Helicobacter pylori infection and chronic gastritis in gastric cancer

P Sipponen, T U Kosunen, J Valle, M Riihelä, K Seppälä

Abstract

Aims: **To investigate the prevalence of *Helicobacter pylori* associated chronic gastritis in patients with gastric cancer.**

Methods: **Serum IgG antibodies for *H pylori* were determined in 54 consecutive patients with gastric carcinoma. The prevalence of *H pylori* in gastric mucosa was also examined histologically (modified Giemsa) in 32 patients from whom adequate biopsy specimens of the antrum and corpus were available. Thirty five patients with gastrointestinal tumours outside the stomach and 48 with non-gastrointestinal malignancies served as controls.**

Results: **Of the 54 patients, 38 (70%) had *H pylori* antibodies (IgG) in their serum (three additional patients had *H pylori* antibodies IgA, class specific but not IgG specific). This prevalence was significantly higher ($p < 0.05$) than that (49%) in the 35 controls. No differences in prevalence of *H pylori* antibodies were found between gastric cancer cases of intestinal (IGCA) or diffuse (DGCA) type, both these types showing *H pylori* antibodies (IgG) in 71% of the patients. In the subgroup of 32 subjects, five patients had normal gastric mucosa and four showed corpus limited atrophy ("pernicious anaemia type" atrophy of type A). All of these nine patients had no evidence of current or previous *H pylori* infection in serum (no IgG antibodies) or in tissue sections (negative Giemsa staining). The remaining 23 patients had antral or pangastritis, and all had evidence of current or previous *H pylori* infection.**

Conclusions: ***H pylori*** **associated chronic gastritis was the associated disease in 75% of the patients with gastric cancer occurring equally often in both IGCA and DGCA groups. About 25% of cases seem to have a normal stomach or severe corpus limited atrophy, neither of which showed evidence of concomitant *H pylori* infection.**

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The role of *Helicobacter pylori* infection in the pathogenesis of gastric cancer is an important but unresolved issue. The importance of *H pylori* infection in gastric carcinoma is supported by recent epidemiological observations which indicate that the prevalence of *H pylori* infection and the incidence of gastric carcinoma are significantly associated.[1–5] It is now accepted that *H pylori* infection is the main cause of chronic gastritis which results in many patients in atrophy and metaplasia of the underlying mucosa.[6–8] Both these conditions are known to be associated with an increased risk of gastric carcinoma.[9–11] It has been assumed that there is a sequence from *H pylori* infection to gastritis and to mucosal alterations which favour the genesis of gastric carcinoma.[12]

But there are several problems with regard to the association between *H pylori* and gastric carcinoma. First, chronic gastritis with subsequent atrophy may arise without concomitant *H pylori* infection.[13] This could be the case particularly in chronic corpus gastritis which leads to severe corpus atrophy of pernicious anaemia type, also well known as a precursor to gastric carcinoma.[10] Secondly, atrophy and metaplasia are implicated in the pathogenesis of gastric carcinoma of the intestinal type,[14] whereas gastric carcinoma of the diffuse type, which comprises 40–50% of all cases of gastric carcinoma, does not clearly coexist with atrophy and metaplasia, and its association with gastritis and *H pylori* infection is, therefore, less clear. Thirdly, gastric carcinoma may also arise in gastric mucosa without histologically demonstrable gastritis or *H pylori* infection,[14] suggesting that not all cases of gastric carcinoma can be related to previous or current gastritis and *H pylori* infection.

Methods

The series consisted of 54 consecutive patients with gastric carcinoma diagnosed in Jorvi Hospital in 1988 and 1989. Cancers of cardiac region of the stomach and those occurring in patients who had already undergone surgery in the stomach were excluded. Upper gastrointestinal endoscopy, taking biopsy specimens from the tumour area, was performed in all the patients, and cancer was diagnosed histologically. In addition to the biopsy specimens from the tumour area, one to three biopsy specimens from both antrum and corpus were available from 32 (59%) patients. The mean age and the male:female ratio of the series are presented in table 1.

