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Helicobacter colonization and histopathological profile of chronic gastritis in patients with or without dyspepsia, mucosal erosion and peptic ulcer: A morphological approach to the study of ulcerogenesis in man

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Summary. *Helicobacter pylori* colonization and the incidence, severity, activity and topography of gastritis were investigated systematically in antrum and corpus mucosal biopsies of 1177 subjects undergoing endoscopy in the absence of gastric complaints (asymptomatic, 49) or for non-ulcer dyspepsia (NUD; 631 patients, 72 of whom had gastric and/or duodenal erosions), active gastric ulcer (GU, 76 patients), active duodenal ulcer (DU, 138 patients), and healed gastric (HGU, 39 cases) or duodenal ulcer (HDU, 230 cases). In the antrum, *H. pylori* colonization and the incidence, severity and activity of gastritis increased progressively in the sequence asymptomatic, erosion-free NUD, erosive NUD, healed ulcer and active ulcer. The same trend was observed in the corpus as regards *H. pylori* and gastritis incidence, whereas the severity and activity of gastritis were lower in active DU and erosive NUD and higher in active, proximal GU than in the remaining patients. Active DU and erosive NUD showed the highest incidence of non-atrophic gastritis and lowest type-A or AB atrophic gastritis, while active GU had lowest normal mucosa or type-A gastritis and highest type-B atrophic gastritis. In conclusion, *H. pylori* colonization and gastritis incidence, severity and, especially, activity of the antrum might all contribute to mucosal erosion and ulceration, whereas the same factors, at least in part and with the exception of proximal GU, seem to have a preventive role when affecting corpus mucosa.

Key words: Chronic gastritis – *Helicobacter pylori* – Peptic ulcer – Mucosal erosions – Dyspepsia

Introduction

Many microbiological, histopathological and clinical studies performed in the last decade strongly indicate *Helicobacter pylori* as a major cause of chronic gastritis (Warren and Marshall 1983; Goodwin et al. 1986; Johnson et al. 1986; Fiocca et al. 1987; Marshall et al. 1988; Rauws et al. 1988; De Giacomo et al. 1990). A few ingestion tests in man support this conclusion (Marshall et al. 1985; Morris and Nicholson 1987). Epidemiological studies also suggest a relationship between *H. pylori* infection and peptic ulcer disease, both in the stomach and duodenum (O'Connor and Axon 1989; Wyatt 1989). In addition, follow-up studies show that chronic gastritis is a risk factor for peptic ulcer (Sipponen et al. 1989, 1990). However, the mechanism leading from gastritis to peptic ulcer is poorly understood. A decrease in the activity (granulocyte infiltrates) of gastritis has been observed after administration of drugs eradicating *H. pylori* (Rauws et al. 1988). Excess activity of gastritis has been also observed in ulcer patients when compared with non-ulcer dyspepsia (NUD) patients (Eidt and Stolte 1990).

In this study, the histological type, activity, topography and *H. pylori* association of gastritis in asymptomatic or NUD patients and in patients with endoscopically proven gastro-duodenal erosions or ulcers were investigated to identify factors potentially involved in the ulcerogenic process.

Materials and methods

The study was carried out in a continous series of 1177 patients (681 males, 496 females, ranging in age from 15 to 88 years) undergoing upper gastrointestinal endoscopy for various indications in the period 1987–1991. Patients were allotted to the following groups, according to symptoms and/or endoscopic findings:

1. Asymptomatics: 49 patients lacking any dyspeptic or ulcer-like symptoms, who were submitted to endoscopy as part of investigations for conditions such as anaemia, oesophageal varices and lymphoproliferative diseases.
2. Non-ulcer dyspepsia (NUD): 631 patients suffering from chronic (more than 3 months) or recurrent, upper abdominal pain or nausea (Talley and Phillips 1988), without endoscopic evidence of ei-

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ther active peptic ulcer scars and without recorded evidence of previous ulcer. This group included 559 erosion-free patients as well as 72 patients with duodenal (46 cases), antropyloric (21 cases, mainly prepyloric) or corpus-fundus (5 cases) erosions.
3. Gastric ulcer (GU): 76 patients with active GU were further subdivided in two groups: those affected with distal, here defined as prepyloric or antral ulcer (44 patients) and those with proximal, body or incisura ulcer (31 patients).
4. Duodenal ulcer (DU): 138 subjects with active DU.
5. Healed gastric ulcer (HGU, 39 cases) or healed duodenal ulcer (HDU, 230 cases): patients with previous endoscopically ascertained ulcer and/or obvious residual scarring, with or without antisecretory drugs and antacid treatment.

Subjects with previous gastric surgery or treated with bismuth and antibiotics or with ongoing non-steroidal anti-inflammatory drug (NSAID) therapy and patients bearing polyps or cancer were excluded. Also excluded were cases showing histological patterns diagnostic for reactive (bile reflux associated, NSAID associated), eosinophilic or granulomatous gastritis (Dixon et al. 1986; Laine et al. 1988; Wyatt and Dixon 1988). In each case three biopsy specimens were taken from the antrum in the prepyloric area and two from the upper body along the greater curve. Focal lesions (i.e. ulcers, erosions) were sampled separately and were not considered in gastritis typing and evaluation.

Formalin-fixed tissues were stained with haematoxylin-eosin, alcian blue-periodic acid Schiff (PAS) and Giemsa stain for *H. pylori*. Cases whose *H. pylori* status was difficult to ascertain due to scarce or heterogeneous bacterial colonization were also stained with Warthin-Starry silver (Thompson 1966).

The presence of *H. pylori* was subjectively scored as follows: 0 = absent; 1 = individual or small groups of *H. pylori* covering less than one-third of superficial and foveolar epithelium (Price 1991); 2 = numerous *H. pylori*, covering more than one-third of the epithelium or forming a continuous layer (Price's grades 2 and 3). The activity of gastritis was graded according to the absence (0), scattered (1) or clustering pattern (2) of intra- and peri-epithelial granulocytes. In a group of 333 patients (146 NUD, 91 DU and 96 GU, including 20 newly added cases) the full spectrum of the Sydney system scores (inflammation, activity, *H. pylori*, gland atrophy, intestinal metaplasia; Price 1991) was applied systematically to the pyloric mucosa.

