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Is typing of metaplasia at the squamocolumnar junction revealing its aetiology?

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Abstract Until recently, intestinal metaplasia (IM) at the squamocolumnar junction (SCJ) was ascribed to Barrett's mucosa (BM), which arises from gastro-oesophageal reflux. Recent studies, however, have shown that IM at the SCJ can also be induced, for example, by *Helicobacter pylori* (HP). The aim of this study was to investigate whether the type of IM might be helpful in the differentiation between these two aetiologies. Biopsies from the antrum, corpus and immediately below the Z-line were taken from 443 patients. Eighty-three of them showed IM below the Z-line. In these, the endoscopic aspect of the Z-line was classified as either unremarkable (n=49) or suspected of BM (n=34). Typing of IM was done using Gomori's aldehyde fuchsin–Alcian blue staining. Overall, age, HP status and erosive oesophagitis had no influence on the IM type. Type-III IM (n=24) was more frequent in men (P=0.0371) and related to endoscopic BM (P<0.0001). Type-I/II IM (n=59) was associated with an unremarkable Z-line (P<0.0001) and was linked to multifocal gastric IM (P=0.016) and HP (P=0.0011). In conclusion, it was shown that, in the presence of a normal Z-line, especially in the absence of HP, type-III IM is suggestive of BM. The diagnosis of short or ultra-short segment BM should therefore include endoscopic, histological and histochemical characteristics.

Key words Intestinal metaplasia · Squamocolumnar junction · Gomori's aldehyde fuchsin · *H. pylori* · Barrett's mucosa

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Introduction

In western industrialised countries, the incidence of gastric carcinoma is decreasing [4]. The incidence of adenocarcinoma at the gastro-oesophageal junction (GOJ), however, is increasing [1, 28]. Carcinomas localised to this latter area often originate from a neoplastic transformation of intestinalised metaplastic mucosa, the so-called Barrett's mucosa (BM), commonly thought to be a consequence of gastro-oesophageal reflux disease [2, 3]. Presently, the endoscopic classification of BM is not only restricted to a definite mucosal segment of a certain length [23, 38], but also includes short segments [19, 35, 40]. The histomorphological problems are related to an unequivocal diagnostic differentiation of short-segment BM versus cardiac intestinal metaplasia (IM) with different genesis. The most important aspect of this question is the fact that only BM has been considered as a pre-neoplastic lesion so far. In contrast, gastric IM does not appear to be a pre-neoplasia [7, 30], although some studies have revealed an association of type-III IM with an increased risk of gastric cancer [9, 33]. The partly multifocal gastric IM, regardless of the type, is mostly induced by *Helicobacter pylori* (HP), whereas the replacement of the squamous epithelium of the lower third of the oesophagus by an intestinalised, goblet-cell-containing columnar epithelium is caused by reflux. The finding of metaplasia with goblet cells at the squamocolumnar junction (SCJ) often gives rise to speculations about its aetiology. An involvement of the cardia region in HP gastritis is obviously frequent [11, 13]. Short-segment BM, however, might also be present [14]. Since BM is associated with a higher risk of carcinogenesis [15], it is important to differentiate these two conditions by means of histology.

Apart from the presence of a goblet-cell-containing intestinalised mucosa, definite histological criteria for diagnosing BM have not yet been established [15, 32]. The fact that the GOJ is not clearly defined complicates this issue. The Z-line (squamocolumnar junction) is not implicitly identical with the GOJ [15]. Cardia- and fundus-

Table 1 Types of intestinal metaplasia (according to Jass and Filipe, 1981 [18]). *GAF-AB* Gomori's aldehyde fuchsin–Alcian blue

Type of metaplasia	Goblet cells (GAF-AB staining)	Columnar cells (GAF-AB staining)
Type I, complete	Sialomucins (blue) a/o sulphomucins (purple)	Absorptive cells with brush border, no mucin
Type II, incomplete	Sialomucins (blue) a/o sulphomucins (purple)	Sialomucins (blue)
Type III, incomplete	Sialomucins (blue) a/o sulphomucins (purple)	Sulphomucins (purple)

type mucosa, without being assigned to BM, can be seen within the distal 3 cm of the oesophagus physiologically [12]. However, mucosa containing goblet cells is not physiological and must lead the pathologist to consider BM [39, 46].

