Gastritis due to spiral shaped bacteria other than *Helicobacter pylori*: clinical, histological, and ultrastructural findings

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Abstract
An intensive histological search for *Helicobacter pylori* in gastric biopsy specimens has led to the detection of other spiral shaped bacteria in the human gastric mucosa. The clinical and morphological findings of 39 cases (0.25% of all gastric biopsies performed in the observation period) are reported for 34 patients (87.2%) complaining of upper abdominal discomfort. Five patients (12.8%) had chronic gastritis and 34 (87.2%) chronic active gastritis. The organisms were seen by light microscopy deep in the gastric foveolae and intracellularly. The scanning and transmission electron microscopic findings show bacteria which invade and damage gastric mucosal cells. These organisms are similar to the spiral shaped bacteria found in the stomachs of cats and dogs and non-human primates. In eight patients organisms were not detected after four weeks of treatment with bismuth salts. The disappearance of the organisms coincided with resolution of the chronic active gastritis and the symptoms.

The ecological niche in the gastric mucosa is probably able to harbour other bacteria besides the well known *Helicobacter pylori*. These ‘other’ organisms share some properties with *H. pylori*. They are helical in shape, have flagellae, produce urease, and their presence is associated with a chronic active type B gastritis.1,2

We present the clinical, morphological, and ultrastructural findings for 39 patients infected with those spiral bacteria.

Patients and methods
Of the 39 patients 24 were men, mean age 54.2 years (range 20–76), and 15 were women, mean age 50.6 years (range 19–79) living in different parts of Germany. Thirty four patients (87.2%) complained of dyspeptic symptoms such as postprandial discomfort, epigastric pain, vomiting, heartburn, and dysphagia, lasting from one month to two years. Four patients were asymptomatic and one patient had diarrhoea due to pancreatic insufficiency. The endoscopic appearances in the antral and corpus mucosa were normal. There was no duodenal or gastric ulcer or tumorous lesion at the time of biopsy. A biopsy urease test was performed in five patients and was positive after 20 minutes.

In our institution all gastric biopsy particles are fixed in 4% neutral formalin, embedded in paraplast, and cut in 3 μm thick sections. The slides are stained routinely by an alcohol haematoxylin and eosin solution. Besides studying the biopsy specimens for morphological changes under low and high power magnification, all slides were screened by one observer (KLH) under oil for the presence of bacterial organisms. By this method it is possible to identify *H pylori* without special stains.3 After identification of spiral shaped bacteria in the specimens, they were stained with Gram, Giemsa, Steiner, and Whartin-Starry silver stains. Tissue for electron microscopy was fixed in buffered glutaraldehyde and postfixed in OsO4. Semi-thin sections were screened for spiral shaped bacteria and selected ultrathin sections further analysed in a Zeiss-EM 109 electron microscope. For scanning electron microscopy, formalin fixed biopsy specimens were postfixed in a similar way, dried with the critical point method, and coated with gold. The specimens were viewed by the Philips SEM 515 scanning electron microscope.

Results

INCIDENCE AND LOCATION OF BACTERIA
The 39 cases represent 0.25% of all antral biopsies performed in the observation period (n=15 180). Spiral shaped bacteria were observed in the antrum in all patients and in five of 25 patients in the fundus. Chronic active type B gastritis was present in 34 patients in the antral mucosa. In four patients there was only a lymphoplasmacytic infiltrate. As in *H pylori* associated gastritis the granulocytes were fre-
with bismuth subsalicylate and were free of symptoms four weeks after the initial diagnosis. Biopsies in these cases, performed between eight and 16 weeks, showed only scattered lymphocytes and a few plasma cells in the lamina propria, but no granulocytes and no colonisation by spiral shaped bacteria (Table).

TRANSMISSION ELECTRON MICROSCOPY

In two patients ultrastructural studies were performed. The spiral shaped bacteria were seen in biopsy specimens of the antral mucosa (Fig 3) and corpus mucosa (Fig 4). The diameter may vary: it usually averages 0·65 μm, but the maximum width was 0·9 μm. The amplitude is about 0·8 μm. Usually up to four spirals are in the plane of section; therefore, the actual length could not be determined by this method. The ends are partly pointed, partly blunt. At the blunt end of the organisms an insertion complex is visible with up to 12 flagellae (Figs 3 and 4 (inserts)). In the region of the insertions the bacterial cell wall shows undulation. The flagellae have swollen ends. Their variable form, with a partial parallel course and partial cord-like twisting, suggest the motility of these organelles. The sickle shaped area next to the insertion complex (Figs 3 and 4) shows less densely packed granular material than elsewhere in the bacterium, but also dense granular structure may occur here. The cell wall is trilaminar (Fig 3). There are no axial filaments and no periplasmic fibres as in *Spirochaetes*. The bacteria were seen on the surface of antral and corpus mucosa, below the mucus, sometimes in close contact to the membranes of surface mucous cells or antral mucoperi cellular cells without a preference for tight junctions. At the point of contact degenerative changes of the cell membrane and the microvilli become apparent (Fig 5). The microvilli show kinking and partial destruction. In the lower mucosa of the corpus the spiral shaped bacteria invade the canalliculi of parietal cells where as many as five can be seen, without obvious damage to their host cells. Bacteria, however, also invade the parietal cells, causing signs of cellular damage such as mitochondrial swelling (Fig 4). In the lower mucosa the bacteria invade mucoperi cellular cells and rarely endothelial cells. The infected cells react with swelling of the mitochondria, the formation of cytoplasmic empty vacuoles around the bacteria, and microvesicular disintegration of organelles, probably partly of lysosomal origin. Once disintegration of a bacterium was seen.

