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PERSPECTIVE

Campylobacter pyloridis and Gastritis

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The successful isolation of *Campylobacter pyloridis* from human gastric mucosa in 1982 [1] marked the turning point in the long but unremarkable career of this organism.

Early Work

Spiral bacteria had been observed in the stomachs of humans and animals by Bizzozero [2] and Salomon [3] at the turn of the century. The first human study was done by Doenges [4], who found the bacterium in 43% of 242 stomachs from postmortem examinations and who described it as "a thick organism with only two or three spirals . . . occasionally within parietal cells," perhaps recognizing that it did not have the thin, multiple coils of the spirochetes. The canaliculi of parietal cells were sometimes invaded, an occurrence suggesting that the organisms were acid tolerant; and in some specimens, infiltration with polymorphs, lymphocytes, and plasma cells was seen in association with the bacteria.

Gastric Urease

Doenges [4] could not culture the gastric bacteria, so he could not have seen the importance of the work done 15 years earlier by Luck and Seth [5]. Luck had observed that the enzyme urease was present in the gastric mucosa of several animals, particularly cats, but also humans. At that time the metabolism of urea and ammonia was not well understood, and the urea cycle of Krebs and Henseleit [6] had not been described. Bliss [7] and Benedict and Nash [8] had noted that the vomitus of persons with nephritis often contained large amounts of ammonia. The presence of urease enzyme in gastric mucosa was thus thought to be a physiological mechanism whereby uremic persons and animals could convert excessive body nitrogen (urea) to ammonia and excrete it in the vomitus. Luck's work indicated that gastric urease was intrinsic to the mucosal cells. Because of his error, the study of gastric urease and gastric spiral bacteria proceeded on different paths for the next 60 years.

Gastrectomy Studies

In 1940, in order to see if the postmortem gastric spirochetes observed by Doenges [4] could also be found during life, Freedberg and Barron [9] examined 35 specimens from partial gastrectomies. They observed the bacteria in 40% of specimens, usually associated with benign or malignant gastric ulcers. Their paper also described what may have been the first use of antibacterial therapy for peptic ulceration. In the discussion, F. D. Gorham stated that he had successfully used intramuscular bismuth as an adjunct to the treatment of gastric ulcers that were difficult to heal, on the basis of its antispirochetal activity and of the work of Doenges [4].

Bismuth and Spirochetes

At the time that Freedberg's paper was published, oral bismuth salts, such as the citrate and the carbonate, had been used to treat dyspepsia and peptic ulceration for ~100 years [10]. Apart from Gorham's brief mention [9], however, the possible antispirochetal action of bismuth salts in the stomach was overlooked. Bismuth salts were denigrated as antacids by Ivy et al. [11] who in 1950 wrote, "They have no significant neutralizing value and if they are of value . . . their mode of action is not clear." Bismuth was relegated to the role of a popular over-the-counter medicine in many countries and was not subjected to adequate clinical trials for many years.

The study of gastric bacteria was curtailed by a paper in 1954 by E. D. Palmer [12]. In an attempt

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to clarify the conflicting points in Freedberg's and Doenges' papers, he examined 1,000 suction biopsy specimens of gastric mucosa but could not see the spirochetes. Perhaps the error was because he did not use silver stains and because the biopsy specimens were from the greater curve of the stomach, not the antrum. Thus Palmer, one of the pioneers of modern thinking on gastritis, may have been responsible for its greatest omission.

Urease and Ulcers

At that time the study of gastric mucosal urease was in its heyday. Still unaware of the bacteria, Fitzgerald and Murphy [13] wrote a thesis on the subject, based on the assumption of Luck and Seth [5] that all human gastric mucosa contained urease. They hypothesized that mucosal urease caused urea to be broken down into ammonia that then neutralized hydrogen ion coming into contact with the stomach wall and thus prevented autodigestion of the normal stomach. They erred because they had no means of examining gastric mucosa from normal persons; all of the partial gastrectomy specimens they studied contained urease (presumedly arising from the spiral gastric bacteria). Although Fitzgerald and Murphy were incorrect in their basic assumptions about urease, they did have some very modern concepts of peptic ulcer disease. They believed that ulcers developed "due to the ill-adjusted interplay of secretion, neutralization, and a third factor—mucosal resistance." They attempted to make their patients with ulcers achlorhydric by feeding them massive doses of urea [13]. Unfortunately, the patients could not tolerate such therapy.