The presence and type of chronic gastritis, and the prevalence of *H pylori* (modified Giemsa) in the 32 patients with biopsy specimens taken from the antrum and corpus were interpreted and presented according to the Sydney system.[15 16]

Gastric carcinoma was classified histologically into intestinal (31 patients), diffuse (21 patients), and unclassified (two patients) according to the criteria of Laurén.[17]

The *H pylori* antibodies were determined from serum samples of all subjects using enzyme immunoassay. The antigen was an acid extract from *H pylori* strain NCTC 11637, and

Table 1 Prevalence of H pylori antibodies in patients with gastric cancer and with other types of gastrointestinal or extra-gastrointestinal cancers

	Total	H pylori antibodies n (%)			Age Mean (SD)	M/F
		IgG	IgA	IgM		
Gastric cancer	54	38 (70)*	29 (54)	3 (6)	65 (16)	26/28
Cancer of gastrointestinal tract						
Oesophagus	6	2 (33)	2 (33)	0	77 (6)	2/4
Pancreas	7	2 (29)	1 (14)	0	62 (14)	4/3
Colon	22	13 (59)	10 (45)	3 (14)	63 (12)	14/8
All	35	17 (49)	13 (37)	3 (9)	65 (12)	20/15
Other cancers	48	26 (54)	20 (42)	1 (2)	66 (12)	34/14

*Difference to "cancer of gastrointestinal tract": p = 0·036 (χ^2).

IgG, IgA, and IgM class antibodies were determined separately as described.[18] The reaction was semiquantitatively estimated as mild (+), moderate (++), or strong (+++). The antibody assays were performed blind without prior knowledge of clinical diagnosis or histology.

Thirty five consecutive patients with histologically verified cancer in gastrointestinal organs other than the stomach and 48 patients with non-gastrointestinal malignancies served as controls. *H pylori* antibodies were determined in all these subjects. The number of patients with different types of cancer, and the demographic data of these series, are given in table 1.

The χ^2 test and Student's *t* test were used to calculate the significance of the differences. Kappa statistics was calculated for evaluation of concordance between histology and serology in the diagnosis of the *H pylori* infection.

Results

H pylori antibodies (IgG) were found in 38 (70%) of the 54 patients with gastric carcinoma (fig 1, table 1). This prevalence was higher (p = 0·036; χ^2) than that in the control subjects with malignant tumour of the gastrointestinal tract outside the stomach (table 1). No differences were found in the prevalence of *H pylori* antibodies among the gastric carcinoma types: antibodies of IgG class were found in 71% of both IGCA and DGCA patients (figs 2 and 3).

The prevalence of *H pylori* antibodies in patients with gastric carcinoma showed a slight negative correlation with age (table 2). The prevalence of patients with *H pylori* antibodies was highest (80%) in the youngest age group (30–49 years) and, in contrast to the prevalence of *H pylori* antibodies in the general population,[18] it tended to decrease slightly with increasing age. Correspondingly, the patients with gastric carcinoma and *H pylori* antibodies were also slightly younger (63 (16) years) than those without the antibodies (67 (18) years). In all age groups the prevalence of *H pylori* antibodies was higher in the patients with gastric carcinoma than in the controls without gastric carcinoma (table 2).

Details of the patients with gastric carcinoma with biopsy specimens available from the antrum and corpus mucosa are listed in table 3. Of these, five (16%) had a normal stomach (both antrum and corpus) and four (13%) patients had chronic corpus gastritis with severe corpus atrophy (A type), two of them also having pernicious anaemia. None of these nine patients had *H pylori* IgG antibodies, or bacteria on histological examination (table 3).

After the nine patients with a normal stomach or with corpus limited severe atrophy had been excluded 23 patients with evidence of *H pylori* infection remained: 22 had IgG antibodies, one had no IgG antibodies but had IgA antibodies and bacteria at histological examination (case 14: table 3). All these subjects had chronic antral gastritis or pangastritis with or without concomitant atrophy. In this group there were no significant differences

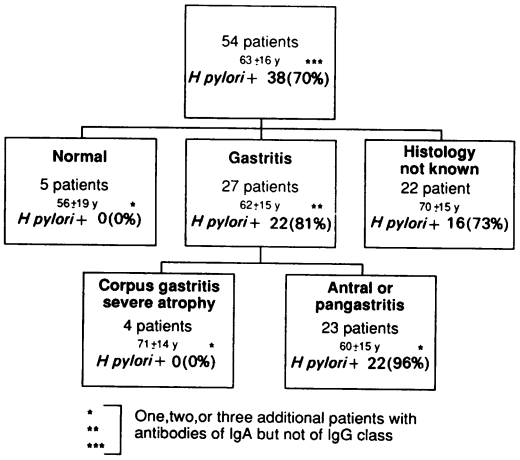

Figure 1 Prevalence (number and percentage) of patients with H pylori IgG antibodies in 54 consecutive cases of gastric cancer: relation to the state of the gastric mucosa.

