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REVIEW

Pathogenesis of columnar-lined esophagus

Kamal E Bani-Hani, Bayan K Bani-Hani

Kamal E Bani-Hani, Bayan K Bani-Hani, Department of Surgery, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan
Correspondence to: Kamal E Bani-Hani, Professor of Surgery, Chairman of Department of Surgery, Faculty of Medicine, Jordan University of Science and Technology, PO Box 3030, Irbid 22110, Jordan. banihani60@yahoo.com
Telephone: +962-2-7060200 Fax: +962-2-7095010
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Abstract

Since its initial description, the pathogenesis of the columnar-lined esophagus (CLE) has been surrounded by many controversies. The first controversy is related to the existence of the condition itself. The second controversy centers on whether the CLE is a congenital or an acquired condition. In this article, we review the congenital and acquired theories of development of CLE and discuss the various factors in acquisition of CLE. The bulk of evidence in the literature suggests that CLE is an acquired condition.

Key words: Barrett's esophagus; Risk factors; Esophageal adenocarcinoma; Pathogenesis; Reflux esophagitis; Gastroesophageal reflux

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INTRODUCTION

The lower esophagus lined by columnar epithelium is a condition poor in fact but rich in theory. It invites speculation but resists laboratory reproduction[1]. Columnar-lined esophagus (CLE) is commonly called "Barrett's esophagus". The same eponym is also used to describe the metaplastic epithelium and complications of this condition. Barrett's epithelium, Barrett's mucosa, Barrett's ulcer, Barrett's stricture and Barrett's carcinoma are used frequently in the literature. It is a pathological premalignant condition in which the lower segment of the esophagus becomes lined by a metaplastic columnar epithelium in the form of either circumferential extension of the gastric columnar epithelium or islands of columnar mucosa or both. The presence of specialized columnar epithelium anywhere in the esophagus represents a true metaplasia of the normal squamous epithelium and is highly suggestive for the diagnosis of CLE.

Since its initial description, the pathogenesis of CLE has been surrounded by many controversies. The first controversy is related to the existence of the condition itself. For more than six years, Norman Barrett[2,3] argued that the columnar-lined structure is an intrathoracic stomach due to a congenitally short esophagus. Earlier in 1943, Allison *et al*[4] described peptic ulceration in the 'short' esophagus. Allison[5] introduced the term reflux esophagitis and showed that peptic ulcer is in the esophagus. Our current concept of CLE is based on the demonstration by both Allison and Johnstone[6]. They have proven that the columnar-lined structure is esophagus on the basis of the following criteria: (1) The tubular structure grossly resembles the esophagus; (2) absence of peritoneal covering; (3) presence of squamous islands within the columnar mucosa; (4) presence of muscularis propria and submucosal glands of esophageal type; and (5) absence of the acid-producing oxyntic cells in the gastric mucous membrane, which line the lower esophagus.

The second controversy center on whether the CLE is a congenital or an acquired condition.

CONGENITAL THEORY OF COLUMNAR-LINED ESOPHAGUS

This theory is based upon the fact that the embryonic esophagus has a columnar epithelial lining, which may later be incompletely replaced with squamous epithelium leaving the lower esophagus lined by the fetal columnar epithelium. Many investigators showed that the embryonic columnar and glandular epithelium might persist in the esophagus after birth. Islets of ciliated columnar epithelium have been reported in post-mortem examination of esophagus from premature and newborn infants. There are four types of congenital columnar epithelium in the esophagus.

Embryonic ciliated columnar epithelium

Johns[7] showed that the fetal esophagus is lined by ciliated columnar epithelium until the 17th wk of development, and is later replaced by squamous epithelium. Initially, this replacement starts in the middle of the esophagus and then extends in both directions. Although, at birth, the esophagus is entirely lined by squamous epithelium, remnants of this embryonic ciliated columnar epithelium sometimes remain in the esophagus after birth. Rector and Connerley[8] found such columnar epithelium in the

esophagus of 7.8% of infants and children. It was more than 8 times commoner in the upper end than the lower end. A sheet of ciliated columnar epithelium has also been found lining the lower esophagus of one asymptomatic adult[9].

Heterotopic or ectopic gastric epithelium

Occasional foci of gastric epithelium were also reported to be present in the esophagus. Carrie[10] reported islands of ectopic gastric mucosa in 50% of his patients. Bosher and Taylor[11] reported the presence of heterotopic gastric mucosa associated with esophageal ulcer and stricture formation. Moreover, Abrams and Heath[12] also showed such epithelium.

Superficial cardiac glands

Normally superficial cardiac glands are present in the lamina propria, particularly in the lower end of the esophagus.

Congenital Barrett's epithelium

Although there is no similarity between the ciliated columnar epithelium and Barrett's epithelium, some investigators considered Barrett's epithelium to be a congenital remnant of the ciliated columnar epithelium.

Initially, Norman Barrett argued that since the early embryonic esophagus is lined by columnar epithelium, and that the metamorphosis to squamous epithelium only occurs after proliferation and recanalization of the original layer, the presence of columnar epithelium in the esophagus of an adult might be explained on the basis of a failure of this process to achieve completion[13]. Later on in 1962, Barrett changed his views and argued that the difficulty in accepting this explanation is that if it were true, one might expect the whole esophagus, and not simply the lower end to be abnormally lined more often than it is[14].

