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Campylobacter pylori: Its Link to Gastritis and Peptic Ulcer Disease

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Bismuth salts have been used to treat acid peptic disease for 150 years. Recently, the discovery of *Campylobacter pylori* and the observation that this bacterium is inhibited by bismuth salts have regenerated interest in the antibacterial properties of bismuth. Bismuth and heavy metals inhibit growth of all *Campylobacter* species and many enteric anaerobes. Bismuth alone cures *C. pylori* infection in only 30% of patients, but in combination with other broad-spectrum antibiotics, it can achieve a cure rate of 80%–90% in 2–4 weeks. Data from several studies indicate that eradication of *C. pylori* is curative for most patients with duodenal ulcer. Epidemiologic studies in the United States suggest that the incidence of new *C. pylori* infections is declining, so antibacterial therapy for symptomatic cases may be adequate therapy. In developing countries, however, curative therapy may not be possible in the presence of environmental sources of reinfection. In these areas intermittent suppressive therapy with bismuth salts may be useful.

Peptic ulcers are defined as ulcers that develop in gastrointestinal epithelium exposed to acid. Thus, peptic ulcers usually occur between the esophagus and the duodenal bulb but in rare cases may be seen in the distal duodenum in Zollinger-Ellison syndrome and in Meckel's diverticula, which may contain ectopic acid-secreting gastric mucosa.

Acidity vs. Mucosal Defect in Peptic Ulcer Disease

Duodenal ulcer, the most common type of peptic ulcer, occurs at some time during the life of ~8% of the population in Western countries [1]. Although some patients with duodenal ulcer have acid hypersecretion, the majority secrete acid within the normal range [2]. In patients with gastric ulcer, acid secretion is often normal or decreased [2]. In these patients and in the majority of patients with duodenal ulcer, an etiology other than hypersecretion of acid must also be present. The other factor is "mucosal defense" and is presumably defective in patients with ulcer disease – so defective that even low or normal amounts of acid can erode the mucosa.

Because of a persistent abnormality of the gastroduodenal mucosa, healing of ulcers by means of acid-reduction therapy has only a temporary benefit. Both duodenal and gastric ulcers usually recur when ulcer therapy is ceased [3].

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One ulcer-healing agent, colloidal bismuth subcitrate (CBS, De-Nol), heals ulcers as effectively as does cimetidine but is associated with a lower rate of ulcer relapse [4]. CBS has been used for more than 100 years in the treatment of dyspepsia and peptic ulceration [5]. When the decreased rate of ulcer relapse following CBS therapy was noted in 1980, investigators could not explain why its ulcer-healing action persisted after administration of the drug was ceased. It is now known that CBS inhibits *C. pylori* and, as a result, heals gastritis [6].

Chronic gastritis (now known to be caused by *C. pylori*) has been proposed by many investigators as the mucosal defect in patients with ulcers. Magnus [7] observed histologic gastritis in 90% of persons with duodenal ulcer and in 75% of persons with gastric ulcer. Other investigators found that ulcers associated with use of nonsteroidal antiinflammatory drugs (NSAIDs) did not have chronic gastritis [8]. These observations suggest that the 30% of gastric ulcers not associated with gastritis are the ones caused by NSAIDs. Thus, except for peptic ulceration occurring in patients who receive NSAIDs, the great majority of peptic ulcers are associated with gastritis.

Gastroduodenal Histology

Normal. The gastric mucosa in healthy persons is confined to a region between the esophagus and the duodenum. The upper portion of the stomach (the gastric "body" or "corpus") secretes acid and

pepsin and consists of unbranched glands that contain parietal cells (for acid) and chief cells (for pepsin). The pores from several of these glands open into a gastric pit lined with mucus-secreting cells. In the antrum there is no substantial secretion of acid or pepsin – the surface epithelium of mucus-secreting cells is folded into mucus-secreting glands. Usually the antral epithelium does not extend further than the pylorus [9].

Unlike the stomach, the duodenal bulb has an intestinal type of epithelium composed of brush-border cells interspersed with goblet cells. In the region immediately distal to the pylorus, various amounts of antral epithelium are mixed with the intestinal-type epithelium [9] so that a transitional zone extends for 1 cm into the duodenum. When biopsy specimens are taken from the duodenal bulb of normal persons, ~25% are found to have gastric tissue present in small amounts [10].

Patients with duodenal ulcer. In a study of patients undergoing pyloroplasty for duodenal ulcer, James [11] found inflamed gastric mucosa in the duodenal bulb in 75% of cases. In a manner analogous to the situation in the ulcer diathesis, this inflammation is unaffected by acid-reduction therapy [12] but may be healed with bismuth salts [13]. In a study of 100 patients with duodenal ulcer, Marshall et al. [14] noted gastric metaplasia of the duodenal ulcer border in 92% of patients, a prevalence much higher than that seen in normal persons.