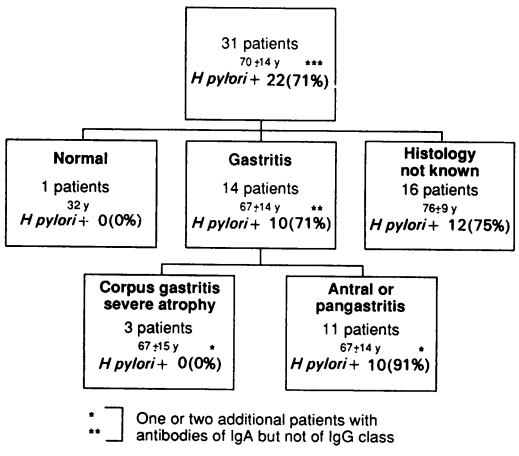

Figure 2 Prevalence (number and percentage) of patients with H pylori IgG antibodies in 31 cases of gastric cancer of intestinal type: relation to the state of the gastric mucosa.

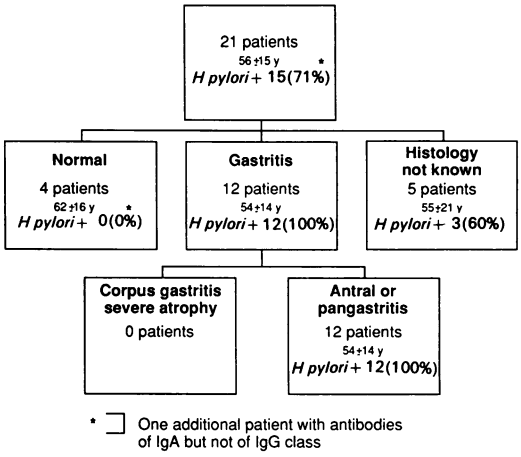

Figure 3 Prevalence (number and percentage) of patients with H pylori IgG antibodies in 21 cases of gastric cancer of diffuse type: relation to the state of the gastric mucosa.

between patients with IGCA or DGCA with regard to prevalence of *H pylori* antibodies (figs 2 and 3): 91% and 100% of the patients had IgG class antibodies, respectively.

In general, the prevalence of *H pylori* in histological specimens agreed with the findings of serology. Except for one, all patients with evidence of *H pylori* in tissue sections also had *H pylori* IgG class antibodies in serum. On the other hand, of the 22 patients with *H pylori* antibodies, only 14 (64%) had the organisms in tissue sections. The overall agreement between the two methods for detecting *H pylori* infection was 72% (κ statistic 0·48).

With regard to the failure to diagnose *H pylori* infection by serology or histology in the 23 patients with antral or pangastritis, atropy in the underlying mucosa seemed to be the most important discriminating factor (table 3). A noticeable atrophy, particularly in corpus mucosa, tended to indicate negative *H pylori* histology (although serology was positive) in these patients. Six out of the eight patients with negative *H pylori* histology showed moderate corpus atrophy; this was not seen in those with positive *H pylori* histology (table 3). Correspondingly, the mean age tended to be higher in subjects with negative *H pylori* histology (69 (9) years) than in those with a positive one (55 (16) years), indicating that the mucosal changes in these *H pylori* negative subjects could have been of longer duration, and be at a more advanced stage than those in *H pylori* positive subjects.

Discussion

H pylori infection is common in patients with gastric carcinoma, but its prevalence varies considerably—from 19% to 80%.[12 19–21] In this study the overall *H pylori* antibody prevalence was 70% in 54 patients with gastric carcinoma. In the analysis of the subgroup of 32 patients with gastric carcinoma with histological biopsy specimens taken from antrum and corpus, and after exclusion of the nine patients with a normal stomach or severe corpus limited atrophy (A type atrophy), all remaining 23 patients with antral gastritis or pangastritis had evidence of *H pylori* infection (22 having *H pylori* IgG class antibodies, one having no IgG antibodies but showing IgA antibodies and organisms in tissue sections). This suggests that *H pylori* associated chronic gastritis is the major contributory factor in patients with gastric carcinoma. This type of gastritis seems to affect about 70–75% of patients with gastric carcinoma.