EVIDENCE SUPPORTING CONGENITAL ORIGIN OF COLUMNAR MUCOSA

Epidemiological evidence

Several studies have reported the cases of CLE in patients who had no GER[21-23]. Many authors reported the cases of CLE in children[24-26]. Two reports showed that a 9-year-old boy[24] and a 10-year old girl[24] had experienced dysphagia since infancy. The authors who favored the congenital theory assumed that the columnar mucosa is present since birth, but it becomes symptomatic later in life as a result of the development of a hiatal hernia and GER. Only a very small proportion of patients with CLE develop esophageal adenocarcinoma.

Morphological evidence

Postlethwait and Musser[27] in an autopsy study described a neonate with CLE. Haque and Merkel[28] reported a case of total CLE, where an adult patient had typical Barrett' s mucosa involving the esophagus. The authors argued that such a case support a congenital origin. However, a review of this case shows that this patient had long-standing, severe GER requiring antireflux surgery. Wolfe *et al*[29] and Mangla[22] described the presence of islands of heterotopic/ectopic gastric mucosa in the esophagus. Mangla[22] also described the cases with squamous epithelium interposed between Barrett's and gastric mucosa. Stadelmann *et al*[23] described patients with a linear, smooth squamo-columnar junction rather than the irregular junction commonly found in patients with CLE, and they argued that this observation support the congenital origin. Other several studies[22,30,31] argued that the presence of parietal and chief cells in Barrett's mucosa, which are highly differentiated cells, is unlikely to be an acquired condition.

Experimental evidence

Failure of experimental models has been reported by Van de Kerckhof and Gahagan by injuring the esophageal mucosa[32]. The absence of reversion of Barrett's mucosa to squamous epithelium after antireflux surgery has been cited as evidence supporting a congenital origin[22].

Details of evidence for production of CLE experimentally will be presented when discussing the acquired origin of columnar mucosa.

ACQUIRED THEORY OF COLUMNAR-LINED ESOPHAGUS

The arguments against the congenital theory include the fact that the embryonic studies have shown that the squamous replacement of the fetal columnar epithelium begins in the mid esophagus and progresses toward each end[7]. In addition, despite the fact that the islets of congenital ectopic gastric mucosa are more common in the cervical region of the esophagus which appears to be the last area to lose the embryonic columnar lining, the columnar epithelium is always found in the lower esophagus.

The association between CLE and gastroesophageal reflux (GER) was recognized early and led to the concept that CLE is an acquired condition. Tileston[15] suggested that the first requisite for the formation of peptic ulcer of the esophagus is an insufficiency of the cardia. He concluded that hyperacidity of the gastric juice plays a part in preventing healing of the esophagus ulcer seems probable. In the same article, he noticed with interest the close resemblance of the mucous membrane around the esophageal ulcer to that normally found in the stomach. In their historical paper, Allison and Johnstone[6] concluded that peptic esophagitis and peptic ulceration of the squamous epithelium of the esophagus are secondary to regurgitation of digestive juices, are most commonly found in those patients in whom the competence of the cardia has been lost through herniation of the stomach into the mediastinum. In the past, there has been some discussion about gastric heterotopia as a cause of peptic ulcer of the esophagus, but this point was very largely settled when the term reflux esophagitis was coined. It describes accurately in two words the pathology and etiology of a condition which are a common cause of digestive disorder. They reported seven patients in whom the lower esophagus

Table 1 Various evidences to support the congenital and acquired theories

Evidences	Congenital theory	Acquired theory
Epidemiological	1 Cases in children	1 Association with gastroesophageal reflux
	2 Cases without demonstrated reflux	2 Usual occurrence after middle age
Morphological	1 Neonate with columnar-lined esophagus	1 Absence of typical cases in fetuses
	2 Adult with involvement of entire esophagus	2 Presence of intestinal-type goblet cells and sulphomucins.
	3 Islands of heterotopic/ectopic gastric mucosa	3 Absence of gastrin-containing cells.
	4 Cases with squamous epithelium interposed between Barrett's and gastric mucosa	4 Endoscopic demonstration of upwards migration of Barrett's mucosa with ongoing gastroesophageal reflux
	5 Cases with linear, smooth squamo-columnar junction	
	6 Presence of parietal and chief cells in Barrett's mucosa	
Experimental	1 Failure of experimental models	1 Animal models.
	2 Absence of reversion to squamous epithelium after antireflux operation	2 Regression after successful antireflux surgery.
		3 Acquisition of Barrett's mucosa after onset of reflux following esophagogastrostomy, Heller myotomy and esophagojejunostomy.

Modified from Hamilton SR. Pathogenesis of columnar cell-lined (Barrett's) esophagus. In: Spechler S J, Goyal R K, (Eds.) Barrett's esophagus: Pathophysiology, diagnosis, and management. New York: Elsevier Science, 1985: 29-37.

was lined by gastric mucous membrane, and all these patients had reflux esophagitis. Four of these patients had progressed to stricture formations and one patient had ulceration in the esophageal part, which was lined by gastric epithelium. They termed such ulcers as Barrett's ulcer although they stressed that the use of this eponym does not imply agreement with Barrett's description of an esophagus lined with gastric mucous membrane as "stomach".

