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REVIEW

The first 5 years of *Helicobacter pylori* research—With an emphasis on the United Kingdom

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Abstract

In the 1970s, 1% of the UK population consulted with dyspepsia; fiberoptic gastroscopy allowed biopsy specimens under direct vision enabling systematic histopathology. Steer et al described clusters of flagellated bacteria closely apposed to the gastric epithelium associated with chronic active gastritis. The first UK series of *Helicobacter pylori* following Marshall's 1983 visit to Worcester confirmed the association of *H. pylori* with gastritis. UK researchers completed much early helicobacter research as there were many UK campylobacteriologists. Steer and Newell proved the *Campylobacter*-like organisms grown on culture were the same as those seen in the gastric mucosa using antiserum raised by inoculating rabbits with *H. pylori* from cultures. Wyatt, Rathbone, and others showed a strong correlation between the number of organisms, type and severity of acute gastritis, immunological response, and bacterial adhesion similar to enteropathogenic *E coli*. Seroprevalence studies indicated *H. pylori* increased with age. Histopathologists also showed peptic duodenitis was in effect "gastritis in the duodenum" caused by *H. pylori*, unifying its role in the pathogenesis of both gastritis and duodenal ulceration. These bacteria were initially called *Campylobacter pyloridis* and then *C. pylori*. However, electron microscopy suggested that the bacteria were not campylobacters, and this was supported by differences in fatty acid and polyacrylamide electrophoresis profiles. In-vitro tests indicated that *H. pylori* was susceptible to penicillins, erythromycin, and quinolones, but not trimethoprim or cefsulodin allowing development of selective media for culture. Monotherapy with erythromycin ethylsuccinate was ineffective, and patients treated with bismuth subsalicylate initially responded with clearance of *H. pylori* and the associated gastritis, but then many relapsed. Thus, pharmacokinetic and treatment studies were important to direct suitable dual and triple treatments. Work optimized serology, and the rapid biopsy urease and urea breath tests. The link between *H.pylori* and gastric cancer was established in large seroprevalence studies, and *H. pylori* test and treat for dyspepsia became routine.

KEYWORDS
Campylobacter-like organisms, chronic gastritis, culture, gastric cancer, Helicobacter pylori, rapid urease test, Serological Diagnosis

1 | DYSPEPSIA IN THE 1970S

The description of the UK's discovery of *Helicobacter pylori*-related gastroduodenal disease needs to start in the gastroenterology clinics of the 1970s, when dyspepsia was a significant problem in both primary and secondary care. In the 1970s, 1% of the UK population consulted their family doctor with food-related upper abdominal pain.[1] At endoscopy one third of these patients had a peptic ulcer, one-third had so called non-ulcer dyspepsia and the remainder had various other much less common disorders including gallstones, gastro-oesophageal reflux disease (GORD), and irritable bowel disease (IBS). Now 50 years later in the 2020s the tide has turned and peptic ulceration is an unusual diagnosis seen in only 5–8% of endoscopies, while GORD is seen in 40% of these patients.[2,3] In the 1970s through the development of fiberoptic gastroscopy, gastroenterologists were able to take biopsy specimens under direct vision, enabling much more detailed gastric diagnostic and histopathological work. Gastric biopsy specimens taken endoscopically from four standard sites throughout the stomach (prepyloric, mid lesser curve, high lesser curve, body greater curve)[4] showed widespread histologically proven gastritis. In patients with chronic gastric ulcer of the body of the stomach; however this gastritis was more localized in chronic prepyloric ulcer.[4] They found that gastritis persisted after medical or surgical healing of the ulcer, suggesting that gastritis was a basic disease process, and that gastric ulceration was a secondary phenomenon.

2 | SIGHTINGS OF *CAMPYLOBACTER*-LIKE ORGANISMS PRE WARREN AND MARSHALL

In 1975 several years before Warren and Marshall's first description of *Campylobacter*-like organisms (CLOs), Steer et al described clusters of unipolar flagellated bacteria in close apposition to the gastric epithelium (Figure 1).[5] Steer indicated that polymorphonuclear leucocytes were migrating through the gastric mucosa in response to some extrinsic factor which he suggested was these bacteria. He also refuted that these bacteria were contaminants introduced at the time of biopsy as some had been phagocytosed by polymorphonuclear leucocytes in the gastric lumen.[5] These early pioneers proved to be very important in the later UK helicobacter story. Steer was able to use his stored histological specimens and detailed investigations to undertake further ground-breaking work, and Gear led the surgical endoscopies in Gloucester where much later helicobacter work was undertaken.

3 | WARREN AND MARSHALL

It was 5 years later in 1980 that Warren first noted CLOs on tissue sections of the gastric antrum in patients with the histopathological appearance of chronic active gastritis. Figure 2.[6] They were not obvious in sections stained with hematoxylin and eosin, but showed up clearly with Warthin-Starry silver staining. They were found in all patients with duodenal ulcers, 80% of patients with gastric ulcer, and 96% of patients with chronic active gastritis.[6] Initially Barry Marshall failed to culture the CLOs from biopsy specimens in a microaerobic atmosphere used for other campylobacters, but their first positive culture occurred when plates were incubated fortuitously for 6 days over the extended Easter break.[6] Thereafter, with this extended incubation, isolation of CLOs became routine.