Mucin production in the columnar and goblet cells of IM has been the subject of several investigations [21, 25, 29, 36]. Whether the type of IM at the SCJ may give a hint of its aetiology has not yet been investigated.

Material and methods

From June 1995 to the end of October 1997 gastric biopsy specimens from 443 patients were routinely obtained and evaluated in a standardised manner according to the updated Sydney System [6]. Biopsy specimens were also obtained immediately below the Z-line. Patients with gastric or oesophageal carcinoma, coagulation defects or oesophageal varices were not included in this study.

Endoscopy was performed in a standardised manner by experienced endoscopists. The appearance of the GOJ was carefully studied in the prograde view after insufflation of air and after retroversion in the stomach. A relatively straight Z-line located within 2 cm above the proximal margin of the gastric mucosal folds was classified as unremarkable. A Z-line that was shifted more than 2 cm proximally and/or showed mucosal tongues of columnar epithelium extending into the distal oesophagus was classified as suggestive of BM. Erosive oesophagitis was diagnosed when there were unequivocal defects in the squamous epithelium. For the purpose of this study, it was only reported as absent or present. Biopsy specimens were taken with a standard forceps including three antral and three corpus specimens. At least two biopsies were taken immediately below the Z-line. All biopsies were fixed in 4% buffered formalin.

The biopsy specimens, separated according to their localisation in the stomach, were routinely prepared. Haematoxylin and Eosin (H+E)-stained sections (4 µm) were classified in accordance with the updated Sydney System [6]. In addition, we used the modified Giemsa staining to reveal HP infection by light microscopy. Subtyping of IM was performed with the use of Gomori's aldehyde fuchsin (GAF)–Alcian blue (AB) staining [42]. Shah et al. validated this staining for typing IM in comparison with the well-known and established high-iron diamine–Alcian blue staining with a sensitivity of 85% and a specificity of 100%. [36]. According to Jass and Filipe [18], three types of IM were distinguished (Table 1). As prior studies had found a predominance of type-III IM with sulphomucin production in columnar cells of BM [21, 29], we evaluated types-I and -II IM without sulphomucins in columnar cells taken together versus type-III IM. For the diagnosis of IM, we did not consider Alcian blue-positive columnar cells alone to be indicative of metaplastic columnar epithelium, because such cells are normally present in the mucous neck region of gastric glands [12, 15]. Therefore, it is speculative to define sialomucin-containing columnar cells as a part of type-II IM versus physiological sialomucin-containing cells between IM of type I.

In addition to histology we performed a validated and commercially available rapid urease test [22] in one antral and in one corpus biopsy specimen. HP infection was assumed when active gastritis with bacteria was found histologically and/or the rapid urease test was positive.

Statistical analysis was performed using the χ^2-test/Fisher's exact test (two tail) and the *t*-test/Mann-Whitney U-test. $P<0.05$ was considered statistically significant. All calculations were performed using the SPSS package.

Table 2 Numbers of patients with different types of intestinal metaplasia at the squamocolumnar junction

	Intestinal metaplasia Type I/II (*n*=59)	Intestinal metaplasia Type III (*n*=24)	*P* value
Median age (range) (years)	62 (30–84)	65 (30–81)	0.8723
Male (%)	35 (59.3)	20 (83.3)	0.0371
H. pylori positive (%)	42 (71.2)	13 (54.2)	0.1394
IM multifocal (%)	32 (54.2)	6 (25)	0.0160
Erosive oesophagitis (%)	17 (28.8)	11 (45.8)	0.1394
Barrett's mucosa at endoscopy (%)	14 (23.7)	20 (83.3)	<0.0001

Results

In 443 patients, the Z-line was endoscopically unremarkable (*n*=385) or suggestive of BM (*n*=58). The median age of patients with an unremarkable Z-line was 54 years (17–89 years) versus 59 years (29–83 years) in patients suspected to have BM. This difference was not significant.