Although Allison and later on Barrett recognized the association between CLE and hiatal hernia and reflux esophagitis, nevertheless, they assumed that the condition is congenital in origin. Moersch *et al*[16] were the first to suggest that the columnar lining might be an acquired condition as a sequel of reflux esophagitis. Hayward[17] suggested that the CLE is an acquired condition due to reflux esophagitis that destroys the squamous epithelium. Moreover, he suggested that the denuded area is re-epithelialized from the columnar cells below, and that the lower 1 to 2 cm of the esophagus is lined by columnar epithelium which acts as a buffer zone of junctional epithelium, does not secrete acid or pepsin but is resistant to them.

The principal of the acquired theory is that the columnar epithelium is an adaptive change in response to the continued harmful environment present in the esophagus due to ongoing GER. Following repeated cycles of destruction and regeneration, in some individuals, a simple columnar epithelium more resistant to digestive action finally replaces the destroyed squamous epithelium[1].

Many earlier observations documented the ascent up the esophagus of a stricture at the squamo-columnar junction as squamous epithelium is replaced by columnar epithelium, supporting the concept of an acquired dynamic epithelium[18,19]. Adler[1] reported a series of 11 patients with CLE associated with strictures, in three of them, progression and ascent of the strictures were documented over 3 to 5 years. Moreover, he also suggested that the occurrence of islets of squamous epithelium within the sheet of columnar epithelium could be interpreted as the more resistant remnants of squamous epithelium that survived the erosive action of the digestive secretions. He stated that the findings of these squamous islets are less easily explained by the congenital theory.

Hamilton[20] summarized the epidemiological, morphological and experimental evidence cited in the literature to support the congenital and acquired theories (Table 1).

EVIDENCE SUPPORTING ACQUIRED ORIGIN OF COLUMNAR MUCOSA

Epidemiological evidence

(1) Many investigators reported the frequent association between CLE and GER[33]. Allison and Johnstone[6] suggested that if gastric reflux occurs, and causes ulceration of squamous epithelium without producing stenosis, is healing of the ulcer in an acid medium more likely to be by overgrowth of gastric rather than of esophageal epithelium? If this were so it might be that some examples of the gastric mucosa in the esophagus were acquired rather than congenital. (2) The usual occurrence of CLE in patients of middle and older ages. If the congenital columnar epithelium lining the esophagus produces acid and pepsin itself as some believe it is difficult to understand why complications do not occur early in life. (3) Dahms and Rothstein[34] reported that CLE in children is a consequence of chronic GER.

Morphological evidence

There is no typical cases of CLE in fetuses[33]. The histopathologic and histochemical characteristics of Barrett' s epithelium have also been quoted to support an acquired origin. The presence of intestinal-type goblet cells, and sulphomucins has suggested an acquired origin[35,36]. Dalton *et al*[37] and Dayal and Wolf[38] suggested that the absence of gastrin-containing cells from Barrett's mucosa as contrasted with congenital gastric heterotopia such as in a Meckel's diverticulum, support an acquired origin for CLE. However, Mangla *et al*[30] have demonstrated the presence of gastrin in Barrett's mucosa. The strongest morphological evidence for acquired origin has been

provided by cases with endoscopic demonstration of cephalic migration of the peptic esophagitis and stricture above an ascending boundary of CLE with continuing GER[19,26,39]. These cases provided strong evidence that the condition could be progressive and result from persistent severe GER and complicating esophagitis. The concept of erosive reflux esophagitis healing by upward migration of adjacent columnar epithelium was advanced by Hayward[17]. Adler[1] reported that out of five patients with CLE associated with strictures, three patients had progression and ascent of the strictures, which were documented over 3 to 5 years. He proposed the possibility of repair by extension from esophageal glands following reflux esophagitis.

Experimental evidence

Bremner *et al*[40] and Wong and Finckh[41] successfully produced columnar-lined mucosa in the esophagi of dogs and rats in the presence of GER, respectively. Li *et al*[42] showed that seven of the 10 dogs developed Barrett's mucosa after a reflux procedure was created, suggesting that a squamous injury in the esophagus is repaired by columnar epithelium in the presence of reflux. The columnar epithelium is acquired when the squamous epithelium is injured and during repair it undergoes columnar metaplasia. Although damage to squamous mucosa is a requisite factor for the development of columnar metaplasia, acute injury alone is not a sufficient stimulus for columnar metaplasia. The acquisition of the columnar epithelium requires a chronically abnormal esophageal environment during the period of mucosal repair. In an experimental study on dog esophagus, Gillen *et al*[43] found that a surgical injury in the esophageal squamous mucosa healed by the regeneration of squamous epithelium in normal dogs. However, if the surgical injury is preceded by alteration of the gastroesophageal junction to cause chronic GER, then the injured squamous mucosa is replaced by a columnar lining. Radigan *et al*[44] and Ransom *et al*[45] reported restoration of squamous mucosa after a successful antireflux operation. The acquisition of Barrett's mucosa after onset of GER following esophagogastrostomy, Heller myotomy, and esophagojejunostomy provide strong evidence for an acquired origin[46-49].

The arguments regarding the etiology of CLE have centered on an acquired *versus* congenital origin; the possibility remains that examples of both do occur[50]. However, the available evidence suggests that the vast majority of cases, if not all, are acquired due to chronic GER. The question remaining to be answered is why Barrett's mucosa develops in only 8-20% of patients with reflux, but not in other patients with reflux of similar severity[20].

