How Man's Commonest Infection Kept Its Secret: The H. pylori story

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In a previous article, I discussed the great prevalence of peptic ulcer disease in the twentieth century (Peptic Ulcer: A Twentieth Century Disease – IFFGD Fact Sheet No. 509). Ulcer researchers became convinced that gastric acid was the cause of peptic ulcer and expended great effort to understand the physiology of acid secretion and to develop diets, drugs and surgical procedures to control acid secretion. So strong was the belief that acid was key that when, beginning in 1983, Marshall and Warren finally proved that a gastric lining bacteria called Helicobacter pylori (H. pylori) was the cause of most peptic ulcers, it took a decade of skeptical debate and a conference at the U.S. National Institutes of Health in 1994 to convince scientists and doctors. Why did it take so long to understand the truth about ulcer disease? Does this history have any implications for the study of the functional gastrointestinal diseases (FGIDs)?

Non-steroidal anti-inflammatory drugs (NSAIDS) cause some peptic ulcers. Very rarely a pancreatic tumor does so. Sometimes the cause is unknown. In this article, we discuss only that majority of peptic ulcers of the stomach and duodenum that are caused by H. pylori.

The Acid Theory

During most of the twentieth century, physicians, surgeons, researchers and pharmaceutical companies maintained an almost obsessive interest in stomach acid as the means by which ulcers occurred. Through the work of Pavlov and others, control of acid secretion was believed to be the clue to ulcer cure. Twentieth century gastroenterologists studied gastric secretion in order to understand better their ulcer patients. Few gastroenterologists of my generation obtained their specialty certificate without measuring their patients' stomach acid under a mentor's watchful eye. "No acid no ulcer!" was the century's ulcer mantra and ever more sophisticated surgical and medical techniques were devised to control acid secretion and permit the ulcer to heal. The requirement for acid in ulcer disease is true. Acid controlling drugs and procedures helped and even saved many. However, we all produce acid in our stomachs, and we do not all get ulcers.

If acid caused peptic ulcers in some people, why not in others? The question received insufficient attention. Nevertheless, the observation that some stomachs failed to resist gastric acid led to a succession of theories as to why the lining of the duodenum and stomach of ulcer patients was vulnerable. A popular notion was that there was a psychological cause. People described an ulcer personality, and ulcers became identified with stressed-out executives. This persona became part of our culture, and when stressed, one might have said, "You'll give me an ulcer!" There were genetic and dietary theories as well, and researchers recognized that smoking was important. All these theories faded into obscurity when at last Marshal and Warren apprehended the real culprit.

Attempts to identify a unique profile of ulcer patients' stomach acid, its secretion in response to a meal, or secretion at night were only partially successful. Many of the theories were true, but insufficient. Subsequent events showed the cause of ulcers lay elsewhere – with bacteria infecting the lining of the ulcer patient's stomach. In retrospect, perhaps the acid theorem delayed the discovery of an ulcer cure. We failed to look "outside the box," even when the real cause was there for pathologists to see through a microscope.

Peptic Ulcer as an Infectious Disease

A great irony of the ulcer story is that bacteria were observed at least three times between 1898 and 1983, but their significance was unrealized – so convinced was the medical establishment that no bacteria could survive a stomach's acid environment. Like others before him, an Australian pathologist, JR Warren saw these organisms in the stomachs of patients with gastritis, but unlike them, he and a gastroenterology resident BJ Marshall connected H. pylori to stomach inflammation (gastritis) and eventually to peptic ulcers. It took almost a decade after their 1983 report before the medical establishment came to believe that H. pylori caused peptic ulcers, and that antibiotics could cure the disease.

The ulcer story is replete with ironies. Peptic ulcers (that we now know were due to infection) were the commonest cause

of rejection from the armed forces in World War II. Now most ulcer complications occur in elderly people taking NSAIDs. General surgeons relied on ulcer surgery for much of their living half a century ago, yet such surgery is rarely necessary now. As the end of the last century approached, effective acid-lowering pharmaceutical and surgical advances appeared at last, only to become almost obsolete as ulcer treatments by 2000. Researchers who built their careers on acid studies were forced to change direction. Meanwhile the final irony: epidemiology research learned that ulcer disease was rapidly declining even before the great discovery. Modern hygiene and less overcrowding in Western countries had already reduced oral transfer of the infection.

