

## Helicobacter pylori in Barrett's esophagus

Joan-Carles Ferreres<sup>1</sup>, Fidel Fernández<sup>1</sup>, Agustín Rodríguez Vives<sup>2</sup>, Irene González-Rodilla<sup>1</sup>, Inmaculada Ursúa<sup>1</sup>, Rafael Ramos<sup>1</sup> and José Fernando Val-Bernal<sup>1</sup>

<sup>1</sup>Department of Pathology and <sup>2</sup>Department of Medicine, Division of Gastroenterology, «Marqués de Valdecilla» National Hospital, Faculty of Medicine, University of Cantabria, Santander, Spain

**Summary.** Barrett's esophagus is an anatomicoclinical state in which, due to the prolonged action of gastroesophageal reflux, the squamous epithelium is replaced by columnar epithelium. *Helicobacter pylori* has been implicated in the pathogenesis of various gastrointestinal disorders and has occasionally been observed in Barrett's esophagus. The aim of this study is to determine the incidence of *H. pylori* in Barrett's esophagus and try to establish its role in the pathogenesis of this disorder. *H. pylori* was observed in 31 biopsies (44.3%) of the 70 studied, mainly when the epithelium is of the gastric atrophic-fundic type ( $p < 0.01$ ). Its presence shows no relation to the degree of inflammatory activity and does not seem, therefore, to play an important role in the pathogenesis of the lesion.

**Key words:** Barrett's esophagus, *Helicobacter*, Esophagitis

### Introduction

*Helicobacter pylori* (*H. pylori*) is a microaerophilic Gram-negative curved or spiral shaped bacillus measuring 2.5 to 3  $\mu\text{m}$  in length and 0.5  $\mu\text{m}$  in diameter. Warren and Marshall (1983) drew attention to its presence in gastric biopsies of patients with active chronic gastritis. Since then it has been related to various gastro-duodenal disorders; acute gastritis (Marshall et al., 1985b; Morris et al., 1987); chronic gastritis (Warren and Marshall, 1983; Marshall and Warren, 1984; Goodwin et al., 1985; Ramírez-Ramos et al., 1987; Wyatt and Dixon 1990); duodenal ulcer (Price et al., 1985; Marshall et al., 1985a; McNulty and Wise, 1985); and gastric ulcer (Price et al., 1985; Marshall et al., 1985a; McNulty and Wise, 1985). In other conditions its

role is still the subject of controversy; e.g. lymphocytic gastritis (Wallez et al., 1987; Dixon et al., 1988).

Barrett's esophagus involves the replacement of the squamous epithelium of the distal end of the esophagus by columnar epithelium similar to that found in the stomach or intestine. This metaplastic change is due to chronic esophagitis caused by reflux (Winters et al., 1987).

Given the affinity of *H. pylori* for gastric mucosa and the proven existence of *H. pylori* in duodenal specimens with gastric metaplasia (Johnston et al., 1986; Walker et al., 1989), it seems reasonable to assume that it will also be detected in specimens from patients with Barrett's esophagus. If this is so, the pathogenic role of the bacillus in this lesion still has to be determined.

The number of articles published on this subjects are few and the results are contradictory (Table 1).

The aim of the present study is to determine the incidence of *H. pylori* in Barrett's esophagus and to see whether there exists a relation with the type of metaplastic epithelium and with the degree of inflammatory activity of the lesion.

### Materials and methods

70 endoscopic specimens, consisting of 1 to 4 biopsies, from the same number of patients with Barrett's esophagus were studied. The age and sex of each patient were recorded.

For the histological analysis, all the specimens were processed routinely in paraffin following fixation in 10% buffered formalin. The 5  $\mu\text{m}$  thick sections were stained with hematoxylin and eosin, periodic acid Schiff-alcian blue (pH 2.5) and Giemsa (Gray et al., 1986).

