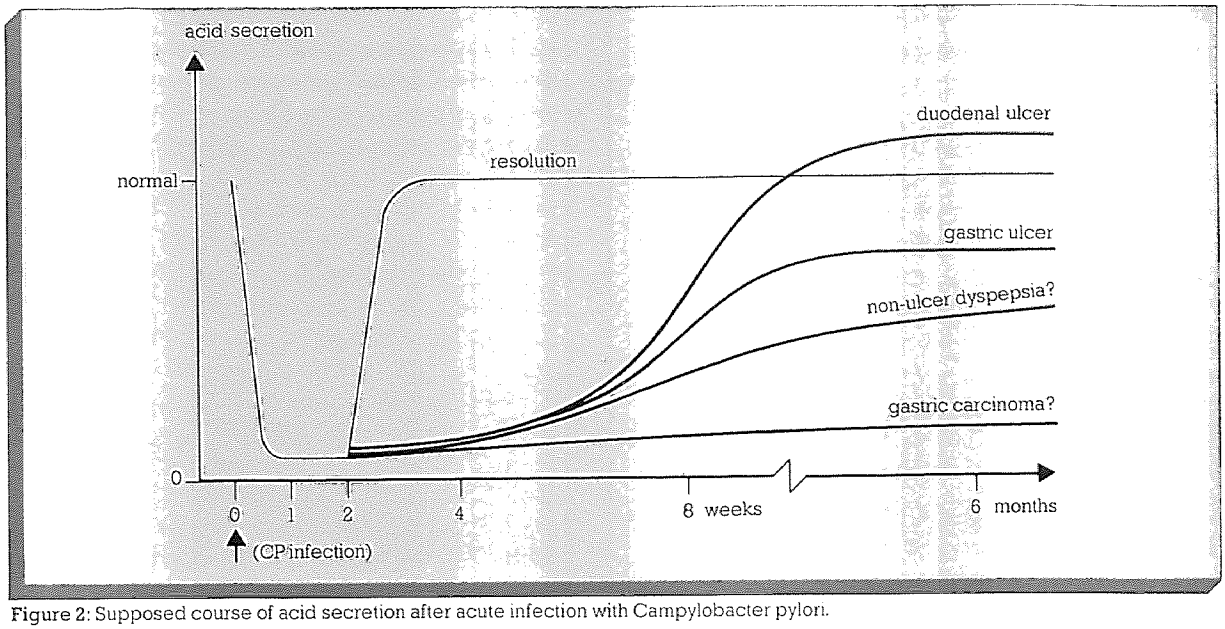

Figure 2: Supposed course of acid secretion after acute infection with Campylobacter pylori.

acid secretion is absent or greatly reduced. If the bacteria are not cleared "spontaneously" (20-50% of cases) the illness enters a chronic phase which may be lifelong. Depending on the amount of inflammation present in the body of the stomach, acid production may be decreased initially, but then returns to normal as chronic gastritis develops (figure 2). Specific IgG antibodies develop four weeks after infection. Peptic ulceration may occur any time after acid secretion has returned, because of the imbalance that now exists between (weakened) mucosal defense and (aggressive) acid secretion (figure 3).