Several histological variables assessed in other classification system have been also considered in the evaluation of gastritis (Whitehead et al. 1972; Strickland and McKay 1973; Glass and Pitchumoni 1975; Fiocca et al. 1987; Kekki et al. 1987; Correa 1988). Thus, based on the intramucosal level of inflammation, *superficial* gastritis was separated from *interstitial* gastritis, including Whitehead's "mildly atrophic" gastritis. The presence of one-third or more of gastric gland loss and/or metaplasic substitution allowed us to identify *atrophic* gastritis, involving less (moderate) or more (severe) than two-thirds of the whole glandular component of biopsy specimens. By combining these histological subtypes of gastritis from both antrum and corpus, gastritis topography was assessed (Kekki et al. 1987; Sipponen et al. 1990). Subjects with normal gastric mucosa were separated from patients with common non-atrophic gastritis, types A, AB and B atrophic gastritis. Occurrence of intestinal metaplasia was recorded independently from its type (complete or incomplete); involvement of more or less than one-third of the biopsy was scored.

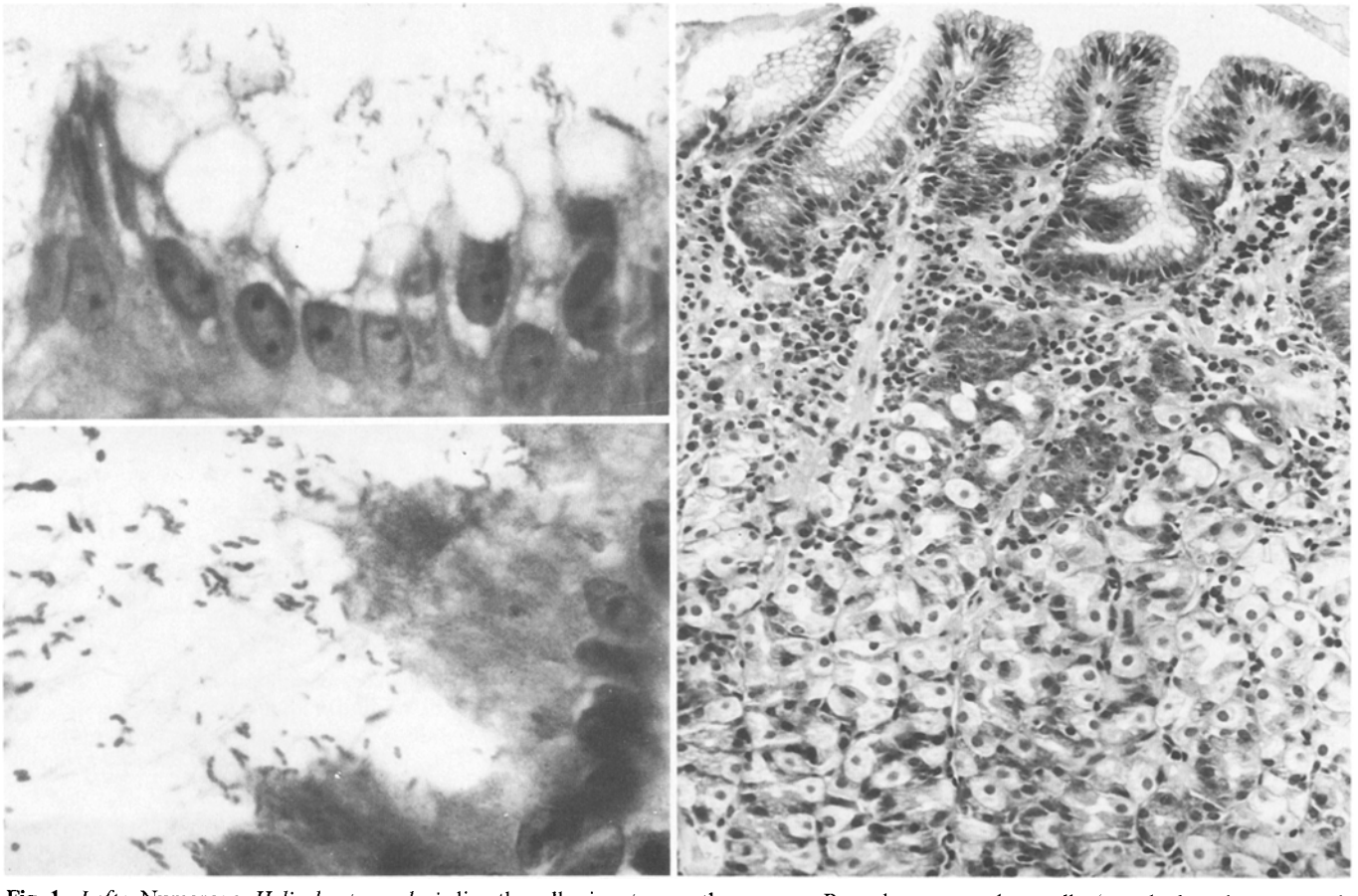

Fig. 1. *Left:* Numerous *Helicobacter pylori* directly adhering to surface gastric epithelium (upper half, Giemsa stain, ×1000) or scattered in the mucous covering the epithelium (lower half, Warthin-Starry silver, ×960). *Right:* Superficial non-active gastritis of the corpus. Round, mononuclear cells (mostly lymphocytes and plasma cells) cluster in the lamina propria in between the foveolae and necks. Haematoxylin and eosin, ×200

Table 1. *Helicobacter pylori* colonization and gastritis in different clinical conditions