Barrett's esophagus was diagnosed by identifying columnar epithelium in specimens taken more than 3 cm above the cardia. The criteria for identification and the measurement of the distance were the same as those previously described (Blackstone, 1984). Three types of epithelium were identified: specialized columnar

Offprint requests to: Dr. D. Fidel Fernández, Departamento de Anatomía Patológica, Hospital Nacional «Marqués de Valdecilla», E-39008 Santander, Cantabria, Spain



epithelium, junctional-type epithelium, and gastric atrophic-fundic type epithelium (Paull et al., 1976). When the different specimens from the same patient belonged to different types of epithelium, they were classified according to the following criteria; presence of chief and parietal cells for the gastric atrophic-fundic type (Fig. 1) and presence of goblet cells with mucin acid production (alcian blue positive) for the specialized columnar type (Fig. 2). When none of the above findings were observed in any of the fragments, these were classified as junctional type (Fig. 3). Cases where only fibrino-leukocytic exudate occurred and where no columnar epithelium was observed were excluded.

The activity of the inflammatory process was evaluated by grouping the specimens into three categories: inactive chronic inflammation, with no polymorphonuclear leukocytes in the lamina propria; active chronic inflammation when these were present in the lamina propria with intraepithelial infiltration (Fig. 3); and erosion-ulceration in terms of the fibrino-leukocytic exudate observed.

*H. pylori* was identified from its morphological characteristics using Giemsa stain (Gray et al., 1986) at a magnification of  $\times 400$  (Fig. 4).

The results were processed statistically using the  $\chi^2$  test.

## Results

The most important results obtained in the study are shown in Table 2.

The mean age of the 70 patients under study was 65 years (range 38-78).

There were no significant differences as far as the presence of *H. pylori* was concerned in relation to the sex and age of the patients or to the degree of inflammatory activity.

There was, however, a statistically significant relationship between the presence of *H. pylori* and the gastric atrophic-fundic type epithelium ( $< 0.01$ ) compared with other types of epithelium.

## Discussion

The proportion of patients with Barrett's esophagus colonised by *H. pylori* in our series agreement with that found by other authors (Talley et al., 1988; Houck and Lucas, 1989).