As the organism seemed so *Campylobacter*-like, it was natural for Marshall to reach out to "Campylobacteriologists." During 1983 Barry Marshall contacted Dr Martin Skirrow in the United Kingdom; Martin had an intense curiosity around microorganisms which persists to this day. He and the lab in Worcester Royal Infirmary were experts at culturing *Campylobacter jejuni*, and were the first to describe a selective medium for it.[7] During 1983 Barry Marshall sent freeze-dried cultures of the proposed CLO to Worcester, UK, and they were able to culture it their too. Martin invited Barry Marshall to submit an abstract to present his work at the Second International Workshop on Campylobacter Infections in Brussels in September 1983. Marshall's presentation at Campylobacter II.[8] stimulated much discussion between the medical microbiologists who had a great interest in *Campylobacter spp*., and the veterinary microbiologists amongst whom there was a wealth of knowledge of animal spiral bacteria adaptations allowing survival in the intestinal tract. How could these CLOs survive in such enormous numbers in the

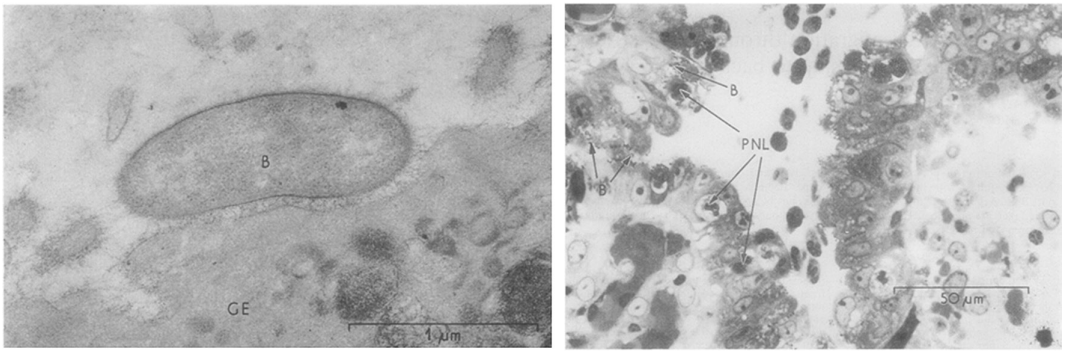

FIGURE 1 Left: Bacterium (B) closely apposed to the gastric epithelium (GE), and right polymorphonuclear leucocytes (PNL) migrating through the gastric epithelium, with bacteria (B) related to the luminal aspect.[5] Copyright Gut.

gastric acid milieu and in the presence of such an intense immune response? Were the CLOs of primary or secondary importance in the etiology of peptic ulceration; were they commensals or pathogens? As Diane Newell a keen campylobacter researcher stated "there *was enthusiasm and success with which microbiologists internationally, previously discouraged by their inability to identify the microbial cause of many causes of acute enteritis had been able to demonstrate in the late 70s many new Campylobacter spps in a wide variety of settings and occasions. The UK Public Health Laboratory Service and others considered that an effort should be made to bring cohesion to a scene that might otherwise become chaotic*."[9] So the UK PHLS sponsored the first and second International workshops on Campylobacter Infections. The workshop format allowed work still in progress to be discussed openly leading to a truly collaborative approach. Thus going forward there were many enthusiastic UK "campylobacteriologists" keen to take on further research.

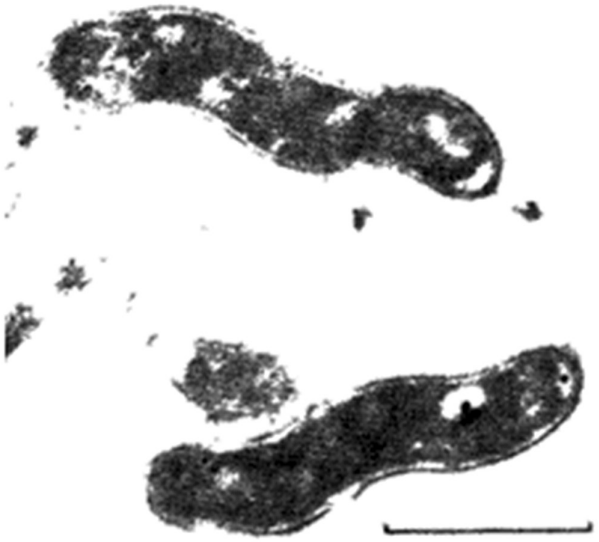

FIGURE 2 *Campylobacter*-like organisms seen in the gastric mucosa by Warren and Marshall[6] (bar 1 μm). Copyright lancet 1983.

4 | FIRST RECOGNITION AND CULTURE OF *CAMPYLOBACTER*-LIKE ORGANISMS OUTSIDE AUSTRALIA

In August 1983, I had just started working as a trainee medical microbiologist in Worcester Royal Infirmary in the United Kingdom. When Barry Marshall visited the hospital just before the Campylobacter workshop in 1983, we wanted to learn more about this new *Campylobacter*-like organisms and were very keen to attempt isolation of the CLO from Worcester patients. We attended an endoscopy session examining patients with dyspepsia, and gastric biopsy specimens were taken. We returned with the specimens to the laboratory and rapidly found numerous spiral organisms in the Gram stained biopsy smears. Figure 3. It seemed incredible that the true significance of these numerous bacteria had been overlooked by most histopathologists previously. The lab soon obtained a positive culture from a woman with gastric ulcer, demonstrating that the organisms were not exclusively Australian.[10] Harry Green at Worcester Royal Infirmary organized Warthin-Starry silver stains, that displayed the CLOs so very clearly and in large numbers.

Helped by a gastroenterology team, a meticulous microbiology team used to culturing campylobacters, and patient histopathologists, I started a series of endoscopy patients, collecting clinical, histological, and cultural characteristics over 3 months from November 1983, publishing an 80 patient series in May 1984 in the Lancet.[10] This confirmed the findings of Marshall and Warren that these CLOs were culturable in a microaerobic atmosphere, and were associated with gastritis. During 1983 Rollason, a histopathologist from Wrexham UK was studying retrospectively a 301 series of dyspeptic patients being investigated by endoscopy. The group found an

