

“Discovery consists of seeing what everybody has seen and thinking what nobody has thought.”
— Albert Szent Györgyi, 1937 Nobel Laureate in Physiology and Medicine

Helicobacter pylori and Ulcers: a Paradigm Revised

by Nancy A. Lynch, Ph.D.

When scientists identified *Helicobacter pylori* as an infectious agent responsible for peptic ulcer disease, it completely transformed our understanding of the microbiology and pathology of the human stomach. That was in 1982. Before then, “no acid, no ulcer” succinctly described the accepted medical paradigm: stomach ulcers occurred when excess acid damaged the gastric mucosa, and treatment should be aimed at reducing or neutralizing that acid. Those who believed in psychosomatic theories of illness postulated even further that overproduction of the ulcer-causing acid was stimulated as a response to life’s stresses—including overambitious mothers. We now know that many ulcers result from a bacterial infection, and that they are readily curable by treatment with antibiotics.

The story of the discovery of *Helicobacter pylori* sounds like a chapter taken from the exciting book, *Microbe Hunters*. Written in 1926 by Paul de Kruif, it chronicled the discovery of the microbes causing the infectious diseases that ravaged the world’s population of the time. It is the tale of two investigators from

Western Australia. One observed a microorganism under his microscope and refused to accept previous explanations for its presence; the other used himself as a guinea pig in order to satisfy Koch’s postulates,

which indisputably establish an organism as causative agent for a specific disease (i.e., a pathogen). In fact, it recalls the story of Robert Koch himself, who conducted his experiments far from the medical

Excerpts from Causes of Peptic Ulcer: a Selective Epidemiological Review by M. Susser, published in the Journal of Chronic Diseases, Vol. 20 pp. 435-456, 1967

“...certain patterns of relationships were more common in ‘ulcer’ families. Thus the mothers of ulcer patients tended to have psychogenic symptoms, and to be striving, obsessional, and dominant in the home; fathers tended to be steady, unassertive, and passive.”

“The description of these families...emphasizes the conflict in duodenal ulcer patients between dependence engendered by a powerful mother and demands of adult roles.”

“The variations in peptic ulcer in different geographical, historical, and social contexts are unequivocal evidence of the influence of ways of life in this disease. The specific elements that contribute to the variations probably include diet, alcohol, cigarette smoking, emotional strain, personality, and genotype... . This does not exclude the possibility that a major single causal effect awaits discovery.”

In discovering the link between H. pylori and stomach ulcers, Drs. Warren and Marshall also liberated mothers from responsibility for causing ulcers in their offspring, as implied by studies reviewed in this article from 1967. In their summary, the reviewers did anticipate the discovery of a single cause for ulcers, but they did not consider the possibility of the cause being an infectious disease.

mainstream in rural Germany, finally convincing the reluctant Berlin professors in 1882 that the bacilli he had isolated and studied actually caused tuberculosis.

But the scientific breakthrough that involved *Helicobacter* occurred in 1982, when J. Robin Warren and Barry Marshall isolated a new bacterium and showed that it caused gastritis and stomach ulcers, diseases that affect millions of humans worldwide. As happens with many scientific advances, this breakthrough initially gained its momentum from the creative insights of an independent investigator.

Although they were the first to succeed in establishing a link between bacteria and ulcers, the Australians were not the first to try. Since the time of Robert Koch in the late 19th century, microscopists observed curved bacteria among the cells under the mucus lining of the stomach, particularly in and around ulcer craters. No one had ever succeeded in isolating the microorganisms, however, and their presence had been explained away as artifact or postmortem contamination. Besides, it was thoroughly accepted among clinical microbiologists of the time that it was unlikely that bacteria could live and grow in the strongly acidic environment of the human stomach.

Warren, a pathologist who examined gastric biopsies, also observed the curved rod-shaped bacteria under his microscope. After examining many such specimens, he realized that the bacteria were always present in tissue that showed signs of inflammation, that the number of organisms correlated with the degree of the inflammation present, and that they occurred in half of the routine gastric biopsy specimens he examined. Convinced that his observations were significant and merited further investigation, he kindled the interest

of Barry Marshall, then a trainee in internal medicine, and together they set out to isolate the source of the infection.