Colonization by *H. pylori* in the stomach is known

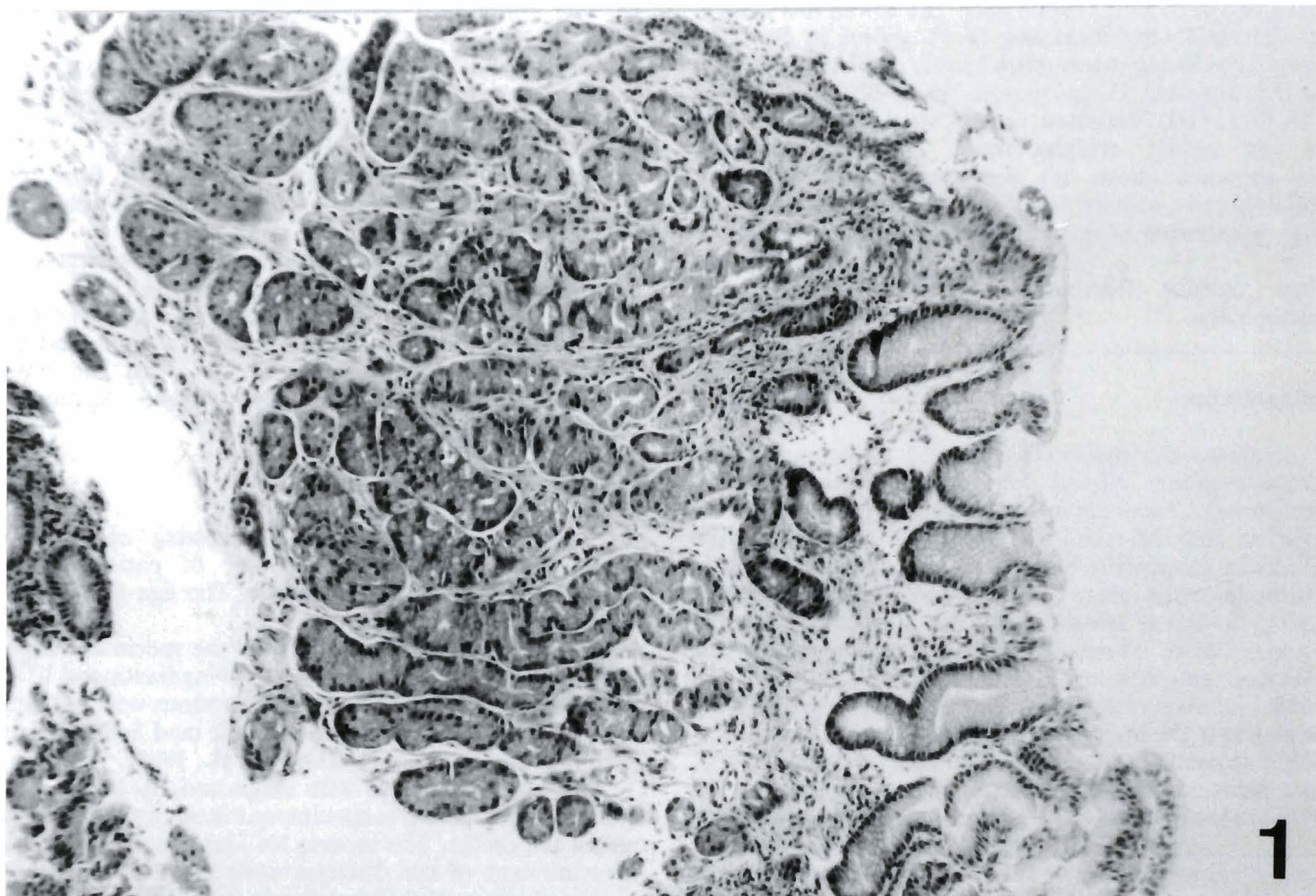