The overall prevalence of *H pylori* antibodies (70%) was significantly higher in patients with gastric carcinoma than in controls (49%) who harboured gastrointestinal malignancies other than gastric carcinoma. The age specific prevalence of *H pylori* antibodies in patients with gastric carcinoma did not show an increase in prevalence with age as is the case in the general population.[18] Even the youngest group of patients with gastric carcinoma (30–49 years) had antibodies in 80% of cases, which is significantly ($p = 0·013$) more than expected (39%).[18] This suggests that *H pylori* infection and subsequent chronic gastritis are specifically associated with gastric carcinoma.

These observations do not necessarily preclude the possibility that *H pylori* infection is a consequence of the altered luminal environment in gastric cancer instead of being a specific precursor for it. On the other hand, several earlier follow up studies have suggested that gastritis and atrophy precede the appearance of cancer,[14] and in addition, the specific absence of *H pylori* infection in patients with gastric carcinoma with normal stomach or in those with corpus limited atrophy contradicts the suggestion that *H pylori* infection would be secondary to gastric carcinoma.

Four patients showed severe corpus limited atrophy, a characteristic feature of pernicious anaemia.[22] In fact, two of these four subjects had clinical evidence of pernicious anaemia. None had *H pylori* class IgG antibodies or

Table 2 Prevalence of patients with H pylori antibodies (positive) of class IgG in gastric carcinoma and other cancer patients (relation to age)

	Age group (years)			
	30–49	50–69	70+	All
Gastric carcinoma patients				
Total	10	19	25	54
H pylori positive	8 (80%)	13 (68%)†	17 (68%)*	38 (70%)‡
Patients with cancer other than gastric carcinoma				
Total	9	38	37	84
H pylori positive	5 56%)	22 (58%)††	16 (43%)†	43 (51%)**

*one additional patient had *H pylori* antibodies of IgA class but not of IgG;
†two additional patients had *H pylori* antibodies of IgA class but not of IgG;
‡three additional patients had *H pylori* antibodies of IgA class but not of IgG;
††four additional patients had *H pylori* antibodies of IgA class but not of IgG;
**six additional patients had *H pylori* antibodies of IgA class but not of IgG.

Table 3 H pylori infection in histology and serology in 32 patients with gastric carcinoma: relation to morphological state of antral and corpus mucosa

Gastric carcinoma	Type*	Age (y)	Sex	Antrum†	Corpus†	H pylori Histology	H pylori Serology		
							IgG	IgA	IgM
1	IGCA	32	M	0	0	−	−	−	−
2	DGCA	67	M	0	0	−	−	−	−
3	DGCA	38	M	0	0	−	−	−	−
4	DGCA	74	F	0	0	−	−	−	−
5	DGCA	69	M	0	0	−	−	+	−
6	IGCA	52	F	0	4	−	−	−	−
7	IGCA	69	M	1	4	−	−	−	−
8	IGCA	81	F	1	4	−	−	+	−
9	uncl	81	F	0	4	−	−	−	−
10	IGCA	67	M	1	1	+	+	++	−
11	IGCA	71	F	1	1	+	++	−	−
12	IGCA	70	M	3	0	+	+++	−	−
13	IGCA	31	M	2	1	+	+++	+	−
14	IGCA	69	F	2	0	+	−	++	+
15	IGCA	86	M	4	2	+	++	+	−
16	DGCA	41	M	1	1	+	++	+	−
17	DGCA	56	F	3	2	+	++	−	−
18	DGCA	61	F	1	1	+	+++	+++	−
19	DGCA	43	F	1	1	+	+++	+	−
20	DGCA	38	M	1	1	+	+	−	−
21	DGCA	57	M	1	1	+	++	−	−
22	DGCA	44	F	2	1	+	+++	+	−
23	DGCA	59	F	1	1	+	+	+	−
24	DGCA	39	F	1	0	+	++	++	−
25	IGCA	64	F	1	3	−	+++	+	−
26	IGCA	66	M	4	3	−	+	+	−
27	IGCA	83	M	1	1	−	+	−	−
28	IGCA	70	M	4	3	−	++	+	+
29	IGCA	60	F	3	3	−	++	++	−
30	DGCA	82	F	1	1	−	+++	+	+
31	DGCA	58	F	1	3	−	+++	+	−
32	DGCA	70	F	4	3	−	+	−	−