Clinical condition	Patients (*n*)	Mean age	With gastritis		*H. pylori positive*		
			n	%	*n*	% all patients[a]	% gastritic[b]
Asymptomatic patients	49	54.4	37	75.5	27	55.1	73.0
NUD	631	54.4	540	85.6	462	73.2	85.6
Erosion-free NUD	559	54.9	475	85.0	406	72.6	85.5
NUD with erosions	67	51.1	61	91.0	53	79.1	86.9
All active ulcers	227	53.2	225	99.1	215	94.7	95.6
All healed ulcers	269	52.2	251	93.3	226	84.0	90.0
Active GU	76	58.3	76	100	71	93.4	93.4
Active proximal GU	31	60.9	31	100	28	90.3	90.3
Active distal GU	44	56.5	44	100	42	95.5	95.5
Healed GU	39	56.3	37	94.9	32	82.1	86.5
Active DU	138	49.9	136	98.6	132	95.7	97.1
Healed DU	230	51.5	214	93.0	194	84.3	90.7
All patients	1177	53.7	1054	89.5	931	79.1	88.3

DU, Duodenal ulcer; GU, gastric ulcer; NUD, non-ulcer dyspesia

[a] Percentage *H. pylori positive* among all patients
[b] *Percentage of H. pylori positive* gastritis patients

Table 2. *Helicobacter pylori* colonization and gastritis type of the antrum in different clinical conditions

Clinical condition	*H. pylori* positive, %		Gastritis, %				Active, %[a]	
	all	grade 2	none	superficial	interstitial	atrophic	all	grade 2
Asymptomatic patients	44.9	10.2	28.6	12.2	40.8	18.4	48.6	11.4
NUD	67.5	27.9	17.4	12.8	53.7	16.1	62.8	19.2
Erosion-free NUD	66.2	25.6	18.2	13.2	51.9	16.7	62.6	18.2
NUD with erosions	79.2	44.8	10.4	10.4	68.7	10.5	63.3	25.0
All active ulcers	91.2	52.0	0.9	5.7	73.1	20.3	86.2	36.9
All healed ulcers	80.3	41.3	7.1	8.9	62.5	21.5	77.6	28.0
Active GU	86.8	51.3	0	1.3	68.4	30.3	81.6	48.7
Active proximal GU	83.9	51.6	0	0	61.3	38.7	83.9	51.6
Active distal GU	88.6	52.3	0	2.3	72.7	25.0	79.6	45.5
Healed GU	77.0	41.0	5.1	5.1	69.2	20.6	78.4	32.4
Active DU	93.5	51.4	1.4	8.7	74.6	15.3	88.2	29.4
Healed DU	80.9	41.3	7.4	9.6	61.3	21.7	77.5	27.2
All patients	74.1	34.9	12.3	10.5	59.0	18.2	71.0	25.0

[a] Active cases among gastritis cases, %

Statistical analysis was performed using the chi-squared test and the StatView statistical pakage.

Results

Of the 1177 patients investigated, 931 (79%) were *H. pylori* positive (Fig. 1); all of these also showed gastritis. Cumulative *H. pylori* colonization of antrum and corpus mucosa was lowest in asymptomatic patients (55%) and increased progressively in erosion-free NUD patients (73%; $P<0.02$) versus asymptomatics), erosive NUD (79%), healed ulcers (84%) and active ulcers (95%; $P<0.001$ versus healed ulcers) (Table 1). The mean age of the various groups ranged from a minimum of 49.9 years in DU to a maximum of 60.9 years in proximal ulcers, a difference unlikely to influence *H. pylori* incidence significantly, which for the whole group of patients remained fairly constant around 80% in the 40–70 years age range. In general, *H. pylori* incidence was higher in the antrum (74%; grade 2=35%) than in the corpus (70%; $P<0.02$; grade 2=20.5%; $P<0.001$) (Tables 2, 3). Maximum incidence of antral *H. pylori* was observed in active ulcer patients (91%). The incidence was significantly lower in healed ulcers (80%; $P<0.01$ versus active ulcers) and erosive NUD (79%; $P<0.02$ versus active ulcers), and decreased further in erosion-free NUD (66%; $P<0.05$ with respect to erosive NUD) and in asymptomatic patients (45%; $P<0.01$ with respect to erosion free NUD) (Table 2). Corresponding values for corpus mucosa showed less prominent changes with highest figures among GU patients (Table 3).

Overall, 1054 of the 1177 patients investigated (89.5%) showed chronic gastritis. *H. pylori* colonization was found in 931 patients with gastritis (88%) and in

Table 3. *Helicobacter pylori* colonization and gastritis type of the corpus in different clinical conditions

Clinical condition	*H. pylori* positive, %		Gastritis, %				Active, %[a]	
	all	grade 2	none	superficial	interstitial	atrophic	all	grade 2
Asymptomatic patients	51.0	12.2	30.6	40.8	20.4	8.2	41.2	8.8
NUD	64.6	19.7	24.1	54.0	14.3	7.6	48.2	12.9
Erosion-free NUD	64.6	19.5	25.0	52.2	14.5	8.3	51.1	14.1
NUD with erosions	65.7	20.9	16.4	67.2	13.4	3.0	26.8	3.6
All active ulcers	81.1	20.7	11.0	76.2	10.1	2.7	33.2	10.4
All healed ulcers	75.1	23.8	16.4	68.0	10.8	4.8	43.6	6.7
Active GU	85.5	26.3	6.6	68.4	18.4	6.6	49.3	21.1
Active proximal GU	80.7	32.3	3.2	51.6	35.5	9.7	60.0	26.7
Active distal GU	88.7	22.7	9.1	81.8	4.5	4.6	40.0	15.0
Healed GU	77.0	17.9	12.8	66.7	12.8	7.7	38.2	5.9
Active DU	80.5	18.8	13.0	81.2	5.1	0.7	24.2	3.3
Healed DU	74.8	24.7	17.0	68.3	10.4	4.3	44.5	6.8
All patients	69.7	20.5	20.1	61.0	12.9	6.0	43.6	10.7

[a] Active cases among gastritis cases, %

none of the 123 patients having normal antral and corpus mucosa. In 46 cases *H. pylori* was detected in a histologically normal corpus mucosa of patients showing *H. pylori*-positive gastritis of the antrum. The relatively small fraction of *H. pylori*-negative gastritis increased progressively with age from 6% in the 15–30 years group to around 20% in the oldest group, without relevant sex difference.