Perseverance—and good luck

The Australians were fortunate, and once more their practice of careful observation paid off. Warren had noticed that the curved microorganisms he saw resembled *Campylobacter*, a type of bacteria known to cause intestinal disease. Their laboratory used the selective growth conditions appropriate for *Campylobacter*, near 37°C (body temperature) with a low level of oxygen present. Still, they tried, without success, to grow the bacteria from stomach biopsies for more than a year—until the cultures were inadvertently left in the incubator over the Easter holidays. This chance prolongation of the incubation period from the usual 2 days to 6 resulted in the successful growth and

isolation of the bacterium. They had discovered serendipitously that *Helicobacter* species grew much more slowly than the other bacteria that were usually cultured in laboratories.

Isolating *H. pylori* (or *Campylobacter pyloridis*, as it was originally called) was significant, but it still did not establish whether the bacteria were the cause of the inflammation with which they were associated or whether they occurred as a result of it.

At first the distinction was unclear, because slides from autopsy specimens showed that the bacteria were present in many individuals with no history of ulcers. To confirm that *H. pylori* caused the gastritis and peptic ulceration, Marshall and another volunteer tried to fulfill Koch's third and fourth postulates by ingesting cultures of the bacteria. Both contracted gastritis (inflammation of the mucus membrane of the stomach), underwent endoscopy (internal examination of the stomach), and provided biopsies from

Koch's Postulates

- I. The organism, a germ, should always be found microscopically in the bodies of animals having the disease and in that disease only; it should occur in such numbers and be distributed in such a manner as to explain the lesions of the disease.
- II. The germ should be obtained from the diseased animal and grown outside the body.
- III. The inoculation of these germs, grown in pure cultures, freed by successive transplantations from the smallest particle of matter taken from the original animal, should produce the same disease in a susceptible animal.
- IV. The germs should be found in the diseased areas so produced in the animal.

Koch's postulates were originally set forth by Friederich Gustav Jakob Henle, a German pathologist and anatomist, and were named for Koch because he was the first to apply the criteria experimentally. Because Marshall and a volunteer did not develop ulcers as a result of their experiment, Dr. Marshall has recently written that for ulcers, all of the postulates have not yet been fulfilled.

which the suspected pathogen was re-isolated. This confirmed the connection between *H. pylori* and gastritis, but since neither scientist developed an ulcer, that link was still unproven. The connection between *H. pylori* and ulcers was eventually deduced from epidemiological studies showed an increased incidence of ulcers in persons infected with the bacteria.

After Warren and Marshall published their work, many other investigators were able to culture the bacteria from the stomachs of their patients who had gastritis and ulcers. This, combined with clinical observations indicating that antimicrobial therapy resulted in ulcer cures, made the weight of the evidence compelling.

Epidemiology

Once the role of *H. pylori* in peptic ulcer disease was firmly established, it was imperative to find out more about the prevalence and distribution of the infection. To do this, investigators needed data about large populations of people all over the world and a way to make feasible such extensive testing. Clearly, the task of culturing bacteria from individuals would be impossible. Not only were specialized equipment and techniques necessary to grow the bacteria, but also the only way to obtain culture material from human sources was by endoscopy, hardly feasible for large-scale studies. The human immune system provided the answer.

Researchers had discovered that specific anti-*H. pylori* antibodies could be detected in the blood serum of individuals who were infected with the organism. That enabled the use of a simple blood test for the important epidemiological studies. Researchers were able to expedite the investigations because they did not have to collect new tissue samples from each person; instead,

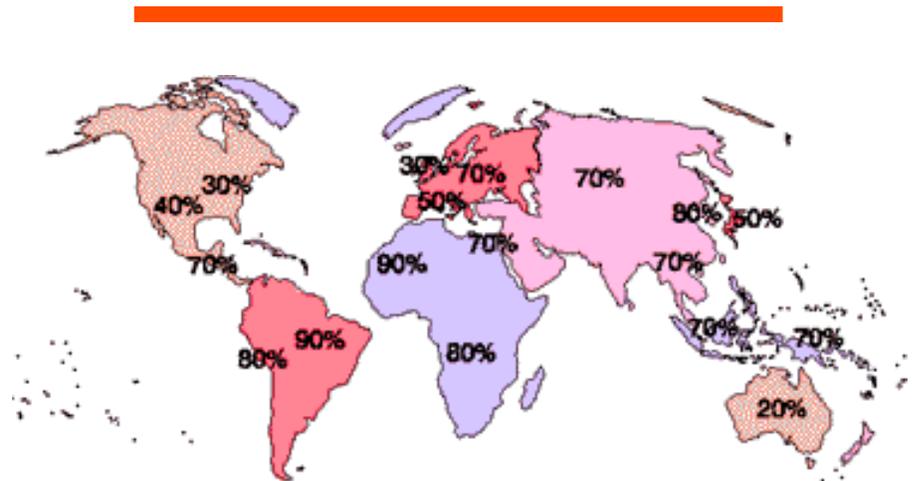
they used blood samples that had already been collected in large numbers at clinics and blood banks, often for other studies and tests.