FACTORS IN ACQUISITION OF CLE

Patients with CLE frequently have anatomical and physiological abnormalities which either predispose to or exaggerate the severe GER, which in turn leads to the acquisition of the columnar epithelium. Another group of these patients acquire the columnar epithelium secondary to esophagitis or mucositis due to irritant or cytotoxic agents. Given the combination of these anatomical and physiological abnormalities, it is not surprising that severe esophagitis commonly accompanies Barrett's epithelium.

The major risk factors that can lead to acquisition of the columnar epithelium are: (1) GER with acid and pepsin; (2) extreme lower esophageal sphincter incompetence; (3) alkaline reflux (duodeno-gastroesophageal reflux of bile and pancreatic juices); (4) gastric acid hypersecretion; (5) abnormal esophageal motility and delayed acid clearance; (6) diminished esophageal pain sensitivity; and (7) alcohol consumption.

The minor risk factors that can lead to acquisition of the columnar epithelium are: (1) Caustic injury by lye; (2) cytotoxic chemotherapy agent; and (3) acid and pepsin secretion by Barrett's epithelium.

GER with acid and pepsin

Much attention has been directed to reflux of the gastric juices containing acid and pepsin. Patients with CLE frequently have an extremely incompetent lower esophageal sphincter, and therefore, are exceptionally predisposed to GER. In most patients with CLE, GER is judged to be the principal factor that causes injury to the squamous epithelium and provides the abnormal esophageal environment necessary for columnar metaplasia. It is now widely accepted that a substantial proportion of patients with Barrett's esophagus do have severe GER. Schnell *et al*[51] conducted a study to test the hypothesis that since acid contact time is related to formation of Barrett' s epithelium, then a greater esophageal acid contact time might result in longer segments of Barrett's epithelium. They studied 116 patients with CLE and demonstrated a definite positive correlation between the length of Barrett' s esophagus and the duration of esophageal acid exposure. Recently some of the published Swedish studies linked adenocarcinoma of esophagus with duration, frequency and severity of GER symptoms[52,53].

Extreme lower esophageal sphincter incompetence

An important factor that contributes to mucosal injury in patients with CLE is lower esophageal sphincter (LES) hypotension. Stein *et al*[54] found that 11 of 12 patients with CLE had an incompetent LES. The abnormalities were defined as LES pressure of less than 6 mm Hg, overall LES length of less than 2 cm, or abdominal LES length of less than 1 cm. They concluded that this predisposes to GER. This study also confirmed earlier reports documenting extreme LES hypotension in patients with CLE. Attwood *et al*[55] reported that 90% of patients with CLE had a mechanically defective LES and 93% had increased esophageal exposure to gastric juice on esophageal pH monitoring.

Alkaline reflux (duodeno-gastro-esophageal reflux of bile and pancreatic juices)

Most of the earlier studies on CLE traditionally focused on the role of gastric acid and pepsin, but other reports suggested that other factors contributed to the esophageal damage in patients with CLE. Bile reflux into the esophagus was reported as an important causative

factor in acquisition of CLE by many investigators[39,47]. DeMeester *et al*[56] using 24-h esophageal pH monitoring found abnormal alkaline reflux (esophageal pH >7 for more than 10.5% of a 24-h period) in 34% (14/41) cases. Gastric secretions normally are not alkaline, suggesting that bile and other alkaline materials in the duodenum frequently reflux into the stomach and esophagus in patients with CLE and this alkaline reflux has a role in the esophageal injury. Waring *et al*[57] also documented the frequent occurrence of duodeno-gastric reflux in patients with CLE. In their study, radionuclide appeared within 95 min of an intravenous injection of ^{99m}Tc-diisopropyl iminodiacetic acid in the stomach of 46% (6/13) patients with CLE. In contrast, 11% (2/19) persons in the control group had radionuclide evidence of duodeno-gastric reflux. The role of alkaline reflux is particularly evident in those cases of CLE acquired after total gastrectomy in which gastric juices were eliminated[49]. Tada *et al*[58] also provided evidence that refluxed substances other than acid and pepsin play a pathogenic role in CLE. They reported a patient with severe GER disease who developed CLE at age 47, 22 years after a total gastrectomy. At age 64, an endoscopic examination revealed adenocarcinoma in Barrett's epithelium. This report confirms previous reports that acid and pepsin are not necessarily the only pathogenic factors for either Barrett's esophagus or esophageal adenocarcinoma, and further supports the important role of alkaline reflux in the development of CLE and adenocarcinoma. Stoker and Williams[59] suggested that a mixture of gastric and duodenal secretions causes esophageal mucosal disruption and intracellular damage through a toxic synergism between the two secretions. The clinical importance of the alkaline reflux is that the treatment of GER in patients with CLE should involve shifting or neutralizing the alkaline substances as well as the acid. As with duodeno-gastric reflux, the stomach contents available for reflux into the esophagus will include bile and pancreatic enzymes in addition to acid. Therefore, suppressing the acids alone may be ineffective in healing esophagitis for patients with CLE. Hetzel *et al*[60] showed that omeprazole, a drug that is dramatically effective in reducing gastric acid secretion and in healing mild esophagitis, was far less reliable for healing ulcerations in Barrett's epithelium. van der Veen *et al*[61] reported that previous gastric surgery represents an increased risk factor for the development of adenocarcinoma in patients with CLE. Attwood *et al*[62] conducted a study to determine the role of intra-esophageal alkalinization in the genesis of complications in Barrett's esophagus. They found that the esophageal acid exposure (% time pH<4) was similar in patients with or without complications (19.2% *vs* 19.3%). In contrast, the esophageal alkaline exposure (% time pH>7) was greater in patients with complications (24.2% *vs* 8.4%). In 81% of patients, there was a clear relationship between gastric and esophageal alkalinization. They concluded that complications in Barrett's esophagus develop in association with increased exposure of the esophagus to an alkaline environment, which appears to be secondary to duodeno-gastric reflux.