H. pylori-positive gastritis was characterized by a mixed population of inflammatory cells (plasma cells, lymphocytes, macrophages, granulocytes) filling the lamina propria interposed between the surface epithelium, the foveolae and gland necks (superficial gastritis) or also involving the lamina propria at the level of the gland body (interstitial gastritis, with or without mild gland atrophy), sometimes associated with substantial (30% or more) atrophy of the glands (atrophic gastritis). Lymphoid aggregates or follicles were often present deep in the mucosa, especially of the antrum. The occurrence of neutrophilic granulocytes inside the epithelium or in the juxta-epithelial lamina propria outlined the activity of gastritis (Figs. 1–3).

In the atrum interstitial gastritis was by far the prevalent type. In the corpus, where the incidence of gastritis was only slightly lower than in the antrum, superficial gastritis was prevalent and evolution of superficial into interstitial gastritis seemed to be a slow process occurring throughout life. Only a relatively small fraction of corpus gastritis progressed further, with time, to atrophic gastritis. From 30 years on, about 0.7% of patients per year entered the "glandular" (interstitial+atrophic) gastritic pool and around 0.2% entered the atrophic pool. However, the latter pool changed markedly according to clinical conditions, ranging from zero rate at whatever age in active DU patients to nearly 0.3% per year starting from 30 years age in NUD, to around 0.5% per year starting from 50 years age in healed DU and active GU.

Of the 1032 patients with antral gastritis, 733 (71%) showed intra- or peri-epithelial granulocytes, that is to say active gastritis. The proportion of active gastritis was fairly stable (around three-quarters of all antral gastritis cases) up to above 70 years, when it declined slightly to 62% ($P<0.05$ with respect to the 60–70 year group). The incidence of *H. pylori* colonization was 96% among active antral gastritis cases, as against 55.5% of the 299 cases with quiescent gastritis ($P<0.001$), thus suggesting a close link between *H. pylori* and active gastritis. However, granulocytes were more abundant inside or around *H. pylori*-free, mucin-poor epithelial of deep foveolae and upper necks than in connection with *H. pylori*-colonized, mucin-rich superficial epithelium. In the corpus, only 44% of gastritis cases were active ($P<0.001$ versus antral gastritis), with activity increasing progressively from 27% in the 15–30 years group to 55% ($P<0.01$) in the oldest group. *H. pylori* colonization was 93% among active and 74% among non-active corpus gastritis ($P<0.001$).

The relationship between activity and histological type of gastritis in the antrum and corpus is illustrated in Table 4. In both antrum and corpus active gastritis prevailed among cases showing interstitial and moderately atrophic gastritis, while quiescent gastritis prevailed among cases of superficial gastritis and the two forms were roughly equivalent in number among severely atrophic cases. The ratio between grade 1 and 2 activity progressively decreased from superficial to atrophic gastritis in both the antrum and corpus.

The relationship between topography and histological type of gastritis (Kekki et al. 1987) has been also analysed. Of the 1177 patients, 123 (10.5%) showed entirely normal gastric mucosa, 709 (67%) had common non-atrophic gastritis, 151 (13%) showed atrophic antral gastritis coupled with no or only superficial gastritis of the corpus (type-B gastritis), 97 (8%) had atrophic gastritis of the antrum or corpus with interstitial or atrophic gastritis of the other site (type-AB gastritis) and 16 (1%) showed atrophic gastritis of the corpus with no or only superficial gastritis of the antrum (type-A gastritis). The median age of patients increased from