This early research on *H. pylori* characterized much of the work to come. The data that emerged from the study of all these samples were unexpected. It showed that *H. pylori* is a common bacterial agent and at least 30-50% of the world's population are colonized with it.

Investigators discovered that the frequency of *H. pylori* presentation was highly variable from country to country and between socioeconomic and ethnic groups. Overall, they found a consistent pattern in most developing nations, where 70 to 90% of adults harbored the bacteria; most individuals acquired the infection as children, before age 10. In developed countries, on the other hand, fewer than 10% of children became infected and although a steady rate of colonization persisted with increasing age, less than half of 60-

year-olds had acquired *H. pylori*. Clear associations could be made with conditions of poor sanitation and crowded living conditions such as those in orphanages or other institutions. In spite of this connection with the signs associated with poverty, the studies failed to establish whether or how transmission from one individual to another actually occurs. Obvious candidates (e.g., oral-oral or fecal-oral pathways) have been considered and investigated. But aside from minor modes of passage, such as through unsterilized endoscopy equipment and from African mothers who pre-masticate food for their children, researchers have been unable to identify a common means for transferring the infection from person to person.

A surprising finding was that most infected individuals were generally asymptomatic and fewer than 20% of people (regardless of age) who tested positive for *H. pylori* had ulcers.



Map showing percentages of population infected with *H. pylori* as determined by epidemiological studies. Within national populations, rates of infection vary across subsets and can be attributed to socioeconomic conditions in childhood. As populations achieve better living conditions, the incidence of *H. pylori* decreases; therefore, the *H. pylori* strain has been dubbed a 'submerging' rather than an 'emerging' pathogen. This image is from the *Helicobacter* Foundation website: www.helico.com

H. pylori and cancer: the importance of archived human samples

Even before the discovery of *H. pylori*, observant medical scientists had noted an association between cancer of the stomach and chronic gastritis, which suggested a possible link between *Helicobacter* infection and cancer. Furthermore, epidemiological studies indicated that *H. pylori* infection was acquired earliest in children from countries where the rates of gastric malignancies were the highest.

It would be difficult to establish a connection between the bacteria and malignancy, because stomach cancer is a disease with a peak incidence in the sixth decade of life. If *H. pylori* caused it, there necessarily would be a long time between initial infection and the development of any malignancy. Fortunately, investigators were able to access sources of archived human samples, which allowed them to implicate *H. pylori* as a cause of gastric carcinoma and lymphoma without waiting for future cancers to develop. These valuable assets were samples of blood that had been collected decades before for other long-term health studies and had been carefully stored for later retrieval and testing.

The 20-year-old archived blood samples of the subjects in that large sample who had eventually developed gastric malignancy were tested for antibodies to *H. pylori* and compared to samples from an otherwise similar, but cancer-free control group. Statistical analysis of the data indicated that those infected with *H. pylori* at the time the blood was collected were up to six times more likely to have subsequently developed a malignancy. The connection of *H. pylori* to stomach cancer became so certain that the World Health Organization Interna-

tional Agency for Research in Cancer has classified it as a Class 1 Carcinogen. Other risk factors, including diet and genetics are important considerations, but if *H. pylori*-induced changes in the stomach can be prevented, it is conceivable that the majority of tumors will not occur. This notion has important implications because gastric cancer is the 14th most common cause of death worldwide, and its incidence is expected to increase in the near future.