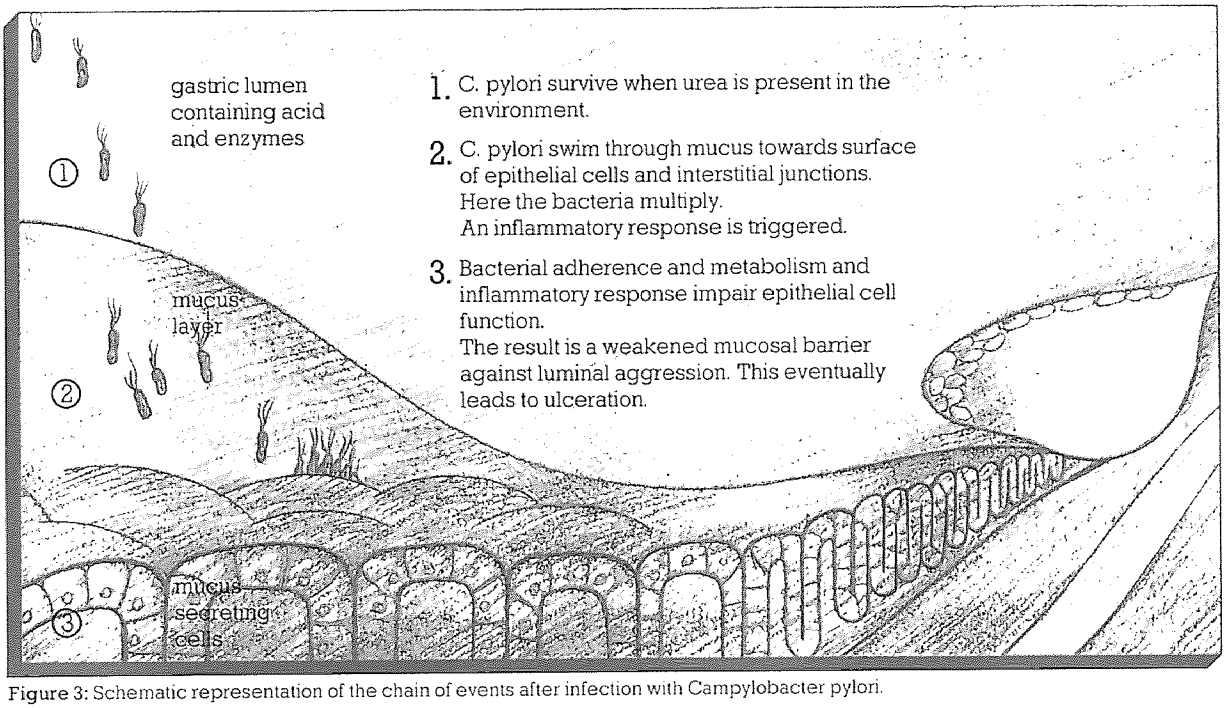

Figure 3: Schematic representation of the chain of events after infection with Campylobacter pylori.

Other evidence of a pathogenic role of CP in gastritis

Histology

CP is not invasive, but wherever it attaches to the gastric epithelial cells, cytopathic changes are seen (7). The cells are unable to maintain their usual flat luminal surface. They round up, their microvilli disappear, and their intracellular mucus contents diminish. Polymorphs, plasma cells and lymphocytes invade the epithelium when CP is present. Together these changes make up the characteristic lesion of CP infection, 'active chronic gastritis'. This appearance rarely occurs in the absence of colonization with CP.

Microbiology and virulence

Intestinal pathogens sometimes secrete cytotoxins which damage the intestinal epithelium. Examples are shigella and aeromonas bacilli. Leunk and coworkers have described a cytotoxin which is present in about half the isolates of CP and which causes vacuolization of gastric epithelial cells (12). Slomiany et al. (13) have investigated the influence of CP on mucus constituents. They observed that CP exhibits a strong proteolytic activity towards gastric mucin polymer. Other possible pathogenic mechanisms for CP include membrane changes due to bacterial attachment and ammonia production due to its powerful urease enzyme.

Immunology

Most patients with gastritis have high titers of IgG antibodies directed against CP. These have been used as the basis for a serological test in patients with dyspepsia (14). In recently acquired CP infection, antibodies can be detected by the fourth week and their presence in serum may indicate that a chronic colonization of the gastric mucosa has developed (6). In patients with chronic gastritis the gastric epithelium can be shown to manufacture CP-specific IgG and IgA antibodies in vitro. It is probable therefore that part of the inflammatory cells present in the gastric mucosa of patients with gastritis are functionally intact, producing antibodies directed against CP.

Therapeutic trials

Non-ulcer dyspepsia (NUD): Active chronic gastritis is reversible with drugs which eradicate CP. Lambert, in a study comparing colloidal bismuth subcitrate (CBS, De-Nol®) and placebo, found that the histology improved when CP infection was suppressed. Furthermore, symptoms of non-ulcer dyspepsia improved significantly in the patients treated with CBS (15). In a similar study in England, bismuth subsalicylate was shown to be superior to placebo and erythromycin in the treatment of gastritis (16). These studies suggest that antibiotic therapy alone will improve symptoms in patients with CP infection. Two other studies comparing CBS and placebo showed similar efficacy in improving active chronic gastritis and dyspeptic symptoms (17,18).
Duodenal Ulcer: About 93% of patients with duodenal ulcer (DU) carry the bacterium (8). In a prospective double-blind trial in which CBS or cimetidine were combined with tinidazole or placebo to eradicate the bacterium, relapse occurred in only 30% of patients cleared of CP. In the group who had continuing CP infection, the relapse rate was about 75% in the same period (19). Overall, in the cimetidine groups the majority of the patients remained CP positive after treatment, while in the CBS groups most patients cleared the microorganism. Interestingly, patients treated with CBS who did not have the bacterium cleared had an ulcer relapse rate similar to those treated with cimetidine. This suggests that for any duodenal ulcer therapy, the relapse rate is a function of the number of patients who still have CP infection after therapy. The results of smaller studies support this hypothesis (20,21).
Gastric Ulcer: About 70% of patients with gastric ulcer (GU) have CP infection (5,8). Clinical trials have not been done to test the effectiveness of antibacterial therapy in GU, but CBS is known to be an effective ulcer healing agent for this disease too. This suggests that eradication of CP infection will be beneficial also in this group. The necessity of excluding malignancy in GU patients means that a gastric biopsy wil still be necessary at initial diagnosis. Once malignancy has been excluded however, serological determinations are one way in which the follow-up of CP associated gastric ulcer patients may be managed.