After Fitzgerald and Murphy's work, the source of gastric urease remained controversial. Lieber and Lefevre [14] showed that the hypoacidity present in many patients with uremia could be reversed with antibiotics, a result suggesting a bacterial origin. Mossberg et al. [15] maintained that Lieber and Lefevre had misinterpreted their data, a view supported by Aoyagi et al. [16], who stated that "(urease) concentration was highest in the stomach and lowest in the large intestine, thus contrasting with the location of the gut flora." Aoyagi et al. had not examined the gastric specimens for bacteria, as they had assumed the stomach was sterile. Subsequently, Delluva et al. [17] demonstrated that urease was not present in mammalian tissue but was solely the product of bacterial metabolism. Delluva's discovery should have resulted in reexamination of the previous work on the origin of gastric urease, but this was never done.

Biopsy Studies of Gastritis

Between 1950 and 1970, new technology enabled blind-suction biopsy specimens to be taken of the stomach in live, conscious patients. Because of the J shape of the stomach, only the body mucosa of the greater curve could reliably be sampled by this means. This was not seen as a handicap, as the emphasis of gastroenterological research was on acid secretion, and the acid-secreting part of the stomach seemed a more likely source of the ulcer diathysis. The observation of Schrager et al. [18] that 90% of peptic ulcers occurred in the non-acid-secreting antrum was ignored.

In the 1970s, gastroenterologists, for the first time, were able to see the mucosa of the stomach and duodenum and take guided biopsy specimens of the gastric antrum. Pathologists recognized that the antrum had been a "blind spot" [19], but most dissertations on gastritis continued to use the confusing terminology developed from the study of the gastric body mucosa.

Gastritis was particularly common in Scandinavian countries where population studies [20, 21] demonstrated that inflammation was often present in the stomach, even in asymptomatic persons. It was found that gastritis was present in 20% of young adults and increased with age, to involve at least 50% of the population by the age of 60 years. In these studies there were several unrecognized deficiencies. Clinical information was not standardized, biopsy specimens were often from body-type mucosa, no distinction was made between active gastritis and chronic gastritis without polymorph infiltration, and epithelial cell changes were usually ignored. They concluded that gastritis was a normal condition that accompanied healthy aging. A more appropriate conclusion would have been that some type of gastric mucosal inflammation was common and that it increased with age and was often asymptomatic.

Type A and Type B Gastritis

An important advance came in 1963 when Strickland and Mackay [22] recognized that antral and body-mucosa gastritis were different diseases. In the body of the stomach there was a type of gastritis as-

sociated with parietal cell antibodies, achlorhydria, and pernicious anemia, in which the parietal cells were gradually destroyed by an infiltrate of plasma cells and lymphocytes. This type of chronic gastritis was usually asymptomatic, and because only parietal cells were affected, the antrum of the stomach was spared. This was called type A, or body-mucosa gastritis. The end stage was referred to as "gastric atrophy." Another feature of type A gastritis was that the mucus-secreting epithelial cells, which line the whole stomach, were not damaged by the process.

There was another, much more common, form of gastritis called type B or antral gastritis. This affected the mucus-secreting antral-type gastric epithelium and often spared the acid-secreting part of the stomach. In retrospect, much of the "superficial gastritis" seen in the body of the stomach was a milder form of the more severe change in the antrum. Although the clinical correlation was unclear, it was subsequently found that ~70% of gastric ulcers and 95% of duodenal ulcers were associated with type B gastritis [18]. Goldner and Boyce [23] and Greenlaw et al. [24] observed that dyspeptic patients without ulcers also tended to have type B gastritis, which was histologically identical to that seen in duodenal ulcer patients. They also proved that the gastritis was unrelated to its supposed cause, i.e., duodenal gastric bile reflux. Despite their work, it remained fashionable to blame type B gastritis on bile reflux, alcohol, dietary indiscretion, smoking, aspirin-like drugs, or even psychosomatic factors. None of these causes was ever proved.

Gastritis and Achlorhydria

One observation by Strickland et al. [25] that highlighted the difference between the two types of gastritis was that in type A gastritis, achlorhydria was accompanied by a raised serum level of gastrin, presumably because these patients had no negative feedback of gastric acid onto the antral gastrin-secreting cells. In type B gastritis, however, where the antrum was usually more severely inflamed than the body of the stomach, no such elevation of serum levels of gastrin occurred, even in severely affected patients who were achlorhydric. The mechanism of the achlorhydria observed in type B gastritis was taken to be the failure of parietal cells, in contrast to the achlorhydria of type A gastritis, in which parietal cells were totally absent. The possible connection between the patients with achlorhydric uremia of Lieber and Lefevre [14] and the achlorhydria present in type B gastritis was never appreciated. In a later study by McConnell et al. [26] it was demonstrated that the achlorhydria present in uremic individuals was extremely labile and could revert to hyperchlorhydria in a matter of days under certain conditions.