In 83 patients (18.7%), the biopsy specimens from the Z-line showed metaplastic mucosa with goblet cells, and only these patients were further evaluated. In 49 of these patients (59.1%), the Z-line was classified as unremarkable and, in this group, there was only a slight preponderance of male gender (female:male =22:27). In the remaining 34 patients (40.9%), the Z-line was suggestive of BM and male patients predominated significantly (fe-

Fig. 1 **A** Intestinal metaplasia at the squamocolumnar junction as a part of *Helicobacter pylori*-induced multifocal intestinal metaplasia in the stomach (Haematoxylin and Eosin, 200×). **B** Detail showing type-I intestinal metaplasia, in which only the goblet cells contain sialomucins (*blue*) and/or sulphomucins (*purple*) (Gomori's aldehyde fuchsin–Alcian blue, 400×)

Fig. 2 **A** Squamocolumnar junction with Barrett's specialised columnar epithelium and goblet cells (Haematoxylin and Eosin, 400×). **B** The columnar cells between the goblet cells contain sulphated mucins (*purple* on Gomori's aldehyde fuchsin–Alcian blue). The goblet cells contain sialomucins and/or sulphomucins (Gomori's aldehyde fuchsin–Alcian blue, 400×)

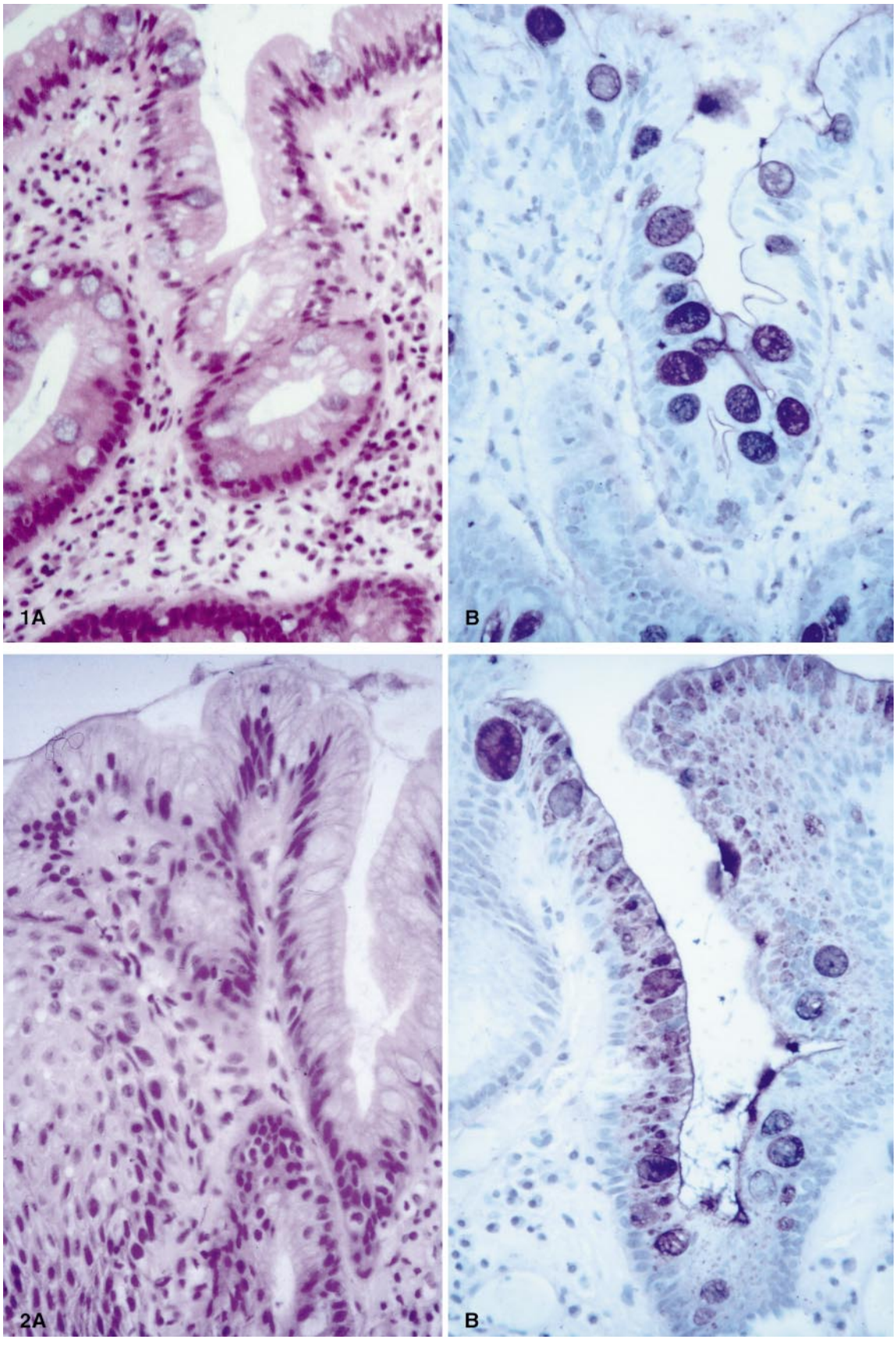
1A
B
2A
B

Table 3 Typing of intestinal metaplasia in patients with an unremarkable Z-line and suspected of Barrett's mucosa (BM)

Intestinal metaplasia	Unremarkable GOJ (n=49)	BM (n=34)
Type I/II	45 (91.8%)	14 (41.2%)
Type III	4 (8.2%)	20 (58.8%)
P value	<0.0001	0.3035

male:male =6:28, P<0.0005). HP infection was detected in 55 of 83 patients (66.3%). Fifteen of 34 patients (44.1%) with endoscopic BM and metaplasia had HP infection compared with 40 of 49 (81.6%) patients with an unremarkable Z-line (P<0.0001).

The results concerning the type of IM in biopsies from the Z-line are summarised in Table 2. Regarding patients' age, the type of IM showed no significant differences. The median age of the patients with type-III IM was 65 years (30–81 years), while those with type-I/II IM had a median age of 62 years (30–84 years). With regard to gender, a significant difference was found between patients with type-I/II relative to type-III IM, as the latter was more frequent in men (P=0.0371). Comparing the HP infection in these two groups, there was no significant difference found (P=0.1394). When analysed separately, type-I/II IM was, however, significantly associated with HP infection (P=0.0011) (Fig. 1), whilst type-III IM was not (P=0.6831).