Theories of the Functional Gastrointestinal Disorders

There are many theories concerning the cause of the functional gastrointestinal disorders. From the nineteenth century, many physicians believed that intestinal spasm was the cause of IBS, yet careful study over the last half century failed to demonstrate the irritable colon in spasm, or to prove any feature of gut movements to be characteristic of the IBS. Despite early acclaim, reports of disturbed electrical rhythms in the colonic muscle, or more recently increased rectal sensitivity have not been connected consistently to IBS. Many physicians and psychologists are equally convinced that IBS patients suffer from a psychological disorder, and that relief is through psychological treatment. Remember the "ulcer personality!" However, no psychological disorder is identifiable in the majority of IBS patients – indeed only a minority seeks medical attention. Some researchers, drawing on the ulcer experience, are convinced that IBS is an infectious disease citing the many instances of IBS occurring after an infection, and "abnormal" amounts of inflammatory chemicals in the intestines of some IBS patients. Others, including many in the pharmaceutical industry, believe fervently that the syndrome results from abnormalities in the enteric nervous system, especially affecting gut serotonin. Still others, using advanced brain imaging technology attribute certain cerebral responses to IBS symptoms. Other functional gastrointestinal disorders provoke similar theories. Functional dyspepsia is blamed, without proof, on reduced stomach emptying, decreased ability of the stomach to relax, and even on H. pylori infection. While such phenomena exist in those with and without functional dyspepsia, none is characteristic of dyspepsia itself. Some researchers claim that IBS, functional dyspepsia, and others have many causes. Others describe subtypes of these disorders, which, without convincing evidence of their existence, create more confusion than enlightenment.

A currently popular theory embraces the idea of visceral hypersensitivity, where through brain-gut interaction, the gut is oversensitive to gut stimulation amplifying symptoms and disordering gut function. While such a theory is a constructive challenge to research, and a convenient way to explain FGID to patients, it is after all just a theory and someday may be discarded. Perhaps several theories are correct since many think IBS and dyspepsia have many causes. Nevertheless, the possibility exists that none of the existing hypotheses is correct. Perhaps, as in the case of peptic ulcer, strongly held theories of doctors and scientists prevent us from recognizing the truth.

Does the Ulcer Story have Lessons for the Functional Gastrointestinal Disorders?

Can we learn from the ulcer experience? Some diseases, like fashions, appear to emerge and decline by whim or heavenly design. The FGID syndromes are human creations because they make sense and are recognized in the real world. However, they lack a scientific underpinning, and very well may be called something else tomorrow. Improved living standards and public health can have unpredictable effects on the prevalence and concept of disease. When existing hypotheses fail to explain an illness after many decades of intensive research, we probably need a new one.

New ideas will emerge from unbiased observers with professional/scientific backgrounds. Warren and Marshall defied established thinking. Dogged adherence to a worn out hypotheses misdirects precious research funding and time. It is wrong for the scientific community to rally round the banner of each new research idea, as most "breakthroughs" are nothing of the sort. Nevertheless, we must not close our minds. Often the truth comes from an unexpected source, recognized through the inspiration of a prepared thinker, often outside the scientific mainstream.

"Be not the first by whom the new are tried, Nor yet the last to lay the old aside."
– Alexander Pope

Someday someone like Marshall and Warren will make the key discovery. Perhaps, like H. pylori, the cause of functional gut disorders is before us now, but our prejudices blind us to its recognition.

Summary

Retrospective judgment is hazardous. Nevertheless, overzealous adherence to the no acid-no ulcer theory narrowed our view, and arguably delayed the discovery of H. pylori as the cause of most non-NSAID ulcers. Even after proof was available, it required almost a decade for acceptance. Those studying the functional gastrointestinal disorders need look beyond their favorite theory, as the truth may lie elsewhere.

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