Cimetidine

In the 1970s, with the advent of the H2 receptor antagonist drugs such as cimetidine, it was possible to test the theory that acid caused peptic ulceration. It was soon discovered that nearly all benign ulcers, whether duodenal or gastric, healed with these agents. The modern fiber-optic instruments were used merely as supplements to the barium meal as gastroenterologists concentrated on the healing of macroscopic ulcer craters in numerous clinical trials of the new drugs. Very few trials included a biopsy of the gastric mucosa as part of the protocol, perhaps as a result of the misinterpreted Scandinavian studies. There were those, however, who saw beyond the macroscopic lesions. McIntyre et al. [27] noted that the histological changes of type B gastritis and duodenitis did not improve when the ulcer craters were healed with cimetidine. The high relapse rates that occurred following cessation of the new drugs indicated that McIntyre's histological impressions were correct—the disease had not been cured.

Spiral Bacteria and Gastritis

At this time the paths of the spiral bacteria and gastritis converged. Steer and Colin-Jones [28] studied the histological effects of carbenoxolone on the gastric mucosa of 50 patients treated for gastric ulcers. They observed that gram-negative bacteria were present on the gastric mucosa of 80% of their patients and that the bacteria did not disappear when the ulcers healed. They also correctly described the association between bacteria and infiltration of the mucosa with polymorphs, a condition known as "active" gastritis. However, the lack of controls in their study, a mistake in the identification of the bacteria, and ignorance of previous literature made it difficult for them to reach any useful conclusions. (Their paper was indexed under carbenoxolone, not bacteria.)

Epidemic Hypochlorhydria and Gastritis

In the 1970s, those who were interested in measuring acid secretion observed strange epidemics of

pentagastrin-fast hypochlorhydria associated with acute gastritis. In a case reported by Wiersinga and Tytgat [29], a man with Zollinger-Ellison syndrome underwent gastroscopic examination and had a biopsy done. Two weeks later, following a brief gastrointestinal illness, his indigestion ceased, and he was found to be achlorhydric. Biopsies demonstrated that active inflammation of the gastric mucosa had developed. In Dallas, Texas, in a study of acid secretion in 39 volunteers, Ramsey et al. [30] observed a similar phenomenon. Nearly half their volunteers developed hypochlorhydria following a mild gastrointestinal disturbance. In one case, the level of liver enzymes was raised. The acid secretion gradually returned to normal after three months in most of the volunteers, but three subjects were still hypochlorhydric after 12 months. Biopsy specimens were not obtained for all of the affected individuals, but when they were obtained, active gastritis was seen. No etiologic agent was found for these epidemics. A virus was presumed to be the cause, probably a rare laboratory event. The modern investigators were unaware that a very similar condition had been described by Sir William Osler years before [31]. Osler's "acute gastritis" consisted of a mild gastroenteritis lasting for a few days and associated with mucousy vomiting. It was Osler's practice to test the vomitus of such cases with litmus paper, and hypochlorhydria was not uncommon. The disease affected adults and children and was thought to progress to a chronic form in some cases, with symptoms of flatulence and dyspepsia. Treatment was often with bismuth salts. The disorder is not described in modern texts [32].

Campylobacter pyloridis

In 1979, at the Royal Perth Hospital in Western Australia, J. R. Warren observed what he termed *Campylobacter*-like organisms on gastric antral mucosa. The bacteria were present on nearly all specimens of gastric mucosa he received, very few of which were normal. Most of the specimens had the histological appearance of "active chronic gastritis," i.e., an infiltration with lymphocytes, plasma cells, and most notably, polymorphs. The polymorphs tended to accumulate around the necks of the antral glands and could often be seen in the lumen. Some of the electron micrographs taken during an earlier study [33] were reexamined, and fine detail of the bacteria could be seen. In 1981, Marshall and Warren [34] began a clinical study of patients undergoing gastroscopic examination, but no matter what disease or symptom the patients presented with, the bacteria were usually present. The gram-negative spirals could be seen in squashed gastric biopsy specimens and in smeared mucus, usually in large numbers. A prospective study was then performed in which 100 consecutive patients undergoing gastroscopic examination had a biopsy done, and the biopsy findings were correlated with the clinical and endoscopic data. During that study, a gram-negative, microaerophilic, catalase-positive bacterium was isolated. It was also observed that 95% of patients with active chronic gastritis had the bacterium, including all 13 who had duodenal ulcers and 14 of 18 with gastric ulcers [34].

