRCP (UK) • J. Guo, MD, PhD (✉)
Department of Pathology, Los Angeles County –
University of Southern California Medical Center,
1100 N. State Street, Room CT7A120,
Los Angeles, CA 90033, USA
e-mail: ptchandr@usc.edu; juanguo9999@gmail.com

During the past five decades, however, there has been an explosion in the incidence of Barrett esophagus and esophageal adenocarcinoma which are columnar epithelial complications of reflux disease. We will explore the possibility that Barrett's esophagus and adenocarcinoma may be promoted by the alkalization of gastric contents that result from acid suppression.

The Offense: Gastric Contents

The composition of gastric contents represents the offensive side of the equation of the pathology of reflux. If gastric contents were not noxious to esophageal squamous epithelium, there would be no "reflux disease" even if reflux were to occur. Gastric contents include gastric secretions which contain acid and pepsin, ingested food and saliva, and duodenal contents if the patient has duodeno-gastric reflux. Duodenal contents include bile and proximal small intestinal enzymes.

Present management with acid suppressive drugs is based on the premise that neutralizing or suppressing secretion of acid in the stomach converts the gastric contents from being noxious to esophageal mucosa to being innocuous. The single minded emphasis on acid suppression in the medical treatment of reflux disease only makes logical sense because the medical community believes that acid is the cause of every pathologic change that occurs in esophageal mucosa. This is likely to be close to the truth for esophageal squamous epithelium, but not for metaplastic columnar epithelium.

In contrast, surgical treatment of reflux disease with some type of repair or augmentation of the function of the lower esophageal sphincter aims at decreasing or preventing reflux. If successful, exposure of both squamous and metaplastic columnar esophageal epithelia to all gastric molecules is prevented.

Converting the strong acid milieu of gastric contents to an alkaline milieu has unintended consequences that are recognized complications of long-term proton pump inhibitor use. Decreased absorption of minerals results in decreased bone density and hip fractures [4]; bacterial infections are increased, notably *Clostridium difficile* colitis [5]. Little attention has been paid, however, to assessing whether gastric alkalization promotes intestinal metaplasia (i.e., Barrett esophagus) and progression to adenocarcinoma in metaplastic esophageal columnar epithelia.

The stomach in its resting state between meals and after it has emptied completely contains the low volume of resting acid secretion by the parietal cells. In the normal individual, the resting state gastric juice has a pH of 1–2. The empty stomach is collapsed, with the mucosal rugae being maximally folded.

With food ingestion the stomach distends, slowly flattening the mucosal rugal folds and the gastric glands are stimu-

lated to rapidly increase acid and enzyme secretion. The secreted acid mixes with the food, which tends to be near the neutral pH range, and results in a pH of the gastric contents that varies with the type and volume of the meal. It has been shown that the gastric pH in the stomach that contains food is not constant throughout the column of food. In particular, there appears to be a very low pH pocket (the "acid pocket") at the top of the food column [6]. When the stomach is full after a heavy meal, this acid pocket is in the proximal stomach, very close to the distal end of the LES and squamous epithelium of the esophagus.

This normal condition of gastric contents can be altered significantly by three relatively common situations that may exist in a large percentage of patients in different populations:

Helicobacter pylori Infection

Helicobacter pylori infection varies greatly in incidence in different populations. It is interesting that in those populations where *H. pylori* is prevalent, such as South Korea and Japan, the incidence of gastric adenocarcinoma is high and that of Barrett esophagus and esophageal adenocarcinoma is low. This has led to the suggestion that *H. pylori* infection is protective against reflux disease. The reason why this could be true is that chronic *H. pylori* gastritis is often associated with atrophic gastritis and hypochlorhydria. The low acid secretion in the stomach acts as a natural acid suppressant.

In populations where *H. pylori* has a high prevalence, infection likely occurs early in life and the hypochlorhydric state prevents squamous epithelial damage and columnar metaplasia.

In populations where *H. pylori* is uncommon such as the USA and Western Europe, reflux usually occurs without the natural acid suppression associated with the infection and results in columnar metaplasia. *H. pylori* infection occurring after columnar metaplasia has been generated can limit further squamous epithelial damage but will not prevent damage to the already established columnar mucosa in the esophagus.

Duodeno-Gastric Reflux

Duodeno-gastric reflux is characterized by alkaline duodenal contents that contain bile salts and acids, bilirubin and duodenal enzymes refluxing into the stomach. Duodeno-gastric reflux is a relatively common phenomenon. Reflux of duodenal contents neutralizes gastric acid to an extent that depends on the volume and frequency of entry of duodenal contents into the stomach. It therefore effectively increases gastric pH.

When duodeno-gastric reflux is present in a patient who has gastroesophageal reflux, the term duodeno-gastro-esophageal

reflux is sometimes used. The presence of duodenal admixture in the refluxate can be measured by placing a sensor in the lower esophagus that recognizes a unique duodenal molecule such as bilirubin. Bilitec is such a probe that was used in the past and provided excellent data on the effect of duodenal admixture in the refluxed gastric contents.

The presence of duodenal elements in gastric contents significantly influences the pathologic changes seen in the esophageal mucosa in reflux disease. The damage to squamous epithelium resulting from a mixture of gastric and duodenal material is greater than gastric material alone. The prevalence of Barrett's esophagus is significantly associated with a positive Bilitec test [7]. Bile salts/acids have been shown in vitro to suppress genes that maintain squamous epithelium and activate genes that promote columnar metaplasia of squamous epithelial cells, intestinal metaplasia in columnar epithelium, and carcinogenesis [8, 9].

Evidence has also been presented that suggest that bile salts/acids entering the stomach have different activity at different gastric pH. In a strong acid milieu, the bile salts/acids become inactivated by precipitation. At a pH above 6, they remain ionized, in solution, and do not produce oncogenic mutations in animals. At a gastric pH of 3–5, the bile salts/acids become un-ionized and capable of producing oncogenic mutations in the esophageal epithelial cells. The typical gastric pH achieved with medical treatment of reflux disease with acid suppressive drugs is also 3–5.

Based on these data, many authorities believe that some derivative of bile salts/acids is the most likely agent involved in the genesis of adenocarcinoma in the esophageal mucosa in patients with reflux. There is no doubt that the carcinogen is present in the gastric contents and delivered to the esophageal mucosa by reflux. A recent radical surgical treatment for Barrett esophagus proposed by Csendes et al. [10] separates the duodenum from the stomach, precluding bile entry into the stomach. In his series with significant follow-up, no patients so treated progressed to adenocarcinoma, suggesting that bile in the refluxed gastric contents plays an important role in carcinogenesis.

Acid Suppressive Drug Therapy

Acid suppressive drug therapy aims to control gastric pH. There is good evidence that maintaining the gastric pH above 4 for greater than 12 h is an effective method of controlling heartburn and causing erosions to heal [3]. When the gastric pH is maintained above this level, symptoms and erosions are effectively prevented in the majority of patients with reflux. Proton pump inhibitors used in adequate dosage have the capability of suppressing acid secretion to a level that maintains pH for 12–18 h of the day [11]. Histamine-2 receptor antagonists are less effective and acid neutralizing agents have only a temporary effect in alkalinizing gastric contents.

The Defense: The Lower Esophageal Sphincter

The lower esophageal sphincter is a high-pressure zone that occupies the distal 3–5 cm of the esophagus, including the entire extent of the abdominal part of the esophagus. Competence of the sphincter depends on its resting pressure, total length, and abdominal length [12]. In the normal person, the sphincter relaxes to permit venting of intra-gastric gas, resulting in belching.

Whenever the lower esophageal sphincter fails to function normally, either because of permanent damage or transient relaxation, free reflux of gastric contents into the esophagus occurs when there is a sufficient pressure gradient from stomach to esophagus that overcomes any residual sphincter function.

Reflux is a dynamic event. It can be likened to a jet of water issuing from a vertically held hose when the tap is opened. In a patient with a mildly damaged sphincter and high-pressure gradient, reflux will have a jet-like form with a low volume and higher progression into the esophagus. With a severely damaged sphincter and a low pressure gradient, the flow will be higher in volume with a lower retrograde propulsive force. The entry of gastric contents into the esophagus results in a response from the esophagus designed to clear the refluxed contents back into the stomach, probably by a stimulation of secondary peristalsis. The effectiveness of this clearing also varies, depending on the structural integrity of the esophageal muscle wall. Variations in the nature of the column of reflux, volume of reflux, and efficiency of clearing greatly influences the time of contact of the refluxed molecules with the esophageal epithelium. Impedance technology permits measurement of the rate of flow and height of the refluxed column. There is no ability to accurately measure volume of reflux.

Whatever the form of reflux, it creates a volume and pressure gradient in the esophagus. In the normal state, the esophagus is empty and at an approximately neutral pH 7. Immediately beyond the distal end of the sphincter the pH is strongly acidic. In both resting stomach and in the full stomach with its acid pocket, the pH immediately distal to the gastroesophageal junction is highly acidic (pH 1–2). The intra-gastric volume near the junction varies with the degree of gastric filling. When reflux occurs, a volume gradient is created in the esophagus as the refluxate is propelled upward. The exposure of the esophageal epithelium to every molecule in gastric juice is highest in the most distal esophagus and lowest at the top of the column of refluxed material, where it is zero (the normal state of the esophagus). This includes hydrogen ions; which means that a pH gradient is created that equals the baseline pH of gastric juice in the most distal esophagus and equal to the neutral esophageal pH at the height of the column. The amount of exposure of

the esophageal epithelium to molecules in the refluxate is dependent on the volume of refluxed material and the efficiency of esophageal clearing, factors that are largely unmeasurable today.

Understanding this pathophysiology of reflux is critical to elucidating the reasons behind the observed pathologic changes that occur in the esophageal epithelium in patients with reflux. The lower esophageal sphincter is a physiological valve. Like any valve, it maintains zero volume and pH 7 on the esophageal side and higher volume (which increases during gastric filling) and a strong acid pH on the gastric side. Like any valve, the result of failure is an obliteration of these sharp gradients [13].

The Target: The Esophageal Squamous Epithelium

Squamous epithelium lining the normal esophagus is a non-keratinizing stratified squamous epithelium. This consists of a basal layer of cells containing stem cells. Above this is a proliferative basal zone consisting of 2–3 layers of cells. In the normal steady state, the basal cell layer is less than 30 % of the thickness of the epithelium. The proliferative cells undergo mitotic division to continually replace cells lost from the surface. A newly produced daughter cell in the proliferative zone is shed 4–6 days later at the surface [14].

The normal differentiation of the squamous epithelium is under the direction of a genetic signal which is most likely a gene in the Wnt complex. The presence of this signal in the dividing cells causes the daughter cells of mitotic division to differentiate towards keratinocytes and move towards the surface.

In addition to the epithelium, the mucosa of the esophagus contains the lamina propria and the muscularis mucosae. The lamina propria of the normal esophagus is scanty and consists largely of collagen with few inflammatory cells. The muscularis mucosa is a thin bi-layered smooth muscle layer. Mucous glands are present in the mucosa and submucosa. The ducts of these mucous glands pass through the mucosa and traverse the squamous epithelium to open at the surface. The mucin secreted by these glands serves to lubricate the squamous epithelium.