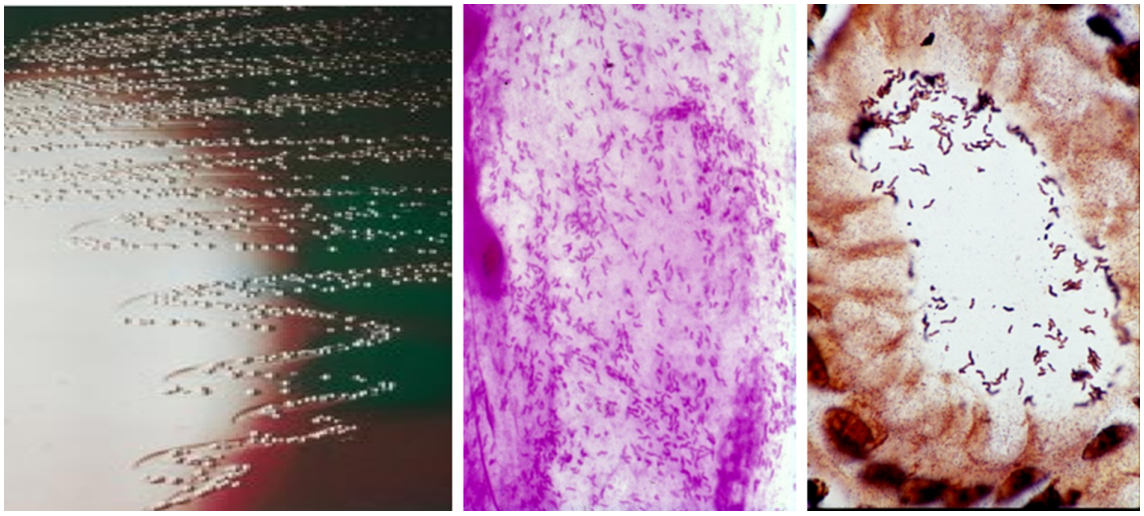

FIGURE 3 Left culture of CLOs on Campylobacter media, middle Gram stain of gastric biopsy smear, and right Warthin Starry Stain of histopathological tissue section showing CLOs in the gastric mucosa.

association of the spiral bacteria with gastritis, but unfortunately a small prospective study of prolonged culture in anaerobic broth rather than microaerobic culture was unsuccessful.[11]

As this new CLO was found most often in the gastric pylorus and was associated with duodenal and gastric ulcers, during informal discussions in 1984 between Dr Martin Skirrow and the dermatologist Dr Newbold in Worcester, the name *Campylobacter pyloridis* was suggested.[12] Figure 4. The word "pyloridis" is derived from the Greek pylorus, "gatekeeper," one who looks both ways, forward to the duodenum and back to the stomach; thus the name *C. pyloridis* was proposed officially by Barry Marshall,[13] and generally accepted.

Following the 1983 Campylobacter II workshop *C. pyloridis* research spread rapidly across the United Kingdom. Only 22 months later at Campylobacter III in Ottawa in July 1985, there were 28 CLO abstracts and 16 were from UK authors, 5 from Australia, 2 USA, 1 Canada, 1 Japan, 1 Netherlands, 1 Spain, 1 Yugoslavia.[14] By this time there were about 30 significant papers published and half were from the United Kingdom. The range of work undertaken and presented at Campylobacter III in July 1985 in Ottawa was extensive, and two UK groups already had patient series of over 200.[15,16]

Why was the United Kingdom so open to campylobacter research? Many of the 1981, and 1983 Campylobacter workshop attendees feature in early publications, as you could relatively easily move from *C. jejuni* research to explore these new *Campylobacter*-like organisms. Many were young researchers with open minds, guided by their older peers, but not blinkered by pharmaceutical sponsorship from the manufacturers of H2 antagonists which were at that time used to treat gastric and peptic ulceration. There was also a readily accessible patient population with chronic relapsing dyspepsia being investigated by endoscopy. In Gloucester UK, for example, we received biopsy specimens from about 1500 patients annually, and these numbers were held in histopathology storage.

However, *C. pyloridis* researchers in the United Kingdom and globally were working amongst some skeptical clinical gastroenterologists. At that time the two main aims of management of peptic ulcer disease were healing of the acute lesion and prevention of recurrence. So, you can therefore understand that the need for investigation and treatment was huge, and gastroenterologists had a large private practice from this recurrent illness. In the late 1970s and early 1980s many studies confirmed that symptomatic relief of dyspepsia could be attained by controlling gastric acid secretion with the histamine H2 antagonists; thus proving Karl Schwarz' 1910 maxim -no acid no ulcer.[17–19] Soon the histamine H2 antagonist became the mainstay of treatment; accounting for a substantial proportion of drug costs worldwide. The significant results of large drug company sponsored multicenter studies, involving gastroenterologists across the world, supported the lifelong use of maintenance H2 antagonists,[20] so many clinicians were skeptical that treating a bacteria would help cure what to them was a chronic disease. Barry Marshall described these gastroenterologists as dinosaurs with their heads in the sand. This did not make him popular with some clinicians for a few years.

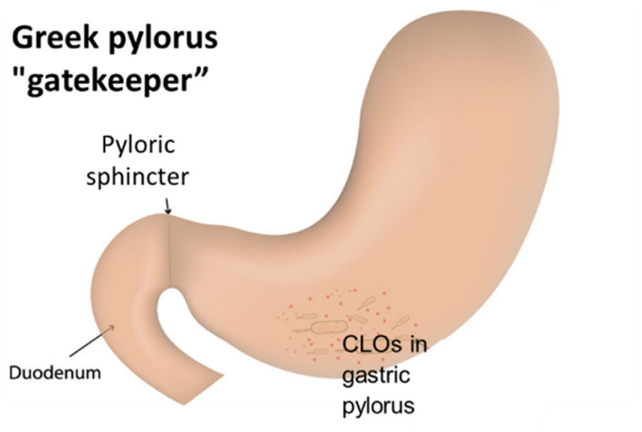

FIGURE 4 Naming of *Campylobacter pyloridis*.

5 | PROVING THE ASSOCIATION BETWEEN *C. PYLORIDIS* AND GASTRITIS

There was very little previous research around these CLOs, so the world was your oyster as far as research was concerned, and it was a very fast-moving time for us all. A bit like the COVID research – but on a much smaller scale. The Lancet was a very important source of information in 1984 and 1985 and its correspondence columns regularly featured new work on CLOs and then *C. pyloridis*. Everyone had easy access to serological methods and so this was the most common area of work in that first year, but there were many histopathological studies and several treatment studies. Steer and Newell set out determine if the *Campylobacter*-like organism grown on culture was the same as that seen in the gastric mucosa.[21] Antiserum was raised by inoculating rabbits with *C. pyloridis* from cultures. They confirmed the specificity of the antiserum by washing and incubating it with *C. pyloridis*, and then incubating it with gold-labeled sheep anti-rabbit. Both the flagella and surface of the *C pyloridis* were labeled with the rabbit anti-*C. pyloridis* serum. Figure 5. Histological sections were than incubated with fluorescent labeled antisera. Fluorescence was present on the luminal surface, gastric mucus and intracellular junctions of the gastric mucus producing cells proving that the cultured organisms were those seen in the gastric specimens and not just laboratory contaminants.[21] Wyatt and Rathbone and others used immunoperoxidase techniques to show IgG, IgM, and IgA attached to CLOs in the gastric mucosa and showed a strong correlation between the number of organisms and severity of acute gastritis, and immunological response (measured by ELISA) with the number of plasma cells in the mucosa; corroborative evidence that the inflammatory response was elicited by the *C. pyloridis*.[22,23]