Abbreviations:
*IGCA, DGCA, uncl = intestinal, diffuse and unclassified;
†grade of chronic gastritis; 0 = normal mucosa; 1 = chronic gastritis without atrophy; 2-4 = chronic gastritis with mild, moderate, or severe atrophy (and metaplasia), respectively.

bacteria in tissue sections, confirming the earlier observations that *H pylori* infection is rarely seen in pernicious anaemia or in severe corpus limited atrophy.[13 23] Current data indicate that in Finland about 5% of gastric carcinoma cases are associated with pernicious anaemia, and that about another 5% could be associated with severe corpus limited atrophy (A type) without concomitant anaemia.

In the subgroup of 32 patients with biopsy specimens taken from antrum and corpus, five did not show gastritis, atrophy, or signs of previous or current *H pylori* infection (no IgG antibodies; no evidence of the organism in biopsy specimens from antrum and corpus), suggesting that probably 10–20% of gastric carcinoma cases developed in a histologically normal stomach. Notably, four out of the five patients had gastric carcinoma of the diffuse type (DGCA) and were relatively young. They may represent genetically determined cases of gastric carcinoma and may not be attributable to *H pylori* infection or gastritis. Hereditary factors have been suggested as important in the pathogenesis of some cases of gastric carcinoma, especially those of DGCA.[24 25]

There was rather good concordance between the findings in tissue sections and serum samples in the detection of *H pylori* infection. All except one with positive *H pylori* histology had *H pylori* IgG class antibodies. The overall agreement between the two methods was therefore 72% (κ statistic 0·48). All gastric carcinoma cases with antral or pangastritis probably represent *H pylori* associated gastritis: all such patients showed either positive serology or histology for *H pylori* infection.

IgA and IgM class antibodies showed a worse concordance with *H pylori* in tissue sections than those of IgG class. Antibodies of IgM class were present only occasionally and those of IgA class gave several false negative and positive results compared with prevalence of *H pylori* in tissue sections. IgG antibodies could be the best determinant of *H pylori* infection in patients with gastric carcinoma.

The histological demonstration of *H pylori* may be difficult in a severely atrophic stomach, particularly in corpus atrophy.[13] Positive serology, however, often occurs in such patients, indicating previous or latent *H pylori* infection.[26] As the infection resolves the number of mucosal lesions increases, resulting in sampling errors in histology (and also later in a reduction in the serological response). Our observations support this; severe corpus atrophy was the main lesion in those in whom *H pylori* were not seen in tissue sections but in whom serum antibodies were present.

An important finding is that the prevalence of *H pylori* infection and gastritis seems to affect gastric carcinoma of both intestinal (IGCA) and diffuse (DGCA) type, these types covering 80–90% of all gastric carcinoma cases in general.[14 27] In fact, the prevalence of *H pylori* antibodies was slightly higher (100% *v* 91%) (figs 2 and 3) in patients with DGCA than in those with IGCA; when the patients with a normal stomach and those with corpus limited atrophy were excluded, the overall prevalence of *H pylori* antibodies was 71% in both.

Several earlier studies have indicated that there are important clinical, histological, and demographic differences between IGCA and DGCA.[27] For instance, DGCA occurs more often in young subjects than IGCA, but equally often in males and females; IGCA tends to be twice as common in males than in females. Histologically, IGCA frequently shows features of intestinal metaplasia in the

malignant mucosa whereas such features are typically absent in DGCA—that is, DGCA occurs more often in non-atrophic, non-metaplastic stomach than IGCA.[28-31]

In spite of the above differences, both types of cancer seem to share common epidemiological features. Both are prevalent in populations with a high incidence of gastric carcinoma but they also seem to occur equally rarely in countries with a low incidence of gastric carcinoma.[32-34] The pronounced decline in incidence of gastric carcinoma, which has occurred throughout the world over the past few decades,[35 36] seems to affect both types of gastric carcinoma, suggesting that both types must have similar common aetiological factors and pathogenic mechanisms.