IM in gastric biopsy specimens from the antrum and/or corpus was found in 32 of 59 patients (54.2%) harbouring type-I/II IM in biopsies from the Z-line. In contrast, of the 24 patients with type-III IM, only six (25%) showed gastric multifocal IM in the antrum and/or corpus. This difference was significant (P=0.016). There was no significant connection between the type of IM and erosive oesophagitis at endoscopy (P=0.1394). We found, however, a highly significant association between the endoscopic aspect of the Z-line and the type of IM (P<0.0001). As summarised in Table 3, patients with an unremarkable Z-line showed type-I/II IM at a significantly higher frequency (P<0.0001).

The diagnosis of type-III IM (Fig. 2) was significantly associated with a Z-line endoscopically suggestive of BM (P<0.0001). However, not all the biopsy specimens with metaplastic mucosa from an endoscopically defined BM were of type-III IM (P=0.3035). As a consequence, the specificity for type-III IM in BM is 91%. Sensitivity, however, amounts only to 58%. The positive predictive value of BM in type-III IM was 0.833; the negative predictive value was 0.762.

Discussion

The aetiology of IM at the SCJ is not uniform [14]. An unremarkable Z-line or only minor macroscopic alterations in the ora serrata, in particular, cause problems when pathogenetically assigning these alterations to IM in biopsy specimens obtained from this area. In terms of BM, reflux-induced metaplasias are pre-neoplastic lesions [15, 39]. Possibly, they are not only found in endoscopically conspicuous tongues and segments of columnar epithelium in the distal oesophagus, but they might also be present as very short segments of BM hardly detectable from the endoscopic point of view. The differentiation of such a "micro BM" from cardiac IM with a different pathogenesis is thus of special importance. This is reflected in the fact that a neoplastic and, finally, malignant transformation may also occur in short segments of BM [2, 3, 35, 47]. Since definite histomorphological criteria for the diagnosis of BM mucosa have not yet been established [31], it is also difficult for the pathologist to differentiate between a short segment of BM and cardiac IM. Biopsies often give no hints of BM, such as the doubling of the muscularis mucosae [43]. Several studies have demonstrated that cardiac IM is not a rare event [13, 41, 45]. Morales et al. [24] found cardiac IM in 23% of the patients, with a significant association to HP infection. Nandurkar et al. [26] reported a prevalence of IM of 36% at the SCJ and no association with HP infection. However, these authors failed to correlate the findings with the presence or absence of HP infection in the antrum and/or corpus, nor was a rapid urease test performed. This fact is important in that the milieu of IM, in particular, offers poor conditions for HP colonisation [37]. Some of our own previous investigations revealed cardiac IM in about 13% of the patients without a macroscopically conspicuous Z-line. This number increased to 34% in patients with endoscopic suspicion of BM [14].