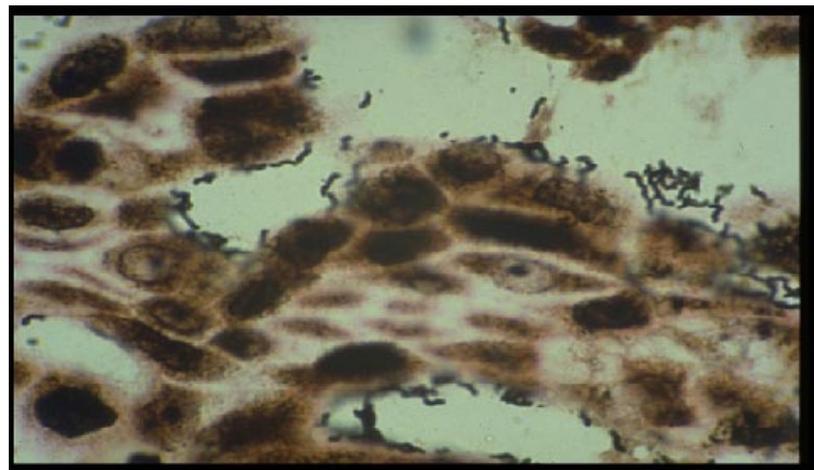
The value of basic research

As scientists gathered and analyzed information about *H. pylori*, they raised confounding questions about the microorganism and the disease processes it caused. Investigators sought answers to many of those questions by applying basic scientific techniques in order to learn more about the bacterium itself.

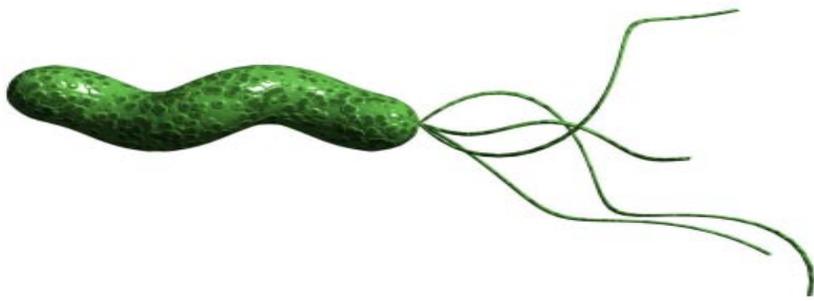
One of the first research goals was to ascertain how *H. pylori* live and grow in an environment so acidic that for years gastroenterologists considered it to be sterile. Microbiologists found that *H. pylori* used a

dual strategy in order to survive in the harsh conditions that prevail in the human stomach. First, the bacteria have multiple polar flagellae (see image of *H. pylori*), tail-like structures with which to propel through the mucus layer lining the stomach until they can attach to the cells at the bottom of the lining. There, protected from direct contact with the hydrochloric acid secreted into the stomach, they create a microenvironment where the balance of acidity and alkalinity (pH) is near neutral. This is accomplished by urease, a powerful enzyme made by *H. pylori*, which converts urea, a chemical made by stomach cells, to carbon dioxide and ammonia. Those chemical products formed by the enzymatic action of urease neutralize the acidity in the mucus immediately surrounding the bacteria, creating a non-acidic microzone that protects the bacteria.

Scientists also needed to find out why people infected with *H. pylori* could not get rid of it, but instead remained infected for life unless they were treated with antibiotics. Early studies of ulcer patients had shown that there was an immune response to the bacteria, because infected



A silver stain (Warthin Starry) of HP (black wiggly lines) on gastric mucus-secreting epithelial cells (x1000). This picture is of Dr. Marshall's stomach biopsy, taken 8 days after he drank a culture of *H. pylori*. This image is from the *Helicobacter* Foundation website: www.helico.com



A 10,000x computer-aided design image of *H. pylori* showing curved shape and flagellae that enable the bacteria to propel themselves into the mucus lining of the stomach. The image by Luke Marshall is from the *H. pylori* Research Laboratory website: www.hpylori.com.au/

people produced antibodies against *H. pylori*, both in the blood and in the mucosal lining of the stomach. For reasons still not clearly understood, the immune response, as vigorous as it is, does not eliminate the bacteria. This may be due in part to the phenomenon, ‘molecular mimicry’, which has been documented in other infectious diseases.

H. pylori produces chemical components in their cell walls that are very much like molecules made by the stomach cells of the host. This creates a problem for the immune system, because it is designed to ignore molecules made by the host (self) and to recognize molecules produced by infectious agents (non-self). Once the immune system recognizes foreign molecules, it directs a vigorous attack that ordinarily destroys the foreign cells. To a certain extent, this mimicry disguises the *Helicobacter* from the immune system so that the immune response is attenuated.