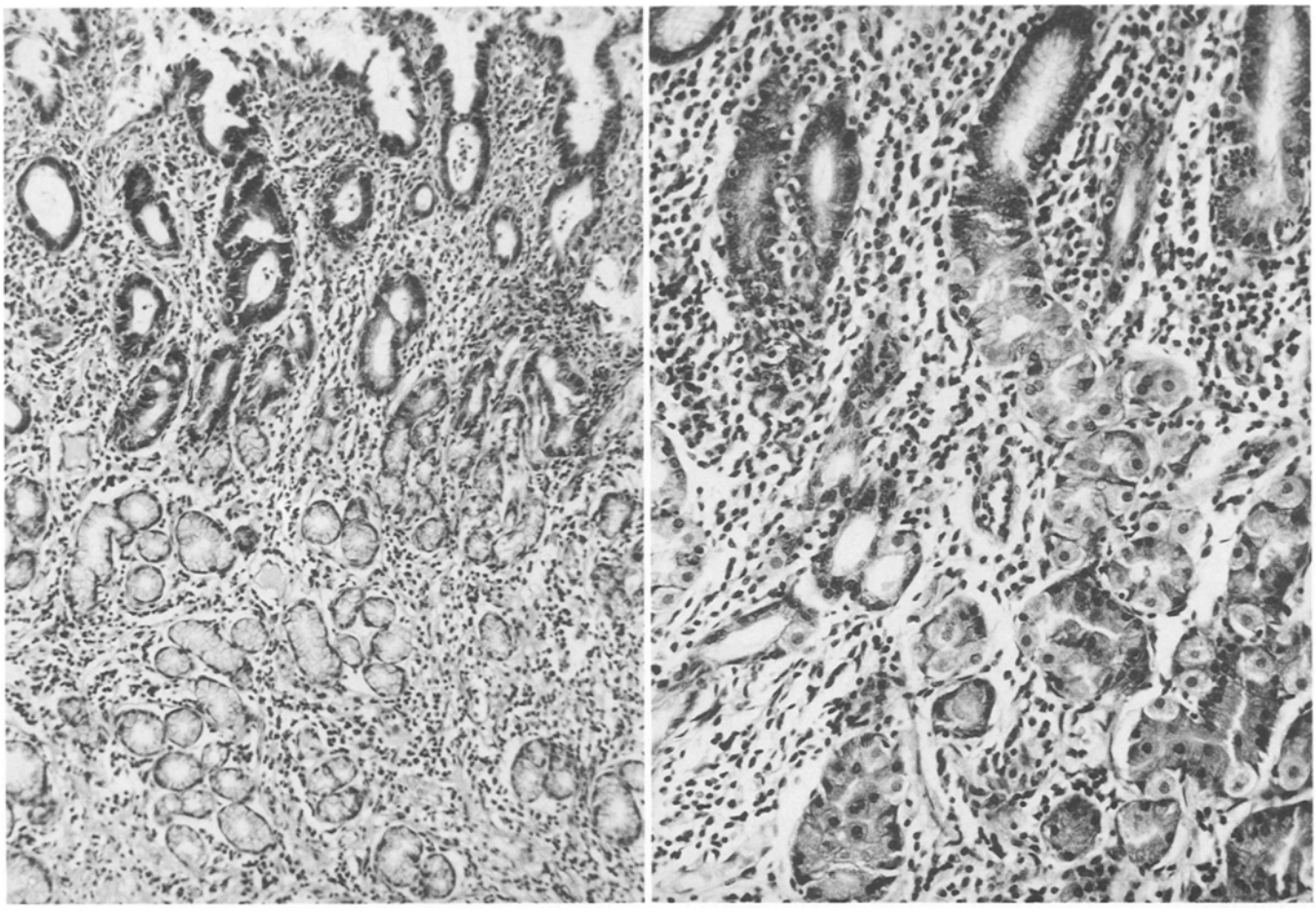

Fig. 2. *Left:* Interstitial gastritis of the antrum showing inflammatory cells in between glandular bodies, necks and foveolae. Haematoxylin and eosin, ×125. *Right:* Pre-atrophic gastritis of the corpus. Note active intraepithelial inflammation of some gland necks (*top left*) coupled with atrophy of underlying gland bodies. Haematoxylin and eosin, ×200

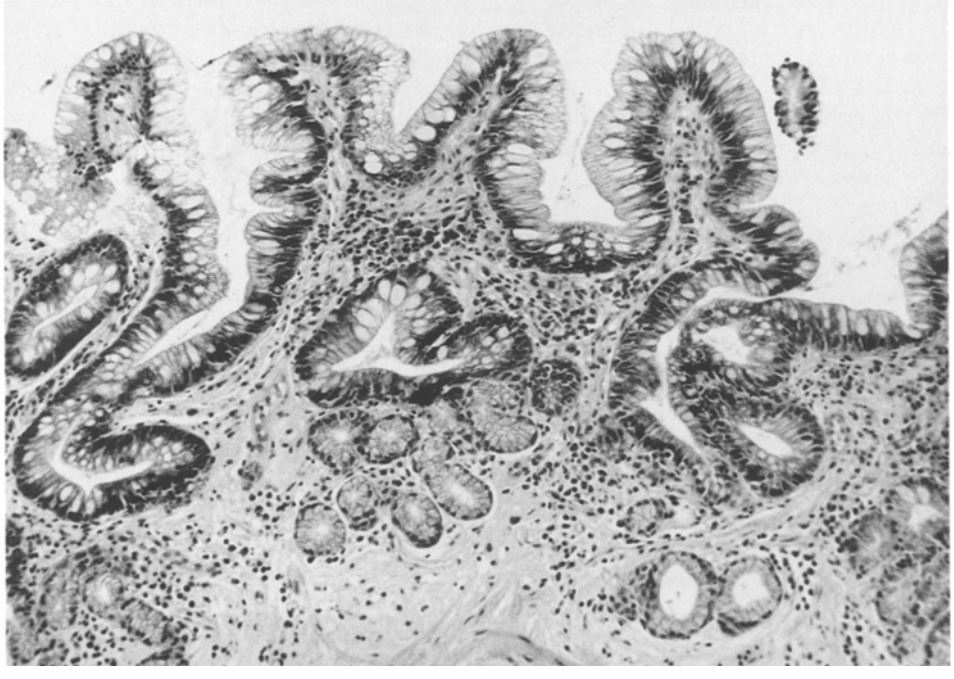

Fig. 3. Atrophic gastritis of the antrum showing severe loss of pyloric gland bodies and extensive intestinal metaplasia of "incomplete" type (goblet cells scattered among foveolar cells). Haematoxylin and eosin, ×125

Table 4. Relationship between activity and histological type of gastritis in antrum and corpus biopsies

Activity	Histological type			
	Superficial	Interstitial	Atrophic	
			moderate	severe
% grade 0	60.5/63.8[a]	25.2/28.9	15.6/30.8	48.9/53.1
% grade 1	33.9/29.0	49.4/50.0	45.5/46.2	29.8/21.9
% grade 2	5.6/7.2	25.4/21.1	38.9/23.1	21.3/25.0
Ratio grade 1:2	6.05/4.03	1.94/2.37	1.17/2.00	1.36/0.88
All cases (0+1+2)	124/718	694/152	167/39	47/32

[a] Percent values for antral/corpus mucosa

44.2 years in the normal mucosa group to 52.5 years in the common gastritis, 60.7 years in type-B, 62.7 years in type-AB and 64.3 years in type-A gastritis groups, suggesting an age-related evolution of some common gastritis cases to atrophic types. *H. pylori* colonization increased from zero in normal mucosa to 90% in common gastritis, remained high in type B (95%) and decreased significantly (76%) in AB gastritis ($P<0.001$ versus type B), while dropping to 31% in type-A gastritis ($P<0.001$ versus type AB).

The relationship between incidence, histological type and activity of gastritis in various clinical conditions is illustrated in Tables 1–3. Among non-ulcer patients, asymptomatic subjects showed a trend towards a lower incidence of gastritis in both the antrum and corpus as well as a lower incidence of active gastritis in the antrum and superficial gastritis in the corpus in dyspeptics. In erosion-free patients, NUD patients with endoscopically ascertained erosions showed increased incidence of gastritis (as a whole) in both antrum and corpus as well as of interstitial and grade-2 active antritis, and of superficial and non-active corpus gastritis. In particular, the 67 NUD patients with duodenal and/or antropyloric erosions showed 69% incidence of interstitial antritis, versus 60% ($P<0.02$) of the 559 erosion-free NUD patients, 67% superficial body gastritis versus 52% ($P<0.05$) and 73% non-active body gastritis versus 49% ($P<0.01$). Among non-erosive NUD patients with gastritis, the 69 *H. pylori*-negative patients, when compared with the 406 *H. pylori*-positive, showed decreased activity of gastritis in both the antrum (7% versus 71%, $P<0.001$) and corpus (28% versus 55%, $P<0.001$), decreased atrophic gastritis (10% versus 21%, $P<0.05$) in the antrum and increased atrophic gastritis (32% versus 6%, $P<0.001$) in the corpus.