IM of the antrum develops during a long-standing HP gastritis [5, 8, 20]. Histologically and functionally, the mucosa of the antrum and cardia show some similarities [44], which are also reflected in a comparable reaction to HP infection [10, 13]. The consequence is that IM at the SCJ may also arise from HP gastritis [11, 13]. A recent study suggested that different cytokeratin subsets may distinguish between BM and IM of the stomach [27]. In our study, we demonstrated that the typing of IM is also useful in the differential diagnosis of IM arising from HP infection relative to BM. There was a highly significant association between the endoscopic finding and the type of IM. Intestinal metaplasia of type I or II at an unremarkable SCJ occurs significantly more often in patients with HP infection and is a part of gastric multifocal IM at the same time. In contrast, if type-III IM was diagnosed, there was a significant association of this finding with a lesion endoscopically suggestive of BM. However, not all the biopsy specimens obtained from the endoscopically definite BM were always recognised as type-III IM. In some cases, more than one mucin type is detectable in BM [29]. As a sign, type-III IM in BM had a low sensitivity that might be improved by more extensive sampling of the SCJ. However, it might be possible that there is a subgroup of BM cases that have only type-I/II IM.

Peuchmaur et al. [29] demonstrated that an incomplete IM with sulphomucin secretion is no rare event in BM. The relationship of metaplastic alterations at the

SCJ with other pathogenetic mechanisms, such as HP infection, could not be taken into account in this early study (1984). Lapertosa et al. [21] also used histochemistry to investigate the mucin production in BM and demonstrated an incomplete colic metaplasia with sulphomucin production in 46 of 69 patients with specialised intestinalised epithelium in the oesophagus. The presence of IM with sulphomucin production appears to be a common event [34]. Jass [17] associated the occurrence of an incomplete colic metaplasia in the specialised columnar epithelium with an increased risk of carcinoma. Haggit et al. [16], however, do not think that there is any relationship between neoplastic transformation and the appearance of sulphomucin in non-goblet cells of BM. All these studies, related only to the typing of IM in BM, did not consider the association of different types of IM at the Z-line with a possible different pathogenetic background. Shah et al. [36] evaluated GAF-AB staining for subtyping IM in gastric and oesophageal biopsy specimens. They concluded that this staining is a simple, cost-saving and safe method for typing IM. As in the investigations mentioned above, they found type-III IM with sulphomucin production in non-goblet cells mostly in biopsies from the oesophagus.

Under consideration of the endoscopic aspect of the SCJ, distal gastric biopsies and the HP status, the type of IM at the SCJ may indicate its pathogenesis. Our results clearly show that the mucosa below the Z-line can be involved in HP-induced multifocal IM of the stomach. If there is no HP infection, no multifocal gastric IM and even an unremarkable Z-line, type-III IM is suggestive of BM. Only the follow-up examinations can answer the question of whether this is an initial BM. The diagnosis of a short segment of BM should therefore include endoscopic, histomorphological and histochemical characteristics.