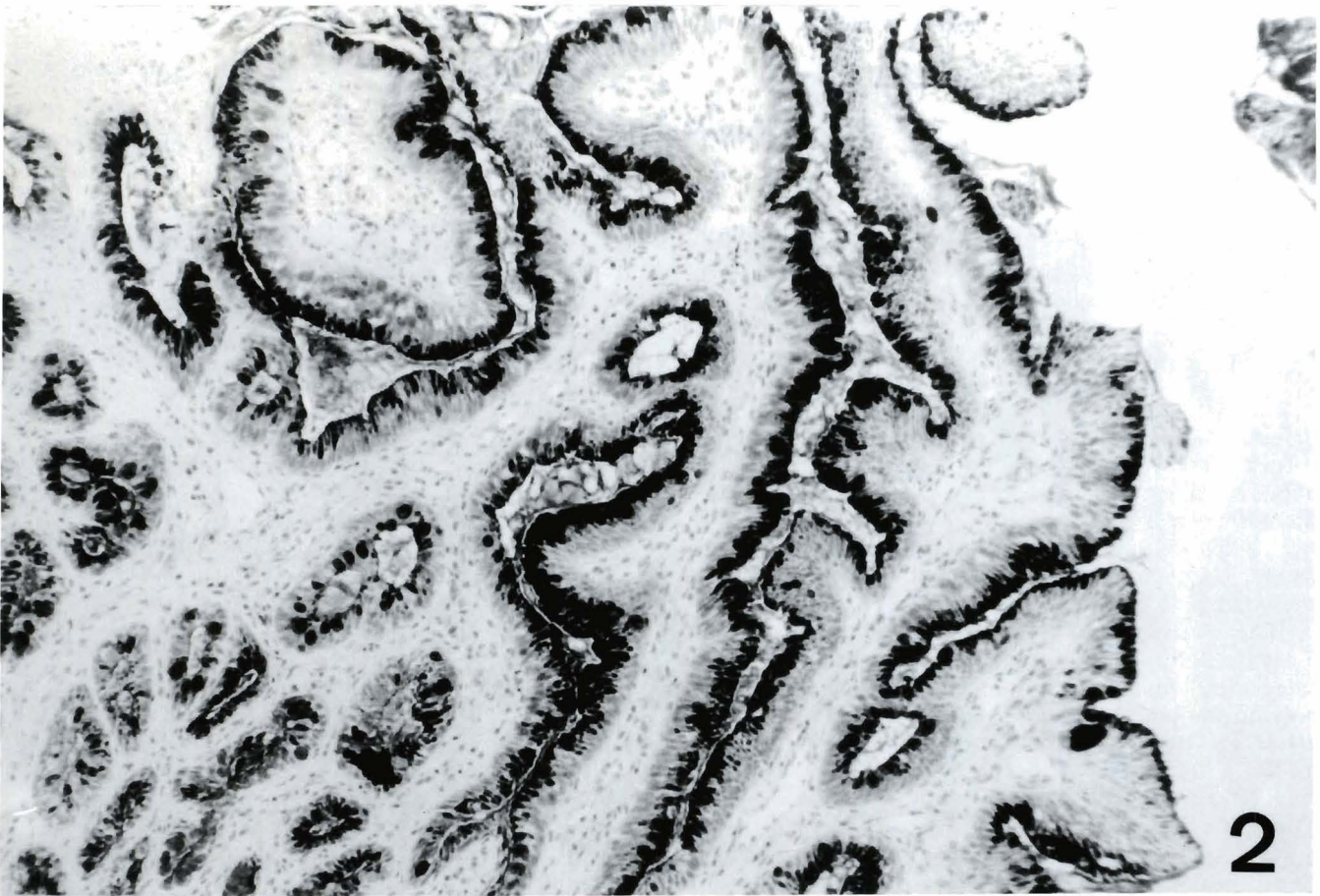
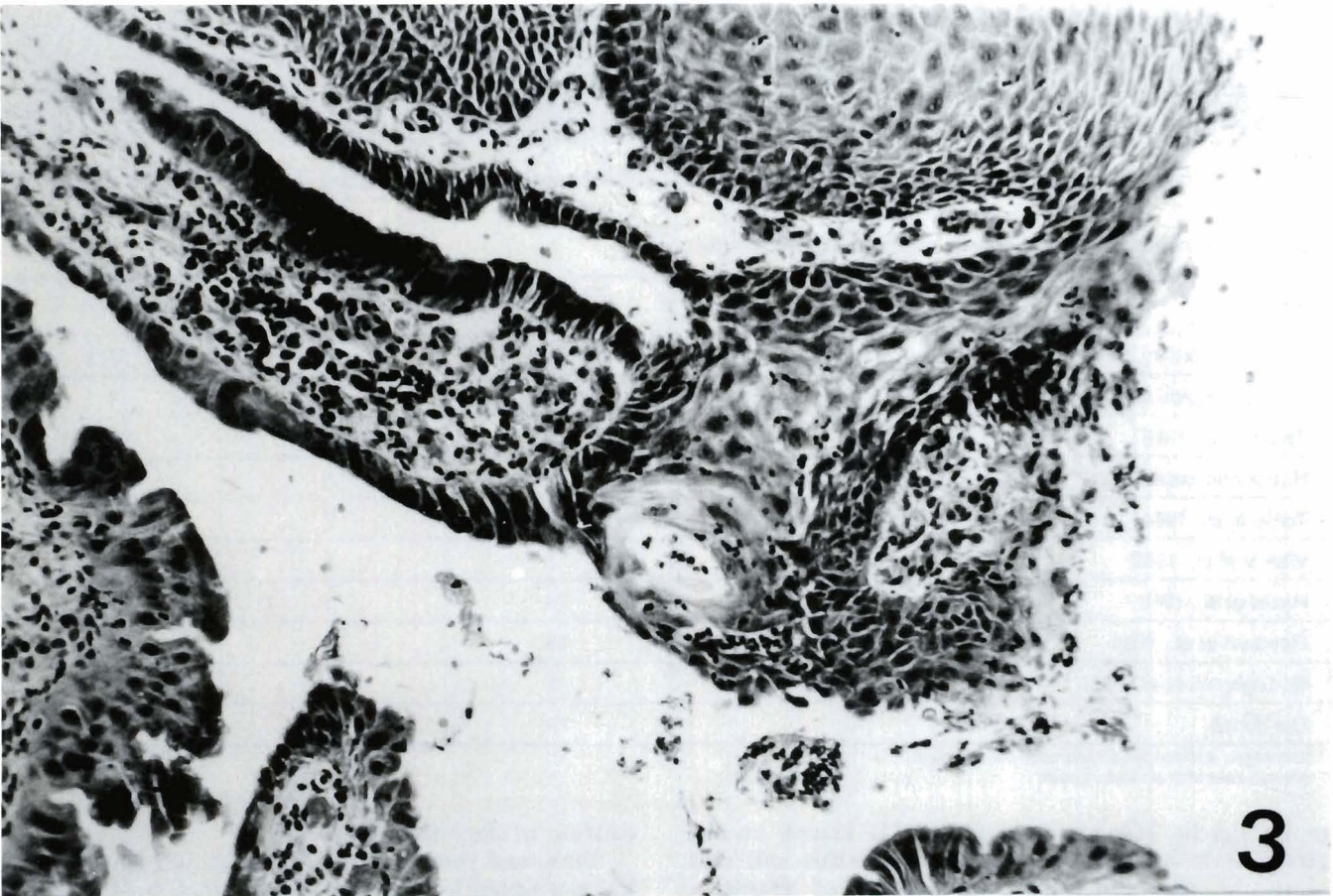