Patients with an active ulcer showed increased cumulative (antrum+body) incidence of *H. pylori* (95%) and gastritis (99%) with respect to both erosion-free NUD (73%, $P<0.001$ and 85%, $P<0.001$, respectively) and erosive NUD (79%, $P<0.001$ and 91%, $P<0.01$ respectively). In active ulcer patients active antritis was especially prominent, with an incidence of 86% versus 63% of both erosion-free NUD ($P<0.001$) and erosive NUD ($P<0.001$). In the same patients, the incidence of normal antral mucosa was sharply reduced (0.9%, $P<0.001$ versus 18% of erosion-free NUD and $P<0.001$ versus 10% of erosive NUD), with a resulting increase of interstitial gastritis (73% in active ulcers versus 52% of erosion-free NUD and 69% of erosive NUD). When compared with GU patients, those with DU were characterized by a lower incidence of grade-2 active antritis (29% versus 49%, $P<0.01$) and of atrophic antritis (15%, as against 30%, $P<0.02$); they also showed a lower incidence of interstitial+atrophic (6% as against 25%, $P<0.001$) and active body gastritis (24% as against 49%, $P<0.001$), with special reference to grade-2 activity (3% versus 21%, $P<0.001$). Active antritis was detected in 88% of duodenal ulcers and 63% ($P<0.001$) of duodenal erosions.

GU patients with proximal (corpus and angulus) ulcer, when compared with antropyloric ulcer patients, had a higher incidence of interstitial+atrophic (45% versus 9%, $P<0.001$) and active (60% versus 40%, $P=0.157$) body gastritis. As a rule, distal GU showed patterns in between those of DU and proximal GU patients.

In general, healed ulcers showed slightly decreased interstitial (62.5% versus 73% $P<0.02$) and grade-2 active antritis (28.0% versus 40%, $P<0.05$) with respect to active ulcers. HDU, compared with their active counterparts, were characterized by decreased interstitial (61% versus 75%, $P<0.02$) and active antritis (77.5% versus 88%, $P<0.02$) as well as decreased superficial (68% versus 81%, $P<0.01$) and increased active body gastritis (44.5% versus 24%, $P<0.001$).

When compared with asymptomatic patients (24.5%) and erosion-free NUD (15%), erosive NUD (9%, $P<0.05$ and $P=0.248$, respectively), HDU (7%, $P<0.001$ and $P<0.01$, respectively), active DU (1%, $P<0.001$ and $P<0.001$, respectively) and active GU (0%) showed progressively decreasing incidence of normal gastric mucosa. This contributed to an increase of common gastritis in both active DU (83%, versus 62% of erosion-free NUD, $P<0.001$, and 49% of asymptomatic patients, $P<0.001$) and erosive NUD (79%, $P<0.01$ with respect to erosion-free NUD and $P<0.001$ with respect to asymptomatic patients) and to increased type-B atrophic gastritis in active GU (22% versus 10% of erosion-free NUD, $P<0.01$). Decreased incidence of AB gastritis was observed in active DU (1.4%, $P<0.01$ versus erosion-free NUD and $P<0.01$ versus asymptomatic patients).

The overall incidence of intestinal metaplasia (IM) in the antrum (25% of all cases) was 3.5 times higher