The association of *H pylori* infection and gastritis with both IGCA and DGCA suggests that *H pylori* associated chronic gastritis is the common general background factor for gastric carcinoma. One hypothesis is that the morphogenesis of gastric carcinoma into different histological subtypes follows the natural course of chronic gastritis in the population.[6-8 37] Inflammation advances gradually and slowly (within years or sometimes decades) towards atrophy (and metaplasia) in both antrum and corpus. The morphogenesis of gastric carcinoma of the intestinal type may be particularly promoted by an atrophic (metaplastic) stomach and that of the diffuse type by a non-atrophic, gastritic stomach.

It is therefore assumed that after initiation of cancer (a gene based event) the morphogenesis of gastric carcinoma into different histological types depends on the stage in the natural course of gastritis from inflammation to atrophy. This assumption would make it understandable why both types of gastric carcinoma share similar epidemiological features: the development of both IGCA and DGCA depends on the occurrence and course of *H pylori* associated chronic gastritis and its sequelae in the general population.

In conclusion, *H pylori* associated chronic gastritis seems to be the background lesion in patients with gastric carcinoma in about 75% of cases. In the remainder it is associated with a normal stomach or with a corpus limited atrophy (atrophy of A type) in which coexistent *H pylori* infection is absent. We further conclude that *H pylori* related gastritis is also associated with both IGCA and DGCA, and suggest that chronic gastritis promotes the genesis of both these major cancer types.