Neural elements present in the mucosa are so fine that they are not visible in routine sections. There are nerve endings in the stratified squamous epithelium that are largely afferent sensory nerves. Some of these are pain-sensitive. Others may be involved in local reflex arcs with the neurons in the submucosa and myenteric plexus that probably coordinate peristalsis and maintain sphincter tone. The vagus nerve innervates the esophagus and influences local neural pathways but are not essential to motor or sphincter function which persist even after complete denervation.

The normal stratified squamous epithelium of the esophagus consists of cells that are bound to each other by tight cell junctions in the cell membranes. This results in an epithelium that is impermeable to molecules in the lumen. The surface epithelium is exposed to luminal molecules during swallowing and if the esophagus is exposed to gastric contents. One function of the normal squamous epithelium is to prevent entry of these luminal molecules into the epithelium; the deep proliferative zone and stem cells are therefore protected.

The stage for epithelial battle with gastric contents when reflux occurs due to failure of the lower esophageal sphincter is now set. There are two epithelia in the normal person's upper digestive tract: normal stratified squamous in the esophagus and normal gastric oxyntic in the stomach. Normal gastric oxyntic mucosa is immune to damage by gastric contents. Esophageal squamous epithelium undergoes damage when exposed to gastric contents.

Definition of Normal Esophagus and Gastroesophageal Junction

The accurate definition of the gastroesophageal junction is critical in understanding the pathologic changes in the mucosa as a result of GERD. At present, the gastroesophageal junction is defined endoscopically as the proximal limit of the rugal folds [15]. It is well known that the inter-observer variability is high amongst clinicians asked to define the gastroesophageal junction using this definition. The American Gastroenterological Association consensus workshop recommended using this definition despite the fact that there was little or no evidence to support it; this was an opinion-based definition [16].

In 2007, Chandrasoma et al. [17], in a study of esophagectomy specimens, proposed that the definition of the true gastroesophageal junction was not possible by endoscopic criteria. The reason for this was that early damage to the abdominal segment of the lower esophageal sphincter and the associated columnar metaplasia results in dilatation of the damaged lower esophagus [2]. The GERD-damaged dilated distal esophagus became part of the gastric reservoir distal to the intact tubal esophagus, eventually developing rugal folds. The dilated distal esophagus has long been mistaken for proximal stomach at endoscopy because it was distal to the proximal limit of rugal folds. This study showed that there exists a variable length of metaplastic columnar epithelium distal to the proximal limit of rugal folds and the end of the tubal esophagus. In full thickness sections, this segment of metaplastic columnar epithelium was concordant with the presence of esophageal submucosal glands, proving that this was dilated distal esophagus rather than proximal stomach. Chandrasoma et al. proposed that the true definition of the gastroesophageal junction was the proximal limit of

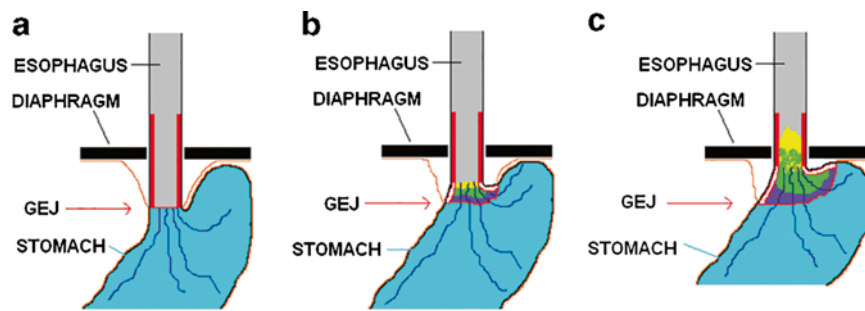


Fig. 2.1 Anatomy and histology in normal and increasing severity of chronic reflux disease. (a) In the normal patient, the esophagus is lined by squamous epithelium (gray) and the stomach is lined by gastric oxyntic mucosa with rugal folds (blue). There is no separation of squamous and oxyntic mucosa. (b): In mild reflux disease, the lower esophageal sphincter is shortened permanently and this is concordant with a dilated distal esophagus that is lined by metaplastic columnar epithe-

lium (shown here as three types—yellow=intestinal metaplasia; green=cardiac mucosa; purple=oxyntocardiac mucosa). Note the partial loss of the acute angle of His and the presence of rugal folds in the dilated distal esophagus. (c): In severe reflux disease, the sphincter damage is greater, the dilated distal esophagus is larger, and there is columnar metaplasia in the distal tubal esophagus. Note the further decrease in the angle of His

gastric oxyntic mucosa, defined histologically. Because it is not possible to distinguish gastric oxyntic mucosa from metaplastic esophageal columnar epithelium in the dilated distal esophagus at endoscopy, it is also not possible to accurately define the true gastroesophageal junction at endoscopy. Submucosal glands are rarely seen in endoscopic mucosal biopsies. However, biopsies from metaplastic columnar epithelium of the esophagus may show the glandular ducts of these glands as they penetrate the mucosa [18].

If this new evidence-based histologic definition of the gastroesophageal junction is accepted over the present opinion-based endoscopic definition, the pathologic changes in the esophagus in early reflux disease become clear [2]. The squamous epithelium normally extends to the end of the esophagus where it transitions to gastric oxyntic mucosa which lines the proximal stomach (Fig. 2.1). This transition point is the gastroesophageal junction. Histologically, there is no other type of epithelium between esophageal squamous epithelium and gastric oxyntic mucosa in the normal gastroesophageal junction, i.e., the squamo-oxyntic gap is normally “zero” [1, 19].

The presence of cardiac mucosa, or non-intestinalized columnar mucosa, as a normal phenomena between the normal epithelium of the proximal stomach and squamous esophagus is a false dogma. This falsehood, based on observations made in the 1960s [20], is still accepted by the medical community despite powerful evidence against it, and prevents correct interpretation of histologic changes in reflux [21]. The new histologic definition of the gastroesophageal junction explains why pathology in the endoscopically defined “gastric cardia” such as intestinal metaplasia and adenocarcinoma has an association with GERD and not with distal gastric pathology. Intestinal metaplasia and adenocarcinoma of the gastric cardia are in reality intestinal metaplasia and sometimes adenocarcinoma of the dilated distal esophagus.

Reflux-Induced Damage to Esophageal Squamous Epithelium

Structural Cellular Changes

Exposure of esophageal squamous epithelium to gastric contents causes damage. It is almost certain that acid is the main cause of squamous epithelial damage although suggestion has been made that a combination of acid and bile and/or pepsin is more potent in producing damage than acid alone.

The first change in the squamous epithelium induced by acid is likely to be intraepithelial edema, referred to as “dilated intercellular spaces [22]” and an increase in the rate of loss of surface keratinocytes from the epithelium as a result of direct damage to the surface cells. This results in a more rapid turnover of the squamous cells. Increased surface loss stimulates the proliferative zone cells to increase in number as well as proliferative activity in order to maintain the structural integrity of the epithelium. This is seen morphologically as an increased thickness of the basal cell zone of the epithelium to greater than 30 % of epithelial thickness. This basal cell hyperplasia is associated with elongation of the papillary processes between the rete pegs; these papillary processes become highly vascularized. Staining of the epithelium with Ki67 shows that the proliferative zone has expanded considerably.

Damage to superficial keratinocytes by acid also results in the release of cytokines. These diffuse across the epithelium into the lamina propria where they have many potential effects. One of these is that many of these cytokines are chemo-attractive to eosinophil leukocytes which migrate into the epithelium, usually in small numbers.

With severe damage to the epithelium, superficial erosions may occur in the epithelium and can progress to ulcers that involve the full thickness of the mucosa. Healing associated with these ulcers can induce fibrous strictures in the esophagus.

It is important to note that reflux disease is not associated with an increased incidence of *squamous* carcinoma of the esophagus. This is fortuitous and implies that gastric contents do not contain molecules that can interact with cell receptors in squamous epithelium and induce mutational changes that result in oncogenic transformation of squamous epithelial cells to squamous dysplasia and carcinoma.

Endoscopic Features

Endoscopic examination of the squamous epithelium is relatively insensitive for the diagnosis of reflux disease. Hyperemia and gross erosions are used as the main diagnostic criteria. The extent of erosions has been used to classify erosive esophagitis into increasing grades of severity (A–D) in the Los Angeles classification [23].

Unfortunately, erosive esophagitis is present in only a minority of patients with symptomatic reflux disease, making it a relatively insensitive endoscopic diagnostic criterion. The presence of erosions is also not specific for reflux disease; erosions may occur in many other esophageal diseases such as infections and pemphigus vulgaris. However, in a patient with clinical reflux disease, the presence of erosions is useful to separate patients into those with and without erosive disease. Patients with erosive esophagitis tend to have more complications and their symptoms are less easily controlled by medical therapy. Patients with clinical reflux disease who have no visible endoscopic abnormality fall into a designation of “non-erosive reflux disease” or NERD.

Biopsy Diagnosis of Reflux Esophagitis

The microscopic changes of squamous epithelial damage represent the presently used criteria for the biopsy diagnosis of reflux disease. A combination of dilated intercellular spaces, basal cell hyperplasia with increased expression of Ki67 by immunoperoxidase staining, increased height of papillary ridges and the presence of intraepithelial eosinophils are histologic features that are associated with reflux esophagitis.

Unfortunately, these morphologic changes in squamous epithelium are of little value in the practical diagnosis of reflux disease. All of these are relatively nonspecific general features of tissue injury rather than specific changes due to reflux. All of these can be seen in esophageal disease other than reflux, notably allergic (eosinophilic) esophagitis [24]. These diagnostic criteria are also not very sensitive; approximately 50 % of patients with symptomatic reflux will not have significant changes on biopsy of their squamous epithelium.

In essence, biopsy of the squamous epithelium has a very low predictive value for the diagnosis of reflux when positive histologic criteria are present. The absence of histologic criteria for reflux also has a very low predictive value for the absence of reflux. Therefore, in and of itself, biopsy of the squamous epithelium is therefore of little value in the evaluation of the patient with reflux disease.

Pathophysiologic Changes

An elegant series of in vitro studies by Tobey et al. [25] has provided excellent evidence of the cellular mechanism involved in acid-induced damage of the squamous epithelium. When the squamous epithelium is exposed to acid in high enough concentration for a sufficient length of time, damage occurs in a highly predictable and progressive manner. The severity and rate of progression of damage is dose-related.

The first visible morphologic change is a separation of the squamous cells due to disruption of the tight junctions between the cells. This is seen electron microscopically as “dilated intercellular spaces” as the earliest morphologic evidence of reflux. With increasing damage, the separation of the squamous cells increases and can easily be recognized by light microscopy in routine sections. The severity of the dilated intercellular spaces correlates with the severity of reflux.