But the disguise is not perfect. Scientists think that this situation results in a modified immune response in which the immune system produces large amounts of antibody and directs them to the *Helicobacter*, but is ineffective in eliminating the infection. Molecular

mimicry of infectious agents may be involved in other diseases, termed ‘autoimmune diseases’. For example, it has been suggested that childhood diabetes is caused by a virus whose surface molecules mimic molecules in the insulin-producing cells of the pancreas. In its effort to eliminate the virus, the immune system injures the insulin-producing cells.

It is interesting that the molecule ‘mimicked’ by *H. pylori* is identical to components of human blood group molecules called Lewis antigens. This may also provide clues to a longstanding enigma—that ulcers were more common in individuals with certain blood groups.

Investigators may have found yet another method used by the bacteria to avoid elimination. Analysis of the *H. pylori* chromosome demonstrated that a high degree of genetic variability exists among different strains of *H. pylori*. This suggests that slight differences among strains might influence the ability of the bacteria to survive. *H. pylori* is able to successfully colonize its human host for a lifetime, because it avoids the defenses of the immune system and because its effects on the hosts are chronic and usually do not kill the host. *H. pylori* resembles some

other pathogens in this way and may represent a special category of infectious diseases that scientists are just beginning to investigate in detail.

Discovery of the genetic variability of *H. pylori* also sheds light on the unexpected finding that only about one in six of those who are infected with *H. pylori* suffers from ulcers; most do not even experience symptoms of chronic gastritis. Microbial geneticists found that the chromosomes of some *H. pylori* strains (about 60% in the U.S.) contained a particular sequence of genes, i.e., a ‘pathogenicity island’. Other strains of this bacterium lacked these genes. After comparing disease outcomes in those from whom the *H. pylori* bacterial strain had been isolated and studied, researchers showed that people infected with a strain containing the pathogenicity island were significantly more likely to develop duodenal ulcers or adenocarcinoma than were people infected with strains that lacked that particular group of genes. We do not yet know how the disease-producing mechanism functions, but the ability to predict disease outcomes by typing *H. pylori* strains could be enormously useful in decisions regarding treatment.

Other studies of the *H. pylori* chromosome found the gene responsible for production of a protein that injures human cells when they are artificially cultured in the laboratory. Although these genes are present in all strains of *H. pylori*, the toxic protein is only produced by some strains and only under certain conditions. Further basic investigations of the mechanisms that regulate gene expression may lead to a better understanding of the variability of effects observed in humans infected with *H. pylori*.

More and more, contemporary studies of bacterial interactions with

their hosts rely heavily on information gained from understanding the genetic characteristics of the pathogen. In August of 1997, research on *H. pylori* was given a boost when the entire DNA sequence of the bacterial genome was published in the journal, *Nature*. Investigators will use this vast amount of data to better understand the metabolism, virulence, and other characteristics of this ubiquitous pathogen by comparing its genetic sequences to similar genes that have been identified and studied in other organisms. The article is a monument to the benefits of a cooperative approach to scientific investigation. When it was published, the paper's 42 authors from six different research institutions released the complete genetic sequence data on the Internet.

The use of other *Helicobacter* species in the development of drugs for *H. pylori*

Once investigators recognized *Helicobacter pylori* as a human pathogen and described techniques for its successful culture, they began to seek new species in the gastrointestinal tracts of other animals. They quickly found them in cats, dogs, mice, ferrets, cheetahs, and birds, among other sources, and to date, have isolated and named at least 17 additional *Helicobacter* species. Some are proving to have important research uses.

Early investigators, especially those interested in testing for antibiotic susceptibility and vaccine development, found that their efforts were hindered, because *Helicobacter pylori* did not colonize the small rodents usually used for that type of research. Fortunately, one of the animal isolates, *H. felis* (named because it was initially isolated from

a cat), also infected the stomachs of mice in a way similar to that in which *Helicobacter pylori* infected humans. It readily became a model for antimicrobial screening and for testing potential immunization schemes.

