Helicobacter pylori and gastroduodenal pathology

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IN 1983, BJ MARSHALL AND JR WARREN UNEARTHED *Helicobacter pylori* (Hp), which – since their historical rediscovery – has been connected with histologically proven gastritis and peptic ulcer disease, as well as with gastric cancer (1). Hp is a Gram-negative multiple polar-sheathed flagellar organism. Initially called *Campylobacter pylori* (because of 16 S rRNA sequencing studies [2]), the organism was reclassified as Hp. Species of Hp are found in a variety of animals, including mice, pigs, dogs, cats and seagulls. Hp usually is found in the stomach and duodenum, but has been described in the rectum.

The Fifth *Helicobacter pylori* Symposium was held at Trinity College, Dublin, Ireland from July 5 to 7, 1992. Under the capable organizational skills of Drs CA O'Morain and HJ O'Connor, topics of a diverse interest relating to Hp and gastroduodenal disease were covered. The meeting was sponsored by over 20 companies. A satellite meeting entitled 'Role of acid inhibition in the management of *Helicobacter pylori* infection' was sponsored by Astra Pharma Inc, and was organized by Drs ART Axon and HJ O'Connor. I was pleased to be a guest at the meeting, together with a dozen other Canadians and an international group of over 800 attendees.

This is the 10th anniversary of the re-discovery of Hp on a holiday weekend in Perth, Western Australia. Hp represents a significant discovery in gastroenterology; 1992 was also an auspicious occasion for Trinity College as it is the quadracentenary year since its foundation. It was the purpose of the Fifth Workshop on Gastroduodenal Pathology and *Helicobacter pylori* that important topics be considered, including microbiology and molecular biology, pathology and pathophysiology, host immune response, clinical epidemiology, as well as clearance and eradication of Hp.

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PHYSIOLOGY AND MOLECULAR BIOLOGY

Interest in Hp has risen exponentially since the rediscovery of this organism 10 years ago because it causes chronic gastritis type B, and it strongly is associated with duodenal and gastric ulcer disease, as well as with gastric cancer. Hp causes a chronic infection which can lead to lifelong inflammation of the gastric antrum. In some individuals, gastric atrophy will develop with its predisposition for gastric cancer, whereas in others gastric metaplasia will occur in the duodenum, leading to a strong association with duodenal ulcer. There may be associated changes in the function of antral G and D cells, with secondary alterations in the gastric secretion of hydrogen and pepsin, and increased G cell responsiveness to food stimulation.

The impaired integrity of the gastric mucosal membrane with Hp infection may be the result of local immunological changes, as well as the result of acetaldehyde secretion arising from the alcohol dehydrogenase of the Hp (3). Acetaldehyde is a highly reactive and toxic substance, and if formed by Hp in vivo, acetaldehyde could be a pathogenic factor behind Hp-associated gastric morbidity. Colloidal bismuth subcitrate is a highly potent inhibitor of alcohol dehydrogenase and prevents oxidation of ethanol to acetaldehyde by Hp. Hp also produces phospholipase A_2 and C, which may damage the phospholipid-rich layer on the human gastric epithelium, thereby acting as a 'barrier breaker' (4). These produce alterations in the gastric membrane and impaired integrity of this interface (5).

Schwartz's dictum of 'no acid – no ulcer' may need to be modified to 'no Hp – no gastritis – no gastric atrophy, cancer or ulcer!' Some forms of therapy of peptic ulcer disease will clear Hp when the presence of Hp is tested very shortly after the termination of acute therapy ('clearance'). However, 'eradication' of Hp (defined as an Hp-negative antral biopsy or negative urea breath test performed one month after treat-