Gastric acid hypersecretion

Patients with CLE may have elevated gastric acid secretion. Collen *et al*[63] suggested that hypersecretion of gastric acid may contribute to the frequency of complications in Barrett's esophagus. In a prospective study, 75% (9/12) patients who had heartburn intractable to treatment with conventional doses of ranitidine (150 mg twice per day) were found to have gastric acid hypersecretion (basal acid output > 10 mEq/h). Among those 12 refractory patients, 10 had Barrett's esophagus, and increasing the conventional dose of ranitidine 2 to 6 times controlled their heartburn, which reduced the gastric acid output to less than 1 mEq/h. With gastric acid hypersecretion and duodeno-gastric reflux of bile and pancreatic enzymes, the gastric material available for reflux can be unusually caustic and harmful.

Abnormal esophageal motility and delayed acid clearance

Many patients with CLE have abnormal motility in the distal esophagus that can delay esophageal clearance, and so the refluxed material may have prolonged contact with the esophageal mucosa. Winter *et al*[64] reported on the importance of delayed acid clearance from the esophagus as a contributory factor in the causation of CLE. Stein *et al*[54] using 24-h esophageal motility monitoring reported that there was an increase in the frequency of abnormally weak contractions (<30 mm Hg) of the distal esophagus in patients with CLE compared with patients with uncomplicated reflux disease. These weak contractions may not empty the esophagus effectively, and could be responsible for the delayed esophageal acid clearance that has been observed in patients with Barrett's esophagus.

Diminished esophageal pain sensitivity

There are large proportions of patients with CLE who are asymptomatic. Cameron *et al*[65] estimated that for every case identified clinically, there are approximately 20 cases in the general population that go unrecognized. Patients with CLE usually seek medical advice when they develop complications, such as esophagitis, stricture, ulcer, bleeding or adenocarcinoma. Many patients with CLE have diminished esophageal pain sensitivity. Skinner *et al*[66] suggested that persistence of severe reflux after antireflux surgery in some patients with Barrett's esophagus who are asymptomatic is due to the Barrett's epithelium not being sensitive to acid after ulceration or strictures heal. Iascone *et al*[67] found that as compared to patients with reflux esophagitis without Barrett's epithelium, patients with Barrett's esophagus have less severe symptoms of heartburn and regurgitation in spite of significantly greater duration of acid reflux in the distal esophagus. Johnson *et al*[68] suggested that the CLE has diminished pain sensitivity and that acid reflux may not cause heartburn for many patients with CLE. Perhaps most patients with Barrett's esophagus escape medical attention because their reflux symptoms are minimal. Diminished pain sensitivity may play a role in the development of the complications that frequently accompany CLE. Patients whose reflux is not heralded by heartburn are unlikely to take antacid or seek medical advice. With no symptomatic warning that caustic material is damaging the esophagus, patients are unlikely to take medications that may prevent further injury[69]. The decrease in pain sensitivity may explain the

lack of reflux symptoms before the onset of dysphagia in some of the patients who develop adenocarcinoma.

Alcohol consumption

Martini and Wienbeck[70] noted the frequent history of chronic alcohol abuse in patients with CLE. Whether this association is related to a direct effect of alcohol on the mucosa or to promotion of GER by the effects of alcohol on the LES is uncertain. It is interesting to notice that alcohol abuse was quoted as early as 1906 as an important cause for peptic ulcer of the esophagus. Tileston[15] in 1906 suggested that the abuse of alcohol deserves a mention among the predisposing causes, occurring with considerable frequency. Alcohol probably acts in two ways: first, by irritation of the esophagus, and second, by the production of gastritis, with vomiting and insufficiency of the cardia.

Caustic injury by lye

Spechler *et al*[71] reported a case with fundic-type Barrett's epithelium in the mid esophagus with sparing of the distal esophagus complicating caustic injury by lye ingestion.

Cytotoxic chemotherapy agent

Cases of CLE have been reported in 63-75% of patients who received a prolonged course of chemotherapy for breast carcinoma. Sartori *et al*[72] reported that CLE could be acquired through an iatrogenic injury by prolonged chemotherapy with anti-neoplastic agents (cyclophosphamide, methotrexate and 5-fluorouracil). These agents injured the esophageal mucosa and caused columnar epithelium secondary to the drug-induced mucositis. In this regard, they published two reports suggesting that chronic chemotherapy with these agents frequently causes columnar metaplasia of the esophagus. In the first report, they described a woman who, because of duodenal ulcer disease, had an endoscopic examination before the beginning of prolonged chemotherapy for breast cancer. The esophagus was normal, but after 4 mo of chemotherapy, a second endoscopy revealed an esophageal ulcer with columnar epithelium. Endoscopic examinations in another eight women who had been treated with the same chemotherapy agents showed columnar epithelium in six of them. The length of the columnar epithelium was more than 3 cm in all six patients[72]. In the second paper, they reported a prospective endoscopic study carried out to document the development of CLE in women receiving the same chemotherapy drugs**.** Ten of sixteen women (63%) who had no endoscopic or histologic evidence of CLE before chemotherapy were found to develop a CLE after 6 mo of chemotherapy[73].