The separation of squamous cells increases the permeability of the epithelium. As reflux-induced damage increases, the normally impervious epithelium becomes increasingly permeable. Luminal molecules of increasing size penetrate the squamous epithelium to an increasing depth [25]. Increased infiltration of luminal molecules into the squamous epithelium has the potential to produce numerous additional effects in the squamous epithelium apart from the morphologic injury.

- (a) Pain: With even mild damage, small molecules like acid (hydrogen ions/protons) can enter the epithelium and stimulate pain-sensitive nerve endings in the epithelium, resulting in “heartburn.” While acid is an extremely powerful pain inducer, other luminal molecules may also enter the damaged squamous epithelium and stimulate nerve endings resulting in discomfort. These other molecules are less effective than acid in causing pain because they are less noxious and larger in size. However, they may be the cause of continuing discomfort in the patients whose symptoms are not completely controlled with acid suppressive drug therapy.
- (b) Eosinophilic esophagitis: The entry of eosinophils into the epithelium is part of the usual pathologic change in reflux disease. This is likely the result of cell damage caused by acid, causing release of chemotactic cytokines

by the damaged cells which causes eosinophil migration into the epithelium [24, 26]. However, the absolute number of eosinophils in patients with reflux is usually small.

Eosinophilic esophagitis is considered to be an atopic type I hypersensitivity reaction of esophageal squamous epithelium to ingested allergens. In this condition, the squamous epithelium typically shows severe damage associated with numerous intraepithelial eosinophils. Atopy results from interaction of ingested allergens with sensitized IgE containing mast cells that are usually found in the lamina propria under the squamous epithelium. In normal epithelium, ingestion of allergens does not evoke the atopic response even in the sensitized individual because the allergen does not penetrate the squamous epithelium and is therefore sequestered from the effector mast cell. When the squamous epithelium is damaged by reflux, the allergen can enter and traverse the epithelium and interact with the mast cell. This causes mast cell degranulation and release of histamine and other cytokines that are extremely chemo-attractive to eosinophils, resulting in the massive intraepithelial eosinophil infiltrate that is typical of eosinophilic esophagitis [26].

As expected from this pathophysiology, eosinophilic (atopic) esophagitis can be treated effectively in many patients with acid suppressive drug therapy. PPIs have anti-inflammatory properties in addition to potent acid suppression and are highly effective in reversing the squamous epithelial damage caused by reflux and restoring the impermeable status of the normal esophageal epithelium. The allergen is therefore prevented access to the effector mast cell, preventing the atopic reaction.

(c) Columnar metaplasia: Entry of large molecules in the gastric juice into the esophageal squamous epithelium because of its increased permeability is the basic reason for columnar metaplasia. These large molecules, when they reach the proliferative and stem cell zone in the deeper part of the epithelium, can interact with cell surface receptors and have the potential to induce alterations in the genetic control mechanisms of the cells.

Cell surface and cytoplasmic receptors usually have complex tertiary structures that require complex complementary molecules for reaction. It is highly unlikely that receptors exist for simple particles like hydrogen ions (protons); acid is not a molecule that is likely to have the capability to cause cell receptor interactions that can result in genetic changes in the cell.

Columnar metaplasia of the esophagus results from the interaction of an unknown molecule in gastric contents that penetrates the damaged squamous epithelium, interacts with the basal region proliferative cells, and causes a switch in the genetic differentiating signal. This switch from the normal signal that dictates squamous differentiation to a new signal that includes BMP-4 (bone morphogenesis protein 4) induces columnar differentiation [27]. The proliferating cell in the deep part of the squamous epithelium, under the BMP-4 signal, differentiates into a columnar epithelium.

There is strong evidence that columnar metaplasia occurs early and is actually seen in most patients with chronic reflux disease [28].

Columnar metaplasia first occurs in the most distal esophagus where the damage to the esophagus is highest in reflux disease. This metaplastic columnar epithelium separates the esophageal squamous epithelium from the normal oxyntic mucosa that lines the proximal stomach, creating a histologic squamo-oxyntic gap [1]. The presence of this metaplastic columnar epithelium and the gap is an absolutely specific and an extremely sensitive marker for reflux disease.

With increasing reflux-induced damage of esophageal squamous epithelium, the amount of columnar metaplasia progressively increases and the squamo-oxyntic gap increases in length as the squamo-columnar junction (Z-line) moves cephalad. In the vast majority of patients with chronic reflux disease, a microscopic squamo-columnar gap with endoscopically invisible columnar metaplasia exists [1, 2]. The length of the squamo-oxyntic gap is lowest in autopsy specimens in patients without a history of reflux disease during life [19, 29]. When the disease becomes severe, the squamo-oxyntic gap becomes visible at endoscopy and is recognized as a visible columnar lined esophagus.

In almost all patients with chronic reflux disease, there are two epithelial types in the esophagus: normal squamous epithelium and metaplastic columnar epithelium. The extent (length) of the latter is directly proportional to the severity of cumulative life-long damage to the esophageal squamous epithelium by reflux [30]. The response of these two epithelial types to reflux is different.

As we treat reflux by altering the composition of the offensive agent (gastric contents) with acid suppressive drug therapy, we must be cognizant about how alkalinization of gastric contents impacts both squamous and columnar epithelia in the esophagus. At present, we do not do this; we concentrate on the great benefit produced in controlling squamous epithelial damage and completely ignore changes that result in the columnar epithelium.

One reason for this is that most physicians harbor the notion that columnar metaplasia does not exist until they can recognize it at endoscopy. This is false. The resolution of endoscopes, even with narrow band imaging and magnification, is too low to see the microscopic columnar epithelium that is present in all patients with chronic reflux disease. What the eye does not behold at endoscopy exists in the patient under the microscope [2]. To not recognize this is a fundamental error.

Effect of Acid Suppressive Drug Therapy on Squamous Epithelium

Acid in gastric contents is responsible for most if not all of the reflux-induced damage produced in the squamous epithelium of the esophagus.

It is probably true that if there was no acid in the stomach, reflux would not cause any damage. At lectures, we have been asked whether the use of acid suppressive agents from birth would prevent reflux-induced damage in the esophageal epithelium. The answer to this is probably affirmative.

Populations who have a high prevalence of *H. pylori* infection have a very low prevalence of reflux disease and GERD-induced adenocarcinoma [31]. This is most likely because the infection causes gastritis with atrophy with achlorhydria early in life and this protects the infected population against reflux disease. Unfortunately, there is a price that is paid in these populations; they have a high incidence of *H. pylori* induced gastric adenocarcinoma.

It is also not feasible to use acid suppressive drugs from early life to prevent reflux disease because gastric acid also has a vital function. In fact, the present long-term use of proton pump inhibitors for treatment of reflux disease has been reported to have significant side effects. Acid suppression with long-term proton pump inhibitor therapy has been reported to increase infections, notably *C. difficile* colitis [5], pneumonia; cause malabsorption of minerals like magnesium and calcium (increased risk of decreased bone density and hip fracture [4]); and produce drug interactions.

Suppressing gastric acid secretion is a highly effective method of treating squamous epithelial damage caused by reflux. In adequate dosage, proton pump inhibitors can maintain gastric pH above a pH of 4 for 12–14 h of the day [11]. At this level of alkalinization of gastric contents, the most potent molecule in the offensive agent in the causation of reflux damage of the squamous epithelium is effectively neutralized.

The most reliably reproducible effect of effective acid suppression in patients with reflux disease is healing of erosive esophagitis in over 90 % of patients, usually within a month of initiation of therapy. Continued acid suppression also prevents recurrence of erosive esophagitis, prevents progression of erosions to deeper ulcers, and markedly decreases the incidence of complex strictures of the esophagus. The practical effect of this change has been obvious; deep and intractable ulcers and fibrous strictures of the esophagus have become rare complications of GERD. This is a dramatic change from five decades ago when these complications were common and very difficult to treat.

The second positive effect of alkalinizing gastric contents with proton pump inhibitors is that it controls pain. Heartburn is reduced significantly in most patients because suppression of acid removes the most potent stimulator of pain-sensitive nerve endings. Control of heartburn improves the quality of life for most patients with reflux disease. The availability of proton pump inhibitors for treating reflux disease has in fact, dramatically decreased the misery index of reflux disease in the past five decades.

When investigated carefully however, acid suppression does not completely eradicate pain in many patients with reflux.

Approximately 30 % of patients continue to have significant pain and few are completely symptom free even with maximum and long terms proton pump inhibitor therapy.

This can be understood by the fact that proton pump inhibitor therapy does not actually stop or decrease reflux [32, 33]. Patients on PPIs continue to have reflux at the same frequency as before. The squamous epithelium is exposed to all the molecules in the refluxate except acid. In many patients whose symptoms persist despite adequate dosage of acid suppressive drugs, the continuing “weak-acid (pH 4–6)” reflux can still cause pain [34].

Effective control of pain in patients with reflux disease is probably most dependent on restoring the normal impermeable state of the squamous epithelium. It is only when this is achieved that the refluxed material in the lumen of the esophagus is kept completely away from the pain-sensitive nerve endings in the esophagus. The fact that some pain and discomfort frequently occurs despite acid suppression can be explained if the squamous epithelial permeability is not fully reversed. Non-acid molecules in the refluxate can also penetrate the epithelium and stimulate nerve endings to cause pain. While this may be at a lower level than acid-induced pain that was present before treatment was instituted, it is often still a source of significant discomfort. It is interesting that studies of symptomatic patients with “weak-acid reflux” show that successful anti-reflux surgery eradicates their pain [35].

Acid suppressive drug therapy is only directed against the acid in the offensive mixture of reflux disease. It does not address the fact that other molecules in the refluxate may continue to cause both symptoms and pathologic changes in the esophageal epithelium. It also does not correct or improve the damaged lower esophageal sphincter or decrease the number or frequency of reflux events [32, 33].

Study of patients treated with acid suppressive drug therapy will therefore show those elements of reflux disease that are poorly controlled: these include symptoms resulting from exposure of the epithelium to weak-acid reflux, regurgitation, and the progression of pathologic changes in the metaplastic columnar epithelium.

Effect of Acid Suppressive Drug Therapy on Metaplastic Esophageal Columnar Epithelium

Gastroesophageal reflux disease has changed its character over the past six decades. In the 1950s, reflux disease was defined almost entirely by its effects on squamous epithelium. The inability to control pain, ulceration, and strictures were the main problems. Approaches to address these issues sometimes require even esophagectomy. The pharmaceutical industry subsequently stepped up to the plate, developing increasingly potent drugs to control acid secretion, which

have proved to be highly successful in controlling pain, ulcers, and strictures.

Columnar metaplasia of the esophagus was common in the 1950s. Examination of detailed descriptions of columnar lined esophagus by Barrett [35, 36] and Allison and Johnstone [37] shows that many patients had extremely long segments of columnar lined esophagus. In fact, evidence suggests that the very long segments of columnar lined esophagus that were common in the 1950s are increasingly rare today. It would be expected that effective acid suppression used early in patients with symptomatic reflux disease would decrease columnar metaplasia of squamous epithelium.