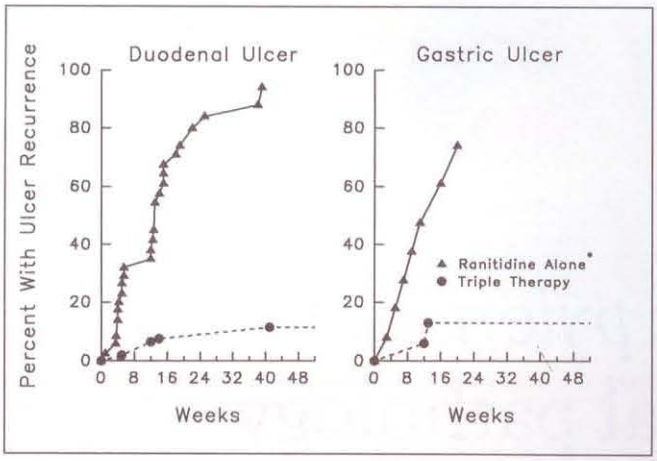

Figure 1) *Lifetable recurrence of duodenal and gastric ulcers for the year after successful loading with ranitidine alone or with triple therapy (five to eight tablets bismuth subsalicylate, 2 g tetracycline and 750 mg metronidazole)*

ment) is the goal of therapy. It is not yet certain how many antral biopsies need to be taken to ensure that all Hp have been eradicated, particularly when small amounts of the bacterium are still present, and whether biopsies also need to be taken from the gastric body; in the presence of reduced gastric acid secretion (such as with the use of a proton pump inhibitor omeprazole), Hp may migrate from the antrum to the gastric body. The relative sensitivity of a urea breath test versus multiple biopsies for Hp needs to be clarified.

Molecular biological methods using polymerase chain reactions suggest that the return of Hp months after eradication likely is due to recrudescence of a suppressed infection rather than reinfection with a different subtype of the organism. Hp is sensitive to many antibiotics in vitro, but not necessarily in vivo. Once Hp has been eradicated, the risk of recurrence within the next year is generally less than 1%, and some patients may go as long as five years without recurrence. When Hp does occasionally recur, it usually does so within the first year after its initial eradication. The high recurrence rates of duodenal ulcer or gastric ulcer in patients in whom Hp is not eradicated (6) (Figure 1) focuses on the importance of eradication of Hp to reduce ulcer recurrence and, therefore, ulcer complications. In fact, once simple single or double agent therapy for Hp has been developed, it may be necessary to perform a urea breath test or endoscopy with biopsy for Hp to determine which patients, if any, require maintenance therapy with acid-suppressing therapy or with Hp-suppressing therapy.

There is partial homology between H^+,-K^+-ATPase (the 'proton pump') and Hp toxin. In vitro, omeprazole may have a direct effect on Hp (7,8) and this effect may be enhanced by the acid conversion products of omeprazole.

Hp may directly affect gastric acid secretion as well as indirectly influence gastrin secretion by way of the antral inflammation and acid suppression. There may also be an increased median pH profile in duodenal ulcer-infected, Hp-positive patients (9). Hp is concentrated in the crypts of the gastric antrum where G cells are present, but the G cells are preserved in Hp infection. In fact, the gastrin concentration per G cell is increased in Hp infection, but antral G cell density is unchanged (10). Basal and food-stimulated gastrin response is greater in Hp-positive than in Hp-negative individuals, possibly due to G cell hyperfunction. The enhanced meal-stimulated gastrin response in duodenal ulcer patients infected with Hp returns to normal after eradication of Hp (11).

Antral gastrin synthesis and release normally are inhibited by somatostatin. The density of G cells does not change with Hp eradication, whereas there is a significant increase in the somatostatin cell density (12), raising the possibility that Hp may increase gastrin concentrations in the serum by inhibiting antral somatostatin-containing cells. Other workers (13) have confirmed that D cells are increased after antibiotic therapy for Hp; while the number of G cells did not change with Hp eradication, serum gastrin concentration declines and antral gastrin concentration rises.

Duodenal ulcer prevalence is related inversely to dietary intake of polyunsaturated fatty acids, and it has been speculated that this may be due to Hp growth inhibition by these acids (14). Hp-positive gastritis, gastric ulcer and duodenal ulcer are associated with increased levels of pepsinogen in the blood, as measured by radioimmunoassay (15).

Hp stimulates the DNA synthesis of human peripheral blood mononuclear cells; this is interleukin (IL)-2 dependent. Human T cells are not able to respond to Hp without antigen-presenting cells like monocytes (by a mechanism which involves the major histocompatibility II complex) (16). In an in vitro organ culture system, it was shown that there is an association between the production of IL-8 and epithelial surface degeneration. The local synthesis of IL-8 may be an important factor in regulating mucosal neutrophil infiltration and activation in patients with Hp infection (17).