1 Forman D, Sitas F, Newell DG, *et al.* Geographic association of Helicobacter pylori antibody prevalence and gastric cancer mortality in rural China. *Int J Cancer* 1990;**46**: 608–11.
2 Correa P, Fox J, Fontham E, *et al.* Helicobacter pylori and gastric carcinoma. Serum antibody prevalence in populations with contrasting cancer risk. *Cancer* 1990;**66**: 2569–74.
3 Sitas F, Forman D, Yarnell JWG, *et al.* Helicobacter pylori infection rates in relation to age and social class in a population of Welsh men. *Gut* 1991;**32**:25–8.
4 Fox JG, Correa P, Taylor NS, *et al.* Campylobacter pylori associated gastritis and immune response in a population at increased risk of gastric carcinoma. *Am J Gastroenterol* 1989;**84**:775–81.
5 Jaskiewicz K, Louwrens HD, Woodroof CW, Van Wyk MJ, Price SK. The association of Campylobacter pylori with mucosal pathological changes in a population at risk for gastric cancer. *S Afr Med J* 1989;**75**:417–19.
6 Siurala M, Sipponen P, Kekki M. Chronic gastritis: dynamic and clinical aspects. *Scand J Gastroenterol* 1985;**20(Suppl 109)**:69–76.
7 Villako K, Siurala M. The behaviour of gastritis and related conditions in different population samples. *Ann Clin Res* 1981;**13**:114–18.
8 Kekki M, Siurala M, Varis K, Sipponen P, Sistonen P, Nevanlinna H. Classification principles and genetics of chronic gastritis. *Scand J Gastroenterol* 1987;**22(Suppl 141)**:1–28.
9 Sipponen P, Kekki M, Haapakoski J, Ihamäki T, Siurala M. Gastric cancer risk in chronic atrophic gastritis: statistical calculations of cross-sectional data. *Int J Cancer* 1985;**35**:173–7.
10 Varis K. Surveillance of pernicious anaemia. In: Sherlock P, Mórson BC, Barbara L, Veronesi U, eds. *Precancerous lesions of the gastrointestinal tract*. New York: Raven Press, 1983:189–94.
11 Morson BC, Sobin LH, Grundmann E, Johansen A, Nagayo T, Serck-Hansen A. Precancerous conditions and epithelial dysplasia in the stomach. *J Clin Pathol* 1980;**33**: 711–21.
12 Correa P, Ruiz B. Campylobacter pylori and gastric cancer. In: Rathbone BJ, Heatley RV, eds. *Campylobacter pylori and gastroduodenal disease*. Oxford: Blackwell Scientific Publications, 1989:139–45.
13 Siurala M, Sipponen P, Kekki M. Campylobacter pylori in a sample of Finnish population: relations to morphology and functional aspects of the gastric mucosa. *Gut* 1988;**29**:909–16.
14 Sipponen P, Kekki M, Siurala M. Precancerous conditions. In: Filipe MI, Jass JR, eds. *Gastric cancer. Currrent problems in tumour pathology*. London: Churchill Livingstone, 1985:152–71.
15 Price AB. The Sydney system: Histological division. *J Gastroenterol Hepatol* 1991;**6**:209–22.
16 Misiewicz JJ. The Sydney system: A new classification of gastritis. Introduction. *J Gastroenterol Hepatol* 1991;**6**:207–8.
17 Laurén P. The two histological main types of gastric carcinoma: diffuse and so called intestinal type carcinoma. *Acta Pathol Microbiol Scand* (A) 1965;**64**:31–49.
18 Kosunen TU, Höök J, Rautelin HI, Myllylä G. Age-dependent increase of Campylobacter pylori antibodies in blood donors. *Scand J Gastroenterol* 1989;**24**:110–14.
19 Loffeld RJLF, Willems I, Flandring JA, Arends JW. Helicobacter pylori and gastric carcinoma. *Histopathology* 1990;**17**:537–41.
20 Andreica V, Dumitrascu D, Sasca N, *et al.* Helicobacter-like organisms in gastroduodenal diseases, *Gastroenterol Clin Biol* 1990;**14**:437–41.
21 Robey-Cafferty SS, Ro JY, Cleary KR. The prevalence of Campylobacter pylori in gastric biopsies from cancer patients. *Mod Pathol* 1989;**2**:473–6.
22 Varis K, Stenman U-H, Lehtola J, Siurala M. Gastric lesion and pernicious anemia. *Acta Hepato-gastroenterol* 1978;**25**:62–7.
23 Flejou JF, Bahame P, Smith AC, Stockbrugger RW, Rode J, Price AB. Pernicious anaemia and Campylobacter like organisms; is the gastric antrum resistant to colonisation? *Gut* 1989;**30**:60–4.
24 Lehtola J. Family study of gastric carcinoma: with special reference to histological types. *Scand J Gastroenterol* 1978;**13(Suppl 50)**:1–73.
25 Mecklin J-P, Nordling S, Saario I. Carcinoma of the stomach and its heredity in young patients. *Scand J Gastroenterol* 1988;**23**:307–11.
26 Karnes WE, Samloff IM, Siurala M, *et al.* Positive serum antibody and negative tissue staining for Helicobacter pylori in subjects with atrophic gastritis. *Gastroenterology* 1991;**101**:167–74.
27 Siurala M, Varis K, Sipponen P. Carcinogenesis in the foregut. Baromn JH, Moody FG, eds. *Gastric carcinoma*. London: Butterworths, 1981:276–312.
28 Järvi O, Laurén P. On the role of heterotopias of the intestinal epithelium in the pathogenesis of gastric cancer. *Acta Pathol Microbiol Scand* (A) 1951;**29**:26–48.
29 Johansen A. Gastric carcinoma. A contribution to the pathology and to cancer histogenesis. Department of Pathology, Bispebjaerg Hospital, Copenhagen 1981.
30 Kato I, Tominaga S, Ito Y, *et al.* A case-control analysis of stomach cancer and atrophic gastritis. *Cancer Res* 1990;**50**:6559–64.
31 Correa P. Chronic gastritis and gastric cancer. In: Ming SC, ed. *Precursors of gastric cancer*. New York: Praeger Publishers, 1984:105–16.
32 Kubo T. Histologic appearance of gastric carcinoma in high and low mortality countries: Comparison between Kyushu, Japan and Minnesota, United States of America. *Cancer* 1971;**28**:726–34.
33 Teh M, Lee Y-S. Intestinal and diffuse carcinoma of the stomach among the ethnic and dialect groups of Singapore. *Cancer* 1987;**60**:921–5.
34 Sipponen P, Kekki M, Siurala M. Increased risk of gastric cancer in males affects the intestinal type of cancer and is independent of age, location of tumour and atrophic gastritis. *Br J Cancer* 1988;57:332–6.
35 Howson CP, Hiyama T, Wynder EL. The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidem Rev* 1986;**8**:1–27.
36 Sipponen P, Järvi O, Kekki M, Siurala M. Decreased incidences of intestinal and diffuse types of gastric carcinoma in Finland during a 20-year period of time. *Scand J Gastroenterol* 1987;**22**:865–71.
37 Siurala M, Varis K, Kekki M. New aspects on epidemiology genetics, and dynamics of chronic gastritis. *Front Gastrointest Res* 1980;**6**:148–65.