Improvement of gastric inflammation and resolution of epithelial damage one year after eradication of *Helicobacter pylori*

E M Witteman, M Mravunac, M J C M Beex, W P M Hopman, J S C Verschoor, G N J Tytgat, R W de Koning

Abstract

Aims—To investigate the effect of eradication of *Helicobacter pylori* infection on gastric epithelial damage and gastritis, scored according to the Sydney system.

Methods—Gastritis scores and epithelial damage were assessed in gastric biopsy specimens before, and five weeks and one year after anti-*H pylori* therapy in 66 patients with *H pylori* related gastritis.

Results—The mean initial levels of activity, inflammation, atrophy, intestinal metaplasia, and *H pylori* scores were higher in the antrum than in the corpus or fundus. Eradication of *H pylori* resulted in an improvement in the mean inflammatory score in antral biopsy specimens from 2.23 before treatment to 1.32 and 1.06, respectively, five weeks and one year after treatment. Corresponding values for fundic biopsy specimens were 1.30,

0.36 and 0.35. Activity scores improved from 1.41 before treatment to 0.13 and zero, respectively, five weeks and one year after treatment in antral biopsy specimens and from 0.60 before treatment to zero in fundic biopsy specimens. Before treatment, epithelial damage was present in 51% of biopsy specimens taken from the antrum and 23% of those from the corpus. Five weeks after eradication of *H pylori* none of the biopsy specimens revealed evidence of epithelial damage.

Conclusion—Eradication of *H pylori* is followed by a rapid, significant improvement in the gastritis score and resolution of epithelial damage in antral and fundic mucosa.

(J Clin Pathol 1995;48:250-256)

Keywords: *Helicobacter pylori*, gastric inflammation, epithelial damage, eradication.

Department of
Gastroenterology and
Hepatology,
Nijmegen University
Hospital, PO Box
9101, 6500 HB
Nijmegen,
The Netherlands
E M Witteman
W P M Hopman

Department of
Pathology
M Mravunac

Department of
Internal Medicine
M J C M Beex
R W de Koning

Statistical
Department,
Brocades Pharma
Yamanouchi Group,
Leiderdorp,
The Netherlands
J S C Verschoor

Department of
Gastroenterology,
Academic Medical
Centre, Amsterdam,
The Netherlands
G N J Tytgat

Correspondence to:
Dr E M Witteman.

Accepted for publication
4 August 1994

Figure 1 *H pylori* associated chronic gastritis of the antrum showing severe active inflammation and epithelial damage. There are cellular tufts (arrow) alternating with depleted apical mucus (modified Giemsa).

Figure 2 *H pylori* associated chronic gastritis of the fundus showing moderate active inflammation with intraepithelial infiltration of neutrophils (arrow) without epithelial damage (modified Giemsa).

Helicobacter pylori is widely accepted as an important cause of chronic gastritis.¹ *H Pylori* associated inflammation plays an important role in the pathogenesis of duodenal ulcer disease and is regarded as a risk factor for gastric carcinoma.²⁻⁴ The prevalence of infection increases with age, with those over 60 years of age having rates approaching 60%. *H pylori* infection usually persists for life and spontaneous recovery from infection is rare. The ecological niche of the micro-organism is the surface epithelium, with clustering at the gastric epithelial intercellular junctions.⁵ The gastric mucosa almost invariably shows evidence of inflammation and epithelial injury. Epithelial damage such as disintegration of apical mucus, epithelial irregularities and microerosions are typical of *H pylori* colonisation.^{6,7}

Gastritis is now scored according to the Sydney system, first introduced in 1990. The histological division of this classification separately assesses, in a semiquantitative manner, acute and chronic inflammatory changes, atrophy and intestinal metaplasia in antral and corpus biopsy specimens.^{8,9} To date, however, few studies on the inflammatory response have been

carried out using the Sydney system of scoring gastritis both before and after eradication of *H pylori* in different parts of the stomach.^{10,11} In particular, no study has systematically assessed the effect of eradication on epithelial damage. Surface epithelial degeneration has been a neglected aspect of *H pylori* associated gastritis.

The aim of this study was to investigate the distribution of *H pylori*, the degree of epithelial injury and the severity of gastritis, graded according to the Sydney system, and to assess improvements in the inflammatory changes and epithelial damage over one year of follow up after eradication of *H pylori* in dyspeptic patients with gastritis.