Inflammatory lesions in the gastric antrum are accompanied by marked lymphocytic infiltration of the lamina propria, suggesting the possibility of an immunological basis. Using monoclonal antibodies specific for surface molecules expressed on distinct T cell subsets, it was shown in human biopsies that there is a marked relative and absolute increase in the number of $CD4^+$ cells, whereas in Hp-negative chronic active gastritis there is only a moderate increase in total T cells without an inversion of the CD4/CD8 ratio (18). These $CD4^+$ T cells may secrete a variety of lymphokines that may recruit inflammatory cells, possibly compromising the functional integrity of the epithelial cells (and thereby the mucosal barrier function). IL-6 and IL-8 levels are also increased in mucosal biopsies from Hp-positive patients (19). T cells of Hp-infected persons may be hyporesponsive to Hp antigen, suggesting a degree of immunosuppression.

DIAGNOSIS

The diagnosis of Hp infection of the stomach usually is based on histology, culture and urease tests of gastric biopsy specimens, all of which are invasive. The ^{13}C-urea breath test may become the future gold standard because it is simple to

perform and may be repeated with ease and without risk to the patient.

Multiple biopsies need to be taken since Hp infection and active chronic gastritis have a patchy distribution; at least four biopsies are required to detect Hp with a sensitivity of 95% (20). Furthermore, eradication of Hp from the gastric antrum may not necessarily lead to its eradication from the body (21), and may be associated with its apparent relocation from gastric antrum to body (necessitating at least two biopsies from each side).

Hp may be detected in the feces of patients with Hp-associated gastritis using a newly developed polymerase chain reaction (22). Serology is an accurate and noninvasive means of diagnosis, and recently developed commercial enzyme-linked immunosorbent assay (ELISA) kits have the potential of standardizing the serodiagnosis and assessing the effects of treatment to eradicate Hp infection (23). The ELISA has a sensitivity of 90.4%, a specificity of 63.6%, a positive predictive value of 85.4% and a negative predicted value of 73.7%. These predictive values are comparable to those of campylobacter-like organism test. Other workers (24) have shown that ELISA has a positive predictive value of 92.3% and a negative predictive value of 100%. If others confirm the very high negative predictive value of ELISA, then this serological test might be used to identify young patients with dyspepsia who could be treated without endoscopy.

Some gastroenterologists may be reluctant to accept serological or breath tests as an alternative to endoscopy for the diagnosis of Hp in dyspeptic patients, but with further pressure on cost containment in our health care system, this represents an interesting concept worthy of further careful study. Indeed, Sobala and co-workers (25) have suggested that in patients under the age of 45 years who present with dyspepsia, are seronegative for Hp and are not taking nonsteroidal anti-inflammatory drugs (NSAIDs), gastroscopy is not required; this approach avoided about 24% of gastroscopies in that study. A similar reduction in the need for gastroscopies has been confirmed in Germany (26), corresponding to a 100% and 97% sensitivity to exclude the presence of gastric ulcer or duodenal ulcer, respectively. This type of study would be important to perform in Canada.

The diagnostic value of four commercially available kits for Hp serology – Malakit *Helicobacter pylori* (Biolab SA, Limal, Belgium), Cobas Core *Helicobacter pylori* EIA (Roche ASA, Basel, Switzerland), Pyloristat (Whittaker Bioproducts, Maryland) and SynElias (Elias, Freiburg, Germany) – has been undertaken (27). The authors concluded that "all four tested kits are quite reliable diagnostic tools for the detection of Hp ... and some 'false positive' results probably are serological traces of a previous Hp infection, whereas false negative results occur in the rare patients who do not seroconvert".

