

Campylobacter-like organisms and *Candida* in peptic ulcers and similar lesions of the upper gastrointestinal tract: a study of 247 cases

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SUMMARY Campylobacter-like organisms were detected by light microscopy in association with 57 of 102 (56%) of gastric ulcers, all the gastric erosions associated with gastritis, three of five (60%) of gastric erosions without gastritis, five of 13 (39%) of mild superficial gastritis and two of 36 (6%) of normal gastric mucosa. They were also seen in four of 20 (20%) of duodenal ulcers, but not in duodenal erosions with duodenitis or normal duodenal biopsy specimens. They were seen in association with 12 of 64 (19%) of cases of Barrett's oesophagus.

Moniliasis was seen in nine of 78 (12%) of the gastric ulcers in which campylobacter-like organisms were found, and the incidence of moniliasis was three of 15 (20%) in association with duodenal ulcers when ulcer debris was present in biopsy material, and in association with six of 25 (24%) of cases of Barrett's oesophagus.

These findings do not support the hypothesis that campylobacter-like organisms cause inflammatory and ulcerative lesions of the upper gastrointestinal tract.

The presence of spiral or curved bacilli in close association with human gastric mucosa was described as early as 1896¹ and noted subsequently on several occasions.²⁻⁷ Recently Marshall and Warren cultured them and drew attention to their similarity to *Campylobacter* species.^{8,9} Subsequently they and others proposed that these organisms produce acute inflammation of the gastric mucosa and are causally related to peptic ulceration. This is plausible in cases of gastric ulcer and duodenal ulcer when other organisms are present. Doubt is raised, however, because they are not present in some gastric ulcers, and they are only seen in association with duodenal ulcers if antral type duodenal mucosa is seen¹⁰⁻¹² even though they may be present in the antral mucosa.¹³

To investigate this possible association further we have correlated the presence of campylobacter-like organisms not only with peptic ulcer and associated inflammation of the stomach and duodenum, but also with erosion of stomach and duodenum with and without associated inflammation, inflammation (superficial gastritis) unassociated with ulceration, normal gastric and duodenal mucosa, and Barrett's oesophagus with and without peptic ulcer. We have also noted the presence or absence of *Candida albicans*

in peptic ulcers of duodenum, stomach, and oesophagus. Candidiasis is generally regarded as an opportunistic infection in peptic ulcers, and it has no aetiological role.^{14,15}

Material and methods

Biopsy tissues were selected from our records of patients investigated for various gastrointestinal symptoms. They were classified according to the usually accepted histological criteria¹⁶ as being normal, or showing acute gastric erosion with or without gastritis, superficial gastritis, peptic ulcer associated with chronic gastritis, normal duodenal mucosa, duodenal erosion with duodenitis, and chronic duodenal ulcer. In cases of duodenal ulcer the presence of antral type mucosa was noted in all cases. Biopsy specimens from patients with Barrett's oesophagus with and without ulceration were also examined.

The investigation of these tissues for campylobacter-like organisms was undertaken in sections stained with haematoxylin and eosin and for *Candida* and other diseases by alcian blue and periodic acid Schiff after diastase digestion. *Candida* spores and pseudohyphae are easily recognised by their size and morphology in ordinary sections stained with haematoxylin and eosin and in all cases their positivity to

periodic acid Schiff was shown. Campylobacter-like organisms as described by others were identified as haematoxyphilic curved or S shaped bacilli or both,^{8,10} depending on the plane of sectioning,¹⁷ in close association with the surface epithelium distributed in either continuous or focal arrangement. A strict definition of Barrett's oesophagus was used and cases were only included if their location was precisely noted at endoscopy and if the histological characteristics of partial intestinal change were present. A total of 269 biopsy specimens from 247 patients were examined. Sections stained with haematoxylin and eosin were screened at a magnification of 40, and verification of suspected campylobacter like organisms was made using a magnification of 1000 under oil immersion. The following stains were used occasionally: Gram, modified Giemsa (without differentiation),¹⁸ Cresyl fast violet,¹⁹ and Warthin-Starry.⁸ The microscopic identification of campylobacter-like organisms in biopsy specimens correlates closely with their isolation on culture,^{13,17,20-22} so as in most previous

studies^{3,10,20,23,24} we used this method of identification. In the cases of peptic ulceration the presence of tissue or debris at the base of the ulcer was also noted. This was presumed to indicate that all the biopsy tissues originated in the edge of or in close proximity to the actual ulcer crater. If the accompanying inflammation was characterised by plasma cells and lymphocytes but no polymorphs it was designated chronic, but if polymorphs were present it was regarded as acute.