Methods

Patients (n = 313) with upper abdominal symptoms of at least one month's duration and without endoscopic abnormalities other than gastritis were considered as candidates for our study. Of the 313 patients, 150 (48%) had histological evidence of gastritis with concomitant *H pylori* infection confirmed by culture or histology, or both. Of these 150 patients, 66 gave their written informed consent for participation in this trial. From this group, 35 patients were randomly selected to be treated with colloidal bismuth subcitrate (CBS) (120 mg four times daily for four weeks) and metronidazole (MTZ) (250 mg four times daily for 10 days); the remaining 31 patients were treated with CBS, 120 mg four times daily, alone for four weeks, a standard regimen at the time of this study.

The patients underwent endoscopic examination before treatment, and five weeks and one year after cessation of treatment. The third endoscopy was performed earlier in cases in whom upper abdominal pain recurred.

On the first occasion, five antral biopsy specimens within a 5 cm radius of the pylorus, four biopsy specimens from the corpus (two proximal and two distal) and two fundic biopsy specimens were taken. Two antral biopsy specimens were cultured and three evaluated histologically. In 15 of the 66 patients only five antral, two fundic and no corpus specimens were taken. On the second and third endoscopies, five antral and two fundic biopsy specimens were taken. Eradication was defined as negative culture and histology at five weeks or more after completion of the therapy. *H pylori* related micro-organisms were cultured as described previously.¹²

HISTOLOGY

The biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin wax and stained with haematoxylin and eosin. *H pylori* infection was assessed in both haematoxylin and eosin stained and modified Giemsa stained sections. All of the biopsy specimens were examined by the same pathologist (MM) who was unaware of the patients' treatment. The different variables for grading gastritis were rated on a four point scale ranging from zero to three; 0, absent; 1, mild; 2, mod-

Figure 3 *H pylori* associated chronic gastritis of the antrum showing severe active inflammation and epithelial damage. There are multiple tufts alternating with depleted apical mucus (modified Giemsa).

erate; and 3, severe, according to the Sydney system.⁹ The following variables were considered. Inflammation was scored according to the presence and density of lymphocytes and plasma cells in the lamina propria; activity was graded according to the presence and density of neutrophil polymorphs in the lamina propria and in the epithelial layer; atrophy was graded according to the loss of gastric glands; presence of *H pylori*-like organisms was graded according to their density and distribution (0, absent; 1, occasional; 2, patchy; 3, layer of bacteria); metaplasia was scored according to severity (0, absent; 1, occasional, 2, severe). The mean score for each variable of the Sydney system was taken for each series of biopsy specimens sampled in the antrum, corpus and fundus.

The presence of a limited number of lymphocytes in the lamina propria in the absence of plasma cells was not considered indicative of inflammation. In addition to the criteria specified in the Sydney system the presence of an irregular gastric surface epithelium, depletion of epithelial cell apical mucus and the presence

of cellular tufts (composed of three to five tall columnar cells and almost always flanked by epithelial defects and areas of depleted mucus) were looked for on light microscopy, according to Chan *et al* (figs 1–4).^{6,7}

STATISTICS

The data were analysed using the non-parametric Wilcoxon signed rank test to determine whether the gastritis scores changed over time—that is, the score at time *t* compared with the pretreatment score (week 0). Comparisons between antral, corpus and fundic biopsy specimens were made using the Wilcoxon rank sum test. Spearman's rank correlation coefficients were computed for the association between the scores for *H pylori* and those for inflammation, activity, atrophy, metaplasia, and epithelial damage in the antral biopsy specimens. The χ^2 test was used to investigate whether there was an association between epithelial damage and other aspects of the Sydney classification.

Because of the gradual withdrawal of a substantial proportion of the patients from the study because of worsening disease the estimates of mean histological parameters became increasingly less reliable towards the end of the study. To compensate for these difficulties, an intention to treat analysis was undertaken. Missing data for patients who withdrew prematurely from the study were generated using the last observation carried forward approach, where the last data collected for patients were fixed until the last time point (that is, one year after treatment). Thus, patients who withdrew because of deteriorating health were considered unchanged for the remaining part of the study.