There was a high seroprevalence (42%) of immunoglobulin (Ig) G to Hp in a large asymptomatic British blood donor population. Endoscopy was offered to all of them, and in the first 100 blood donors who underwent upper gastrointestinal endoscopy, the endoscopic findings were: one gastric cancer,

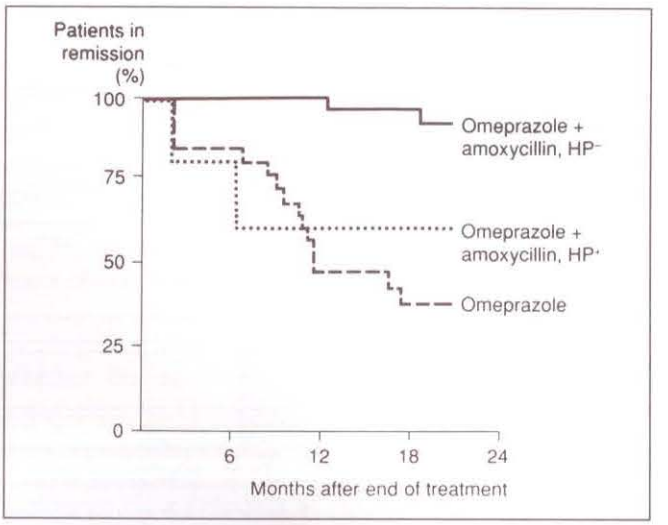

Figure 2) *Cumulative remission rates in patients with duodenal ulcer who were initially given a combination of omeprazole and amoxicillin, or omeprazole alone. HP–* Helicobacter pylori*-negative; HP+* H pylori*-positive*

one leiomyoma, 17 duodenal ulcers, five gastric ulcers, six antral polyps, 17 erosive duodenitis, 18 antral erosions, 25 antral gastritis and only 10 normal endoscopies. Endoscopies were not performed in consecutive Hp-negative individuals, but these data highlight the surprisingly high prevalence of previously unsuspected lesions in Hp-positive individuals (28). The study also raises the possible consideration of the clinical importance of high levels of IgG to Hp in screening persons for endoscopy.

TREATMENT

Results from seven independent studies from different centres on the effect of Hp eradication on peptic ulcer disease have been summarized (29). We need simple safe inexpensive therapy for the treatment of Hp infections because there continues to be concern about compliance, resistance and side effects of the current triple-agent therapeutic programs.

The combination of omeprazole 40 mg bid plus amoxicillin 500 mg bid may eradicate Hp in up to 82% of patients (30). The combination of omeprazole/amoxicillin (40 mg every morning plus 750 mg bid, respectively) was examined in a double-blind, randomized, placebo controlled study involving 428 Hp-positive patients with doudenal ulcer (31). One month eradication rates of 82% with double therapy and 65% with omeprazole alone were obtained, with these remission rates falling to 70 and 36%, respectively, at six months. Better Hp eradication with omeprazole/amoxicillin was noted in nonsmokers than in smokers. This was a finding different from that reported by a Belgian group (32), and the discrepancy may have been due to a different formulation, or different dosing intervals of omeprazole or of amoxicillin (for example, the suspension is preferable to capsules and twice a day dosing is better than once a day). Dosing conditions are likely critical in achieving eradication. For example, initial treatment with 40 mg omeprazole for one week followed by a combined amoxicillin/omeprazole treat-

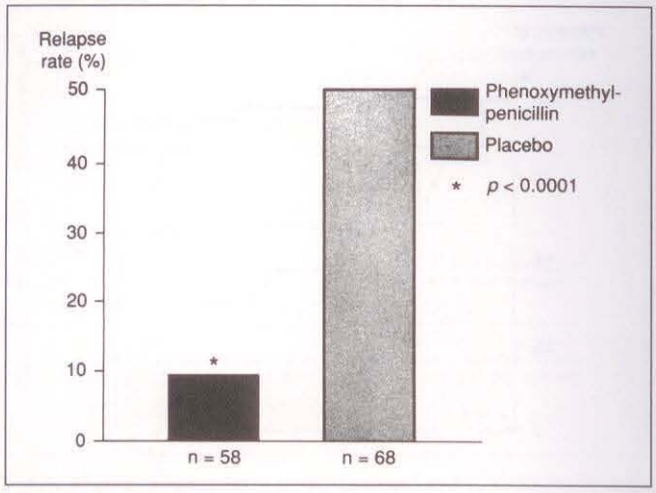

Figure 3) *Relapse rates in patients with duodenal ulcer after 14 weeks of phenoxymethylpenicillin treatment*

ment provides disappointing eradication rates in patients with Hp-related disease of the gastroduodenum (33). With ingestion of three antimicrobial agents for at least two weeks, compliance rates are low, adverse effects are frequent and eradication is not always achieved.