Gastric metaplasia present in the duodenum of patients with duodenal ulcers is associated with inflammation (duodenitis), which may lead to an appearance identical to gastritis in the antrum. In patients with duodenal ulcers, gastritis affects the duodenal bulb and antrum but spares the body of the stomach. Thus, acid secretion is not affected by the histologic lesion [15].

Patients with gastric ulcer. Patients with gastric ulcers are older than patients with duodenal ulcers. This may be because gastritis worsens and extends into the body mucosa with age [16]. Thus, as a person with duodenal ulcer ages, gastritis extends into the body mucosa and acid secretion decreases. Although the tendency for duodenal ulcer decreases with age, the severe gastritis in the gastric antrum may lead to ulceration in the stomach. Additionally, the junctional zone between antrum and duodenum moves proximally with age [17], so there is less gastric metaplasia in the duodenum and less tendency for duodenal ulceration.

Natural progression of gastritis. Ultimately, gastritis leads to atrophy of gastric mucosa (antrum and body), with replacement of acid-secreting epithelium by intestinal- or pyloric-type epithelium (atrophic gastritis). In this stage acid secretion is so low that peptic ulcer disease is no longer possible.

Campylobacter pylori and Gastritis

The observation that *Campylobacter*-like organisms were present on inflamed gastric mucosa and that the inflammation depended on persistence of the organism [18, 19] prompted studies that led to the isolation of *C. pylori*. The new bacterium is present in 95% of patients with duodenal ulcers and in 70% of patients with gastric ulcers [8], the same proportions of peptic ulcer disease that are associated with gastritis.

In vitro studies reveal a new genus of gram-negative bacteria that is related to *Campylobacter* in morphology, biochemistry, and cultural requirements but that has an unusual ultrastructure (sheathed flagella). The massive urease production of *C. pylori* [20] is unique among the *Campylobacter* species and permits its survival in gastric acid [21].

Campylobacter pylori and most other *Campylobacter* species are inhibited by bismuth salts (MIC, <25 mg/L [22]). CBS inhibits *C. pylori* in vitro and in vivo and eradicates the bacterium completely in 30% of patients [14]. Bismuth subsalicylate (BSS, Pepto-Bismol) has similar in vitro activity, and its popularity as an over-the-counter therapy for dyspepsia [23] may be due to healing of symptomatic gastritis.

Acute C. pylori infection. Acute *C. pylori* infection may have been quite common at the turn of the century, when it was described by William Osler [24]. In acute *C. pylori* infection [25], widespread gastritis is associated with transient vomiting and abdominal pain; the symptoms usually resolve within a week [26] (figure 1). Most recent reports of the illness have concerned iatrogenic *C. pylori* infections, where volunteers have been infected by endoscopes or pH electrodes. In India, and perhaps in other developing countries, acute *C. pylori* infection may still be quite common [27, 28].

Epidemiology of *C. pylori* and Peptic Ulceration

Campylobacter pylori gastritis is by far the most common form of chronic gastritis. Therefore, studies

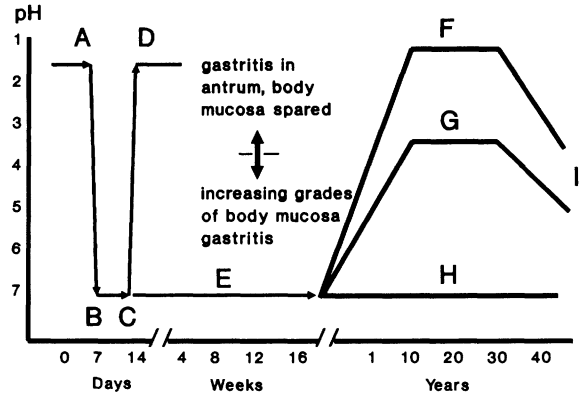

Figure 1. Time-line of *C. pylori* infection. In acute *C. pylori* infection, ingestion of the organism (*A*) is followed in 3–7 days by vomiting and epigastric discomfort. At this time, widespread gastritis is present and histamine-fast achlorhydria may be noted (*B*). After 1 week (*C*), gastric histology and acid secretion may return to normal if the bacterium is cleared by the host defenses (*D*). In most cases, severe chronic gastritis of the antrum and body mucosa persists for 3–12 months (*C–E*). Usually, *C. pylori* and gastritis decrease in the body mucosa, allowing acid secretion to return (*F*). This gives the pattern seen in duodenal ulcer, i.e., high or normal acid secretion, mild body-mucosa gastritis, severe antral gastritis, and duodenitis (with gastric metaplasia). In gastric ulcer, gastritis is severe in antral and body mucosa and acid secretion tends to be normal or decreased (*G*). In gastric carcinoma, acid secretion is usually decreased. This may be a result of gradual atrophy of body mucosa associated with long-standing gastritis (*F–I, G–I*) or may occur in some persons who never regain acid secretion after the acute *C. pylori* episode (*B–C–H*). Lifelong *C. pylori*-associated gastritis probably leads to chronic atrophic gastritis and hyposecretion of acid in older persons (*E–F–I, E–G–I*). This hypoacidity could explain the reported "burn out" of peptic ulcer disease.