The biggest and most dramatic change in the last six decades has been the explosion in the incidence of intestinal metaplasia and adenocarcinoma within the columnar lined esophagus. In the 1950s, histologic descriptions of the epithelium show that intestinal metaplasia defined by the presence of goblet cells was very uncommon even in very long segments of columnar lined esophagus [35, 37]. Adenocarcinoma was so rare that single cases were reported. The first case was reported in 1952 by Morson and Belcher [38]. Allison and Johnstone's 1953 paper had the second case [37].

Today, Barrett's esophagus, defined as intestinal metaplasia in a biopsy taken from visible columnar lined esophagus, is present in an estimated 5–10 % of adults in the population [39]. If symptomatic patients with normal endoscopy are biopsied, intestinal metaplasia is found in up to 25 % of patients in some studies [40]. The increase in the prevalence of intestinal metaplasia in the population from 1950 to 2012 has been astounding.

Similarly, the incidence of esophageal adenocarcinoma has shown an increase not seen for any other human cancer type in human history over such a short period. From the first reported case in 1952, the incidence has increased exponentially. In 1982, Rodger Haggitt declared esophageal adenocarcinoma “an epidemic” [41]. From 1975 to 2003, the incidence of esophageal adenocarcinoma increased six-fold [42]. In 1995, the incidence of adenocarcinoma of the esophagus overtook that of esophageal squamous carcinoma in the USA [42]. Today, I see adenocarcinoma of the esophagus ten times more frequently than squamous carcinoma. Of the 16,000 patients who developed esophageal carcinoma in 2010, it is likely that 90 % (over 14,000) were adenocarcinomas. When adenocarcinoma of the gastroesophageal junctional region and gastric cardia (which are, in reality adenocarcinomas of the distal esophagus [43] and so classified by the AJCC 7th edition [44]) are added to this number, an astonishing 20,000 people in the USA developed adenocarcinoma in 2010. The number is still increasing in an incidence curve that is still upward. A sobering thought is that, with an overall mortality of 85 %, esophageal adenocarcinomas are responsible for the death of nearly 17,000 people every year in the USA alone.

Barrett's esophagus and esophageal adenocarcinoma are solely the result of gastroesophageal reflux disease. There is no other cause for either of these entities despite some associations with obesity and smoking.

Despite what must be the most dramatic increase in the mortality from a single cancer type in the history of medicine, there has been little or no attempt to address this problem by the medical community at large. The treatment of reflux disease is still aimed at controlling heartburn and healing erosive esophagitis with acid suppressive drugs. While this goal has been met and the medical community declares self-satisfied success at the wonder of their drugs and their ability to control reflux disease and improve quality of life, the number of people dying from cancer that is the complication of reflux disease is increasing exponentially.

As pathologists, we tend to view every disease from a different viewpoint. To us, the criterion of success of treatment of any disease is the mortality rate from that disease. By that criterion, the treatment of reflux disease rivals the worst failures in the history of medicine. From having an occasional death resulting from intractable ulceration or hemorrhage in the 1950s, reflux disease in 2010 is responsible for approximately 17,000 deaths from adenocarcinoma in the USA and many more in Europe.

The goal of a treatment of a disease should be to prevent death at all costs; everything else is secondary. The present treatment algorithms for reflux disease have as their goal the improvement of the quality of life of millions of people who have heartburn caused by reflux. This is an easy goal to achieve but should not be mistaken for an attempt at preventing cancer in the many thousands of patients every year. It is merely the treatment of the squamous manifestations of the disease when the development of cancer is in fact a disease of the columnar metaplastic epithelium.

We need to set a new goal for patients with reflux disease. We need to tell ourselves that our primary goal in this disease is to prevent cancer and death. When we do this, we will stop ignoring the columnar lined esophagus; rather we will focus on it with all the technology that is available.

Metaplastic Esophageal Columnar Epithelial Types

The change in the differentiating genetic signal from the postulated Wnt to BMP-4 in the proliferating cells of the esophageal epithelium results in the transformation of the stratified squamous epithelium to a columnar epithelium composed entirely of undifferentiated mucous cells. These cells line the surface and form a foveolar pit and glands, all composed of morphologically similar mucous cells. This is *cardiac epithelium* which is defined as an epithelium composed entirely of mucous cells without parietal or goblet cells [45].

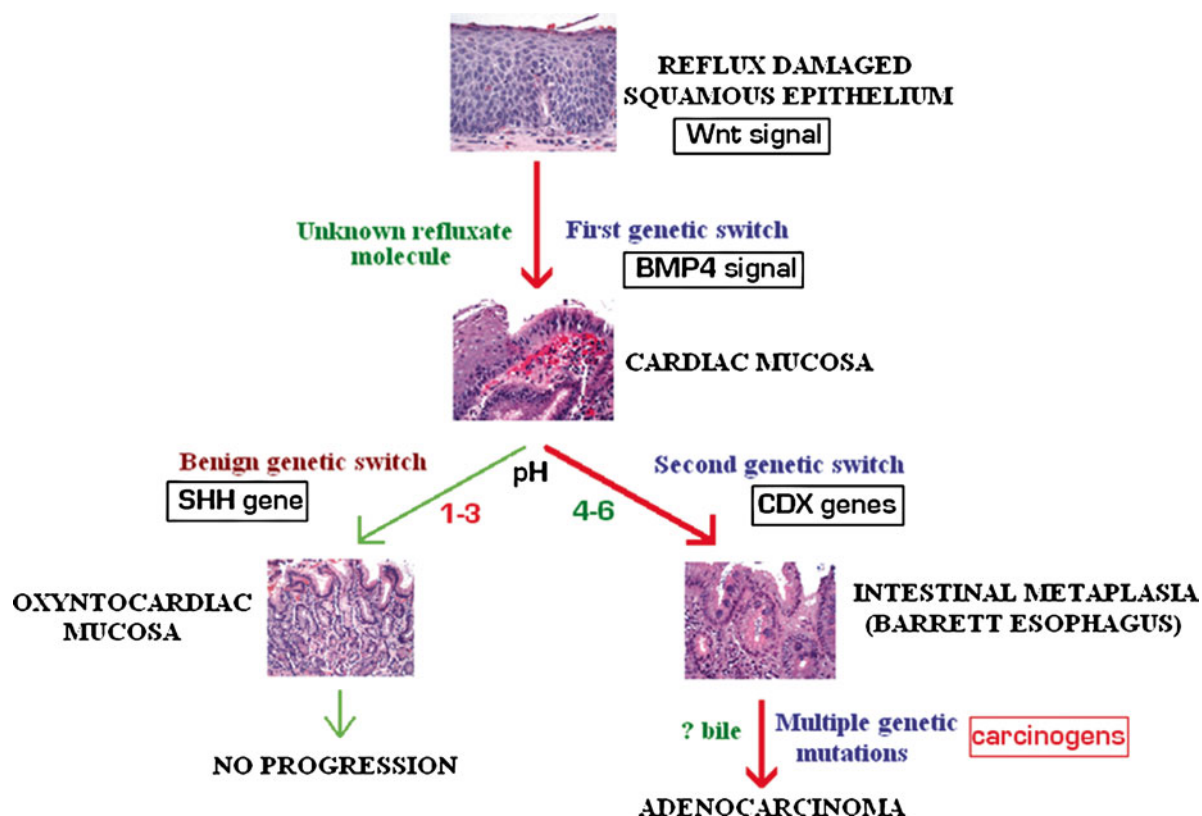


Fig. 2.2 Sequence of epithelial changes in the esophagus caused by reflux disease. In the initial step, squamous epithelium undergoes columnar metaplasia to cardiac mucosa. The cardiac mucosa then evolves in one of two directions: (a) in a strong acid milieu, Sonic Hedgehog gene is

activated leading to parietal cells and oxyntocardiac mucosa. This is a stable epithelium that does not progress to cancer. (b) In a weaker acid milieu, CDX2 is activated and intestinal metaplasia results

Cardiac epithelium has also been called “junctional epithelium” and “mucous-cell only epithelium.”

Cardiac epithelium is subjected to attack by gastric contents as a result of continuing reflux disease. As a result, it has the potential to evolve into two other significant epithelial types within the columnar lined esophagus—oxyntocardiac and intestinal epithelia [46]. These are defined by the presence of parietal cells and goblet cells. Figure 2.1 Many other differentiated cell types can be seen in metaplastic esophageal columnar epithelium—neuroendocrine cells, pancreatic cells, chief cells, Paneth cells, ciliated cells. At present, these cell types have no known significance and are pretty much ignored in the definition of the three basic types of metaplastic epithelia.

The first type of change in cardiac mucosa occurs as a result of development of parietal (oxyntic) cells within its glands (Fig. 2.2). The presence of parietal cells in cardiac mucosa converts the epithelium to *oxyntocardiac epithelium*. This is defined as a columnar epithelium where the glands contain a mixture of mucous cells and parietal cells. It does not have goblet cells. Like the cardiac metaplasia of squamous epithelium resulted from a genetic switch, oxyntocardiac mucosa is generated in cardiac mucosa by activation of

a different differentiating genetic signal—possibly a combination of BMP-4 and the Sonic Hedgehog gene [47]. Sonic hedgehog gene is the usual genetic signal in the gastric oxyntic mucosa and is required for development of parietal cells in gastrointestinal columnar epithelia [48]. Oxyntocardiac epithelium has also been called “gastric fundic-type epithelium” and “mixed mucous and parietal cell epithelium.”

The second type of change in cardiac epithelium occurs as a result of development of goblet cells which can appear in the surface, foveolar region, or in the glands. This is *intestinal metaplastic epithelium* (Fig. 2.2). Intestinal epithelium is generated in cardiac mucosa by activation of yet another different differentiating genetic signal—the homeobox gene complex that includes CDX2 [8, 49]. CDX2 is the usual genetic signal in the intestine with CDX2 being dominant for colonic differentiation [50]. Intestinal epithelium in the esophagus has also been called “specialized columnar epithelium” or “Barrett’s Esophagus.”

These three columnar epithelia are the only significant columnar epithelial types that occur in the esophagus. Because the criteria for their definition are simple (based on the presence or absence of three easily recognizable cell type: mucous cells, parietal cells, and goblet cells), their

identification in biopsies is easy, precise, and accurate with little inter-observer variation after minimal training.

Together, various combinations of these three columnar epithelial types comprise the entire pathologic metaplastic gap that results from columnar metaplasia of squamous epithelium [1, 40]. Because this process requires two steps (damage to squamous epithelium with increased permeability and a cellular reaction between molecules in gastric contents and esophageal epithelium that produces highly specific changes in differentiating genetic signals), the presence of any or all these epithelia are absolutely specific for reflux disease.