When patients with Hp-positive duodenal ulcer were treated with omeprazole 40 mg bid for 10 days followed by 20 mg daily for six weeks, the cumulative relapse rates within 12 months were 52%, while the relapse rates were only 4% when treatment was with a combination of omeprazole and amoxicillin 1 g bid for 10 days followed by 20 mg omeprazole daily monotherapy for six weeks (34). At 18 months, the cumulative relapse rates were 64% and 14%, respectively (Figure 2). Relapse rates were much lower in patients with mild (grade II) gastritis than in those with severe (grade IV) gastritis. The dose of amoxicillin may be important; amoxicillin 3 g/day plus omeprazole 40 mg daily may be superior to amoxicillin 2 g/day in eradicating Hp (35).

While maintenance of ulcer remission can be achieved by prolonged acid secretion with an H_2 receptor antagonist or with a proton pump inhibitor, it also is possible to prevent the recurrence of duodenal ulcer using phenoxymethylpenicillin (PEN) 2.4 g bid when acute healing has first been achieved with omeprazole 40 mg daily (36). Relapse rates in patients with duodenal ulcer after 14 weeks PEN remained low for five months after this treatment (Figure 3).

When Hp is eradicated from the antrum by the use of omeprazole and an antibiotic, the antral gastritis will improve, but body gastritis may worsen. Omeprazole will increase the concentration and half-life of immunoglobulins in gastric juice. Transient hypochlorhydria may occur with Hp infection. Omeprazole raises the intragastric pH to a greater extent than H_2 receptor antagonists to enhance the effect of acid-labile antibiotics acting on Hp.

The cause of nonulcer dyspepsia may be obscure; in individuals with symptoms lasting more than three months, normal biochemistry and a normal abdominal ultrasound, evidence for Hp infection was determined, and when identified was treated with colloidal bismuth subcitrate (120 mg qid for four weeks), colloidal bismuth subcitrate plus triple antibiotics or placebo (37). In Hp-positive nonulcer dyspepsia patients in whom Hp persisted, 95% of the patients required additional treatment over the next year, whereas only 12% of those in whom the organism had been eradicated required additional treatment. The long term response appears to be associated with the eradication of Hp, whereas initial improvement in symptom score is not a consequence of Hp eradication. Because peptic ulcer disease is a recurrent disease and usually is associated with Hp, it is unknown whether some patients with nonulcer dyspepsia may, in fact, have peptic ulcer disease and do not have duodenal ulcer or gastric ulcer when they are examined radiologically or endoscopically. This possibility needs to be carefully examined as we begin to consider Hp status as an important consideration in the management of patients with nonulcer dyspepsia. It is not yet reported whether omeprazole plus amoxicillin is useful in the treatment of Hp-positive nonulcer dyspepsia.

GASTRITIS, ATROPHY AND CANCER

Approximately one-half of patients with Hp-associated chronic active gastritis will progress over two years to develop chronic atrophic gastritis with intestinal metaplasia (38). Follicular gastritis is characterized by lymphoid follicular hyperplasia in the antral mucosa, and the presence of this recently described form of gastritis is correlated highly with the presence of Hp infection (39). In adults, Hp infection is associated with active chronic gastritis; in children the histopathology is usually only chronic gastritis, often with associated lymphoid aggregates. Host factors must be important in the induction of gastritis. The development of gastric metaplasia and heterotopia in the duodenum likely predisposes this tissue to acid-related damage.