Table 1. Eradication of *C. pylori* with bismuth and/or antibiotics.

Antibiotic(s)	Eradication rate (%)	Reference(s)
Amoxicillin	<20	51
Erythromycin	<20	6
Bismuth subcitrate (CBS)	30–40	14, 40, 51
Bismuth subsalicylate (BSS)	<20	*
Nitrofurans	20	45
Nitroimidazoles	0	46
Quinolones	0–20	41
CBS + amoxicillin	30–40	46
CBS + erythromycin	40–60	46
CBS + tinidazole	75	14
CBS + tetracycline + metronidazole	70–90	42, 44
BSS + amoxicillin	40	47
BSS + erythromycin	30	47
BSS + metronidazole	70	47
BSS + tetracycline + metronidazole	90†	43
Amoxicillin + tinidazole	70†	48
Amoxicillin + omeprazole	62†	49

NOTE. Data are from studies in which patients were reassessed no sooner than 14 days after completion of therapy.

* Author's unpublished observations.

† Preliminary data from a small study.

of gastritis accurately reflect the presence of *C. pylori*. Similarly, serologic studies of the prevalence of *C. pylori* disclose the prevalence of gastritis.

In the United States *C. pylori* affects 20%–30% of the adult population. The prevalence is age related—5%–20% in young persons and 30%–50% in middle-aged persons [29, 30]. *C. pylori* is uncommon in affluent white communities but is quite common in economically disadvantaged groups. For example, 75% of paid Hispanic volunteers were found to have *C. pylori* [31]. The prevalence of *C. pylori* in volunteer studies varies depending on the source of the subjects. Infection with *C. pylori* is found more frequently in paid volunteers than in unpaid volunteers, perhaps because paid volunteers tend to be from a lower socioeconomic group [29–32]. In developing countries *C. pylori* is common and the majority of the adult population may carry the infection [28].

In the United States, the age-related increase in *C. pylori* infections may mean that the infection is ubiquitous and that the adult population is infected with the bacterium at the rate of 1% per annum after the age of 20 years, as proposed by Perez-Perez et al. [29].

An alternative explanation is that the infection is usually acquired in childhood and that the age-related increase in prevalence is really a cohort effect. For example, if *C. pylori* was a common pediatric infection before 1940, persons >50 years old would still be likely to carry the infection. If *C. pylori* infections were infrequent in children born after 1950, today the infection would be uncommon in adults <40 years of age (figure 2).

The literature concerning the epidemiology of peptic ulcer tends to support a cohort effect rather than the gradual acquisition of *C. pylori* during adult life. Cohort analysis suggests that the incidence of peptic ulcer disease, particularly of duodenal ulcer, was related to an acquired environmental factor that was

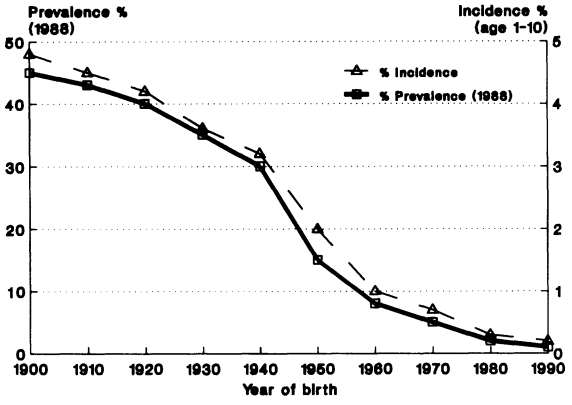

Figure 2. The prevalence of *C. pylori* infection in adults in the United States is plotted on the *Y* axis against year of birth on the *X* axis. As a result of acquisition of *C. pylori* in childhood, persons born in 1920 have a much higher carriage rate of *C. pylori* than do persons born in 1960. The prevalence of chronic *C. pylori* infection in persons >50 years old may reflect a high incidence of acute infection during childhood, the time at which enteric pathogens usually are acquired. The dashed line indicates the hypothetical incidence of acute *C. pylori* infections in children during the years indicated on the *X* axis. If these years were presented in reverse chronologic order, the *X* axis would represent age and the graph would more closely resemble illustrations of the prevalence of gastritis as described by Kekki et al. [33].

common between 1870 and 1900 [34]. This factor was acquired before the age of 15 years and conferred a lifelong predisposition towards peptic ulceration [35].