We therefore have a new definition of reflux disease at a cellular level: *Reflux disease is the presence of a gap between esophageal squamous epithelium and gastric oxyntic mucosa composed of any combination of cardiac, oxyntocardiac and intestinal epithelia.* This is the squamo-oxyntic gap [1]. This definition is 100 % specific for reflux disease; columnar metaplasia does not occur in any other esophageal disease. Having a precisely reproducible definition of reflux disease based on examination of routine biopsy specimens taken at endoscopy has enormous value.

Of the three types of metaplastic columnar epithelium in the esophagus, the only epithelium that is at risk for progression to dysplasia and adenocarcinoma is intestinal epithelium [51]. This defines Barrett esophagus. Patients who have intestinal metaplasia in a biopsy taken from a visible columnar lined esophagus are estimated to have a risk of future cancer of ~0.5 % per year.

Present guidelines for biopsy at endoscopy do not emphasize a complete examination of the epithelium between the Z-line and gastric oxyntic mucosa. Biopsies are not recommended for patients who do not have a visible columnar lined esophagus. This results in early changes of GERD limited to the dilated distal esophagus being ignored [2]. In patients with a visible columnar lined esophagus, biopsies stop at the proximal limit of rugal folds, thereby missing the pathology in the dilated distal esophagus.

The Amount (Length) of the Squamo-Oxyntic Gap

From its normal length of zero cm, the squamo-oxyntic gap progressively increases in length in patients with reflux disease due to increasing amounts of columnar metaplasia of their squamous epithelium. Columnar metaplasia is usually a “permanent” change. Once it has occurred, reversal will not usually occur unless there has been a significant treatment induced alteration such as ablation of the epithelium. Although minor decreases in the presence of goblet cell metaplasia have been reported with therapy, neither acid suppressive drug therapy nor successful anti-reflux surgery reliably reverses

columnar metaplasia. As such, the squamo-oxyntic gap changes in only one direction—increase in length.

In autopsy studies of people who have died without symptoms of reflux disease during life, the squamo-oxyntic gap varies from zero to less than 1 cm [19, 29]. If assessed by measured biopsies distal to the endoscopic gastroesophageal junction in patients with heartburn undergoing endoscopy, the gap is usually also less than 1 cm. This gap is limited to the *dilated distal esophagus* that is often mistaken for proximal stomach by present endoscopic criteria [2]. When a visible columnar epithelium is present, the squamo-oxyntic gap is equal to the length of the endoscopically visible columnar segment (measured by the Prague criteria [52]) plus the endoscopically invisible area within the dilated distal esophagus [1, 17].

The measured length of the squamo-oxyntic gap is an accurate measure of cumulative reflux damage to squamous epithelium during life. Because further metaplasia is prevented by acid suppression, the length of the gap usually remains constant after the first endoscopy because patients who have a visible columnar lined esophagus are almost invariably placed on acid suppressive drug therapy.

The length of the squamo-oxyntic gap at first presentation is an exquisitely accurate measure of the severity of reflux. Oberg et al. [53] from our unit showed that the presence of cardiac and/or oxyntocardiac mucosa in biopsies of endoscopically normal patients compared with their absence correlated significantly with a greater likelihood of an abnormal 24-h pH test and lower esophageal sphincter abnormalities. In a study of pediatric patients at Harvard, Glickman et al. [54] showed that children who had greater than 1 mm of measured cardiac mucosa between the squamous epithelium and the first observed parietal cell had significantly greater evidence of reflux than those with less than 1 mm of cardiac mucosa. The presence of cardiac mucosa is therefore sensitive to within a measurement of 1 mm. Chandrasoma et al. [30] showed that there was a hugely significant difference in the amount of reflux as measured by a 24-h pH test in patients with a squamo-oxyntic gap that was greater than 20 mm (2 cm) compared with lengths less than 20 mm.

Based on this evidence we can now accurately define the severity of chronic life-long reflux in a patient by pathologic criteria. *Severity of reflux disease is defined by the length of the squamo-oxyntic gap.* Based on this, we recognize the following grades of severity of reflux disease:

Mild reflux disease: Endoscopically normal; squamo-oxyntic gap less than 1 cm limited to the dilated distal esophagus; with heartburn (mild symptomatic reflux disease) or without heartburn (asymptomatic reflux disease).

Moderate reflux disease: Endoscopically visible columnar lined esophagus; squamo-oxyntic gap of 1–2 cm; with heartburn

(moderate symptomatic reflux disease) or without heartburn (asymptomatic moderate reflux disease).

Severe reflux disease: Endoscopically visible columnar lined esophagus; squamo-oxyntic gap of greater than 2 cm; with heartburn (severe symptomatic reflux disease) or without heartburn (asymptomatic severe reflux disease).

This new grading system is of great value because it rates reflux disease by chronic, irreversible changes in columnar epithelium that may ultimately result in adenocarcinoma. Unlike the present Los Angeles system for grading the severity of reflux disease which is based on reversible squamous epithelial changes, this system uses chronic changes in GERD and will demonstrate an uncomfortable truth: *reflux disease defined by the squamo-oxyntic gap is a chronic irreversible change that is not improved by medical therapy.*

Distribution of Columnar Epithelia in the Squamo-Oxyntic Gap

The three types of columnar epithelium in the squamo-oxyntic gap show infinite variation. Oxyntocardiac epithelium is present in all people. At autopsy in people without reflux and in patients with an oxyntic gap of less than 1 cm, oxyntocardiac epithelium is often the only columnar epithelium in the gap [19]. In patients with an oxyntic gap that is 1–2 cm (moderate reflux disease), cardiac epithelium is almost always present in the gap [40].

Intestinal metaplasia is present in the squamo-oxyntic gap in a minority of patients. The prevalence of intestinal metaplasia varies with the length of the squamo-oxyntic gap; the longer the gap, the greater the prevalence of intestinal metaplasia [40]. In the new millennium, intestinal metaplasia is present in 90 % of patients with a gap exceeding 3 cm and 100 % of patients when the gap exceeds 5 cm [1, 40].

The most dramatic historical change in reflux disease is in the prevalence of intestinal metaplasia in the squamo-oxyntic gap. In the 1950s intestinal metaplasia was rare even in long segments of columnar lined epithelium [35, 37]. In Paull et al.'s mapping study of 1976 [55], intestinal metaplasia was more prevalent than in the 1950s, but much less than at the present time. In 1994, Spechler et al. [56] reported a prevalence of 19.4 % of intestinal metaplasia in patients with visible columnar lined epithelium less than 2 cm in length. In our study from 2003, intestinal metaplasia was present in 70 % of patients with a squamo-oxyntic gap of 1–2 cm [40]. It should be noted that endoscopically visible columnar epithelium in the esophagus is shorter than the actual histologic squamo-oxyntic gap, making this difference highly significant. These data provide powerful evidence that the prevalence of intestinal metaplasia in columnar epithelium has increased greatly in the past 60 years. This increase is very likely to be

the most likely basis for the increased incidence of adenocarcinoma in patients with reflux disease.

Mapping studies of the squamo-oxyntic gap shows that the three epithelia are distributed in a remarkably non-random and constant manner [57]. Oxyntocardiac epithelium dominates the distal part of the gap. If intestinal metaplasia is present, it is almost always present in the most proximal region of the gap immediately adjacent to the squamo-columnar junction. When present, the amount of intestinal metaplasia varies greatly in different patients. In some patients intestinal metaplasia is limited to the most proximal region of the gap; in others, the intestinal metaplasia extends distally to involve an increasing part of the gap. The involvement is usually contiguous without skip areas. In a few patients, intestinal metaplasia is present in the entire gap but there is usually non-intestinalized cardiac and oxyntocardiac mucosa in the most distal part of the gap separating intestinal from gastric oxyntic mucosa.

Cause of Intestinal Metaplasia in Columnar Epithelia

The distribution of intestinal metaplasia in the columnar epithelium provides insight as to its causation (Fig. 2.3).

All changes that occur in the esophagus except intestinal metaplasia tend to be maximal in the distal esophagus. The reason for this is easy to understand; the concentration of all injurious molecules is greatest in the distal esophagus and decreases from distal to proximal. For this reason, most injuries like erosions and columnar metaplasia are maximal distally.

The only thing that increases from distal to proximal in the esophagus is the pH (i.e., the concentration of hydrogen ions decreases from distal to proximal). Reflux of acid gastric contents into the esophagus creates a pH gradient from baseline gastric pH (normally 1–2) in the most distal esophagus to neutral (pH 7) at the height of the column of reflux.

The fact that the prevalence of intestinal metaplasia increases as the length of columnar lined esophagus increases and the fact that intestinal metaplasia always begins in the proximal region adjacent to the squamous epithelium is powerful evidence that intestinal metaplasia is favored in a pH environment that is closer to neutral (pH 4–7) (Fig. 2.3). Stated in another way, CDX2 activation is favored in a higher than lower pH milieu [49].

In contrast, the fact that oxyntocardiac epithelium occurs in the most distal region of the squamo-oxyntic gap suggests that Sonic Hedgehog gene activation and development of parietal cells in cardiac mucosa is favored by a strong acid milieu.

The concept of evolution of cardiac epithelium in two directions based on the pH milieu of the esophagus has logic in its favor [47]. In the gastrointestinal tract, CDX genes are normally expressed in the small and large intestine which are

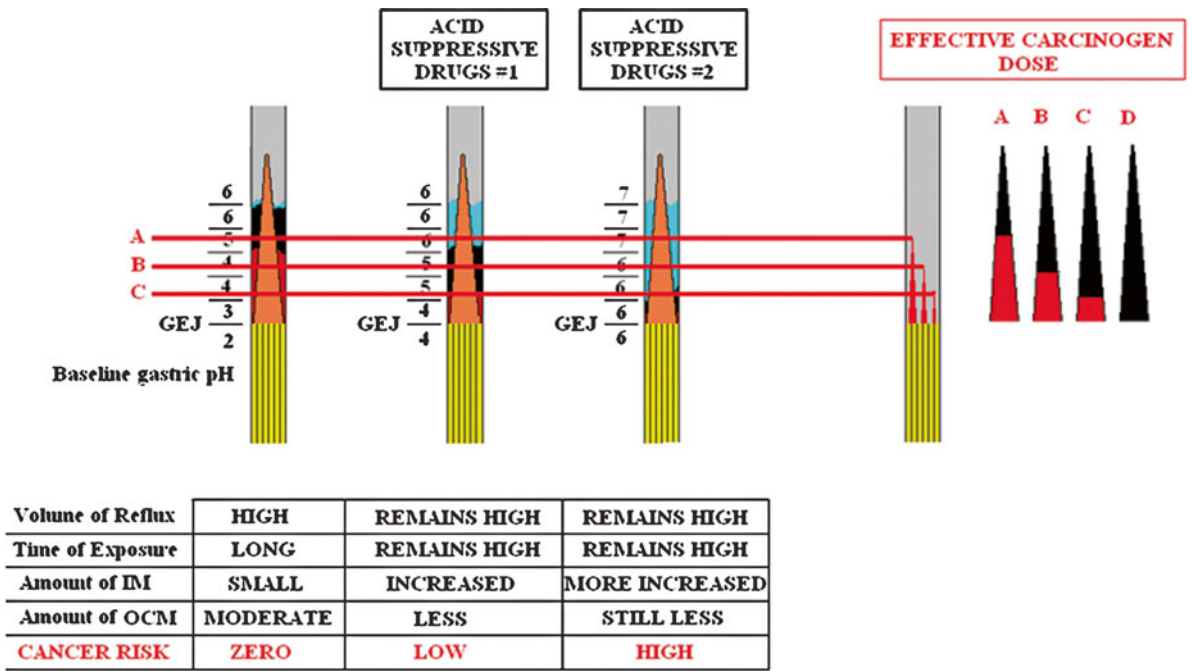


Fig. 2.3 Theoretical representation of a patient with severe reflux disease. During a reflux episode, a column of gastric contents is propelled into the esophagus, setting up a gradient of decreasing volume and increasing pH in the esophagus. The reflux has caused columnar metaplasia in the esophagus. If one assumes that intestinal metaplasia occurs in cardiac mucosa at pH 6, it can be seen that the extent of intestinal metaplasia progressively increases from normal (left) to partially