Researchers found that some of the newly discovered *Helicobacter* species colonized regions of their hosts' digestive systems other than their stomachs. *H. hepaticus* and *H. bilis* both infect the liver or intestines of mice. Both have been used in animal models of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. These models have been particularly valuable when the bacteria are used to infect mice in which genes for particular cytokines (molecules that regulate the immune system) have been disabled. These genetically engineered mice develop inflammatory bowel disease spontaneously when housed under normal conditions, but do so much more quickly when they are infected with *Helicobacter*, offering a golden opportunity to study the etiology of these debilitating diseases.

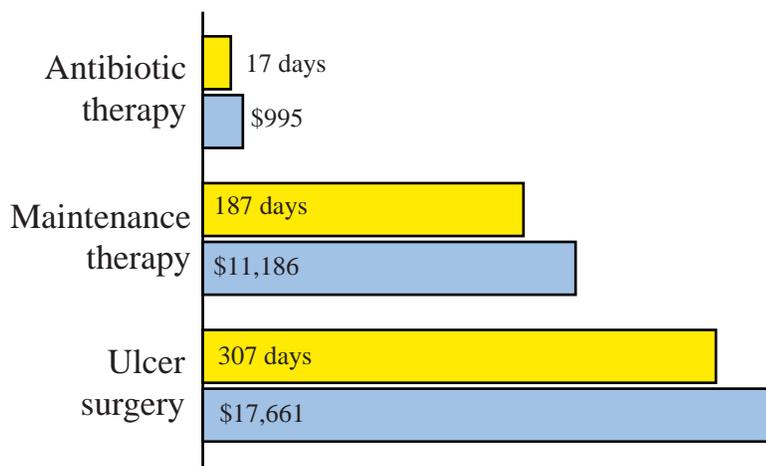
Since additional *Helicobacter* species have been found in other animals, there has been interest that some of them might be a reservoir for human infection. So far, no non-human or environmental reservoir has been proven, nor has any definitive means of transmission been established. *H. pylori* has been found in monkeys and in laboratory cats, and there have been reports of other gastric *Helicobacter*-like organisms in those species as well as in dogs. More studies will be needed to determine whether *H. pylori* naturally colonizes domestic dogs and cats and whether these pets can transmit *H. pylori* or other animal-associated helicobacter to humans. Recent evidence from Chile

supports the theory of human colonization by *Helicobacter* species originally found in animals. In those studies, investigators demonstrated genetic evidence for the presence of several species of animal-associated intestinal *Helicobacter* in the gall bladders of individuals with chronic cholecystitis.

What the *Helicobacter* story tells us

The *Helicobacter* story illustrates many of the issues that generate extensive interest and debate among present-day scientific researchers. In a time of 'big science' and 'mega' research projects, there is still opportunity for individual investigators to challenge accepted theories and to change them, with great benefit to society and science. In spite of concerns regarding privacy, the availability of human subjects and of archival tissues for research can have immense benefit for understanding human disease and its causes. Animal models may offer the only way to test methods in order to prevent an infection that afflicts half the world's human population, primarily the least advantaged among us. The technological advances coming from basic research have allowed both rapid advancements in clinical research and rapid dissemination of the results.

An important lesson learned from Warren and Marshall's discovery is that not all infectious agents are easy to culture and isolate. In this regard, it is interesting that the colon, gall bladder, esophagus, and salivary glands are other sites in the gastrointestinal system where long-standing chronic inflammation predisposes to the development of cancer. Scientists still need to determine whether a 'slow bacterium' like *Helicobacter* is related to any of these diseases.



Expected costs and days of treatment for ulcer therapy under three different protocols; treatment with antibiotics, maintenance therapy with acid-blocking drugs, and surgery (vagotomy). Costs include hospital care and procedures, laboratory tests, medications, and office visits to physicians and are based on fees for 1993. Since neither maintenance therapy nor vagotomy terminates the underlying disease, a time period of 15 years was used to calculate costs and treatment duration for those strategies. The economic effect of ulcer disease in the United States, as measured in a study of 1989 data, showed that the illness cost nearly \$6 billion annually. (\$2.66 billion for hospitalization, not including physician's fees), outpatient care (\$1.62 billion), and work loss (\$1.37 billion). Reprinted with permission from the American College of Gastroenterology (American Journal of Gastroenterology, 1997, volume 92, pages 614-620) and the Archives of Internal Medicine, volume 155, pages 922-928.