Fig. 1. Barrett's esophagus; gastric atrophic-fundic type. Presence of chief and parietal cells. Hematoxylin-eosin.  $\times 63$



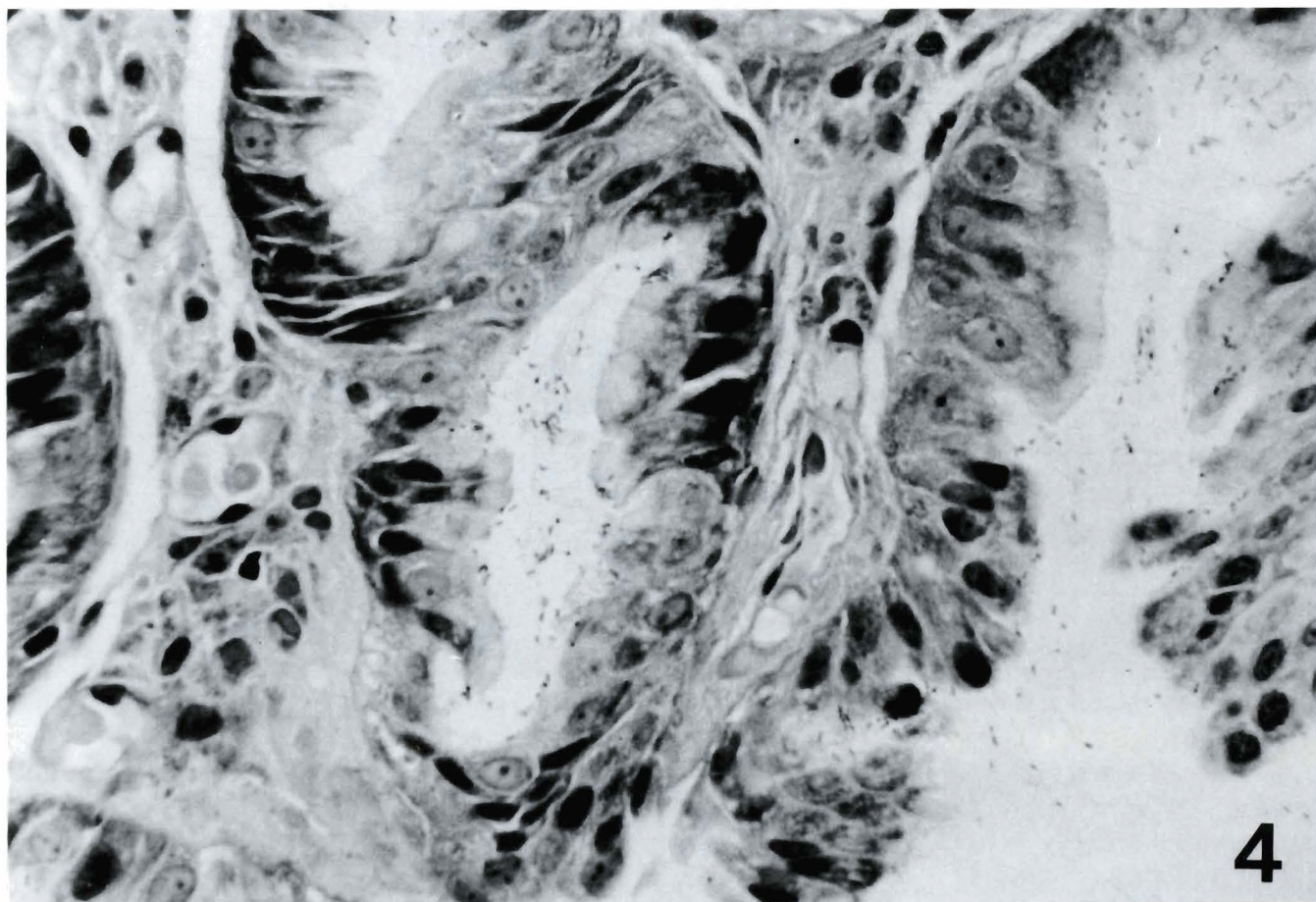


**Fig. 2.** Barrett's esophagus; specialized columnar type. Presence of goblet cells with mucin acid production. Periodic acid Schiff-alcian blue, pH 2.5.  $\times 63$



**Fig. 3.** Barrett's esophagus; junctional type. Superficial epithelium, similar to the normal squamous-columnar junction. Polymorphonuclear leukocytes are observed in the lamina propria with intraepithelial infiltration. Hematoxylin-eosin stain.  $\times 100$





**Fig. 4.** *H. pylori* in Barrett's esophagus. Curved on spiral shaped bacillus in superficial and intraglandular mucus. Giemsa stain,  $\times 400$

**Table 1.** *Helicobacter pylori* in patients with Barrett's esophagus.

Authors	No. patients studied	No. patients with <i>H. pylori</i>	%
Paull and Yardley, 1988	26	4	15.3
Kalogeropoulos and Whiterhead, 1988	64	12	19
Talley et al., 1988	23	12	52
Houck and Lucas, 1989	38	0	0
Talley et al., 1984	47	7	14.9
Walker et al., 1989	7	2	29
Hazell et al., 1988	20	3	15
Goodwin et al., 1985	13	4	*
De Giacomo et al., 1988	1	1	**
Our series	70	31	44.3

\* esophagus and duodenal specimens not specified

\*\* isolated case in a pediatric patient

to be patchy (Goodwin et al., 1985; Hazell et al., 1987). It is reasonable to assume that this will also occur in the metaplastic epithelium of Barrett's esophagus, which might account for the differences

existing in the different series.

Only one previous study (Houck and Lucas, 1989) has attempted to associate the presence of *H. pylori* in Barrett's esophagus with the type of metaplastic

**Table 2.** *Helicobacter pylori* in 70 patients with Barrett's esophagus studied at Valdecilla Hospital, Santander.

	No. patients with Barrett's esophagus (%)	C. pylori (%)