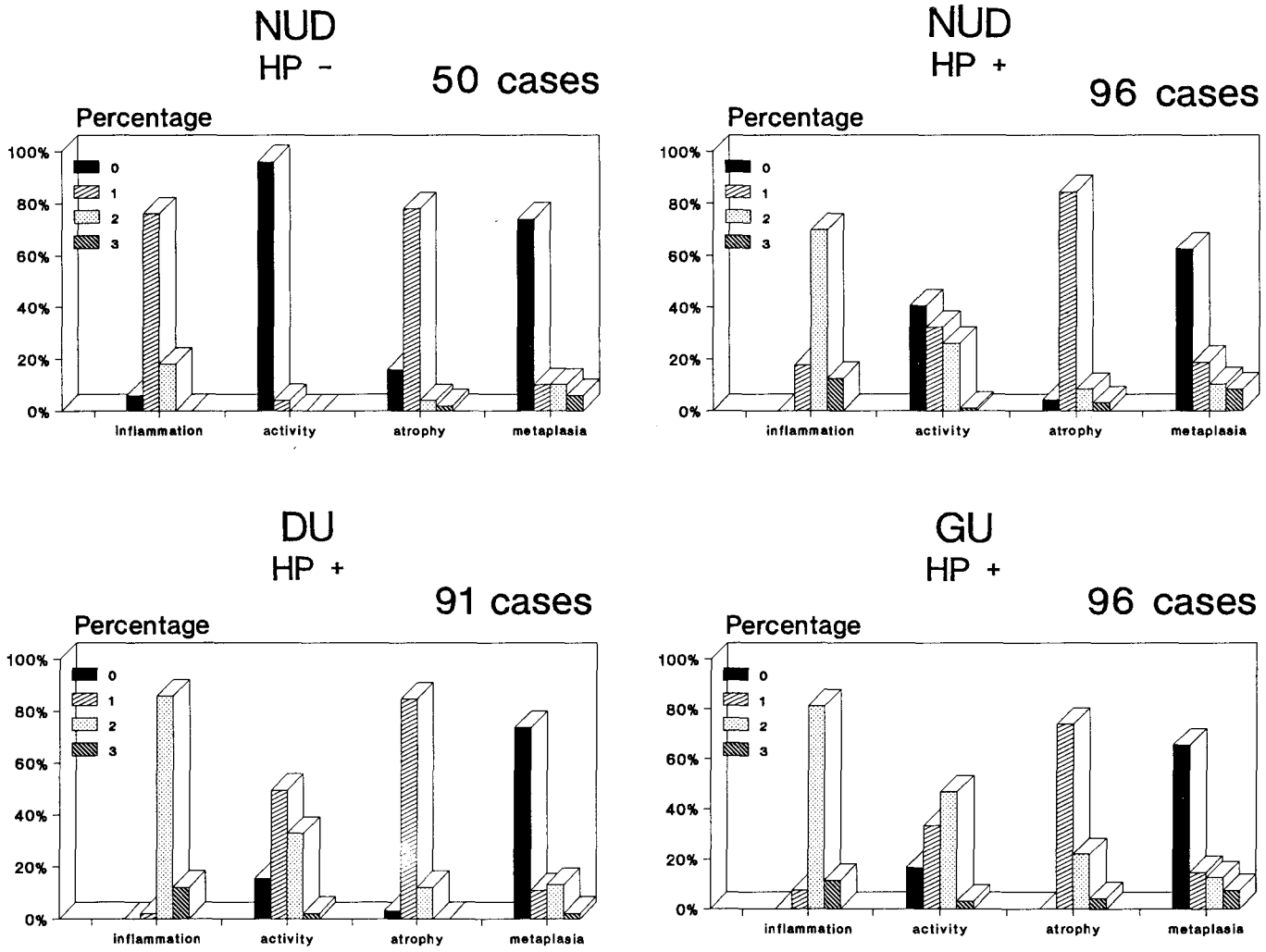

Fig. 4. Sidney system's scores of antral mucosa in some clinical conditions. NUD, Non-ulcer dyspepsia; DU, duodenal ulcer; GU, gastric ulcer

than in the corpus (7%). It increased from 0% in normal mucosa to 20% (1% "extensive", that is to say, involving more than one-third of the biopsied mucosa) in common gastritis, 63% (28% extensive) in type-B, 70% (37% extensive) in type-AB, and 81% (31% extensive) in type-A gastritis. IM incidence was fairly constant at 27–32% in most clinical conditions, with the exception of NUD with antropyloro-duodenal erosions, which showed a much lower figure (10%, $P<0.01$ versus erosion-free NUD, 29%), of *H. pylori*-negative NUD, showing an increased incidence (54%, $P<0.001$ versus *H. pylori*-positive NUD, 30%) and of proximal GU, showing an increased rate (55%, $P<0.05$ versus distal GU, 32%, and $P<0.01$ versus duodenal ulcers, 29%). In *H. pylori*-negative NUD the IM increase was exclusively due to increased incidence in the corpus mucosa, while in proximal GU it was mainly due to the antral mucosa.

Results obtained by the application of the Sydney system of gastritis scoring (Price 1991) to the antral mucosa of *H. pylori*-negative or positive NUD and *H. pylori*-positive DU or GU are outlined in Fig. 4. Statistical analysis covering the four scoring grades (0–3) showed a highly significant ($P<0.001$) increase of activity and inflammation as well as a non-significant decrease of gland atrophy and IM, when *H. pylori*-positive NUD were compared with *H. pylori*-negative NUD of the same mean age (58 years). Further increase of activity was seen when *H. pylori*-positive DU ($P<0.01$) or GU ($P<0.001$) were compared with *H. pylori*-positive NUD, while inflammation and *H. pylori* scores were increased in DU patients ($P<0.01$ for both scores) only and gland atrophy in GU patients ($P<0.05$) only. Only atrophy was significantly increased ($P<0.05$) in GU versus DU patients, a finding partly related to their age difference (mean of 60 years in GU and 49 in DU).

Discussion

A variety of histological criteria (including the new Sydney system) for the evaluation of gastritis and its relationship with ulcerogenesis gave substantially unequivocal results, stressing the importance of granulocyte infil-

trates and *H. pylori* colonization in addition to the total number of inflammatory cells, the extent of gland atrophy, IM and the topography of the lesion. In general the Sydney classification seems to offer a more complete, accurate and sensitive scoring system. The advantage of some traditional classifications lies in their description of the intramucosa level of inflammation, whether superficial or involving the whole depth of the mucosa (Whitehead et al. 1972; Fiocca et al. 1987). In general inflammatory involvement of the glandular compartment is much more prominent in the antrum than in the corpus mucosa. Acidopeptic glands were substantially spared in as many as 76% of our 1177 patients, as against 12% of pyloric glands. This finding may be functionally important considering that lymphokine-producing T-lymphocytes and macrophages are abundant in deep "interstitial" gastritis (Solcia et al. 1992), that some lymphokines are powerful inhibitors of acid secretion (Cucala et al. 1991) and that acidopeptic glands are substantially free of inflammation in most patients with active DU and distal GU. The recently ascertained production of anti-inflammatory and trophic factors like transforming growth factor-alpha (TGF-α; Beachamp et al. 1989) and prostaglandin E_2 (PGE_2; Higuchi et al. 1988) by parietal cells might have a role in protecting acidopeptic glands from inflammatory involvement.

Among the variables used in the assessment of gastritis in this study, intra- and peri-epithelial granulocyte infiltration (activity) seems to be the one most predictive of progression of gastritis. The lower (about half) activity of corpus with respect to antral gastritis fits with the milder, superficial nature of most corpus gastritis with respect to the more severe, deeper type of most antral gastritis. The age-increased activity in the corpus may also be related to (and, indeed, anticipate) a parallel behaviour of more severe (interstitial and atrophic) types of gastritis at this site (Ihamaki et al. 1985). With the exception of those with severe (end-stage) atrophy and type-A topography, gastritis types of higher severity (interstitial and atrophic, with B or AB topography) usually had higher incidence and grade of activity. In fact, aggression of renewal zone epithelium by granulocytes, a prominent finding in many interstitial and moderately atrophic gastritis, might interfere with epithelial regeneration and cause progressive gland atrophy.