acid suppressed with baseline gastric pH 4 (center) to severely acid suppressed with baseline gastric pH 6 (right). The three horizontal red lines indicate the effective carcinogen dose delivered to the esophagus by reflux in three patients with different carcinogen levels. It can be seen that the risk of carcinoma increases with increasing acid suppression because the interaction between the target epithelium (intestinal metaplasia) and carcinogen increases

high pH environments [50]. In the normal stomach, a low pH environment, Sonic Hedgehog gene is active [48]. In patients with atrophic chronic gastritis, a disease process that destroys parietal cells and decreases gastric acidity (i.e., increases pH), CDX2 is activated and results in intestinal metaplasia [58].

The fact that intestinal metaplasia in columnar lined esophagus is promoted by a pH in the 4–7 range has profound implications. The therapeutic goal of treating reflux disease with acid suppressive drugs is to alkalinize gastric contents to the pH 4–7 range over a large part of the 24 h period [3, 11]. The alkalinization of gastric juice in patients on acid suppressive drug therapy means that the esophageal pH gradient that is produced when reflux occurs is shifted. Instead of the gradient ranging from pH 1–2 in the distal esophagus to 7 at the height of the reflux column, the distal esophagus in the patients on proton pump inhibitor therapy is the altered baseline gastric pH which is over 4. The entire esophagus is now at a pH of 4–7.

This may well explain the greater extent of intestinal metaplasia today than existed in the past (Fig. 2.3). In a mapping study of ten esophagectomy cases in 2007, we showed that intestinal metaplasia extended from the top of the columnar lined segment all the way into the dilated distal

esophagus [17]. This contrasts with the mapping data of Paull et al. [55] where patients with long segments of columnar lined esophagus either had no intestinal metaplasia or intestinal metaplasia limited to the proximal part of the segment. The distal 3–4 cm of the segment in Paull et al. consisted of cardiac and oxyntocardiac epithelia [55].

The goal of treating reflux with acid suppressive drugs is to alkalinize gastric juice; the unintended consequence of this is that the esophagus is exposed to alkalinized material during reflux. This results in increased prevalence and extent of intestinal metaplasia in the columnar lined segment.

Carcinogenesis in Columnar Lined Esophagus

The only epithelium in the esophagus that is susceptible to carcinogenesis is intestinal epithelium [51]. Squamous, cardiac, and oxyntocardiac epithelia do not develop cancer.

Oxyntocardiac epithelium is particularly immune to cancer because it does not develop intestinal metaplasia [28]. It is therefore a stable epithelium that is highly desirable because it is resistant to acid, carcinogens, and agents in the gastric contents that induce intestinal metaplasia. Cardiac epithelium is

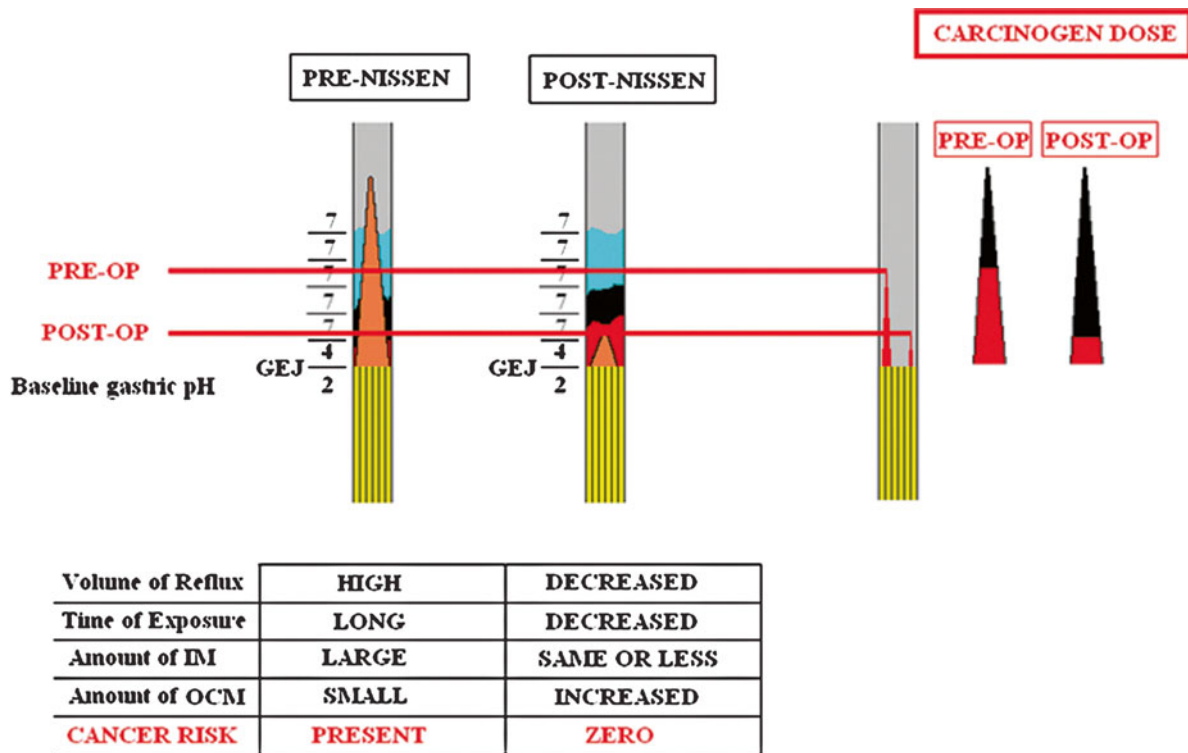


Fig. 2.4 Similar diagram of a patient with severe reflux and a long segment of columnar lined esophagus with intestinal metaplasia limited to the proximal region. Pre-operatively, carcinogen is delivered to the intestinal metaplastic region by the severe reflux. After Nissen

fundoplication, the reflux has decreased and effective carcinogen delivery is limited to the distal esophagus, never reaching the level of intestinal metaplasia. This would theoretically reduce the risk of carcinoma

also resistant to acid and carcinogens but can transform into intestinal metaplasia [28]. There is a time lag of many years between the occurrence of cardiac metaplasia and intestinal metaplasia. Children with reflux disease often develop cardiac mucosa but intestinal metaplasia only rarely develops before the third decade of life [59]. In patients who have undergone esophagectomy, cardiac mucosa commonly develops proximal to the anastomotic line. In some patients, intestinal metaplasia occurs in the cardiac mucosa, often many months to years later [60].

The carcinogen that induces oncogenic changes in esophageal intestinal metaplasia is uncertain. There is some evidence that it is a derivative of bile salts/acids that enters the stomach via duodeno-gastric reflux. Carcinogenesis is likely to be largely dependent on the concentration of carcinogen in the gastric contents. Because this cannot be measured, the risk of cancer in reflux cannot be accurately assessed. A patient who has no carcinogen will never develop cancer irrespective of any condition in the esophagus. A patient with a high carcinogen level can develop cancer only if there is intestinal metaplasia in the esophagus.

The carcinogen is delivered to the esophagus by reflux. As with all other molecules that are refluxed into the esophagus, the highest concentration of carcinogen is in the distal

esophagus and progressively decreases from distal to proximal [61]. The distal esophagus is therefore at greatest risk for cancer development (Figs. 2.3 and 2.4). However, the carcinogen acts only on intestinal epithelium. This must mean that the risk of adenocarcinoma increases significantly as the distal part of the columnar lined esophagus becomes intestinalized. The role played by alkalization of gastric contents with acid suppressive drugs in increasing the extent of intestinal metaplasia in the esophagus would therefore promote carcinogenesis in reflux (Fig. 2.3).

The most common location of reflux-induced adenocarcinoma is in the distal part of the intestinal metaplasia within the columnar lined segment near the junction of intestinal epithelium and non-intestinalized cardiac mucosa [62]. In the 1950s, adenocarcinoma was rare because intestinal metaplasia was rare and when it was present it was limited to the most proximal region of long segments of columnar lined esophagus, commonly in the mid-esophagus [37, 38]. Theoretically, carcinogen concentration in this proximal region was sufficient only if the patient had a very high carcinogen level. With increasingly effective alkalization by drugs, the location where adenocarcinoma occurs has moved increasingly to the more distal part of the esophagus. This is the result of extension of intestinal metaplasia into lower

regions of the columnar lined esophagus as a result of alkalinization of the refluxate [61].

At the present time, cancer risk is defined by the presence of intestinal metaplasia in the columnar lined esophagus. No effort is made to stratify risk in the patients with intestinal metaplasia by mapping the extent of intestinal metaplasia and the proximity of intestinal metaplasia to the distal esophagus. It can be predicted that the patients who have more reflux (i.e., a longer squamo-oxyntic gap) with its attendant higher carcinogen exposure, more intestinal metaplasia and extension of intestinal metaplasia to the more distal esophagus where carcinogen concentration is highest are at the greatest risk for cancer. If the prevalence and extent of intestinal metaplasia is promoted by alkalization of gastric juice, the use of drugs that suppress or neutralize acid may be responsible for at least some of the increased incidence of Barrett esophagus and adenocarcinoma that has been seen in the past six decades [61].

Effect of Anti-reflux Surgery on Esophageal Epithelia

Anti-reflux surgery typically consists of some type of fundoplication which artificially augments the function of the damaged lower esophageal sphincter. The most common operation is a Nissen fundoplication, which is a complete wrap of the gastric fundus around the distal esophagus, commonly with a crural repair. Partial fundoplications that produce a lesser sphincter augmentation than a Nissen are also used. Lesser procedures than surgical fundoplication are available as anti-reflux procedures. Endoscopic fundoplication has been attempted but not with sustained success. The only procedure presently being used is the transoral incisionless fundoplication which has had limited success in a small number of patients. A newer technique is LINX, a magnetic ring placed laparoscopically around the distal esophagus to augment sphincter function.