Results

The results are shown in tables 1 and 2. Campylobacter-like organisms were detected in 56% of gastric ulcers and there was no significant difference in the incidence between cases which included ulcer debris and those that did not. When there was no ulcer debris, however (table 2), 92% of those with acute inflammation contained campylobacter-like organisms, whereas in those with a chronic component of gastritis

Table 1 Incidence of campylobacter-like organisms and *Candida albicans* in various gastrointestinal lesions (269 biopsy specimens from 247 patients)††

No	Histology	No patients	Campylobacter-like organisms		Candida albicans	
			No	%	No	%
1	Gastric ulcer:	102	57	55.8	NE	NE
	Ulcer debris present*	78	44	56.4	20	25.6
	Ulcer debris absent	24	13	54.2	NE	NE
2	Gastric erosions with gastritis:	5	5	100	NE	NE
	Gastric erosions without gastritis:	5	3	60	NE	NE
4	Mild superficial gastritis:	13	5	38.5	NE	NE
	Acute	2	1	50		
	Chronic	8	2	25		
	Acute and chronic	3	2	66.6		
5	Normal gastric mucosa:	36	2	5.5	NE	NE
6	Duodenal ulcer:	20	4	20	NE	NE
	Ulcer debris present	15	4†	26.6	3	20
	Under treatment	8	2	25.0		12.5
	No treatment	7	2	28.5	1	28.5
	Ulcer debris absent	5	0	0	NE	NE
	Under treatment	4	0	0		
	No treatment	1	0	0		
7	Duodenal erosions‡ with duodenitis:	2	0	0	NE	NE
8	Normal duodenal mucosa:§	5	0	0	NE	NE
9	Barrett's oesophagus:¶	64	12	18.7	NE	NE
	Ulcerated**	25	6	24	6	24
	Non-ulcerated	35	6	17.1	NE	NE
	Dysplasia	1	0	0	NE	NE
	Candida-ulcerated	1	0	0	1	100
	Candida-non-ulcerated	2	0	0	NE	NE
Total††		247	87	35.2	NE	NE

NE = not estimated.

††Two patients had three biopsies and another 14 patients had two biopsies.

*Coincidence of campylobacter-like organisms and *Candida albicans* was noticed in nine from 78 (11.5%) cases.

†Three of the campylobacter-like organisms (+) cases had also campylobacter-like organisms (+) gastritis (the second biopsy specimen is not included in another group).

‡One of the cases is also included in gastric ulcer-campylobacter-like organisms (+) group.

§One patient is also included in the MSG-chronic campylobacter-like organisms (-) group.

¶Two patients are also included in gastric ulcer-campylobacter-like organisms (+) group, one with campylobacter-like organisms (+) and one with campylobacter-like organisms (-) in oesophageal biopsy specimen.

**Coincidence of campylobacter-like organism and *Candida albicans* was noticed in one from 25 cases (4%).

+ = positive; - = negative.

Table 2 Incidence of campylobacter-like organisms in gastric ulcers present at endoscopy without ulcer debris in biopsy material

Histological appearance	No of patients	No (%) with campylobacter-like organisms
Healing ulcer	6	1 (17)
Ulcer margins with acute inflammation	12	11 (92)
Ulcer margins with chronic inflammation	6	1 (17)
Total	24	13 (54)

only 17% showed campylobacter-like organisms. The incidence of the organisms in gastric erosions with and without associated gastritis was 100% and 60%, respectively. Campylobacter-like organisms were also detected in five of 13 (39%) with associated mild superficial gastritis but no ulcer, and in only two of 36 (6%) of samples of normal gastric mucosa.

Campylobacter-like organisms were not seen in the biopsy specimens of normal duodenal mucosa, nor were they seen in either of the two erosions associated with duodenitis. Campylobacter-like organisms were detected in four of 20 (20%) duodenal ulcers, and in three of these campylobacter-like organisms were also seen in gastric biopsy specimens taken at the same examinations in which there was a mild superficial gastritis in one case, and atrophic gastritis in two. One patient with a duodenal erosion without campylobacter-like organisms and two patients with duodenal ulcers without campylobacter-like organisms had campylobacter-like organisms in the gastric mucosa. Campylobacter-like organisms were only seen in tissue from duodenal ulcers in association with foci of antral type epithelium.

Of the 64 cases of Barrett's oesophagus (19%) were associated with campylobacter-like organisms but it was noticeable that in the presence of ulceration the percentage rose to 24%.