Several groups confirmed the strong correlation between the presence of *C. pyloridis*, with chronic active gastritis, the strong serological response, and validity of using antibody detection as a predictor of the presence of *C. pyloridis*.[24,25] Researchers were really interested in the relative lack of IgM found, this and the stability of IgG over many

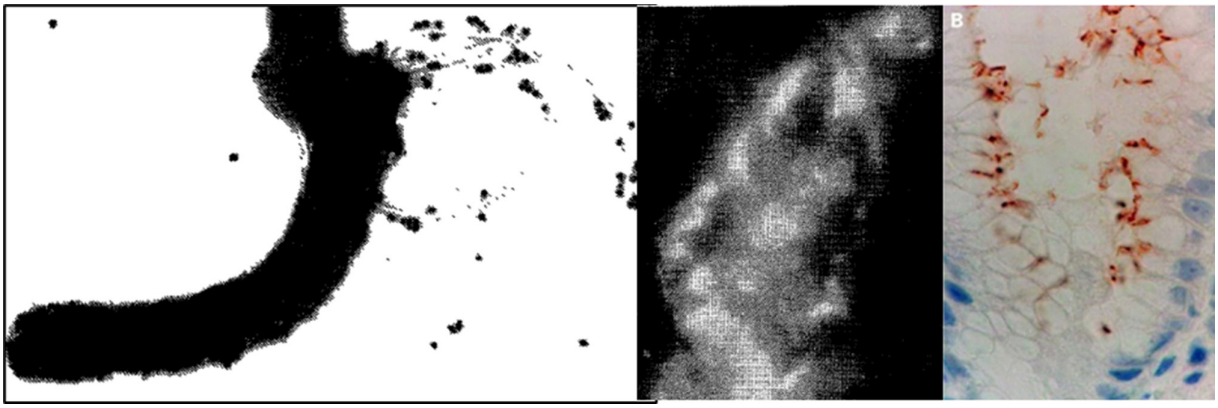

FIGURE 5 Left: Electron micrograph with gold label rabbit anti-*C. pyloridis* serum attached to surface of the body and flagella of *C. pyloridis*, middle photomicromicrograph with fluorescence related to luminal surface of gastric epithelial cells. Copyright Lancet 1985.[21] Right: Immunoperoxidase–techniques showed IgG, IgM, and IgA attached to *C. pyloridis* in the gastric mucosa (courtesy of Rathbone and Wyatt).

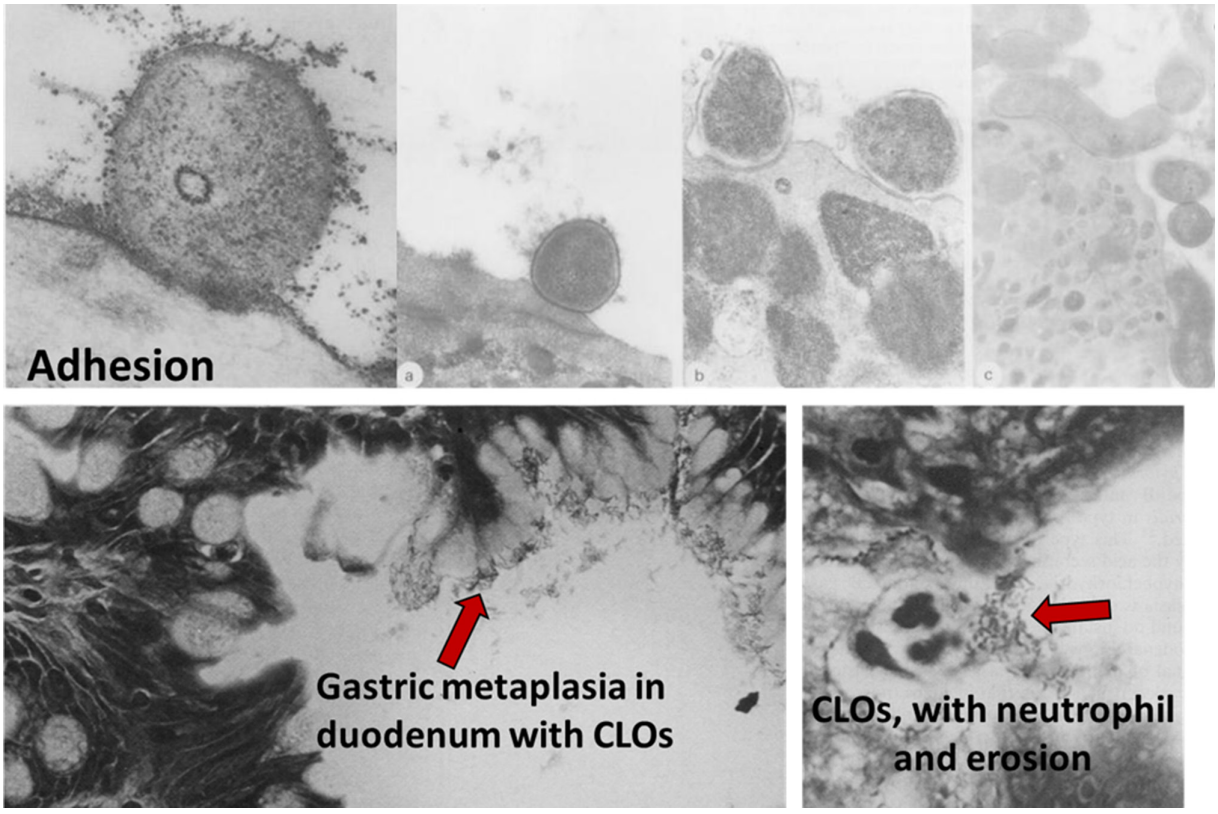

FIGURE 6 Top: Electron micrograph showing adherence of *Campylobacter pyloridis* bacteria to the gastric epithelial cells.[29] Copyright Gut 1990. Bottom left: histopathological section showing gastric type cells in the duodenum (gastric metaplasia) with CLOs present on this gastric epithelium.[30] Bottom right: gastric metaplasia in the duodenum with CLOs present causing a polymorphonuclear reaction and an erosion.[30] Copyright J Clin Pathol 1987.