TOTAL	70	31 (44.3)
SEX		
Males	48	21 (44.8)
Females	22	10 (45.5)
AGE		
> 50	60	27 (45)
< 50	9	4 (44.4)
EPITHELIUM TYPE		
Columnar	34 (48.6)	11 (32.4)
Junctional	28 (40)	12 (42.9)
G. atrophic-fundic	8 (11.4)	8 (100)*
INFLAMMATORY ACTIVITY		
Inactive	23 (32.9)	10 (43.5)
Active	13 (18.6)	7 (53.8)
Ulceration-erosion	34 (48.6)	14 (41.2)

\*  $p < 0.01$ 

epithelium. Inexplicably, no bacilli were found in any of the 40 patients studied and no association could be established.

When the epithelium is of the specialized columnar type with villi-bearing structures and mucin acid production from the goblet cells, as occurs in the intestine, the presence of *H. pylori* is rare. This, however, does not occur when the other types of metaplasia are involved (junctional-type and gastric atrophic-fundic type). This agrees with the fact that *H. pylori* is not usually observed in areas of intestinal metaplasia in connection with chronic atrophic gastritis (Goodwin et al., 1985; Wyatt and Dixon, 1990) or in duodenal specimens where there is no gastric metaplasia (Johnston et al., 1986; Walker et al., 1989). The 32.4% which showed positive in Barrett's esophagus with specialized columnar type epithelium is probably due to the fact that fairly often in the same patient the specialized columnar epithelium is associated with junctional-type epithelium (Paull et al., 1976). In many of these cases *H. pylori* has been observed in the luminal surface of the junctional-type foveolar epithelium, although with our restrictive classification criteria these were considered to be of the specialized columnar type. Another factor which might explain the presence of *H. pylori* in this and other type of Barrett's esophagus is possible contamination from the dragging effect of the gastroscope (Fallingborg et al., 1989) or from reflux (Walker et al., 1989; Coelho et al., 1989).