Candidiasis was present in 20 of 78 (26%) gastric ulcers if ulcer debris was present, and if only gastrectomy specimens are considered the incidence was 38%. In nine cases of ulcers positive for *Candida* (12%) campylobacter-like organisms were also detected. In duodenal ulcers candidiasis occurred in 20% without accompanying campylobacter-like organisms. In cases in which there was ulcer debris in the biopsy material, the incidence of campylobacter-like organisms was almost equal to that of *Candida*. Interestingly, in one case with both duodenal ulcer and Barrett's ulcer only the duodenal ulcer contained *Candida*. *Candida* was, however, also seen in six of the 25 cases of ulcerated Barrett's oesophagus (24%). There was a similar incidence of campylobacter-like organisms, but campylobacter-like organisms and *Candida* were seen together in only one case.

Discussion

"Can these spirochaetes, which exist in man, and in animals commonly employed for experiments and which are ordinarily harmless, be ignored in physiologic and pathologic studies on the stomach?" This question posed by Doenges³ was addressed 50 years later by Marshall and Warren,⁹ who stated that campylobacter-like organisms are "aetiologically related to chronic antral gastritis and, probably, to peptic ulceration also".

Since that time it has been claimed in support of this statement that campylobacter-like organisms occur in the antrum in almost all patients with duodenal ulcers and in up to 90% of those with non-autoimmune gastritis.^{9,25} In comparison campylobacter-like organisms are found in only 3.4 to 24% of normal subjects^{9,13} and in about 21% of patients with type A gastritis.²⁶ Antibodies to campylobacter-like organisms can be detected in serum samples^{20,27,28} and gastric juice¹⁸ of patients who harbour the organism, and after ingestion of campylobacter-like organisms it is claimed that a gastritis can be induced in previously normal volunteers.²⁹ The organism is sensitive to antimicrobials including metronidazole,^{30,31} and it has been claimed that metronidazole heals peptic ulcers³², bismuth compounds are also effective.³³⁻³⁶ It is also said that colonisation by campylobacter-like organisms persists in patients treated with H₂ receptor antagonists, the use of which is known to be associated with a higher incidence of relapse of ulcers than other agents.³⁷

There is, however, evidence that campylobacter-like organisms do not have a causal role in peptic ulcer disease. They are not present in all lesions, and there is a better association with a history of ulcer (53%) than with active ulceration (46%).²⁵ The correlation with the acute inflammatory activity of gastritis has been disputed^{17,20} and campylobacter-like organisms persist despite the healing of the ulcer.^{17,21,38,39} They are sometimes present even when the mucosa is histologically normal^{13,40} and they occur in about 24% of asymptomatic healthy volunteers with histological evidence of gastritis.²² Gastric ulcers from which campylobacter-like organisms are found have similar clinical courses to those in which they are not found,⁴¹ and in a study from Hong Kong³⁹ 51% of duodenal ulcers healed after placebo treatment despite the persistence of campylobacter-like organisms in the antrum. Finally in a study of duodenal biopsy specimens there was no correlation between the presence of campylobacter-like organisms and active inflammation.²³

The previously claimed association between the presence of campylobacter-like organisms and gastric ulcer has varied between 35%⁴⁰ and 80%,^{7,9,42} but other

investigators^{13 17 21} report an incidence similar to that in the present study (56%). The presence of ulcer debris does not influence the result, but in its absence an acute inflammatory component was associated with campylobacter-like organisms in 92% of cases compared with 17% when the inflammation was chronic. This is similar to some previous reports^{9 23 39 42} but not all.^{17 20}

Gastric erosions (particularly those not associated with gastritis—for example, in aspirin abusers) have hitherto received scant attention, though about 7% are said to contain campylobacter-like organisms.²³ In this study all the gastric erosions associated with gastritis showed campylobacter-like organisms, which were also present in 60% of those without gastritis. This clearly weakens the argument that campylobacter-like organisms are the only cause of gastric ulceration, but would favour the theory that gastric erosions (especially if accompanied by inflammation) form a suitable milieu for colonisation by campylobacter-like organisms.

In mucosa showing mild superficial gastritis 38% of specimens showed campylobacter-like organisms and there was a good correlation with acute inflammation. Though the numbers are small, it is an unusual lesion to find alone in routine upper gastrointestinal biopsy material. Our findings contrast with those of Jones *et al.*²⁰ and Andersen *et al.*²³ however, who found that 83% of superficial gastritis specimens contained campylobacter-like organisms. In the first of these studies there was no association with the type of inflammation, and in the second there was no grading of the superficial gastritis. If cases of mild chronic superficial gastritis are excluded from our study the incidence of campylobacter-like organisms in mild superficial gastritis with an acute component rises to 60%.