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References

1. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF (1991) Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 265:1287–1289
2. Cameron AJ, Lomboy CT, Pera M, Carpenter HA (1995) Adenocarcinoma of the esophagogastric junction and Barrett's esophagus. Gastroenterology 109:1541–1546
3. Clark GWB, Smyrk TC, Burdiles P, Hoeft SF, Peters JH, Kiyabu M, Hindler RA, Bremner CG, DeMeester TR (1994) Is Barrett's metaplasia the source of adenocarcinomas of the cardia? Arch Surg 129:609–614
4. Correa P (1991) The epidemiology of gastric cancer. World J Surg 15:228–234
5. Craanen ME, Dekker W, Blok P, Ferweda J, Tytgat GNJ (1992) Intestinal metaplasia and *Helicobacter pylori*: an endoscopic bioptic study of the gastric antrum. Gut 33:16–20
6. Dixon MF, Genta RM, Yardley JH, Correa P and the participants in the International Workshop on the Histopathology of Gastritis, Houston 1994 (1996) Classification and grading of gastritis. Am J Surg Pathol 20:1161–1181
7. Ectors N, Dixon MF (1986) The prognostic value of sulphomucin positive intestinal metaplasia in the development of gastric cancer. Histopathology 10:1271–1277
8. Eidt S, Stolte M (1994) Prevalence of intestinal metaplasia in *Helicobacter pylori* gastritis. Scand J Gastroenterol 29:607–610
9. Filipe MI, Munoz N, Matko I, Kato I, Pompe-Kirn V, Jutersek A, Teuchmann S, Benz M, Prijon T (1994) Intestinal metaplasia types and the risk of gastric cancer: a cohort study in Slovenia. Int J Cancer 57:324–329
10. Genta RM, Huberman RM, Graham DY (1994) The gastric cardia in *Helicobacter pylori* infection. Hum Pathol 25:915–919
11. Goldblum JR, Vicari JJ, Falk GW, Rice TW, Peek RM, Easley K, Richter JE (1998) Inflammation and intestinal metaplasia of the gastric cardia: the role of gastrooesophageal reflux and *H. pylori* infection. Gastroenterology 114:633–639
12. Gottfried MR, McClave SA, Boyce HW (1989) Incomplete intestinal metaplasia in the diagnosis of columnar lined esophagus (Barrett's esophagus). Am J Clin Pathol 92:741–746
13. Hackelsberger A, Günther T, Schultze V, Labenz J, Roessner A, Malfertheiner P (1997) Prevalence and pattern of *Helicobacter pylori* gastritis in the gastric cardia. Am J Gastroenterol 92:2220–2224
14. Hackelsberger A, Günther T, Schultze V, Manes G, Dominguez-Muñoz J-E, Roessner A, Malfertheiner P (1998) Intestinal metaplasia at the gastrooesophageal junction: *Helicobacter pylori* gastritis or gastrooesophageal reflux disease? Gut 43:17–21
15. Haggitt RC (1994) Barrett's esophagus, dysplasia and adenocarcinoma. Hum Pathol 25:982–993
16. Haggitt RC, Reid BJ, Rabinovitch PS, Rubin CE (1988) Barrett's esophagus: correlation between mucin histochemistry, flow cytometry and histologic diagnosis for predicting increased cancer risk. Am J Pathol 131:53–61
17. Jass JR (1981) Mucin histochemistry of the columnar epithelium of the oesophagus: a retrospective study. J Clin Pathol 34:866–870
18. Jass JR, Filipe MI (1981) The mucin profiles of normal gastric mucosa, intestinal metaplasia and ist variants and gastric carcinoma. Histochem J 13:913–939
19. Kim SL, Waring PJ, Spechler SJ, Sampliner RE, Doos WG, Krol WF, Williford WO (1994) Diagnostic inconsistencies in Barrett's esophagus. Gastroenterology 107:945–949
20. Kuipers EJ, Uyterlinde AM, Peña AS, Rosendaal R, Pals G, Nelis GF, Festen HPM, Meuwissen SGM (1995) Long-term sequelae of *Helicobacter pylori* gastritis. Lancet 345:1525–1528
21. Lapertosa G, Baracchini P, Fulcheri E and the operative group for the study of esophageal precancer (1992) Mucin histochemical analysis in the interpretation of Barrett's esophagus. Results of a multicenter study. Am J Clin Pathol 98:61–66
22. Malfertheiner P, Dominguez-Muñoz JE, Heckenmüller H, Neubrand M, Fischer HP, Sauerbruch T (1996) Modified rapid urease test for detection of *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 8:53–56
23. McClave SA, Worth-Boyce H, Gottfried MR (1987) Early diagnosis of columnar-lined esophagus. A new endoscopic diagnostic criterion. Gastrointest Endosc 33:413–416
24. Morales TG, Sampliner RE, Bhattacharyya A (1997) Intestinal metaplasia of the gastric cardia. Am J Gastroenterol 92:414–418
25. Mullen PJ, Carr N, Milton JD, Rhodes JM (1995) Immunhistochemical detection of O-acetylated sialomucins in intestinal metaplasia and carcinoma of the stomach. Histopathology 27:161–167
26. Nandurkar S, Talley NJ, Martin CJ, Ng THK, Adams S (1997) Short segment Barrett's oesophagus: prevalence, diagnosis and associations. Gut 40:710–715
27. Ormsby AH, Goldblum JR, Rice TW, Richter JE, Falk GW, Vaezi MF, Gramlich TL (1999) Cytokeratin subsets can reliably distinguish Barrett's esophagus from intestinal metaplasia of the stomach. Hum Pathol 30:288–294