months suggested a chronic infection. Furthermore *C. pyloridis* were less common in patients with atrophic gastritis, and the organism increased in prevalence with age; but was not associated with other GI diseases.[24] Hawtin et al in Southampton UK presented similar findings in a endoscopy/seroprevalence study of 222 patients showing that only 1% of under 15 year olds were seropositive for *C. pyloridis*, increasing to 8% 15–44 years, 55% 45–64 years, and 68% over 65 years.[26]

6 | THE IMPORTANT ROLE OF HISTOPATHOLOGISTS

Initially the organisms' effect on the gastric physiology and immunology was not understood and some of the data seemed conflicting. How could this organism persist in the presence of such a good immune response? Why did this *Campylobacter* species cause

dyspepsia in some patients and not others, and how was it associated with duodenal ulcers? Histopathologists were pivotal in this search for the truth. There was already an interest in Leeds in the pathophysiology of peptic ulcer disease (PUD) and the post-operative stomach, and the investigation of non-ulcer dyspepsia (NUD). Thus, they were "primed" for the discovery of *C. pyloridis* and held well-documented archival material that kick-started their investigations. Dixon and Wyatt in a series of studies found that *C. pyloridis* were much less associated with autoimmune/pernicious anemia type gastritis, reflux gastritis, and lymphocytic gastritis than with the "usual" active chronic gastritis—confirming that *C. pyloridis* was disease specific and not a commensal.[27,28] Their ultrastructural and histological study of epithelial adherence by *C. pyloridis* in gastritis revealed patterns of adhesion akin to those found with enteropathogenic *E.coli* elsewhere in the gut. The presence of adhesion sites was related to the degree of surface epithelial degeneration strengthening the case for *C. pyloridis* as a pathogen.[29] Figure 6. Their copious biopsy material from NUD patients permitted them to show the association between *C. pyloridis* positive gastritis, gastric metaplasia with associated *C. pyloridis* in the duodenal cap, and *C. pyloridis* associated active duodenitis.[30,31] So peptic duodenitis in patients with or without an actual duodenal ulcer was in effect "gastritis in the duodenum" caused by *C. pyloridis*. They thus hypothesized that gastric metaplasia results from increased acid reaching the duodenum, so proposing a unifying hypothesis for the role of *C. pyloridis* in the pathogenesis of both gastritis and duodenal ulceration.[32]

7 | THE GASTRIN LINK

To test the unifying hypothesis that *C. pyloridis* in the gastric antrum increases gastrin release and thereby acid secretion leading to duodenitis, Levi et al studied meal-stimulated gastrin release, and the presence or absence of antral *C. pyloridis* in patients with duodenal ulcers.[33] Gastric acid secretion was determined before and during infusion of pentagastrin (6 tig/kg/h) for 105 min. Both mean basal and mean pentagastrin, and meal stimulated rates of gastric acid secretion were significantly higher in the *C. pyloridis* positive than in the *C. pyloridis* negative patients.[33] Figure 7. McColl et al extended this work showing that gastrin concentrations significantly decreased after eradication of the bacteria.[34]

8 | WAS *C. PYLORIDIS* A TRUE *CAMPYLOBACTER?*

Curry et al sought to determine if the so-called *C. pyloridis* ultrastructure seen by electron microscopy was similar to other campylobacters. The flagella were multiple unlike campylobacters and sheathed unlike Aquaspirillum; unlike campylobacters the ends of these bacteria did not taper, nor did they have a terminal concavity; the outer membrane was closely adherent unlike campylobacters which were loose; the large flagellar discs did not have the radial structures characteristic of those seen in *C.jejuni and C.fetus;* the large number of 12 nm "doughnut"-like structures seen on the surface and released in very large quantities had not been seen in similar extracts of campylobacters. Thus, a new separate genus was suggested for *C. pyloridis*.[35] Figure 8.

Other UK work also suggested that *C. pyloridis* was different to other campylobacters, in 1984 several groups showed that the polypeptide profiles on polyacrylamide electrophoresis were unlike those of other campylobacter, allowing the development of diagnostic tests using the more immunogenic outer membrane proteins.[36–38] Hudson and Wait in 1985 showed that *C. pyloridis* possessed very different proportions of individual cellular fatty acids detected by gas liquid chromatography.[39]

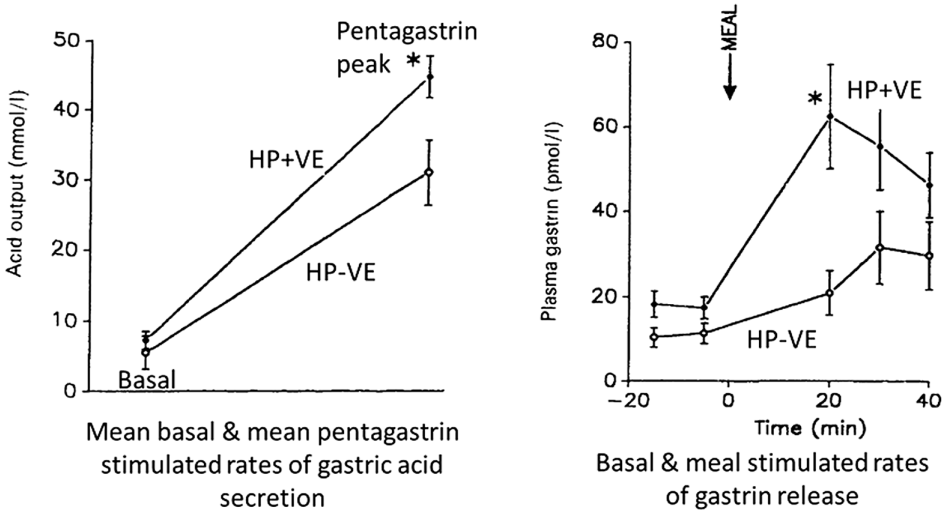

FIGURE 7 Mean basal and pentagastrin stimulated acid secretion (left) and basal and meal stimulated gastrin release (right) in *H.pylori*-positive (HP+VE) and *H.pylori*-negative (HP-VE) patients with duodenal ulcers. Vertical bars indicate SEM; $^*p < 0.05$.[33] Copyright Lancet 1989.