In 1983, these findings were confirmed and extended [35]. The bacteria were present in 70% of 40 patients with gastric ulcers and in 90% of 70 patients with duodenal ulcers. Culture techniques were refined that enabled the investigators to confidently state that the bacteria were not present on histologically normal gastric mucosa. Also, the bacteria were still present in patients whose ulcers had healed with cimetidine therapy but who still had gastritis [35].

Epidemic Hypochlorhydria and Spiral Bacteria

Once it was recognized that the presence of polymorphs in gastric mucosa was virtually pathognomonic of infection with the bacteria, the cases of epidemic gastritis with hypochlorhydria stood out as possible acute infections. Examination of biopsy specimens from Weirsinga's [29] and Ramsey's [30] patients revealed spiral organisms. It was presumed that the bacteria were transferred from one case to another on a wet pH electrode, with the source of the infection probably being one of the volunteers or a previously studied patient with gastritis.

Antibacterial Action of Bismuth

In 1983 bismuth was still a component of over-the-counter remedies, recommended for the treatment of "gastritis," "gas," "dyspepsia," and the like. In the study of Marshall and Warren [34], the only symptom that correlated with the bacteria was "burping." At that time, one bismuth salt, colloidal bismuth subcitrate (CBS; DeNol; Gist Brocades), had been proven to heal duodenal ulcers. Patients with ulcers healed by this drug relapsed less often than those treated with H2 receptor antagonists [36], a finding since confirmed by Lee et al. [37]. Although CBS

had not been used to treat gastritis, ultrastructural studies had shown that healing of duodenal ulcer mucosa with CBS was better than healing with cimetidine [38]. In one of these studies [39], metaplastic gastric epithelium and spiral bacteria were included in an electron micrograph of a pretreatment duodenal ulcer border but were not present in the posttreatment photographs, a finding suggesting that they had disappeared. This observation led to the hypothesis that the lower relapse rates observed for patients with ulcers healed by CBS were due to an antibacterial effect, as had been proposed in 1940 [9]. In laboratory tests, it was observed that the MIC for the spiral bacteria was <25 mg/liter for CBS [35], a concentration lower than that for any of the other ulcer-healing drugs. In studies using CBS or antibiotics [35, 40, 41] and in a controlled study using Peptobismol® [42], it has now been demonstrated that type B gastritis is reversible. The active inflammation and most of the chronic inflammation disappear following eradication of the bacterium.

Recent Work

In 1984, McNulty and Watson [43] confirmed the association with duodenal ulcers, but a link with gastric ulcers was difficult to demonstrate because the proportion of patients with gastric ulcers and the bacteria was hardly more than that of patients examined by endoscopy who were without ulcers. Steer [44, 45] has accurately described the histological changes of duodenal and gastric mucosa infected with the bacteria. A major feature in the "active" form of gastritis not noted in some papers, was epithelial cell damage. Above all else, the presence of epithelial cell changes and the accompanying polymorph infiltration of the lamina propria distinguished gastritis associated with spiral bacteria from other forms of gastritis.

Urease Explained

The puzzle of the gastric urease was solved with the observation by Langenberg et al. [46] that the bacteria had remarkable urease activity; by McNulty and Wise [47], who observed that the urease in the human stomach could be detected with a urease test; and by Langton and Marshall [48], who observed low levels of urea and high levels of ammonia in the gastric juice of patients with gastritis.

More Recent Work

Like the Scandinavian population studies [20, 21], serological studies [49–51] have indicated that the spiral bacteria (and presumably gastritis) are common in healthy individuals, such as blood donors. However, in one study [52], symptoms of dyspepsia were twice as common in donors with the bacteria. In general, the epidemiology of the infection appeared to parallel that of gastritis, as had been seen in the Scandinavian biopsy studies [20, 21].

During 1984, an attempt was made to fulfill Koch's postulates for the bacterium. A volunteer infected with the bacterium developed a heavy colonization of previously normal gastric epithelium that was associated with hypochlorhydria, halitosis, and mild gastrointestinal disturbance. Biopsies demonstrated active inflammation identical to the lesions illustrated by Wiersinga and Tytgat [29] and Ramsay et al. [30]. The typical ultrastructural abnormalities associated with the spiral bacteria were also seen [53]. In 1985, Gledhill et al. [54] reported another epidemic of hypochlorhydria in which the initial "active" gastritis was seen to progress to "chronic gastritis" in two cases. Biopsy specimens containing spiral bacteria were obtained only after the hypochlorhydria had developed, so the initial presence of gastritis or of the organism could not be excluded.