SCANNING ELECTRON MICROSCOPY

The organisms were aggregated in small clusters of 3–10 bacteria, some without any contact, partly lying parallel and close to each other (Fig 6). While most of the organisms were straight, bent forms were also noted. The bacteria have an average length of 6–17 μm (range 4·8–6·7 μm) and a thickness of about 1 μm.

Discussion

The identification of spiral bacterial organisms

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**Figure 2: Several Gastrospirillum hominis in the middle of the corpus mucosa partly invading parietal cells. (Steiner silver stain. Original magnification ×800.)**

**Effect of treatment with bismuth salts on Gastrospirillum hominis and the cellular infiltrate**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Sex</th>
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<th>G hominis</th>
<th>Granulocytes</th>
<th>Lympho- plasma cells</th>
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B = before treatment; A = after treatment.
Gastritis due to spiral shaped bacteria

chronic gastritis. It was proposed that these spiral organisms should be called 'Gastrospirillum hominis.' Until now, the colonisation of the human gastric mucosa by Gastrospirillum hominis seems to be a rare event. We found 39 cases among 15 180 antral biopsies—that is, roughly 0.25%. This is about the same incidence as the 0.36% reported from England and 0.3% from New Zealand, whereas the 0.6% reported from France exceeds these numbers. An intensive search for these organisms could probably show many more cases since the commonly used Whartin-Starry stain impregnates the organisms irregularly so that they may be falsely interpreted as H pylori. As we and others could show that at least some of the organisms seem to produce urease, patients with Gastrospirillum hominis and a positive urease test could be falsely diagnosed as having an H pylori infection without further histological studies. Since all attempts at culture have been unsuccessful until now, the diagnosis of this bacterial infection relies on a careful histological examination of the gastric biopsy specimens, either under high power or oil in haematoxylin and eosin, Gram, or Giemsa stained sections.

The distribution of the spiral shaped bacteria in the human gastric mucosa differs from that seen in H pylori infection. Whereas they may be observed above the surface cells in the mucous layer, they appear more commonly deeply within the gastric pits. In contrast to light microscopy the spiral shaped bacteria ultrastructurally sometimes seem to be attached to the membranes of the surface cells with a possible effect on the membrane structures. There is, however, no attachment or penetration of the intercellular tight junctions as is seen in H pylori colonisation. In contrast to the behaviour of H pylori, the spiral shaped bacteria obviously cannot only damage cell membranes but penetrate them as well. We found the organisms intracellularly in mucous and endocrine cells in the antral mucosa as well as in the parietal cells in the fundic mucosa.

Similar to the other reported cases we could also prove that infection with spiral shaped bacteria is almost always associated with an active chronic gastritis generally less severe than in H pylori infection. There was one case in which H pylori and the spiral shaped organisms could be identified together, as was reported by the French group. This patient had a more severe chronic active gastritis. After treatment with bismuth salts, Gastrospirillum hominis could not longer be found, while H pylori persisted. Gastrospirillum hominis infection is not necessarily temporary, but can persist for a long time, maintaining chronic active gastritis, as the two cases prove, where it was found 10 and five years before the last biopsy. There are several points which favour the aetiopathogenetic importance of Gastrospirillum hominis in inducing and maintaining gastritis in the human stomach: (a) The presence of the organisms is always associated with gastritis. (b) The suppression of Gastrospirillum hominis coincides with the disappearance of the gastric changes.

Figure 3: Gastrospirillum hominis lying on the surface of a mucopuctive cell. Degeneration of microvilli. (Transmission electron microscope. Original magnification × 32 000.) Filaments partly attached to the 'end' of another bacterium. (Box × 110 000 original magnification.)

Figure 4: Three bacteria within a parietal cell: while one is still in the canalicular system, the other bacteria have invaded the cytoplasm causing degeneration-like mitochondrial swelling. (Transmission electron microscope. Original magnification × 20 000.) The inset shows twisting of bacterial filaments. (Box × 110 000 original magnification.)

Figure 5: Attachment of a bacterial 'end' to the cytoplasmic surface with kinking of microvilli. (Transmission electron microscope. Original magnification × 100 000.)

other than H pylori in the human gastric mucosa associated clinically with the symptoms of non-ulcer dyspepsia and morphologically with an active chronic gastritis suggests that H pylori is not the only bacterial organism causing active
Serological studies by Lee et al. in patients with *Gastrospirillum hominis* showed cross reacting antibodies against the cat derived organisms. It seems that the human gastric mucosa always reacts with an inflammatory response to the infection with these animal derived mucosa associated organisms. There is a clear association of the presence of spiral shaped bacteria with a chronic active gastritis and probably the symptoms of non-ulcer dyspepsia in humans. Thus, besides the well recognised infectious gastritis caused by *H. pylori*, there exists another type of gastritis caused by animal derived organisms, the frequency and the importance of which have to be further elucidated.

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Figure 6: *Gastrospirillum hominis* on the mucosal surface of the gastric body; most are straight, a few are bent (white arrows), and some lie parallel, close to each other (black arrow). (Scanning electron microscope. Original magnification x8000.)