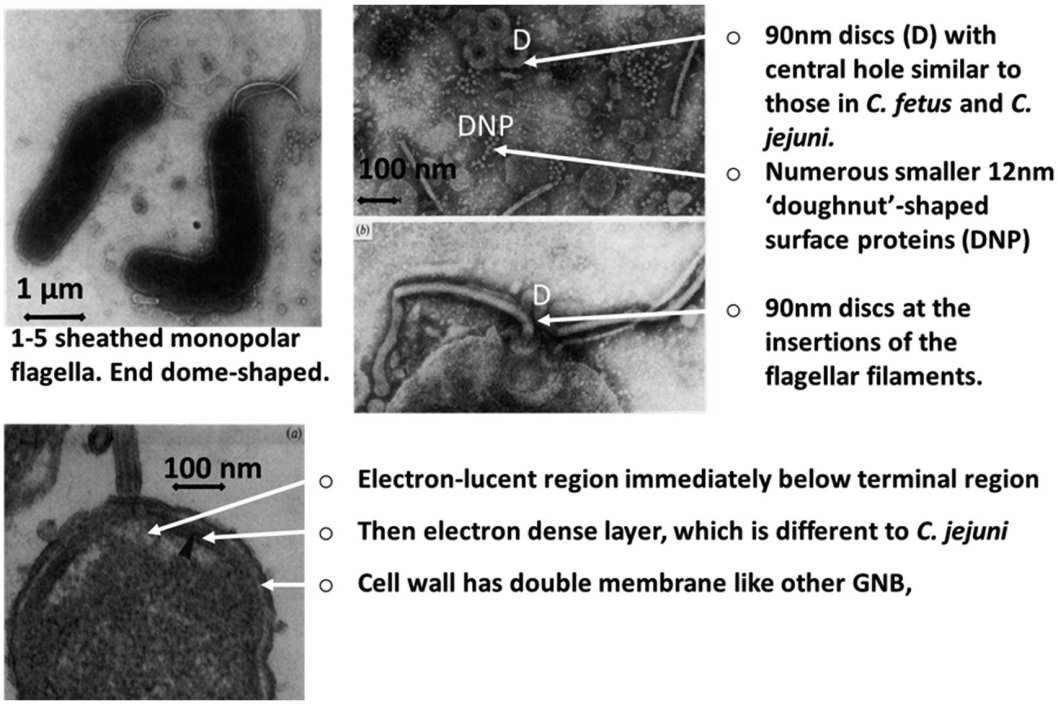

FIGURE 8 Electron microscopy work indicating that *C. pyloridis* was unlike other campylobacters.[35] Copyright J Gen Microbiol 1985.

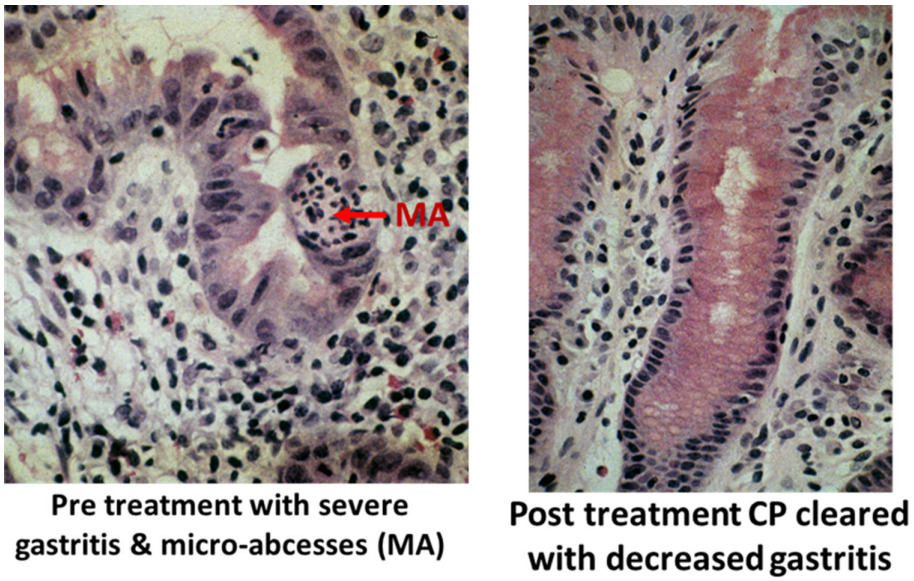

FIGURE 9 Resolving chronic active gastritis seen in patient (Birmingham UK) cleared of *C. pyloridis*.

9 | ANTIMICROBIAL SUSCEPTIBILITY

In 1984, it was not yet known if antimicrobial chemotherapy was an appropriate alternative to antacid or gastric acid reduction in the therapy of *C. pyloridis*. McNulty et al examined susceptibility of clinical isolates to a number of potential chemotherapeutic agents, including two bismuth salts.[40] Like other campylobacters *C. pyloridis* was very susceptible in-vitro to erythromycin (MIC 90, 0.12 µg/mL) and ciprofloxacin (MIC 90, 0.25 µg/mL) which were already used for treatment of *Campylobacter enteritis*. In contrast to other campylobacters and most other bacteria, all the *C. pyloridis* strains were highly susceptible to penicillin (MIC 90 0.03 µg/mL)—so this and amoxicillin would be possible therapeutic agents. The majority of *C. pyloridis* strains were susceptible to metronidazole, but demonstrated a bimodal distribution as 20% had an MIC 90 greater than 1 µg/mL, which has been described for other members of the *Campylobacter* genus. Like other campylobacters, all strains were resistant to trimethoprim and sulfamethoxazole (MIC 90 > 256 µg/mL) explaining why Skirrow's Campylobacter medium, which contains these antimicrobials was so effective as a selective medium for culturing the organisms. The bismuth salts which had been used historically for the successful treatment of peptic ulcers and dyspepsia

both had MICs in the range of 4–32 μg/mL; this in-vitro activity of bismuth salts helped to explain why they yielded a lower relapse rate of peptic ulcers than the H2 antagonists.[41] It was thought that bismuth salts acted locally by coating peptic ulcers, and erosions promoting healing. We and others wondered if this was due to their local antibacterial action in the gastric lining.