At the present time, anti-reflux surgery is recommended only to improve the quality of life in patients with GERD who fail to achieve adequate symptom control with maximum doses of acid suppressive drugs. As such, patients who undergo surgery are likely to be those with the greatest damage to their sphincter. Anti-reflux surgery is presently not recommended as a cancer-preventive surgery for patients with Barrett's esophagus.

Anti-reflux surgery differs fundamentally from medical therapy with acid suppressive drugs in that it addresses the cause of reflux. By restoring or augmenting sphincter function, surgery not only prevents acid from reaching the esophagus; it prevents reflux and sequesters the esophagus from all molecules in the gastric contents (Fig. 2.4).

At the present time, the success or failure of anti-reflux surgery is defined by:

- (a) Symptom relief and improvement of quality of life: This is a low bar to achieve by anti-reflux surgery. In general, anti-reflux surgery controls symptoms in approximately 85 % of patients who have failed medical therapy. A relatively small reduction in the exposure of the esophageal epithelium to refluxate can probably achieve this objective.
- (b) The ability of the patient to withdraw from proton pump inhibitor therapy: Approximately 30 % of patients require continued proton pump inhibitor therapy after anti-reflux surgery. This is commonly regarded as a failed surgery. However, it is known that many patients are placed on drug therapy without certainty that the symptoms are caused by reflux, suggesting that being on drug treatment after surgery does not equate to failure of the operation.
- (c) Normalization of the 24-h pH test: Post-operative 24-h pH testing is rarely undertaken in patients after anti-reflux surgery outside academic centers and in patients where the objective of symptom control has been met. In general, normalization of the 24-h pH test is a criterion for success of surgery that is more difficult to achieve than symptom control. Nissen fundoplication has a 75-85 % probability of normalizing the 24-h pH test. Initial studies with LINX suggest that patients with early reflux disease have a high rate of success in controlling symptoms as well as normalizing the 24-h pH test. It is likely that the success of fundoplication will be greater if the operation is done earlier in the course of the disease where sphincter damage is less.
- (d) Cessation of all reflux: While complete cessation of reflux with a totally flat line on a 24-h pH study is achieved in some patients after a fundoplication, this is not the stated objective for this surgery.
- (e) Regression or prevention of progression of histologic changes: Anti-reflux surgery is as or more successful than the best medical therapy in reversing and preventing histologic changes in squamous epithelium caused by reflux. This is usually measured as control of heartburn and healing and prevention of erosive esophagitis. The effect of anti-reflux surgery on the histologic composition of columnar epithelium has not been studied adequately. Oberg et al. [63] reported a series of 69 patients with columnar lined esophagus without intestinal metaplasia who were treated with either long-term proton pump inhibitor therapy or anti-reflux surgery. On follow-up, 80 % of 49 patients who were treated medically developed intestinal metaplasia at 8 years, significantly higher than 40 % of 20 patients treated by anti-reflux surgery after 16 years. This suggests that

anti-reflux surgery has a protective effect, at least compared with proton pump inhibitor therapy, in preventing progression of cardiac mucosa to Barrett esophagus. The significant number of patients developing Barrett esophagus after surgery indicates that the protection is incomplete but could be explained by less than complete cessation of reflux after surgery.

Anti-reflux surgery has been shown to reverse intestinal metaplasia in the columnar lined esophagus in patients with Barrett esophagus. This occurs uncommonly in patients with long segment Barrett esophagus, but was reported in 73 % of patients with intestinal metaplasia limited to a dilated distal esophagus [64, 65].

The most important question is whether anti-reflux surgery can prevent progression of reflux disease and particularly reflux disease complicated by Barrett's esophagus to adenocarcinoma. Several small individual studies with prolonged follow-up have shown that patients with non-dysplastic Barrett's esophagus were shown to remain stable without progression to high grade dysplasia and cancer after fundoplication [64, 65]. In a controlled study by Parrilla et al. [66], the protective effect of anti-reflux surgery was seen only in those patients who normalized their 24-h pH study after the surgery. In patients who did not normalize their 24-h pH test, the incidence of cancer was not significantly less than patients who were treated with acid suppressive drug therapy without surgery.

Chang et al. [67], in a meta-analysis of the literature, showed that there was a significant cancer-preventive role for anti-reflux surgery when controlled and uncontrolled studies were combined. However, when only controlled studies were included, the data supporting such a role did not reach statistical significance, possibly because the number of these studies was small.

Lagergren et al. [68] reported that the odds ratio for adenocarcinoma in patients with Barrett's esophagus who had anti-reflux surgery was 12 times the general population, and concluded that surgery did not prevent cancer. However, in a prior epidemiologic study of a similar population, Lagergren et al. [69] showed that the odds ratio for adenocarcinoma was 43.5 times the general population in the most severely symptomatic GERD patients. If one recognizes that it is likely that anti-reflux surgery is performed in the most severe GERD patients, i.e., those with Barrett's, this study actually suggests that anti-reflux surgery may play a partially protective role against cancer in severe GERD patients.

In both Chang et al. [67] and Lagergren et al. [68], there is no reporting of the success or failure of the surgery in any objective way. The available data only shows that with fundoplications being performed with the objective of symptom control and without the aim of stopping reflux completely, it possibly has a partial cancer-preventive effect in patients with severe GERD and Barrett esophagus. Lagergren et al.

[70], in fact showed that one reason for failure of anti-reflux surgery to prevent adenocarcinoma may be persistent reflux after surgery, i.e., an ailed surgery.

Theoretically, if an anti-reflux surgical procedure can be refined to completely stop reflux, and if post-operative testing proves that this has indeed happened, the likelihood is that progression of columnar epithelial changes to cancer will be prevented. This is based only on the fact that carcinogenesis in metaplastic columnar epithelium in the esophagus is the result of luminal exposure of the target epithelium to oncogenic molecules in gastric contents delivered to it by reflux. If reflux is stopped completely and the required mutations for carcinogenesis have not occurred at the time of surgery, there is a near certainty that cancer will be prevented (Fig. 2.4).

The failure of studies to show that anti-reflux surgery does not conclusively prevent cancer in patients with GERD is likely due to the fact that surgery is not designed to achieve this objective and falls short of complete or even adequate control of reflux in many cases. When this failure is at a level where symptom control is achieved but carcinogens still bombard the target epithelium in the esophagus, we declare the procedure a success. A successful surgery defined by the achievement of symptom control is not necessarily a success in terms of cancer prevention. If we are to use anti-reflux surgery to prevent adenocarcinoma in patients with GERD, we must refine surgical technique to satisfy the objective of stopping reflux almost completely while maintaining the complication rate at a level that is acceptable.

References

1. Chandrasoma PT, Wijetunge S, DeMeester SR, Hagen JA, DeMeester TR. The histologic squamo-oxync gap: an accurate and reproducible diagnostic marker of gastroesophageal reflux disease. *Am J Surg Pathol*. 2010;34:1574–81.
2. Chandrasoma P, Wijetunge S, Ma Y, DeMeester S, Hagen J, DeMeester T. The dilated distal esophagus: a new entity that is the pathologic basis of early gastroesophageal reflux disease. *Am J Surg Pathol*. 2011;35:1873–81.
3. Katz PO, Ginsberg GG, Hoyle PE, Sostek MB, Monyak JT, Silberg DG. Relationship between intragastric acid control and healing status in the treatment of moderate to severe erosive oesophagitis. *Aliment Pharmacol Ther*. 2007;25:617–28.
4. Yu EW, Bauer SR, Bain PA, Bauer DC. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. *Am J Med*. 2011;124:519–26.
5. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. *Clostridium difficile*-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *Am J Gastroenterol*. 2012;107:1001–10.
6. Herbella FA, Vicentine FP, Silva LC, Patti MG. Postprandial proximal gastric acid pocket and gastroesophageal reflux disease. *Dis Esophagus*. 2012;25:652–5.
7. Kauer WK, Burdiles P, Ireland AP, Clark GW, Peters JH, Bremner CG, DeMeester TR. Does duodenal juice reflux into the esophagus of patients with complicated GERD? Evaluation of a fiberoptic sensor for bilirubin. *Am J Surg*. 1995;169:98–103.