28. Pera M, Cameron AJ, Trastek VF, Carpenter HA, Zinsmeister AR (1993) Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. Gastroenterology 104:510–513
29. Peuchmaur M, Potet F, Goldfain D (1984) Mucin histochemistry of the columnar epithelium of the oesophagus (Barrett's oesophagus): a prospective biopsy study. J Clin Pathol 37:607–610
30. Ramesar KCRB, Sanders DAS, Hopwood D (1987) Limited value of type III intestinal metaplasia in predicting risk of gastric carcinoma. J Clin Pathol 40:1287–1290
31. Riddell RH (1996) Early detection of neoplasia of the esophagus and gastroesophageal junction. Am J Gastroenterol 91:853–863
32. Riddell RH (1996) The biopsy diagnosis of gastroesophageal reflux disease, "carditis", and Barrett's esophagus, and sequelae of therapy. Am J Surg Pathol 20[suppl]:31–50
33. Rokkas T, Filipe MI, Sladen GE (1991) Detection of an increased incidence of early gastric cancer in patients with intestinal metaplasia type III who are closely followed up. Gut 32:1110–1113
34. Rothery GA, Patterson JE, Stoddard CJ, Day DW (1986) Histological and histochemical changes in the columnar lined (Barrett's) esophagus. Gut 27:1062–1068
35. Schnell TG, Sontag SJ, Chejfec G (1992) Adenocarcinoma arising in tongues or short segments of Barrett's esophagus. Dig Dis Sci 37:137–143
36. Shah KA, Deacon AJ, Dunscombe P, Price AB (1997) Intestinal metaplasia subtyping: evaluation of Gomori's aldehyde fuchsin for routine diagnostic use. Histopathology 31:277–283
37. Siurala P, Sipponen P, Kekki M (1988) *Campylobacter pylori* in a sample of Finnish population: relations to morphology and functions of the gastric mucosa. Gut 29:909–915
38. Skinner DB, Walther BC, Riddell RH, Schmidt H, Iascone C, DeMeester TR (1983) Barrett's esophagus: comparison of benign and malignant cases. Ann Surg 198:554–565
39. Spechler SJ, Goyal RK (1986) Barrett's esophagus. N Engl J Med 315:362–371
40. Spechler SJ, Goyal RK (1996) The columnar-lined esophagus, intestinal metaplasia, and Norman Barrett. Gastroenterology 110:614–621
41. Spechler SJ, Zeroogian JM, Antonioli DA, Wang HH, Goyal RK (1994) Prevalence of metaplasia at the gastroesophageal junction. Lancet 344:1533–1536
42. Spicer SS, Meyer DB (1960) Histochemical differentiation of acid mucopolysaccharides by means of combined aldehyde fuchsin-alcian blue staining. Am J Clin Pathol 33:453–460
43. Takubo K, Sasajima K, Yamashita K, Tanaka Y, Fujita K (1991) Double muscularis mucosae in Barrett's esophagus. Hum Pathol 22:1158–1161
44. Toner PG, Cameron CHS (1995) The gastric mucosa. In: Whitehead R (ed) Gastrointestinal and oesophageal pathology, 2nd edn. Churchill Livingstone, Edinburgh, pp 15–32
45. Trudgill NJ, Suvarna SK, Kapur KC, Riley SA (1997) Intestinal metaplasia at the squamocolumnar junction in patients attending for diagnostic gastroscopy. Gut 41:585–589
46. Weinstein WM, Ippoliti AF (1996) The diagnosis of Barrett's esophagus: goblets, goblets, goblets. Gastrointest Endosc 44:91–95
47. Weston AP, Krmpotich PT, Cherian R, Dixon A, Topalovski M (1997) Prospective long term endoscopic and histologic follow-up of short segment Barrett's esophagus: comparison with traditional long segment Barrett's esophagus. Am J Gastroenterol 92:407–413