The gastric atrophic-fundic epithelium is the type which contains most «normal» gastric mucosa elements

(parietal cells, chief cells, mucous cells, foveolae) (Paull et al., 1976) and this type *H. pylori* was observed in all cases ( $p < 0.01$ ).

As for the relationship between presence or absence of *H. pylori* and the degree of inflammatory activity of Barrett's esophagus, our results are not conclusive (Table 2). Although we observed a higher proportion of active chronic inflammation in patients with *H. pylori* (53.8%) compared to those who showed no signs of activity (43%), this difference was not statistically significant.

The idea that *H. pylori* is responsible for the «gastritis» of Barrett's esophagus similar to that produced in gastric mucosa has its advocates (Hazell et al., 1988) and we should recognise that it is at least tempting.

However, our results lead us to believe, like other authors (Talley et al., 1984; Kalogeropoulos and Whitehead, 1988; Paull and Yardley, 1988; Talley et al., 1988; Coelho et al., 1989; Cheng et al., 1989; Walker et al., 1989), that *H. pylori* does not play an important role in the genesis of Barrett's esophagus and that it may not take part in the activity of the disorder either; it may in fact be a colonizer of previously damaged mucosa and find in the metaplastic epithelium a microenvironment with similar characteristics to that found in the stomach.

## References

- Blackstone M.O. (1984). The esophagus: Endoscopic appearance, technique of examination, and normal appearance, in Endoscopic Interpretation: Normal and