8. Tamagawa Y, Ishimura N, Uno G, Yuki T, Kazumori H, Ishihara S, Amano Y, Kinoshita Y. Notch signaling pathway and Cdx2 expression in the development of Barrett's esophagus. *Lab Invest.* 2012;92:896–909.
9. Jürgens S, Meyer F, Spechler SJ, Souza R. The role of bile acids in the neoplastic progression of Barrett's esophagus – a short representative overview. *Z Gastroenterol.* 2012;50:1028–34.
10. Csendes A, Smok G, Burdiles P, Braghetto I, Castro C, Korn O. Effect of duodenal diversion on low-grade dysplasia in patients with Barrett's esophagus: analysis of 37 patients. *J Gastrointest Surg.* 2002;6:645–52.
11. Miner Jr P, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am J Gastroenterol.* 2003;98:2616–20.
12. DeMeester TR, Peters JH, Bremner CG, Chandrasoma P. Biology of gastroesophageal reflux disease: pathophysiology relating to medical and surgical treatment. *Annu Rev Med.* 1999;50:469–506.
13. Theodorou D, Ayazi S, DeMeester SR, Zehetner J, Peyre CG, Grant KS, Augustin F, Oh DS, Lipham JC, Chandrasoma PT, Hagen JA, DeMeester TR. Intraluminal pH and goblet cell density in Barrett's esophagus. *J Gastrointest Surg.* 2012;16:469–74.
14. Karam SM. Lineage commitment and maturation of epithelial cells in the gut. *Front Biosci.* 1999;4:286–98.
15. McClave SA, Boyce Jr HW, Gottfried MR. Early diagnosis of columnar lined esophagus: a new endoscopic diagnostic criterion. *Gastrointest Endosc.* 1987;33:413–6.
16. Sharma P, McQuaid K, Dent J, Fennerty B, Sampliner R, Spechler S, Cameron A, Corley D, Falk G, Goldblum J, Hunter J, Jankowski J, Lundell L, Reid B, Shaheen N, Sonnenberg A, Wang K, Weinstein W. A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago Workshop. *Gastroenterology.* 2004;127:310–30.
17. Chandrasoma P, Makarewicz K, Wickramasinghe K, Ma YL, DeMeester TR. A proposal for a new validated histologic definition of the gastroesophageal junction. *Hum Pathol.* 2006;37:40–7.
18. Shi L, Der R, Ma Y, Peters J, DeMeester T, Chandrasoma P. Gland ducts and multilayered epithelium in mucosal biopsies from gastroesophageal-junction region are useful in characterizing esophageal location. *Dis Esophagus.* 2005;18:87–92.
19. Chandrasoma PT, Der R, Ma Y, et al. Histology of the gastroesophageal junction: an autopsy study. *Am J Surg Pathol.* 2000;24:402–9.
20. Hayward J. The lower end of the oesophagus. *Thorax* 1961;16:36–41.
21. Odze RD. Unraveling the mystery of the gastroesophageal junction: a pathologist's perspective. *Am J Gastroenterol.* 2005;100:1853–67.
22. Tobey NA, Carson JL, Alkiek RA, et al. Dilated intercellular spaces: a morphological feature of acid reflux-damaged human esophageal epithelium. *Gastroenterology.* 1996;111:1200–5.
23. Genta RM, Spechler SJ, Kielhorn AF. The Los Angeles and Savary-Miller systems for grading esophagitis: utilization and correlation with histology. *Dis Esophagus.* 2011;24:10–7.
24. Rodrigo S, Abboud G, Oh D, DeMeester SR, Hagen JA, Lipham J, DeMeester TR, Chandrasoma P. High intraepithelial counts in esophageal squamous epithelium are not specific for eosinophilic esophagitis in adults. *Am J Gastroenterol.* 2008;103:435–42.
25. Tobey NA, Hosseini SS, Argore CM, Dobrucali AM, Awayda MS, Orlando RC. Dilated intercellular spaces and shunt permeability in non-erosive acid-damaged esophageal epithelium. *Am J Gastroenterol.* 2004;99:13–22.
26. Bhattacharya B, Carlsten J, Sabo E, Kethu S, Meitner P, Tavares R, Jakate S, Mangray S, Aswad B, Resnick MB. Increased expression of eotaxin-3 distinguishes between eosinophilic esophagitis and gastroesophageal reflux disease. *Hum Pathol.* 2007;38:1744–53.
27. Castillo D, Puig S, Iglesias M, Seoane A, de Bolós C, Munitiz V, Parrilla P, Comerma L, Poulsom R, Krishnadath KK, Grande L, Pera M. Activation of the BMP4 pathway and early expression of CDX2 characterize non-specialized columnar metaplasia in a human model of Barrett's esophagus. *J Gastrointest Surg.* 2012;16:227–37.
28. Chandrasoma P. Controversies of the cardiac mucosa and Barrett's esophagus. *Histopathol.* 2005;46:361–73.
29. Kilgore SP, Ormsby AH, Gramlich TL, et al. The gastric cardia: fact or fiction? *Am J Gastroenterol.* 2000;95:921–4.
30. Chandrasoma PT, Lokuhetty DM, DeMeester TR, et al. Definition of histopathologic changes in gastroesophageal reflux disease. *Am J Surg Pathol.* 2000;24:344–51.
31. Chow WH, Blaser MJ, Blot WJ, et al. An inverse relation between cagA+ strains of *Helicobacter pylori* infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res.* 1998;58:588–90.
32. Blonski W, Vela MF, Castell DO. Comparison of reflux frequency during prolonged multichannel intraluminal impedance and pH monitoring on and off acid suppression therapy. *J Clin Gastroenterol.* 2009;43:816–20.
33. Tamhankar AP, Peters JH, Portale G, Hsieh C-C, Hagen JA, Bremner CG, DeMeester TR. Omeprazole does not reduce gastroesophageal reflux: new insights using multichannel intraluminal impedance technology. *J Gastrointest Surg.* 2004;8:890–8.
34. Agrawal A, Roberts J, Sharma N, Tutuian R, Vela M, Castell DO. Symptoms with acid and nonacid reflux may be produced by different mechanisms. *Dis Esophagus.* 2009;22:467–70.
35. Barrett NR. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. *Br J Surg.* 1950;38:175–82.
36. Barrett NR. The lower esophagus lined by columnar epithelium. *Surgery.* 1957;41:881–94.
37. Allison PR, Johnstone AS. The oesophagus lined with gastric mucous membrane. *Thorax.* 1953;8:87–101.
38. Morson BC, Belcher BR. Adenocarcinoma of the oesophagus and ectopic gastric mucosa. *Br J Cancer.* 1952;6:127–30.
39. Rex DK, Cummings OW, Shaw M, Cumings MD, Wong RKH, Vasudeva RS, Dunne D, Rahmani EY, Helper DJ. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. *Gastroenterology.* 2003;125:1670–7.
40. Chandrasoma PT, Der R, Ma Y, Peters J, DeMeester T. Histologic classification of patients based on mapping biopsies of the gastroesophageal junction. *Am J Surg Pathol.* 2003;27:929–36.
41. Haggitt RC. Adenocarcinoma in Barrett's esophagus: a new epidemic? *Hum Pathol.* 1992;23:475–6.
42. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst.* 2005;97:142–6.
43. Chandrasoma PT, Wickramasinghe K, Ma Y, DeMeester TR. Adenocarcinomas of the distal esophagus and "gastric cardia" are predominantly esophageal adenocarcinomas. *Am J Surg Pathol.* 2007;31:569–75.
44. Rice TW, Blackstone EW, Rusch VW. 7th edition of the AJCC cancer staging manual: esophagus and esophagogastric junction. *Ann Surg Oncol.* 2010;17:1721–4.
45. Chandrasoma PT, DeMeester TR. Chapter 5: histologic definitions and diagnosis of epithelial types. In: Chandrasoma PT, DeMeester TR, editors. GERD: reflux to esophageal adenocarcinoma. San Diego: Academic; 2006. p. 89–106.
46. Chandrasoma PT, DeMeester TR. Chapter 9: the pathology of reflux disease at a cellular level: part 2 – evolution of cardiac mucosa to oxyntocardiac mucosa and intestinal metaplasia. In: Chandrasoma PT, DeMeester TR, editors. GERD: reflux to esophageal adenocarcinoma. San Diego: Academic; 2006. p. 169–200.

47. Yamanaka Y, Shiotani A, Fujimura Y, Ishii M, Fujita M, Matsumoto H, Tarumi K, Kamada T, Hata J, Haruma K. Expression of Sonic hedgehog (SHH) and CDX2 in the columnar epithelium of the lower oesophagus. *Dig Liver Dis.* 2011;43:54–9.
48. Feng R, Xiao C, Zavros Y. The role of Sonic Hedgehog as a regulator of gastric function and differentiation. *Vitam Horm.* 2012; 88:473–89.
49. Vallbohmer D, DeMeester SR, Peters JH, Oh DS, Kuramochi H, Shimizu D, Hagen JA, Danenberg KD, Danenberg PV, DeMeester TR, Chandrasoma PT. Cdx-2 expression in squamous and metaplastic columnar epithelia of the esophagus. *Dis Esophagus.* 2006;19:260–6.
50. Silberg DG, Swain GP, Suh ER, Traber PG. Cdx1 and Cdx2 during intestinal development. *Gastroenterology.* 2000;119:961–71.
51. Chandrasoma P, Wijetunge S, DeMeester S, Ma Y, Hagen J, Zamis L, DeMeester T. Columnar lined esophagus without intestinal metaplasia has no proven risk of adenocarcinoma. *Am J Surg Pathol.* 2012;36:1–7.
52. Vahabzadeh B, Seetharam AB, Cook MB, Wani S, Rastogi A, Bansal A, Early DS, Sharma P. Validation of the Prague C & M criteria for the endoscopic grading of Barrett's esophagus by gastroenterology trainees: a multicenter study. *Gastrointest Endosc.* 2012;75:236–41.
53. Oberg S, Peters JH, DeMeester TR, et al. Inflammation and specialized intestinal metaplasia of cardiac mucosa is a manifestation of gastroesophageal reflux disease. *Ann Surg.* 1997;226:522–32.
54. Glickman JN, Fox V, Antonioli DA, Wang HH, Odze RD. Morphology of the cardia and significance of carditis in pediatric patients. *Am J Surg Pathol.* 2002;26:1032–9.
55. Paull A, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RK. The histologic spectrum of Barrett's esophagus. *N Engl J Med.* 1976; 295:476–80.
56. Spechler SJ, Zeroogian JM, Antonioli DA, Wang HH, Goyal RK. Prevalence of metaplasia at the gastroesophageal junction. *Lancet.* 1994;344:1533–6.
57. Chandrasoma PT, Der R, Dalton P, Kobayashi G, Ma Y, Peters J, DeMeester T. Distribution and significance of epithelial types in columnar lined esophagus. *Am J Surg Pathol.* 2001;25:1188–93.
58. Barros R, Freund JN, David L, Almeida R. Gastric intestinal metaplasia revisited: function and regulation of CDX2. *Trends Mol Med.* 2012;18:555–63.
59. Hassall E. Columnar lined esophagus in children. *Gastroenterol Clin North Am.* 1997;26:533–48.
60. Dresner SM, Griffin SM, Wayman J, Bennett MK, Hayes N, Raimes SA. Human model of duodenogastro-oesophageal reflux in the development of Barrett's metaplasia. *Br J Surg.* 2003;90: 1120–8.
61. Chandrasoma PT, DeMeester TR. Chapter 10: the pathology of reflux disease at a cellular level: part 3 – Intestinal (Barrett) metaplasia to carcinoma. In: Chandrasoma PT, DeMeester TR, editors. *GERD: reflux to esophageal adenocarcinoma.* San Diego: Academic; 2006. p. 201–40.
62. Thiesen J, Stein HJ, Feith M, Kauer WK, Dittler HJ, Pirchi D, Siewert JR. Preferred location for the development of esophageal adenocarcinoma within a segment of intestinal metaplasia. *Surg Endosc.* 2006;20:235–8.
63. Oberg S, Johansson J, Wenner J, Johansson F, Zilling T, von Holstein CS, Nilsson J, Walther B. Endoscopic surveillance of columnar-lined esophagus: frequency of intestinal metaplasia detection and impact of antireflux surgery. *Ann Surg.* 2001;234: 619–26.
64. Hofstetter WL, Peters JH, DeMeester TR, Hagen JA, DeMeester SR, Crookes PF, Tsai P, Banki F, Bremner CG. Long-term outcome of antireflux surgery in patients with Barrett's esophagus. *Ann Surg.* 2001;234:532–8.
65. DeMeester SR, Campos GMR, DeMeester TR, Bremner CG, Hagen JA, Peters JH, Crookes PF. The impact of antireflux procedure on intestinal metaplasia of the cardia. *Ann Surg.* 1998;228: 547–56.
66. Parrilla P, deHaro LFM, Ortiz A, Munitiz V, Molina J, Bermejo J, Canteras M. Long term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. *Ann Surg.* 2003;237:291–8.
67. Chang EY, Morris CD, Seltman AK, O'Rourke RW, Chan BK, Hunter JG, Jobe BA. The effect of antireflux surgery on esophageal carcinogenesis in patients with Barrett esophagus: a systematic review. *Ann Surg.* 2007;246:11–21.
68. Lagergren J, Ye W, Lagergren P, Lu Y. The risk of esophageal adenocarcinoma after antireflux surgery. *Gastroenterology.* 2010; 138:1297–301.
69. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med.* 1999;340:825–31.
70. Lagergren J, Viklund P. Is esophageal adenocarcinoma occurring late after antireflux surgery due to persistent postoperative reflux? *World J Surg.* 2007;31:465–9.

Antireflux Surgery

Swanstrom, L.L.; Dunst, C.M. (Eds.)

2015, XV, 245 p. 170 illus., 85 illus. in color., Hardcover

ISBN: 978-1-4939-1748-8