Results

PRETREATMENT (MORPHOLOGICAL DATA)

Of the 66 patients, 62 had pangastritis, occurring most prominently in the antrum. The mean levels of all five different variables of the Sydney classification were significantly higher in the antral compared with the corpus and fundic biopsy specimens (Wilcoxon rank sum test, $p < 0.05$; fig 5). In one of the 66 patients more than two antral biopsy specimens were necessary to detect *H pylori*-like microorganisms. In 43% of the patients there was activity in the antral biopsy specimens only and in 7% of the patients activity was present in corpus or fundic biopsy specimens only. In all patients antral biopsy specimens revealed chronic inflammation (68% had grade 2 inflammation).

Lymphoid follicles were found in 38, 5 and 11%, respectively, of the antral, corpus and fundic biopsy specimens from the *H pylori* positive patients. There was a direct correlation between the presence of lymphoid follicles and presence of epithelial damage (χ^2 test, $p < 0.05$). No significant correlation between the degree of *H pylori* colonisation and the prevalence of lymphoid follicles was found.

Irregular surface epithelium, loss of apical mucus and cellular tufts were detected sig-

Figure 4 Chronic gastritis of the antrum showing multiple *H pylori* related micro-organisms, intraepithelial neutrophils and loss of mucus (arrow) (modified Giemsa).

Table 1 Mean ratings for the histological parameters, graded according to the Sydney system in antral and fundic biopsy specimens before therapy (week 0) and five weeks and one year after treatment in patients in whom *H pylori* eradication was successful compared with those with persistent infection (intention to treat analysis)

	CBS (not-eradicated) n = 31	CBS + MTZ (not-eradicated) n = 12	CBS + MTZ (eradicated) n = 23	Eradicated + / -
Antrum				
activity				
0	1.4	1.3	1.4	
5 weeks	1.3	1.3	0.3*	†
1 year	1.3	1.3	0.3*	†
inflammation				
0	2.2	2.2	2.3	
5 weeks	2.1	2.1	1.5*	†
1 year	2.2	2.2	1.2*	†
metaplasia				
0	0.5	0.4	0.3	
5 weeks	0.5	0.6	0.1	
1 year	0.6	0.7	0.2	
atrophy				
0	0.2	0.1	0.3	
5 weeks	0.1	0.0	0.2	
1 year	0.1	0.0	0.2	
Fundus				
activity				
0	0.9	0.3	0.5	
5 weeks	0.6	0.1	0.1*	
1 year	0.7	0.1	0.0*	
inflammation				
0	1.6	1.4	1.0	
5 weeks	1.4	1.3	0.5*	†
1 year	1.4	1.3	0.4*	†
metaplasia				
0	0.0	0.0	0.0	
5 weeks	0.0	0.1	0.0	
1 year	0.1	0.1	0.0	
atrophy				
0	0.0	0.0	0.0	
5 weeks	0.0	0.0	0.0	
1 year	0.0	0.0	0.0	

* p<0.05 from baseline (pretreatment); † p<0.05 between patients with and without *H pylori* infection.

Figure 5 Mean scores of histological parameters according to the Sydney system on gastric biopsy specimens from patients with *H pylori* related gastritis. The mean level of all five variables was significantly higher in antral compared with corpus and fundic biopsy specimens (Wilcoxon rank-sum test; $p < 0.05$).

Figure 6 Percentage of biopsy specimens with epithelial damage in patients with *H pylori* related gastritis in antrum, corpus and gastric fundus. Irregular surface epithelium, loss of apical mucus and cellular tufts occurred significantly more frequently in the antrum than in the corpus or fundic mucosa (χ^2 test; $p < 0.01$).

nificantly more frequently in the antral than in the corpus and fundic mucosa (χ^2 test, $p < 0.01$; fig 6).

A significant, positive association (Spearman's rank correlation) was detected between the *H pylori* score (Sydney system) and the score for inflammation ($p < 0.001$) and for activity ($p < 0.001$). No statistically significant association was observed between the grade of *H pylori* infection and the scores for atrophy or intestinal metaplasia. Patients without epithelial damage had significantly lower scores for chronic inflammation ($p = 0.05$), activity ($p = 0.02$), atrophy ($p = 0.04$), and intestinal metaplasia ($p = 0.0005$). No statistically significant association could be found with respect to the *H pylori* score ($p = 0.18$).