Our results from normal gastric mucosa (6%) seem to be similar to those of Marshall and Warren⁹ (6%), Andersen *et al.*²³ (5%) and Taylor *et al.*²⁴ (5%), but cases of mild superficial gastritis are often included in this category. This could account for the higher incidences of 9–14% campylobacter-like organisms in normal mucosa reported by others.^{10 13 40} If the mild superficial gastritis and normal mucosal biopsy specimens in our study are considered together, the incidence of campylobacter-like organisms rises to 15%. Though numbers are comparatively small, campylobacter-like organisms are not usually found in specimens from normal mucosa. Jones *et al.*²⁰ for example, were unable to find campylobacter-like organisms in 15 cases, but found one patient with a positive culture and circulating serum antibodies (7%), and McNulty and Watson²¹ could not find campylobacter-like organisms in 21 cases. In duodenal ulcers, campylobacter-like organisms occurred in 20%

of all cases, but their presence correlated with the coexistence of ulcer debris. This is in keeping with the fact that accompanying mucosa was likely to have been taken from the acutely inflamed ulcer margin and is indicative of the association between campylobacter-like organisms and intraepithelial infiltration of polymorphonuclear leucocytes.⁴² In biopsy specimens of duodenal ulcers that are accompanied by ulcer debris therefore, campylobacter-like organisms were seen in 27%.

Infiltration by polymorphonuclear leucocytes is generally extensive⁴¹ and this is in keeping with the observation that campylobacter-like organisms were present in equal numbers in the two subgroups of gastric biopsy specimens (table 1). The reported incidence of campylobacter-like organisms in biopsy specimens from the duodenal cap show pronounced variations. Some workers claim that they are absent¹³ despite campylobacter-like organisms being present in the antral biopsy specimens (as was the case in two of three patients in our study) but others claim that they are present in up to 85% of cases.^{10–12} In this series their presence varied between 0 and 30% depending on the presence of ulcer debris, acute inflammation, and previous treatment (table 1). In most other studies of duodenal ulcers, only gastric mucosal biopsy specimens were examined and this adds to the confusion.^{9 17 21 22 39} As reported by others, however,^{10 12 13} normal duodenal mucosa was not associated with the presence of campylobacter-like organisms. We were also unable to see campylobacter-like organisms in biopsy specimens from the duodenal caps of patients with duodenal erosions with duodenitis, an entity not considered in previous studies.

Barrett's oesophagus has not previously been studied for the presence of campylobacter-like organisms, which were present in 19% of 64 cases. If ulceration was present, they were slightly more frequent (24%) compared with 17% in non-ulcerated cases, but this is not significant. The presence of campylobacter-like organisms in Barrett's oesophagus with or without ulceration (as in peptic ulceration elsewhere) obviously introduces the possibility that they have an aetiological importance. In view of the established place of gastric reflux in the acquisition of Barrett's epithelium, the part played by campylobacter-like organisms in the ulcerative process itself must be considered, but our results do not support this and it seems much more likely that the campylobacter like organisms are commensals.

Although the overall incidence of *Candida* in gastric ulcers was 26% (which is higher than that found by Scott and Jenkins (16%)¹⁵ and lower than that reported by Katzenstein and Maksem (33%)¹⁴ and Gotlieb-Jensen and Andersen (36%)³⁹) if only gastrectomy specimens were considered the incidence was 38%,

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which is similar to the 33% found by Katzenstein and Maksem,¹⁴ who also examined only gastrectomy specimens.

This study is unique in that we know of no previous data about the coexistence of campylobacter-like organisms and *Candida* in upper gastrointestinal biopsy tissue. In gastric ulcers both organisms were seen in 12% of biopsy specimens. In duodenal ulcers with ulcer debris in the biopsy material, *Candida* and campylobacter-like organisms were seen with almost equal regularity. Similarly, in Barrett's oesophagus with ulcers *Candida* was seen in 24% (an incidence similar to campylobacter-like organisms), but they occurred together in only one case. These findings probably indicate that the organisms prefer different environmental conditions for colonisation and growth. If some forms of peptic ulcer are caused by campylobacter-like organisms, however, then the same argument could apply to *Candida*, but against this is the finding of *Candida* in a duodenal ulcer when a coexistent Barrett's oesophageal ulcer was not affected. *Candida* is found only in association with necrotic ulcer debris and not neighbouring mucosa, and both organisms—which are probably ubiquitous—may colonise the upper gastrointestinal tract and multiply under the right circumstances.

In conclusion, our findings—particularly in erosions without inflammation, mild superficial gastritis, and Barrett's oesophagus—and the equal incidence of campylobacter-like organisms and *Candida* in ulcerated Barrett's oesophagus and duodenal ulcers, do not support the argument that campylobacter-like organisms cause gastritis and peptic ulceration. Indeed, it is more logical to propose that the presence of these lesions in some way promotes colonisation by these organisms.

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