*H. pylori in Barrett's esophagus*

- pathologic appearances of the gastrointestinal tract. Raven Press, New York, 12-13.
- Cheng E.H., Bermanski P.B., Silversmith M., Valenstein P. and Kawanishi H. (1989). Prevalence of *Campylobacter pylori* in esophagitis, gastritis and duodenal disease. *Arch. Intern. Med.* 149, 1373-1375.
- Coelho L.G.V., Das S.S., Payne A., Karim Q.N., Baron J.H. and Walker M.M. (1989). *Campylobacter pylori* in esophagus, antrum and duodenum. *Dig. Dis. Sci.* 34, 445-448.
- De Giacomo C., Fiocca R., Villani L., Bertolotti L. and Maggiore G. (1988). Barrett's ulcer and *Campylobacter*-like organisms infection in a child. *J. Pediatr. Gastroenterol. Nutr.* 7, 766-768.
- Dixon M.F., Wyatt J.I., Burke D.A. and Rathbone B.J. (1988). Lymphocytic gastritis-relationship to *Campylobacter pylori* infection. *J. Pathol.* 154, 125-132.
- Fallingborg J., Agnholt J., Miller-Petersen J., Christensen L.A., Lomborg S., Sndergaard G., Teglbjaerg P.T. and Rasmussen S.N. (1989). *Campylobacter pylori* in esophagus (letter). *Dig. Dis. Sci.* 34, 1802-1803.
- Goodwin C.S., Blincow E.D., Warren J.R., Waters T.E., Sanderson C.R. and Easton L. (1985). Evaluation of cultural techniques for isolating *Campylobacter pyloridis* from endoscopic biopsies of gastric mucosa. *J. Clin. Pathol.* 38, 1127-1131.
- Gray S.F., Wyatt J.I. and Rathbone B.J. (1986). Simplified techniques for identifying *Campylobacter pyloridis*. *J. Clin. Pathol.* 39, 1280.
- Hazell S.L., Hennessy W.B., Borody T.J., Carrick J., Ralston M., Brady L. and Lee A. (1987). *Campylobacter pyloridis* gastritis II: distribution of bacteria and associated inflammation in the gastroduodenal environment. *Am. J. Gastroenterol.* 82, 297-301.
- Hazell S.L., Carrick J. and Lee A. (1988). *Campylobacter pylori* can infect the oesophagus when gastric tissue is present (abstract). *Gastroenterology*. 94, 178.
- Houck J.A. and Lucas J.G. (1989). Absence of *Campylobacter*-like organisms in Barrett's esophagus. *Arch. Pathol. Lab. Med.* 113, 470-472.
- Johnston B.J., Reed P.I. and Ali M.H. (1986). *Campylobacter*-like organisms in duodenal and antral endoscopic biopsies: relationship to inflammation. *Gut*. 27, 1132-1137.
- Kalogeropoulos N.K. and Whitehead R. (1988). *Campylobacter*-like organisms and *Candida* in peptic ulcers and similar lesions of the upper gastrointestinal tract: a study of 247 cases. *J. Clin. Pathol.* 41, 1093-1098.
- McNulty C.A.M. and Wise R. (1985). Rapid diagnosis of *Campylobacter*-associated gastritis (letter). *Lancet*. 1, 1443-1444.
- Marshall B.J. and Warren L.R. (1984). Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1, 1311-1314.
- Marshall B.J., Armstrong J.A., McGeachie D.B. and Glancy R.J. (1985a). Attempt to fulfill Koch's postulates for pyloric *Campylobacter*. *Med. J. Aust.* 142, 436-439.
- Marshall B.J., McGeachie D.B., Rogers P.A. and Glancy R.J. (1985b). Pyloric *Campylobacter* infection and gastroduodenal disease. *Med. J. Aust.* 142, 439-444.
- Morris A. and Nicholson G. (1987). Ingestion of *Campylobacter pyloridis* causes gastritis and raised fasting gastric pH. *Am. J. Gastroenterol.* 82, 192-199.
- Paull A., Trier J.S., Dalton M.D., Camp R.C., Loeb P. and Goyal R.K. (1976). The histologic spectrum of Barrett's esophagus. *N. Engl. J. Med.* 295, 476-480.
- Paull G. and Yardley J.H. (1988). Gastric and esophageal *Campylobacter pylori* in patients with Barrett's esophagus. *Gastroenterology*. 95, 216-218.
- Price A.B., Levi J., Dolby J.M., Dunscombe P.L., Smith A., Clark J. and Stephenson M.L. (1985). *Campylobacter pyloridis* in peptic ulcer disease: microbiology, pathology, and scanning electron microscopy. *Gut*. 26, 1183-1188.
- Ramírez-Ramos A., Gilman R.H., Recavarren S., Watanabe J., Cok J., León-Barua R. and Spira W.M. (1987). *Campylobacter pyloridis* in a developing country (Abstract). *Gastroenterology*. 92, 1588.
- Talley N.J., Cameron A.J., Shorter R.G., Zinsmeister A.R. and Phillips S.F. (1988). *Campylobacter pylori* and Barrett's esophagus. *Mayo Clin. Proc.* 63, 1176-1180.
- Talley R., Weinstein W.M., Marin-Sorensen M., Schneidman D., Reedy T.J. and Van Deventer G. (1984). *Campylobacter pylori* colonization of Barrett's esophagus (abstract). *Gastroenterology*. 94, 454.
- Walker S.J., Birch P.J., Stewart M., Stoddard C.J., Hart C.A. and Day D.W. (1989). Patterns of colonisation of *Campylobacter pylori* in the esophagus, stomach and duodenum. *Gut*. 30, 1334-1338.
- Wallez L., Weynaud B. and Haot J. (1987). Evaluation histologique de la presence d'organismes de type *Campylobacter* dans les gastrites lymphocytaires. *Acta. Endoscop.* 17, 41.
- Warren J.R. and Marshall B.J. (1983). Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1, 1272-1273.
- Winters Ch., Spurling T.J., Chobanian S.J., Curtis D.J., Esposito R.L., Hacker J.F., Johnson D.A., Cruess D.F., Cotelingam J.D., Gurney M.S. and Cattau E.L. (1987). Barrett's esophagus-A prevalent, occult complication of gastroesophageal reflux disease. *Gastroenterology*. 92, 118-124.
- Wyatt J.I. and Dixon M.F. (1990). *Campylobacter*-Associated chronic gastritis. *Pathol. Annu.* 25, (pt 1) 75-98.

Accepted March 1, 1991