10 | FIRST THERAPEUTIC STUDIES

To investigate if bismuth salts were indeed active in-vivo and to further explore the direct causative relationship between *C. pyloridis* and chronic active gastritis McNulty et al undertook a prospective, randomized, investigator blind study comparing a locally active agent (bismuth salicylate liquid 30 mL four times daily for 3 weeks), an antimicrobial agent (erythromycin ethylsuccinate liquid 500 mg four times daily, an inactive ester active only after absorption four times daily for 1 week followed by matched placebo for 2 weeks), and placebo liquid (matched in dose, color and packaging), in eradicating the organism from the gastric mucosa.[42] Associated changes in histological and endoscopic appearances were examined before and within 48 h of treatment completion. Clearance of *C. pyloridis* had a rapid healing effect on the chronic active gastritis seen on histopathology, it seemed to melt away with decreasing gastritis scores in nearly all patients cleared of *C. pyloridis*; with greater improvement in endoscopic appearances than observed in patients with persistent infection. Figure 9. This was the first randomized controlled trial. The difference in resolution of gastritis between the cleared group and the patients with persistent infection was highly significant ($X^2 = 25.7$; $p < 0.0001$). Gastritis resolved in 13 out of 16 patients (81%) treated with bismuth compared with only 3 of 13 receiving erythromycin ($X^2 = 9.8$; $p = 0.001$) and none of 16 patients given placebo ($X^2 = 21.3$; $p < 0.001$). The lack of effect of the erythromycin was surprising and disappointed us, but the use of the inactive antimicrobial ester indicated the importance of using an agent which would be either locally active (like the bismuth) and/or be able to penetrate into the gastric mucosa, crypts and mucus where *C. pyloridis* resides. Interestingly a small open treatment study by Jones et al showed that at 6 month follow-up patients initially cleared of *C. pyloridis* with tripotassium dicitrato-bismuthate again had bacteria present, indicating that a combination of local and systemic treatment may be needed.[43] Subsequent pharmacokinetic work showed that several antimicrobials (including erythromycin) active in-vitro did not reach adequate concentrations in the gastric mucus to inhibit *C. pyloridis*.[44] So by 1988 clinicians were already into an era of triple treatment.

11 | DIAGNOSTIC TESTS

11.1 | Gram stains and culture

To aid the diagnostic process clinicians and researchers needed a sensitive and specific test for *C. pyloridis*, thus over those first years there were many diagnostic studies.[45] Gram stained smears of fresh gastric biopsy smears were the first method used in the microbiology lab for the rapid identification of *C. pyloridis* positive patients. In my experience patients with numerous organisms on an antral biopsy usually had a severe chronic active gastritis. Culture in a microaerobic atmosphere was needed and initially researchers were using Skirrow's medium. A modification of Skirrow's medium was developed informed by the in-vitro antimicrobial susceptibility results.[46] Cefsulodin (5 mg/1) was substituted for polymyxin, and amphotericin B (5 rag/l) was added to inhibit *Candida* spp., a common contaminant of the stomach. Dent's medium is still available commercially from Oxoid.

11.2 | Biopsy urease test

As Langenberg described, the intense urease reaction displayed when you touched a *C. pyloridis* colony with Christensen's urea broth was striking.[47] Owen et al confirmed this rapid positive reaction and showed that all other enteric campylobacters were urease negative.[48] The urease reaction of *C. pyloridis* was so intense that I could readily believe that a gastric biopsy specimen could be used to produce a rapid, less laborious, diagnostic test. I left some gastric biopsy specimens I had used for Gram and culture in Christensens urea broth—and I was surprised to see that they yielded positive results in under an hour—then ensued an initial description,[49] and a 1400 series to prove it was a very reliable diagnostic method.[50] The test was commercialized globally by Barry Marshall (who independently in Australia discovered the usefulness of the test) as the CLO test.[51]

11.3 | Confirmatory laboratory tests

It was important for microbiologists to be able to confirm that colonies grown in the lab were indeed *C. pyloridis*—we and others started with simple routine lab tests. As indicated urease was the most useful lab test, but others were needed. All strains of *C. pyloridis* produced oxidase, catalase, urease, and demonstrated weak hemolysis that could facilitate acquisition of hemin. Rapid identification schemes that detect the presence of preformed enzymes indicated that these could be used to differentiate *C. pyloridis* from other campylobacters,[52] but it was a very homogeneous species and so enzyme tests would not be useful in any biotyping scheme.[53]

11.4 | Urea breath test

Both histology and microbiology needed gastric biopsy material, and as IgG persisted, the serological tests described by many could not show whether gastric colonization was still present. Bell solved this diagnostic conundrum for UK routine NHS care, when he had the idea for the carbon 14 urea breath test,[54] which was incredibly reliable for the diagnosis of *C.pylori*. The 13C-urea breath test had been reported in the Lancet a month earlier by David Graham and his US colleagues.[55] The 13C is not radioactive, but required a mass spectrometer not available to district general hospitals in the UK. Bell

emphasized that the scintillation counter, required for the radioactive C14 radioisotope test breath test was inexpensive and readily available; the test could also accurately indicate if treatment was effective.[54] Breath tests have now become the most commonly used tests to follow treatment effectiveness.