In a review article, Goodwin et al. [55] point out that the spiral gastric bacterium, now named *C. pyloridis*, has many features that would qualify it as the initial member of a new genus: It has selected an ecological niche where there is no competition—the gastric mucosa. Whether it is taxonomically similar to the gastric bacteria present in animals [56] will depend on culture and on study of the latter, most of which have been difficult to isolate. Ultrastructural studies show that *C. pyloridis* has multiple sheathed flagella with terminal bulbs similar to those seen in vibrios, and it has a smooth cell wall unlike the "wrinkly" appearance of *Campylobacter jejuni* [57]. Axial filaments are not present on *C. pyloridis*, a feature that differentiates it from the gastric bacteria of animals [56] and the spirochetes [1].

PAGE of sonicated *C. pyloridis* isolates gives a pattern quite different from that of *C. jejuni* [58]. Also, unusual fatty acids make up its cell wall: tetradecanoic (14:0), and *cis*-methylene octadecanoic (19:0); whereas the other campylobacters have hexadecanoic (16:0), octadecenoic (18:1), and hexadecenoic (16:1)

[57]. It also lacks the respiratory quinone-methylated menaquinone-6 that is found in the other campylobacters. Very high urease and catalase activity are also unusual in the campylobacters [55].

On the other hand, *C. pyloridis* resembles the known campylobacters in many ways. Its shape in fresh specimens is distinctly that of a *Campylobacter*, and it is microaerophilic (although it also grows well in standard CO_2 incubators using 90% room air plus 10% CO_2, if the humidity is high [35]). It is unable to metabolize sugars and has a similar G+C content of ~36%. It is best approached as an abberrant *Campylobacter* that grows in three days at 37 C in a very humid environment, in *Campylobacter* atmospheres, on media containing whole or lysed blood, and perhaps on selective antibiotics such as trimethoprim, vancomycin, nalidixic acid, and amphotericin [35].

In practice, there is very little difficulty in identifying *C. pyloridis*. It is the predominent organism isolated from gastric mucosal biopsy specimens, and a urease test applied to a bacterial colony gives a red reaction in a few minutes [46]. Factors that impair its isolation are usually preventable. These are concurrent antibiotic use, recent oral medications (cimetidine or bismuth-containing drugs), and agents used to facilitate endoscopy, such as simethicone [35]. In the author's view, elective endoscopy should be postponed for at least seven days if the patient has taken antibiotics (i.e., penicillins, cephalosporins, metronidazole, gentamicin, or tetracyclines [35]) to which the bacterium is sensitive.

As described by Buck et al. [59] in this issue of the *Journal*, *C. pyloridis* has very unusual morphology when subcultured, with long, curved cells and U shapes. Perhaps this indicates that ideal conditions for its growth have not yet been obtained in vitro. One of the factors not reproduced in normal media is a high viscosity, as seen in gastric mucus. In the description of their motility studies, Hazell et al. [60] state that "even at 200 centipoise, the spiral organisms could still move," a finding implying that in a viscous medium the spiral *Campylobacter* shape was present. Buck's illustrations also lend weight to the hypothesis of Hazell by showing an electron micrograph of *C. pyloridis* organisms finding their way down between the epithelial cells. This illustration also demonstrates some of the ultrastructural cytopathic changes that are seen when *C. pyloridis* colonizes the gastric mucosal cells: the bulging of mucous cells, the loss of microvilli, and the development of attachment pedestals [55].

The Future

In the next two years we can expect to see a number of clinical trials that will decide the importance of this new pathogen. The first of these is likely to be observation of the healing and relapse rates of duodenal ulcers following the eradication of *C. pyloridis*. Subsequently, double-blind studies of antibiotic therapy for patients with chronic vague gastrointestinal syndromes, such as "non-ulcer–dyspepsia" and "flatulent dyspepsia," will decide whether these poorly understood disorders are as functional as some clinicians would have us believe [61].

At the present time the least that can be said about infection with *C. pyloridis* is that it is common in patients undergoing gastroscopic examination and in asymptomatic adults but that its presence confers an ~10-fold risk of developing duodenal ulceration.

The alternative view is that infection of the gastric mucosa with *C. pyloridis* is the most common gastrointestinal disease of modern persons. It is the most probable cause of active chronic gastritis, a disorder associated with nearly all forms of chronic dyspepsia. It is associated with a forgotten form of acute bacterial gastroenteritis causing hypochlorhydria. Finally, its ability to digest urea and produce ammonia in the stomach is a metabolic disorder of particular relevance to patients with renal or hepatic disease.

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