As previously shown (Marshall and Warren 1984; Fiocca et al. 1987, 1989; Rauws et al. 1988), a correlation was found between *H. pylori* colonization and the activity of gastritis. However, other factors besides *H. pylori* colonization must also be involved in granulocyte chemotaxis to explain, for instance, the unusually low activity of corpus gastritis in DU and erosive NUD patients despite their high incidence of *H. pylori*. Often variations of gastritis activity were more prominent than those expected from concomitant changes of *H. pylori* colonization, although both variables usually changed in the same direction. In our experience granulocytes concentrate more in deep foveolae and necks (near to IgG-producing plasma cells filling the lamina propria) in *H. pylori*-free epithelia than in *H. pylori*-colonized superficial epithelium (Solcia et al. 1992). This suggests that in chronic *H. pylori* gastritis granulocyte chemotaxis is mainly due to complement fixation by locally released IgG (especially IgG_1; Stacey et al. 1990) antibodies interacting with *H. pylori* antigens. The latter have been suggested to be preferentially processed and presented at the level of deep foveolae and necks (Kirchner et al. 1990; Solcia et al. 1992).

Asymptomatic and erosion-free NUD subjects were the main contributors of normal mucosa, while most active DU (83%) and erosive NUD (79%) patients fitted in the common gastritis group. Active GU patients were prominent among cases with type-B gastritis. It seems clear from our findings that gastric *H. pylori* colonization decreases when atrophic gastritis affects acido-peptid glands, either with (type-AB gastritis) or without (type-A gastritis) antral involvement, but does not decrease when the atrophic process affects pyloric glands only (type-B gastritis). The usually higher incidence of IM in the antrum with respect to the body and its substantially similar prevalence in the three main types of atrophic gastritis seem to rule out extensive IM while favouring decreased acid secretion (Siurala et al. 1988) as a causative factor in this behaviour of *H. pylori* colonization. The low *H. pylori* colonization in type-A gastritis fits with previous reports (Fong et al. 1991).

Our finding of significantly higher antral *H. pylori* colonization (coupled with a parallel but non-significant trend of gastritis incidence and activity) in non-ulcer dyspepsia with respect to asymptomatic subjects suggests that *H. pylori*-associated antral gastritis may have a role in the pathogenesis of NUD. In a previous study (Siurala et al. 1985) a similar difference concerning the incidence of antral gastritis was shown to be accounted for by a subgroup of NUD patients with gastric stump, hiatus hernia or biliary tract disease. Gastric stump patients have been excluded from the present study, while no significant difference was noted in the gastritis of NUD patients with or without evidence of bile reflux during endoscopy. Improvement of dyspeptic symptoms after eradication of *H. pylori* and regression of antral gastritis has been reported in children (De Giacomo et al. 1990). Important differences in the variables used to assess gastritis have been found in this study between *H. pylori*-positive and *H. pylori*-negative NUD patients. This suggests the need for more work on possible relationships between *H. pylori* gastritis and various clinical subtypes of NUD.

Recent follow-up studies have clearly shown that antral chronic gastritis predisposes to peptic ulcer disease of both duodenum and stomach (Sipponen et al. 1989, 1990). The exact factors and mechanisms involved in this predisposition are not known. Our investigations show that *H. pylori* colonization and active gastritis of the antrum, progressively and significantly increase from erosion-free asymptomatic patients to non-erosive NUD, NUD with gastroduodenal erosions and active gastroduodenal ulcers, thus suggesting a role for these factors. In fact, nearly all active ulcers had associated *H. pylori*-positve antritis of active type, while healed ulcers had slightly reduced *H. pylori* colonization, antritis incidence and activity. Higher incidence in grade-2

active antritis, despite somewhat lower *H. pylori* colonization, seems to distinguish GU from DU.

Of special interest is the significantly lower proportion of active corpus gastritis in DU patients when compared with GU or NUD, a difference no longer observed in HDU. A factor protecting the structure and function of the oxyntic glands in active DU (and distal GU) patients has been postulated previously (Kekki et al. 1984; Ihamaki et al. 1985; Siurala et al. 1985). The possible involvement of cytoprotective and trophic factors, like PGE_2 or TGFα produced by parietal cells (Beachamp et al. 1989; Higuchi et al. 1988) should be investigated.

Although the overall incidence of *H. pylori* in corpus mucosa (80.5%) was only moderately lower among DU patients than in antral mucosa (93.5%), grade-2 colonization was more obviously reduced (19% versus 51%, $P<0.001$). Low density colonization was usually coupled with mild superficial, non-active gastritis or even with normal mucosa. Heavy *H. pylori* colonization seems to be necessary in the oxyntic mucosa to induce a type of active superficial gastritis progressing to more severe atrophic forms. Thus, lack of heavy *H. pylori* colonization and active gastritis involving glandular bodies (or, at least, the renewal zone of the mucosa) may account in part for the integrity of oxyntic glands in DU patients.

Patients with duodenal erosions resembled DU patients in many respects, including low incidence of active corpus gastritis. This suggests that a common pathogenetic background and histogenetic link may exist between the two lesions (Sircus 1985). Flat gastric erosions of antropyloric mucosa, which have also been linked to peptic ulcer disease at the same site (Karvonen 1982; Karvonen et al. 1983), are also coupled with low incidence of corpus active gastritis as well as high incidence of active antritis.

Thus, from our findings and some previous observations (Fiocca et al. 1987, 1989, 1991; Rauws et al. 1988; Sipponen et al. 1989; De Giacomo et al. 1990; Eidt and Stolte 1990) it seems clear that progressively increasing severity of both *H. pylori* colonization and active antral gastritis marks the appearance of NUD, erosions and ulcers and may have an important role in their pathogenesis. The dual role of corpus-fundus mucosa (Siurala et al. 1985) also seems to be important, with normal mucosa or superficial, inactive gastritis favouring the development of pyloroduodenal ulcers or erosions, and active interstitial/atrophic gastritis preventing such lesions while favouring the development of proximal ulcers. Although by themselves gastritis-related factors are far from fully predictive of ulcer/erosion formation and localization, their role may appear more crucial when considered in combination with *H. pylori*-associated epithelial lesions (Chen et al. 1986; Tricottet et al. 1986; Fiocca et al. 1987; Wyatt et al. 1987; Solcia et al. 1992) and other factors like gastric secretion and cytoprotective agents.

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