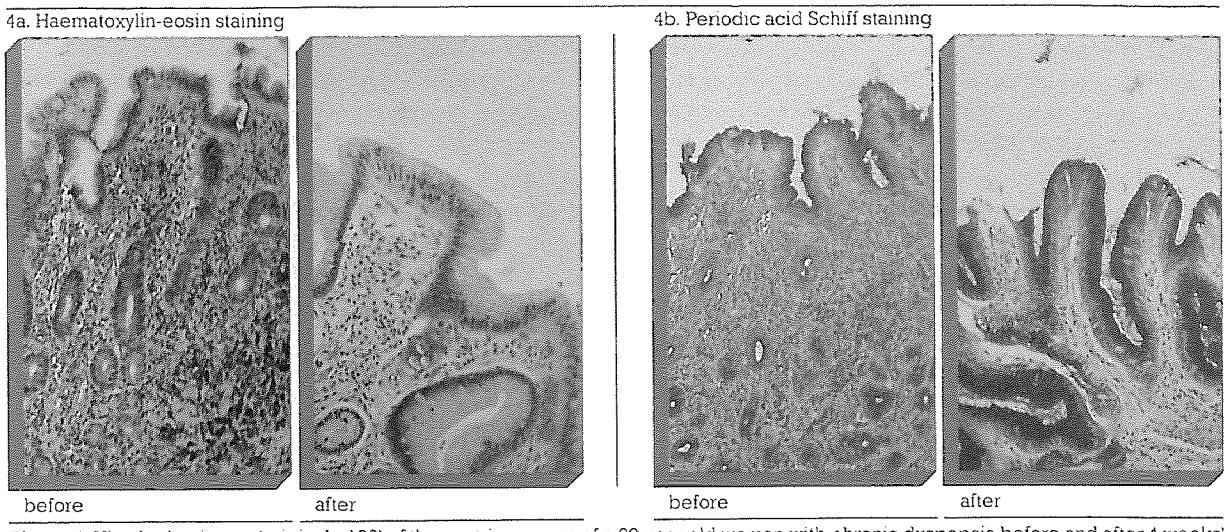

Figure 4: Histologic picture (original x 100) of the gastric mucosa of a 60-year old woman with chronic dyspepsia before and after 4 weeks' treatment with colloidal bismuth subcitrate.

Patients should be warned that the long-term benefits of antibacterial therapy for gastritis have not yet been proven, and that antibiotic therapy is not without risk. When CP associated gastritis exists and other medical therapy has failed, many patients with chronic dyspeptic complaints will wish to try an antibacterial regimen. To properly evaluate such therapy the diagnosis of CP should be made by biopsy, and eradication of the infection should be the therapeutic goal.

The use of a course of CBS or bismuth subsalicylate alone has had varying success (figure 4). Given alone, these drugs eradicate approximately 30% of infections. In combination with an antibiotic CP can be eradicated in 50-75% of cases.
In Australia we have observed that combining 21-28 days' CBS therapy with the administration of an antibiotic between day 7 and 21, improves clearance rates.
The following antibiotics have been used:

Drug	Dose	Times/day	Start day	Stop day	Cure %
tinidazole	500 mg	2	15	21	>70
amoxicillin	500 mg	4	7	21	>50
erythromycin	250-500 mg	4	7	21	>60
doxycycline	100 mg	2	7	21	>50?

When antibiotics or bismuth are used alone, the bacteria are usually only suppressed, and recrudescent infection often occurs within a month or so, with subsequent relapse of the patient's symptoms. Therefore, to assess the efficacy of therapy, gastric antral biopsies can best be taken 21-28 days after completing the course of antibacterial drugs. Negative culture and histology at this time is followed by reinfection in less than 10% of the patients per annum.

Suggestions for treatment

Until recently no effective treatment for gastritis was known and the treatment of dyspepsia concentrated on the reduction of, or protection from, gastric acid. This narrow approach is no longer appropriate. In patients with chronic gastritis there is an identifiable etiological agent which may be responsible for their symptoms, whether or not an ulcer is present. Endoscopists must therefore include an antral biopsy in the routine diagnostic evaluation of all dyspeptic patients.

General practitioners should consider the possibility of CP infection before 'giving up' on patients with vague intestinal symptoms and a negative X-ray. Clues to the diagnosis are a family history of dyspepsia, relief in the past after antibiotic therapy, response to bismuth containing drugs, previous ulcer disease in the patient or spouse, or an episode of gastroenteritis in the year before the onset of the symptoms.

Such patients may be helped by administration for a 4 weeks course of CBS combined with a 2 weeks course of a suitable antibiotic such as amoxicillin 500 mg q.i.d. from the second week onwards. Colloidal bismuth subcitrate should be given on an empty stomach, a half to one hour before meals or before going to bed. The choice of antibiotic can be made easier by determining the sensitivity of the patient's C. pylori strain to various antibiotics during the first week of treatment. Alternatives are erythromycin 500 mg q.i.d. during the second and third week or tinidazole or metronidazole, 500 mg b.i.d. or t.i.d. respectively, from day 7 to 17. Amoxicillin causes the least side-effects. Erythromycin causes an exacerbation of abdominal pain in ± 40% of the patients. And finally, the imidazole-derivatives should not be given to patients who have taken them before, because their C. pylori strains will probably have become resistant.

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