12 | FIRST DESCRIPTION OF OTHER CLOS—*GASTROSPIRILLUM HOMINIS/ HELICOBACTER HEILLMANNII*

Through examining so many gastric biopsy smears and histology tissue sections, it was only a matter of time that one of us gastric campylobacter researchers came across another one! So it was that we found a new large tightly spiraled gastric organism on a Gram stained gastric biopsy smear.[56] Over the next 10 months with meticulous search through gastric biopsy specimen, Gram smears and histopathological sections we found 6 patients out of 1650 with these new helical organisms; they too were associated with chronic active gastritis. This new bacterium was much larger and had truncated poles with flattened ends unlike *C. pyloridis*, sheathed flagella like *C. pyloridis*, and had the electron lucent zone seen in *C. pyloridis*. Figure 10. At that time we suggested the name *Gastrospirillum hominis*.[57] Following our description, others worldwide found this larger gastric spiral bacteria in man and in the gastric mucosa of other animals, and it was later named *Helicobacter heillmannii*, posthumously after Heillmann who described a large series of 39 patients with the bacterium.[58]

13 | IMPORTANCE OF UREASE

The intense urease activity in *C. pylori* was investigated by many. Diane Newell and colleagues used monoclonal antibodies to show that many these spiral and helical organisms, colonizing the gastric mucosa in animals and man, expressed antigenically identical ureases.[59] Newell et al. suggested that the conservation of urease antigenicity across these animals was related in part to the evolutionary relatedness of these gastric bacteria and also to the importance of urease activity in gastric colonization allowing these bacteria to reside in the gastric mucus with its relatively acidic PH and migrate through this to colonize deep within the gastric crypts.

14 | NOMENCLATURE; *CAMPYLOBACTER PYLORI* RENAMED *HELICOBACTER PYLORI*

As stated above, Skirrow and Newbold originally suggested the Greek species name *pyloridis*, as it was based on the Greek word pylorus. However The International Code states that "*scientific names of all taxa are latin or latinized words regardless of their origin*." Therefore in late 1987 *C. pyloridis* was latinized and renamed as *C. pylori*.[60] Later the work of taxonomists indicated that differences from the other *Campylobacter* species justified the creation of a new genus, and in 1989 the genus name *Helicobacter* was proposed and accepted.[61]

15 | *HELICOBACTER* AND CANCER

In 1929 Hurst from Guy's Hospital in London, suggested the term gastritis-cancer for gastric cancers occurring secondary to gastritis.[62] He suggested that "*the actual development of cancer must be due either to a constitutional or inherited liability to the disease, or to the chance invasion by some external stimulant*." Forman an epidemiologist specializing in cancers, produced some of the first evidence that chronic *Helicobacter pylori* infection was indeed this "stimulant" and the precursor to gastric cancer. A Chinese study found a positive association between gastric cancer rates across China with *H. pylori* prevalence.[63] Then in a prospective UK cohort study all subjects had serum stored at the onset of the observation period. Cases of gastric cancer that were identified within the cohorts in subsequent

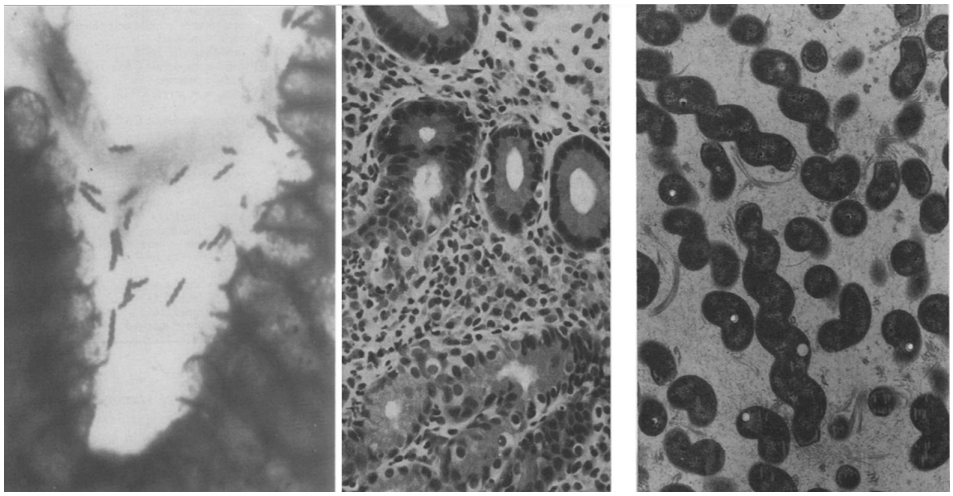

FIGURE 10 Left: Section through pyloric gland showing groups of spiral organisms in neck and on mucosal surface (Half-Gram.). Middle: section through lamina propria showing neutrophil infiltration into pyloric glands. (Hemotoxylin and eosin.) Right: Large group of spiral organisms showing terminal bunches of sheathed flagellar filaments.[57] Copyright J Clin pathol 1989.

years were matched to controls by age and date of serum collection, and the sera was tested in a blinded fashion for *H. pylori* infection. Median IgG concentrations to *H. pylori* were significantly higher in Cancer subjects, who also had significantly higher risk of prior infection with *H. pylori* than did controls (OR 2.8).[64]

16 | TEST AND TREAT FOR *HELICOBACTER* BECOMES ROUTINE

So the theater was set for consideration of diagnostic test and treat protocols for *H. pylori* in patients with dyspepsia. Sobala and the team in Leeds assessed the likely effect of screening dyspeptic patients for *H pylori* infection by serology on diagnostic accuracy for peptic ulcer disease and endoscopic workload. Overall, the screening strategy would have reduced endoscopy workload by 23·3% (95% confidence interval 20·9–25·8%) and would have had a sensitivity for detection of peptic ulcer of 97·4% (94·5–99·1%). No peptic ulcer or malignant disease was missed in the patients studied prospectively. Individuals who were seronegative for *H. pylori* and who were not taking NSAIDs could be reassured that they did not have peptic ulcer disease.[65] This work supported a policy of screening young dyspeptic patients before endoscopy for *H. pylori* by serology rather than the symptom-based screening strategies used historically. This test and treat policy was then introduced in the United Kingdom and beyond. I think this is a good place to pause the story as *H. pylori* moved from the research setting to the routine, though the research around this topic will continue beyond 2023, shown by the ongoing popularity of the biannual Helicobacter meeting.

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