The earliest detectable morphological change leading to cancer is an increased rate of cellular proliferation. Using the bromodeoxyuridine histochemical technique, labelling indices were calculated and found to be higher in patients with Hp-positive gastritis than in those with Hp-negative gastritis or in normal control tissue (40). There is a correlation between mucosal cell proliferation and the intensity of body gastritis caused by Hp (41). Based on 1984-88 American cancer statistics, 1.3% of persons with Hp infection will develop gastric cancer in their life compared with 0.2% of persons without Hp (42). While the risk of atropic gastritis increases with age, the Hp-associated development of chronic gastritis may lead to gastric atrophy in some individuals – this greatly increases the risk of gastric cancer, with a change in relative risk of 2.5-fold if there is chronic gastritis and 15-fold if there is gastric atrophy (43). In fact, it has been estimated that 60% of the risk of development of gastric cancer may be due to Hp infection, and Hp seropositivity predicts the increased risk of gastric cancer (44,45). In a low gastric cancer risk country such as Canada it remains unclear whether Hp screening and treatment could be cost-effective in preventing gastric cancer.

Hp is the major causative factor of acute and chronic

gastritis, a condition that over many years may develop into chronic atrophic gastritis, the precursor lesion of intestinal type gastric cancer. Intestinal metaplasia is thought to be a sequel to inflammation. Intestinal metaplasia is found more often in Hp-positive than in Hp-negative patients (46), but a causal relationship between it and Hp is not a universal finding (47).

Hp-positive chronic gastritis and gastric cancer associated with Hp may be the major background phenomena in the pathogenesis of both intestinal and diffuse types of gastric cancer (48). In a case-control analysis of approximately 100 consecutive gastric cancer patients and 500 outpatient non-cancer controls, the age-adjusted relative risk (relative risk: odds ratio) of gastric cancer is three in chronic nonatrophic gastritis, and 15 in the presence of atrophy and atrophic gastritis (intestinal metaplasia). The gastritis-related increased risk of gastric cancer is related to both intestinal and diffuse types of gastric cancer. Hp is associated with gastritis in 71% of both intestinal and diffuse gastric cancer, and only 16% of cases of gastric cancer are not associated with Hp.

Gastric juice ascorbic acid levels are lower in Hp-positive than Hp-negative individuals (49), raising the possibility that reduced levels of this powerful anti-oxidant in gastric juice may have a role in the development of gastric cancer.

Human Hp has been inoculated long term in monkeys. If Hp infection is an essential prerequisite of gastric cancer, intervention becomes a possibility. Oral immunization has been undertaken in mice (50) and ferrets (51). While immunization to Hp might protect against gastritis, peptic ulceration and gastric cancer, an unsophisticated vaccine might contain heat shock protein analogues and might cause autoimmune gastritis. This important developing area will be followed with interest.

OTHER CONDITIONS

In patients with endoscopically confirmed gastroesophageal reflux disease and esophagitis, 55% were Hp-positive on antral biopsy, although there was no significant correlation between Hp status and either patient symptoms or esophagitis grade (52). Of 62 patients with a hiatus hernia, 28 (45%) had histological evidence of Hp on the hernia mucosa and 96% had Hp in the gastric antrum. The role of Hp in the recurrence of erosive esophagitis needs to be explored. Omeprazole is recognized to benefit the treatment of patients with erosive esophagitis (this is a recurrent disease, and it is unknown whether the use of the combination of omeprazole plus amoxicillin would reduce the risk of these recurrences or the need for continued acid inhibitory therapy).

The prevalence of Hp in the postoperative stomach is controversial, and the role of bile gastritis needs to be established. In 68 Hungarian patients who later underwent proximal selective vagotomy the preoperative Hp infection rate was 70% in the antrum and was 51% in the duodenal bulb. Following proximal selective vagotomy, the Hp infection rate was unchanged in the stomach, while it decreased to 6.8% in the duodenal bulb (53).

The prevalence of Hp-positive gastritis is no different in immunologically compromised patients with acquired immune deficiency syndrome (AIDS) and with AIDS-related complex (as in human imunodeficiency virus seronegative patients). Interestingly, gastritis in Hp-positive AIDS/AIDS-related complex patients is often mild (54), and cell-mediated immune deficiency does not appear to increase the risk of infection with Hp (55). Median $CD4^+$ T cells were significantly lower in Hp-positive patients, and a lower percentage of patients treated with zidovudine were Hp-positive compared with the nontreated group (8 versus 60%, respectively) (56).

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