Acid and pepsin secretion by Barrett's epithelium

Secretion of acid and pepsin by the parietal and chief cells in the Barrett's mucosa has been considered as possible factors in development of CLE by some investigators like Mangla *et al*[30] and Ustach *et al*[74]. However, there are no recent data to support this.

SUMMARY

The incidence of CLE and adenocarcinoma is rising at an epidemic rate, and the cause for this rapid rise is unclear and the answer to this principle question remains to be determined. Due to the causal relationship between CLE and GER, risk factors which enhance reflux such as tobacco smoking, alcohol consumption, dietary changes including high fat diet, obesity, and the wide spread usage of the medications that affect the upper gastrointestinal tract could be partially responsible for this rise. Although other several factors can be offered as possible explanations for this rise in incidence such as increased awareness of the condition, widespread use of endoscopy, and improved diagnostic techniques, this rapid increase in the incidence of CLE and adenocarcinoma raises serious concern that the current management for GER is inadequate and deserves reassessment.

REFERENCES

1 **Adler RH**. The lower esophagus lined by columnar epithelium. Its association with hiatal hernia, ulcer, stricture, and tumor. *J Thorac Cardiovasc Surg* 1963; **45**: 13-34
2 **BARRETT NR.** Chronic peptic ulcer of the oesophagus and 'oesophagitis'. *Br J Surg* 1950; **38**: 175-182
3 **Barrett NR**. Hiatus hernia. *Proc R Soc Med* 1952; **45**: 279-286
4 **Allison PR**, Johnstone AS, Royce GM. Short esophagus with simple peptic ulceration. *J Thorac Surg* 1943; **12**: 432-457
5 **Allison PR**. Peptic ulcer of the esophagus. *J Thorac Surg* 1946; **15**: 308
6 **Allison PR**, Johnstone AS. The oesophagus lined with gastric mucous membrane. *Thorax* 1953; **8**: 87-101
7 **Johns BA**. Developmental changes in the oesophageal epithelium in man. *J Anat* 1952; **86**: 431-442
8 **Rector LE**, Connerley ML. Aberrant mucosa in esophagus in infants and in children. *Arch Pathol* 1941; **31**: 285-294
9 **Raeburn C**. Columnar ciliated epithelium in the adult oesophagus. *J Pathol Bacteriol* 1951; **63**: 157-158
10 **Carrie A**. Adenocarcinoma of the upper end of the oesophagus arising from ectopic gastric epithelium. *Br J Surg* 1950; **37**: 474
11 **Bosher LH**, Taylor FH. Heterotopic gastric mucosa in the esophagus with ulceration and stricture formation. *J Thorac Surg* 1951; **21**: 306-312
12 **Abrams L**, Heath D. Lower oesophagus lined with intestinal and gastric epithelia. *Thorax* 1965; **20**: 66-72
13 **Barrett NR**. The lower oesophagus lined by columnar epithelium. In: Modern Trends in Gastroenterology ed. Jones FA, Butterworth & Co., London, 1958: 147
14 **Barrett NR**. Benign stricture in the lower esophagus. *J West Soc Periodontol Periodontal Abstr* 1962; **43**: 703-715
15 **Tileston W**. Peptic ulcer of the esophagus. *American Journal of the Medical Sciences* 1906; **132**: 240-265
16 **Moersch RN**, Ellis FH Jr, McDonald JR. Pathologic changes occurring in severe reflux esophagitis. *Surg Gynecol Obstet* 1959; **108**: 476-484
17 **Hayward J**. The treatment of fibrous stricture of the oesophagus associated with hiatal hernia. *Thorax* 1961; **16**: 45-55
18 **Morris KN**. Gastric mucosa within the oesophagus. *Aust N Z J Surg* 1955; **25**: 24-30
19 **Goldman MC**, Beckman RC. Barrett syndrome: Case report with discussion about concepts of pathogenesis. *Gastroenterology* 1960; **39**: 104-110
20 **Hamilton SR**. Pathogenesis of columnar cell-lined (Barrett's) esophagus. In: Barrett's esophagus: Pathophysiology, diagnosis, and management ed. Spechler, SJ, Goyal RK, Elsevier Science Publishing Co, New York, 1985: 29-37