POST-TREATMENT MORPHOLOGICAL DATA

At five weeks, *H pylori* was eradicated in 23 of the 35 patients (66%) treated with dual therapy, but in none of the 31 patients treated with CBS alone. Fifty of the 66 patients underwent a third endoscopy. Patients who withdraw from the study included those with persisting *H pylori* infection (10 of 43) and those in whom *H pylori* infection had been eradicated (six of 23). Nine patients underwent the third endoscopy within nine months of finishing therapy because their symptoms recurred.

H pylori-like micro-organisms persisted in all 33 patients positive at five weeks who underwent the third endoscopy. Reinfection had not occurred in any of the 17 *H pylori* negative patients who underwent the third endoscopy. Statistically significant improvements in activity and chronic inflammation were observed in patients with successful *H pylori* eradication following combination therapy (table). Such improvement was not observed in persistently *H pylori* positive patients on either treatment regimen.

In patients whose *H pylori* infection had been successfully eradicated epithelial injury (characterised by surface epithelial irregularity, loss of apical mucus or cellular tufts) in the fundic and antral mucosa was resolved, five weeks and one year after treatment, whereas epithelial injury was still present in patients with persistent *H pylori* infection.

Five weeks and one year after treatment, lymphoid follicles were still present in seven of 23 (30%) and one of 17 (6%), respectively, antral biopsy specimens from *H pylori* negative patients. No corresponding decrease in the prevalence of lymphoid follicles was seen in those with persistent *H pylori* infection.

There were no significant changes in atrophy or intestinal metaplasia scores in antral and fundic biopsy specimens during follow up in patients with (non-eradicated) and without (eradicated) persistent *H pylori* infection.

Discussion

H pylori associated chronic inflammation may lead to the development of atrophy and intestinal metaplasia in the gastric mucosa.¹³ However, there remain many unanswered

questions about the progression and distribution of chronic *H pylori* related inflammation, activity, atrophy, and intestinal metaplasia and potential reversibility after *H pylori* eradication.

The histological divisions of the Sydney classification permit the separate examination of the behaviour of acute and chronic inflammation in different parts of the stomach following *H pylori* therapy.

Our results suggest that activity and epithelial damage resolve quite rapidly after eradication of *H pylori* and therefore can be used as markers of successful therapy, confirming conclusions reached by other authors.^{10,11} Resolution of chronic inflammation is a much slower process in all parts of the stomach and in most patients regression is still incomplete one year after eradication. In contrast to the study of Di Napoli *et al.*,¹⁰ in this study failure to eradicate *H pylori* did not result in even a temporary improvement in antral gastritis scores after five weeks. The inflammatory reaction, the density of the layer of the bacteria and epithelial damage was greater in fundic than in antral biopsy specimens, confirming the findings of other authors.¹⁴⁻¹⁷ The reduction in inflammation in the corpus and fundus may be related to a lower density of *H pylori* colonisation. We found that the intensity of gastritis was significantly related to the density of *H pylori*, which is consistent with the findings reported by other investigators.¹⁶⁻¹⁹

In 48% of our patients with upper abdominal symptoms and no endoscopic abnormalities there was histological evidence of chronic gastritis. *H pylori* negative antral gastritis represented 23% of all gastritis cases. All other patients with gastritis were positive for *H pylori* infection. In the literature the incidence of *H pylori* negative gastritis has been reported to vary from zero to 28%.^{14,15,20} *H pylori* was detected in biopsy specimens from the corpus and fundus in a few patients. It is possible that *H pylori* infection cleared spontaneously in some patients because of an unfavourable gastric environment. In fact, in 60% of patients with *H pylori* negative gastritis and moderate inflammation and activity there was evidence of intestinal metaplasia or atrophy, which are often associated with low acid output.

