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Helicobacter pylori causes peptic ulcers

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Abstract

Thomas Borody describes how he and his colleagues developed the Triple Therapy to eliminate the bacteria from the human body, hence confirming their role in ulcer formation.

Introduction

I graduated from the University of New South Wales, and trained in gastroenterology at St Vincent's Hospital in Sydney, followed by a short tropical medicine course at Sydney University, leading to a year of extraordinary life and medicine in the Solomon Islands. This was followed by a period in North America for further training in gastroenterology at the Mayo Clinic.

Returning to Sydney in the early 1980s, I established the Centre for Digestive Diseases, where we were seeing through the gastroscope 2 to 3 new peptic ulcers a day. Acute and chronic peptic ulcers with the complications of the disease and its medical and surgical management was the major part of gastroenterological practise.

A first breakthrough

A breakthrough had occurred with discovery of H2 Blockers, such as Tagamet, which inhibited acid secretion and healed ulcers. This was seen as proof for the prevailing mantra that hypersecretion of acid was the cause of duodenal ulcers, confirming, as though it was needed, that the research focus on acid secretion was the way to go. When ulcers returned within a year of stopping the H2 Blocker, the basic tenet simply became a little more sophisticated, adopting the ulcer equation of Wilfred Card: "*acid + pepsin vs. mucosal resistance*." British research even determined a threshold for acid secretion rate, below which you could not develop a duodenal ulcer.

The history of peptic ulcers

The question which no one had an answer for was "what damaged the stomach mucosa to facilitate digestion by acid and pepsin." The history of peptic ulcers had been forgotten.

In 1889, the Polish physician Walery Jaworski swept up in the "germ theory" wave where there was a new bacterium for every disease, described spiral organisms in the stomach wall, which he called *Vibrio rugula*, and he considered these caused gastric ulcers and cancers. It was not till Warren and Marshall associated spiral organisms with peptic ulcers in 1981 that infection challenged one of the most established "cause and effect" relationships in medicine, as the cause of impaired mucosal resistance.

The problem was that, while Marshall's heroic self-experiment — swallowing the bacteria — showed that they could damage the mucosa, ulcers were not induced. The only way to prove that *Helicobacter pylori*

bacteria (as they came to be called) caused ulcers was to develop treatment that eradicated the bacteria, and show that ulcers not only healed, but stayed healed (unlike the situation with H2 Blockers, where ulcers would recur). Many attempts using one or two antibiotic combinations were tried, but, at best, were capable of eradicating the bacteria only in a minority of patients.

The Triple Therapy

Helped by the high number of patients with peptic ulcers in the clinic, we explored 36 different combinations of antibiotics, before finding a combination, dose, and duration for therapy that eradicated *Helicobacter pylori* in most patients: Bismuth, Metronidazole, and Tetracycline. Later, we showed that acid suppression further facilitated eradication, and added a Proton Pump Inhibitor to the original "Triple Therapy."

Three key papers published in the *Medical Journal of Australia* documented the success of Triple Therapy. Two were included in the "ten most quoted papers in the MJA," published to celebrate 90 years of publication. Two other papers in the "top ten" were those by Warren and Marshall, illustrating the extraordinary contribution made by Australian scientists in Peptic Ulcer disease. The first of our papers was published in 1989, describing the quantitative eradication of *H. pylori* with Triple Therapy, and the healing of ulcers (Borody et al., 1989). The second, in 1990, gave proof that eradication led to cure of duodenal ulcers (George et al., 1990). In 1994, we published a 4–6 year post-eradication report, confirming ulcers remained healed, and that the re-infection rate was of the order of 0.1% per annum (Borody et al., 1994).

Triple therapy, and commercial variants of this therapy, were quickly adopted in all countries. Most popular was a dual antibiotic with a proton pump inhibitor (Nexium Hp-7), which was less effective, leading to the problem of antibiotic resistance. Cure rates fell, while an increasing pool of resistant bacteria and persistent ulcers became a major clinical problem. By then, the link with gastric cancer (involving Adrian Lee[1]) was established, and eradication of resistant *H. pylori* took on added importance (Enno et al., 1995).

Quad Therapy and beyond

We developed the next therapeutic milestone of "escape" therapy (or Quad Therapy) based on Rifabutin, which successfully eradicated *H. pylori* in 90% of those with resistant bacteria (Borody et al., 2006). Recently, this number has been increased to 97% by our group, using a potassium channel blocker (Vonoprazan) (Borody et al., 2019).

A recent study examined the impact of *H. pylori* eradication in Australia over a 16-year period, and concluded that Triple Therapy has prevented 18,665 deaths, and saved 258,887 "life years." Direct and indirect cost savings were estimated, over this period, at in excess of ten billion dollars (Eslick et al., 2020).

Gut biome diseases

Our studies on *Helicobacter pylori* began a long-term research programme in identifying and treating gut disease caused by a disturbed gut microbiome. We developed the idea and then the practical value, of "bulk microbiome replacement" (obtained from normal faeces) for Irritable Bowel

1 Enno et al. (1995).

Syndrome, *Clostridium difficile* infection, and most recently, chronic ulcerative colitis. Although these Faecal Microbiome Transplant therapies are crude, better definition of specific bacteria using new technologies, and improved replacement bacteria methodology, will transform our understanding and management of a range of gut — and systemic — diseases. We have noted significant improvement in a number of systemic diseases including Parkinson's disease and autism. These exciting observations not only give hope for new therapies for many diseases not previously linked to an abnormal microbiome, but focus attention on the role played by the microbiome in both normal and abnormal body function.

Most recently, we initiated the first effective randomised controlled trial of a combination antibiotic triple therapy for Crohn's disease, often resulting in years of remission (Agrawal et al., 2020).

The future

The focus on managing host-parasite relationships at mucosal surfaces has been extended to the airways, with current studies focussed on triple therapies for late-onset asthma, and COVID-19 infection (based on Ivermectin). Thus, research to improve management of cryptic intracellular infections at mucosal sites has a continuous history at the Centre for Digestive Diseases, for over 40 years.

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