21 **Hennessy TP**, Edlich RF, Buchin RJ, Tsung MS, Prevost M, Wangensteen OH. Influence on gastroesophageal incompetence on regeneration of esophageal mucosa. *Arch Surg* 1968; **97**: 105-107
22 **Mangla JC**. Barrett's esophagus: an old entity rediscovered. *J Clin Gastroenterol* 1981; **3**: 347-356
23 **Stadelmann O**, Elster K, Kuhn HA. Columnar-lined oesophagus (Barrett's syndrome) - congenital or acquired? *Endoscopy* 1981; **13**: 140-147
24 **Wyndham N**. The significance of gastric mucosa in the oesophagus. *Br J Surg* 1956; **43**: 409-412
25 **Postlethwait RW**, Sealy WC. In: Surgery of the esophagus. Springfield, 1II, Charles C Thomas, Publisher 1961
26 **Borrie J**, Goldwater L. Columnar cell-lined esophagus: assessment of etiology and treatment. A 22 year experience. *J Thorac Cardiovasc Surg* 1976; **71**: 825-834
27 **Postlethwait RW**, Musser AW. Changes in the esophagus in 1,000 autopsy specimens. *J Thorac Cardiovasc Surg* 1974; **68**: 953-956
28 **Haque AK**, Merkel M. Total columnar-lined esophagus: a case for congenital origin? *Arch Pathol Lab Med* 1981; **105**: 546-548
29 **Wolf BS**, Marshak RH, Som ML. Peptic esophagitis and peptic ulceration of the esophagus. *Am J Roentgenol Radium Ther Nucl Med* 1958; **79**: 741-759
30 **Mangla JC,** Schenk EA, Desbaillets L, Guarasci G, Kubasik NP, Turner MD. Pepsin secretion, pepsinogen, and gastrin in "Barrett's esophagus." Clinical and morphological characteristics. *Gastroenterology* 1976; **70**: 669-676
31 **Csendes A,** Larrain A, Uribe P. Gastric acid secretion in patients with a symptomatic gastroesophageal reflux and patients with esophageal strictures. *Ann Surg* 1974; **179**: 119-122
32 **van de Kerckhof J**, Gahagan T. Regeneration of the mucosal lining of the esophagus. *Henry Ford Hosp Med Bull* 1963; **11**: 129-134
33 **Sjogren RW Jr,** Johnson LF. Barrett's esophagus: a review. *Am J Med* 1983; **74**: 313-321
34 **Dahms BB**, Rothstein FC. Barrett's esophagus in children: a consequence of chronic gastroesophageal reflux. *Gastroenterology* 1984; **86**: 318-323
35 **Berenson MM**, Herbst JJ, Freston JW. Enzyme and ultrastructural characteristics of esophageal columnar epithelium. *Am J Dig Dis* 1974; **19**: 895-907
36 **Jass JR**. Mucin histochemistry of the columnar epithelium of the oesophagus: a retrospective study. *J Clin Pathol* 1981; **34**: 866-870
37 **Dalton MD,** McGuigan JE, Camp RC, Goyal RK. Gastrin content of columnar mucosal lining the lower (Barrett's) esophagus. *Am J Dig Dis* 1977; **22**: 970-972
38 **Dayal Y**, Wolfe HJ. Gastrin-producing cells in ectopic gastric mucosa of developmental and metaplastic origins. *Gastroenterology* 1978; **75**: 655-660
39 **Halvorsen JF**, Semb BK. The "Barrett syndrome" (the columnar-lined lower oesophagus): an acquired condition secondary to reflux oesophagitis. A case report with discussion of pathogenesis. *Acta Chir Scand* 1975; **141**: 683-687
40 **Bremner CG**, Lynch VP, Ellis FH Jr. Barrett's esophagus: congenital or acquired? An experimental study of esophageal mucosal regeneration in the dog. *Surgery* 1970; **68**: 209-216
41 **Wong J**, Finckh ES. Heterotopia and ectopia of gastric epithelium produced by mucosal wounding in the rat. *Gastroenterology* 1971; **60**: 279-287
42 **Li H,** Walsh TN, O'Dowd G, Gillen P, Byrne PJ, Hennessy TP. Mechanisms of columnar metaplasia and squamous regeneration in experimental Barrett's esophagus. *Surgery* 1994; **115**: 176-181
43 **Gillen P,** Keeling P, Byrne PJ, West AB, Hennessy TP. Experimental columnar metaplasia in the canine oesophagus. *Br J Surg* 1988; **75**: 113-115
44 **Radigan LR,** Glover JL, Shipley FE, Shoemaker RE. Barrett esophagus. *Arch Surg* 1977; **112**: 486-491
45 **Ransom JM**, Patel GK, Clift SA, Womble NE, Read RC. Extended and limited types of Barrett's esophagus in the adult. *Ann Thorac Surg* 1982; **33**: 19-27
46 **Naef AP**, Savary M, Ozzello L. Columnar-lined lower esophagus: an acquired lesion with malignant predisposition. Report on 140 cases of Barrett's esophagus with 12 adenocarcinomas. *J Thorac Cardiovasc Surg* 1975; **70**: 826-835
47 **Hamilton SR**, Yardley JH. Regnerative of cardiac type mucosa and acquisition of Barrett mucosa after esophagogastrostomy. *Gastroenterology* 1977; **72**: 669-675
48 **Kortan P,** Warren RE, Gardner J, Ginsberg RJ, Diamant NE. Barrett's esophagus in a patient with surgically tested achalasia. *J Clin Gastroenterol* 1981; **3**: 357-360
49 **Meyer W**, Vollmar F, Bar W. Barrett-esophagus following total gastrectomy. A contribution to it's pathogenesis. *Endoscopy* 1979; **11**: 121-126
50 **Berardi RS**, Devaiah KA. Barrett's esophagus. *Surg Gynecol Obstet* 1983; **156**: 521-538
51 **Schnell T**, Sontag S, O'Connell S, Chejfec G, Miller T, Serlovsky R, Brand L, Kurucar C. Esophageal acid exposure time correlates with the length (L) of Barrett's esophagus (BE). *Gastroenterology* 1990; **98**: A120
52 **Lagergren J**, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; **340**: 825-831
53 **Ye W**, Chow WH, Lagergren J, Yin L, Nyren O. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. *Gastroenterology* 2001; **121**: 1286-1293
54 **Stein HJ,** Eypasch EP, DeMeester TR, Smyrk TC, Attwood SE. Circadian esophageal motor function in patients with gastroesophageal reflux disease. *Surgery* 1990; **108**: 769-77; discussion 777-778
55 **Attwood SE,** DeMeester TR, Bremner CG, Barlow AP, Hinder RA. Alkaline gastroesophageal reflux: implications in the development of complications in Barrett's columnar-lined lower esophagus. *Surgery* 1989; **106**: 764-770
56 **DeMeester TR,** Attwood SE, Smyrk TC, Therkildsen DH, Hinder RA. Surgical therapy in Barrett's esophagus. *Ann Surg* 1990; **212**: 528-40; discussion 540-542
57 **Waring JP**, Legrand J, Chinichian A, Sanowski RA. Duodenogastric reflux in patients with Barrett's esophagus. *Dig Dis Sci* 1990; **35**: 759-762
58 **Tada T**, Suzuki T, Iwafuchi M, Watanabe H, Katayanagi N, Aizawa K, Nishimaki T, Tanaka O, Muto T. Adenocarcinoma arising in Barrett's esophagus after total gastrectomy. *Am J Gastroenterol* 1990; **85**: 1503-1506
59 **Stoker DL**, Williams JG. Alkaline reflux oesophagitis. *Gut* 1991; **32**: 1090-1092
60 **Hetzel DJ**, Dent J, Reed WD, Narielvala FM, Mackinnon M, McCarthy JH, Mitchell B, Beveridge BR, Laurence BH, Gibson GG. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. *Gastroenterology* 1988; **95**: 903-912
61 **Van der Veen AH**, Dees J, Blankensteijn JD, Van Blankenstein M. Adenocarcinoma in Barrett's oesophagus: an overrated risk. *Gut* 1989; **30**: 14-18
62 **Attwood SE**, Ball CS, Barlow AP, Jenkinson L, Norris TL, Watson A. Role of intragastric and intraoesophageal alkalinisation in the genesis of complications in Barrett's columnar lined lower oesophagus. *Gut* 1993; **34**: 11-15
63 **Collen MJ**, Lewis JH, Benjamin SB. Gastric acid hypersecretion in refractory gastroesophageal reflux disease. *Gastroenterology* 1990; **98**: 654-661
64 **Winter HS**, Madara JL, Stafford RJ, Tapper D, Goldman H. Delayed acid clearance and esophagitis after repair of esophageal atresia. *Gastroenterology* 1981; **80**: 1317
65 **Cameron AJ,** Zinsmeister AR, Ballard DJ, Carney JA. Prevalence of columnar-lined (Barrett's) esophagus. Comparison of population-based clinical and autopsy findings. *Gastroenterology* 1990; **99**: 918-922
66 **Skinner DB,** Walther BC, Riddell RH, Schmidt H, Iascone C, DeMeester TR. Barrett's esophagus. Comparison of benign and malignant cases. *Ann Surg* 1983; **198**: 554-565
67 **Iascone C**, DeMeester TR, Little AG, Skinner DB. Barrett's esophagus. Functional assessment, proposed pathogenesis, and surgical therapy. *Arch Surg* 1983; **118**: 543-549