In addition to explaining the declining incidence of duodenal ulcer in the United States, an infective cause for peptic ulcer (*C. pylori*) could also account for the familial aggregation of duodenal ulcer in families with raised levels of serum pepsinogen [36]. The level of pepsinogen was raised during an epidemic of *C. pylori*-associated gastritis reported in Texas [16], and (as is true in ulcer disease) *C. pylori* gastritis runs in families. A familial tendency for gastric metaplasia in the duodenal bulb could explain the clustering of certain types of ulcers (duodenal or gastric) in families infected with *C. pylori* [37].

Bismuth Salts and Therapy for *C. pylori* Infection

The mode of action of bismuth salts on bacteria is not well understood. Bismuth has broad-spectrum antibacterial activity against anaerobes (*Clostridium difficile, Bacteroides fragilis*) and *Campylobacter* species (*Campylobacter jejuni, Campylobacter coli, C. pylori*) [38]. Heavy metals bind to sulfhydryl groups on proteins and disturb their tertiary structure [39].

The persistence of *C. pylori* after ulcer healing with H_2-receptor antagonists is well known, and eradication of the organism is associated with decreased recurrence of ulcer [14, 40]. Bismuth salts alone will eradicate *C. pylori* in 20%–40% of patients, an observation that may explain the decreased rate of ulcer relapse [14, 40]. If duodenal ulcers positive for *C. pylori* relapse at the usual rate (80% per annum) and duodenal ulcers negative for *C. pylori* relapse at only a rate of 10% per annum, it can be predicted that with CBS therapy the overall relapse rate will be 50%–60%.

Single-agent therapy with antibiotics alone has also been relatively unsuccessful in the eradication of *C. pylori* [41]. Penicillins, erythromycin, and tetracyclines are ineffective in spite of the continued in vitro sensitivity of *C. pylori* to these agents. The use of nitroimidazoles and quinolones results in the emergence of resistant *C. pylori* isolates without eradication of the bacterium, so these agents should only be used in combination with other drugs.

Most effective antibacterial regimens for *C. pylori* utilize two or three agents. Bismuth salts, if given concurrently with nitroimidazoles, prevent the development of resistant isolates and result in a cure rate of 70%–75%. In one large Australian series, Borody et al. [42] claimed a cure rate of 94% in more than 100 patients treated with triple therapy consisting of CBS (one tablet four times daily for 1 month), tetracycline (2 g daily for 1 month), and metronidazole (200 mg four times daily for 10 days). Graham et al. [43] have had similar success using BSS as the bismuth salt.

It is not known whether metronidazole-resistant *C. pylori* isolates are eradicated with triple-therapy regimens. The high cure rate reported may be due to a low prevalence of metronidazole resistance in Houston, Texas, and Sydney, Australia. The success of triple therapy was not duplicated in a study by McNulty et al. in the United Kingdom [44], in which a cure rate of only 68% was obtained (see table 1) [45–49].

Monitoring Therapy for *C. pylori* Infection

In some early studies of *C. pylori* infection, only short-term clearance of *C. pylori* was monitored. As

a result, "eradication" rates were unusually high [6] and "relapse" of infection was the rule. In studies in which patients were reexamined ≥2 weeks after cessation of therapy and sensitive methods for detecting *C. pylori* were used, relapse of infection was uncommon [14, 50, 51].

For these reasons eradication of *C. pylori* can be confirmed only by reexamination of the gastric mucosa 4 weeks after completion of antibacterial therapy. The method used must be sensitive, have few false-negative results, and should detect the presence of *C. pylori* organisms, rather than antibody. Suggested methods include examination of multiple biopsy specimens (two to four) of gastric mucosa with use of Giemsa stain, determination of the presence of urease in multiple biopsy specimens (two to four), or a urea breath test [52, 53]. In most medical centers culture is less sensitive than these methods, so culture cannot be used to exclude *C. pylori* infection.

The Future

Studies of *C. pylori* are difficult to perform at present because we do not have a convenient therapy with a 100% cure rate. If such a therapy can be found, double-blind therapeutic trials will be simplified and the role of *C. pylori* in gastroduodenal disease will be unveiled.

In the United States, therapy for *C. pylori* may be worthwhile only in symptomatic persons. Preliminary data suggest that reinfection is rare after successful eradication of the bacterium (author's unpublished observations), so it may not be necessary to treat infected family contacts or search for a source of infection.

In developing countries, however, *C. pylori* is common in children and, as with other enteric infections, reinfections may be prevalent after effective therapy. In these areas, vaccination and public health measures may be successful in controlling *C. pylori*. In areas where *C. pylori* reinfection is common, intermittent suppressive therapy with noncurative agents such as bismuth salts may be a useful long-term alternative to combination antibiotic therapy.

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