Chan and Hui⁶ described characteristic surface changes such as loss of cell mucus, epithelial erosions and cellular tufts around gastric ulcers of patients with *H pylori* infection in contrast to the changes present in *H pylori* negative patients with gastric ulcer disease. We found similar epithelial changes in many patients with *H pylori* related gastritis in the absence of gastric ulceration. The sensitivity of the presence of cellular tufts and depletion of apical mucus on microscopy as markers for the presence of *H pylori* (29 and 49%, respectively) was much lower in the patients with gastritis in this study compared with the corresponding patient group in the study by Chan and Hui.⁶ We were surprised not to find a correlation between the density of *H pylori* infection and evidence of epithelial damage. Leung *et al.*²¹ reported an association between the degree

of *H pylori* colonisation and the severity of epithelial damage. A possible explanation for this discrepancy is that their scoring system graded both focal maximal severity as well as the overall extent of bacterial colonisation. The specificity of epithelial damage as a marker of eradication in our study was very high. In all biopsy specimens of patients in whom *H pylori* had been eradicated epithelial damage resolved rapidly within five weeks of cessation of therapy. There was a significant association between the inflammatory reaction and the degree of epithelial damage.

Gastric lymphoid tissue is reported to develop in response to chronic infection by *H pylori* and is associated with low grade B cell gastric lymphoma.²²⁻²⁴ Lymphoid follicles were found in 38% of antral biopsy specimens in this study and appeared to be pathognomonic of *H pylori* infection.²⁵ Lymphoid follicles disappeared slowly after eradication of *H pylori*.

Atrophy and intestinal metaplasia did not resolve, at least during the short follow up period in this study. The development of atrophy and intestinal metaplasia is multifactorial and factors other than bacterial infection alone are presumably involved (for example, diet induced injury and bile reflux).^{26,27} However, longitudinal studies report the increased prevalence of chronic gastritis and *H pylori* infection as well as an increased prevalence of atrophy and intestinal metaplasia with increasing age.²⁸ Furthermore, changes in the epidemiology of *H pylori* have also resulted in changes in the epidemiology of atrophic gastritis and intestinal metaplasia and subsequently in the occurrence of gastric carcinoma or peptic ulcer disease.^{29,30} Many questions about the natural history of chronic gastritis remain unanswered. The natural progression of chronic gastritis and the possible resolution of atrophy and intestinal metaplasia following the eradication of *H pylori* merits further study.

We are grateful to Mr T Hagendoorn for taking the photographs.

- 1 Dooley CP, Cohen H, Fitzgibbons PL, Bauer M, Appleman MD, Perez-Perez GI, *et al.* Prevalence of *Helicobacter pylori* infection and histologic gastritis in asymptomatic persons. *N Engl J Med* 1989;321:1562-6.
- 2 Graham DY, Lew GM, Klein PD, Evans DG, Evans DJ, Saeed ZA, *et al.* Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study. *Ann Intern Med* 1992;116:705-8.
- 3 Nomura A, Stemmerman GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. *N Engl J Med* 1991;325:1132-6.
- 4 Eurogast Study Group. An international association between *Helicobacter pylori* infection and gastric cancer. *Lancet* 1993;341:1359-62.
- 5 Chen XG, Correa P, Offerhaus J, Rodriguez E, Fanney F, Hoffman E, *et al.* Ultrastructure of the gastric mucosa harboring *Campylobacter*-like organisms. *Am J Clin Pathol* 1986;86:575-82.
- 6 Chan WY, Hui PK, Chan JKC, Cheung PS, Ng CS, Sham CH, *et al.* Epithelial damage by *Helicobacter pylori* in gastric ulcers. *Histopathology* 1991;19:47-53.
- 7 Hui PK, Chan WY, Cheung PS, Chan JKC, Ng CS. Pathological changes of gastric mucosa colonized by *Helicobacter pylori*. *Hum Pathol* 1992;23:548-56.
- 8 Misiewicz JJ, Tytgat GNJ, Goodwin CS, Price A, Sipponen P, Strickland R. The Sydney system: A new classification of gastritis. Working Party Reports. Sydney: World Congress of Gastroenterology, 1990:1-10.
- 9 Price AB. The Sydney System: Histological division. *J Gastroenterol Hepatol* 1991;6:209-22.
- 10 Di Napoli A, Petrino R, Boero M, Bellis D, Chiandussi L. Quantitative assessment of histological changes in chronic gastritis after eradication of *Helicobacter pylori*. *J Clin Pathol* 1992;45:796-8.