68 **Johnson DA**, Winters C, Spurling TJ, Chobanian SJ, Cattau EL Jr. Esophageal acid sensitivity in Barrett's esophagus. *J Clin Gastroenterol* 1987; **9**: 23-27
69 **Spechler SJ**. Columnar-lined (Barrett's) esophagus. Curr Opinion *Gastroenterol* 1991; **7**: 557-561
70 **Martini GA,** Wienbeck M. Does alcohol favour the development of Barret's syndrome (endobrachy-oesophagus) (author' s transl)? *Dtsch Med Wochenschr* 1974; **99**: 434-439
71 **Spechler SJ**, Schimmel EM, Dalton JW, Doos W, Trier JS. Barrett's epithelium complicating lye ingestion with sparing of the distal esophagus. *Gastroenterology* 1981; **81**: 580-583
72 **Sartori S**, Nielsen I, Trevisani L, Pazzi P, Malacarne P. Barrett' s esophagus after antineoplastic chemotherapy. *Endoscopy* 1990; **22**: 152
73 **Sartori S,** Nielsen I, Indelli M, Trevisani L, Pazzi P, Grandi E. Barrett esophagus after chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF): an iatrogenic injury? *Ann Intern Med* 1991; **114**: 210-211
74 **Ustach TJ**, Tobon F, Schuster MM. Demonstration of acid secretion from esophageal mucosa in Barrett's ulcer. *Gastrointest Endosc* 1969; **16**: 98-100

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