- 11 Valle J, Seppälä K, Sipponen P, Kosunen T. Disappearance of gastritis after eradication of *Helicobacter pylori*. *Scand J Gastroenterol* 1991;26:1057-65.
- 12 Witteman EM, Hopman WPM, Becx MJCM, De Koning RW, Tytgat GNJ, Janssen AJHM, et al. Smoking habits and the acquisition of metronidazole resistance in patients with *Helicobacter pylori*-related gastritis. *Aliment Pharmacol Ther* 1993;7:683-7.
- 13 Craanen ME, Dekker W, Block P, Ferwerda J, Tytgat GNJ. Intestinal metaplasia and *Helicobacter pylori*: an endoscopic bioptic study of the gastric antrum. *Gut* 1992;33:16-20.
- 14 Hazell SL, Hennessy WB, Borody TJ, Carrick J, Ralston M, Brady L, et al. *Campylobacter pyloridis* gastritis. Distribution of bacteria and associated inflammation in the gastroduodenal environment. *Am J Gastroenterol* 1987;82:297-301.
- 15 Li YY, Hu PJ, Du GG, Hazell SL. The prevalence of *Helicobacter pylori* infection in the People's Republic of China. *Am J Gastroenterol* 1991;86:446-9.
- 16 Loffeld RJLF, Potters HVPJ, Arends JW, Stobberingh E, Flendrig JA, van Spreuwel WP. *Campylobacter* associated gastritis in patients with non-ulcer dyspepsia. *J Clin Pathol* 1988;41:85-8.
- 17 Satch K, Kimura K, Yoshida Y, Kasano T, Kihira K, Taniguchi Y. A topographical relationship between *H pylori* and gastritis: quantitative assessment of *H pylori* in the gastric mucosa. *Am J Gastroenterol* 1991;86:285-91.
- 18 Stolte M, Eidt S, Ohnsmann A. Differences in *Helicobacter pylori* associated gastritis in the antrum and body of the stomach. *Z Gastroenterol* 1990;28:229-33.
- 19 Bayerdörffer E, Lehn N, Hatz R, Mannes GA, Dertel H, Sauerbruch T, et al. Difference in expression of *Helicobacter pylori* gastritis in antrum and body. *Gastroenterology* 1992;102:1575-82.
- 20 Hu PJ, Li YY, Mitchell HM, Zhou MH, Chen MH, Du GG, et al. Oxyntic and antral gastritis in the People's Republic of China: diagnosis and relationship of *Helicobacter pylori*. *Am J Gastroenterol* 1992;87:741-45.
- 21 Leung KM, Hui PK, Chan WY, Thomas TMM. *Helicobacter pylori*-related gastritis and gastric ulcer. *Am J Clin Pathol* 1992;98:569-74.
- 22 Stolte M, Eidt S. Lymphoid follicles in the antral mucosa: immune response to *Campylobacter pylori*? *J Clin Pathol* 1989;42:1269-71.
- 23 Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, et al. *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med* 1994;330:1267-71.
- 24 Hussell T, Isaacson PG, Crabtree JE, Spencer J. The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to *Helicobacter pylori*. *Lancet* 1993;341:571-4.
- 25 Wyatt JL, Rathbone BJ. Immune response of the gastric mucosa to *Campylobacter pylori*. *Scand J Gastroenterol Suppl* 1988;142:44-9.
- 26 Sobala GM, Pignatelli B, Schorah CJ, Bartsch H, Sanderson M, Dixon MF, et al. Levels of nitrite, N-nitroso compounds, ascorbic acid and total bile acids in gastric juice of patients with and without precancerous conditions of the stomach. *Carcinogenesis* 1991;12:193-8.
- 27 Correa P, Cuello C, Fajardo LF, Haenszel W, Bolanos O, De Ramirez B. Diet and gastric cancer: nutrition survey in a high risk area. *J Natl Cancer Inst* 1983;70:673-8.
- 28 Sipponen P, Kekki M, Siurala M. The Sydney System: Epidemiology and natural history of chronic gastritis. *J Gastroenterol Hepatol* 1991;6:244-51.
- 29 Dixon MF, Sobala GM. Gastritis and duodenitis: the histopathological spectrum. *Eur J Gastroenterol Hepatol* 1992;4 (Suppl 2):S17-23.
- 30 Sipponen P. *Helicobacter pylori* infection—a common worldwide environmental risk factor of gastric cancer? *Endoscopy* 1992;24:424-7.