Benefits and questions

The impact of Warren and Marshall's work is extremely important. We no longer consider stomach ulcers a chronic, incurable disease, but one that may be cured quickly, at a fraction of the expense of the previous palliative or surgical methods and with the expectation of full recovery. Recent reports indicate that antimicrobial treatment can cause regression of gastric lymphomas and possibly early gastric cancer.

These successes raise the inevitable question of how much testing and treatment of non-symptomatic individuals there should be. Although reliable screening methods are available, mass testing programs will be expensive and should not occur without the intent to treat those who are infected.

There is little question about the benefits of antimicrobial treatment for individuals who suffer from ulcers. From an economic view alone, curative rather than palliative treatment is desirable. But there is much to debate about the benefits and hazards of universal testing and treatment. Certainly, eradication of *H. pylori* would be considered beneficial in preventing suffering from gastritis, ulcers, and cancer. And there may be other, as yet unknown adverse effects on infected children, such as retarded growth or loss of energy.

On the other hand, there is great concern about the extensive use of antimicrobial drugs that would be required to treat all infected individuals. Clearing *H. pylori* from the stomach requires therapy for at least 1-2 weeks with multiple drugs, and

the cost is probably prohibitive, particularly in the developing countries where incidence is highest. Furthermore, if antibiotics are used so extensively, it is very likely that the target bacteria would develop resistance to effective drugs within a few years. Prolonged treatment alters the normal microbial population of the gastrointestinal tract, eliminating some beneficial bacteria as well as pathogens.

A vaccine, which would make prevention of this disease a feasible public health goal, could prevent infection in millions of children and greatly reduce the worldwide incidence of gastritis, ulcers, and stomach cancer. Scientists have developed vaccines for *Helicobacter* by using a mouse model; pilot studies have shown that these vaccines prevent infection and may eventually eliminate the bacteria in already colonized animals. Many biotechnology companies are working to develop such a therapeutic vaccine for human protection. Finding a human vaccine to *H. pylori* may be more difficult because of the bacteria's characteristic genetic variability and molecular mimicry, which were previously described. It is likely to take years for the basic research to develop a vaccine and for the necessary clinical trials before commercial production and widespread distribution of an effective vaccine becomes a reality.

The *Helicobacter pylori* story illustrates so well how the knowledge and sophisticated technology developed by basic scientists evolve into advances in understanding human disease and ameliorating it. Fundamental to this process of discovery is the insight of the individual, independent investigator, a point inherent in Albert Szent Györgyi's remark.

RESOURCES

For a well written and interesting personal overview of the historical and clinical aspects of *Helicobacter pylori*, see “The Bacteria behind Ulcers,” by Martin J. Blaser, in the February 1996, issue of the *Scientific American*, pp. 104-107.

If you are interested in the history of gastric microbiology, including early reports of stomach bacteria, see “A Century of *Helicobacter pylori*: Paradigms Lost—Paradigms Regained” by Mark Kidd and Irvin M. Modlin in *Digestion* (1998) Vol. 59, pp.1-15.

Information about other *Helicobacter* species can be found in “The Role of *Helicobacter* Species in Newly Recognized Gastrointestinal Tract Diseases of Animals,” by James G. Fox and Adrian Lee in *Laboratory Animal Science* (1997) Vol. 47, pp. 222-255.

If you are concerned about the possibility of acquiring *H. pylori* from a pet or have other questions, access the website of the *Helicobacter* Foundation. This is an excellent resource for both scientists and the public where you can find much information about *H. pylori*, its diagnosis, and treatment, a list of frequently asked questions, and an ongoing discussion where your questions can be posted. There are also links to many other useful Internet sites concerned with *H. pylori*. It can be found at www.helico.com.

If you would like to know more about the work of Dr. Barry Marshall, access the *H. pylori* research laboratory website at www.hpylori.com/au/htm, where you will find an interesting *H. pylori* picture gallery, photos of his laboratory in Australia, and more informative links.

For thoughtful viewpoints on the question of who should be tested or treated for *H. pylori*, consider:

1. “Not all *Helicobacter pylori* strains are created equal; should all be eliminated?” by Martin J. Blaser in *Lancet* (1997) Vol. 349, pp. 1020-22.
2. “To intervene or not to intervene? That is the question,” by Adrian Lee in *Mucosal Immunology Update* (December 1997) Vol. 5, pp. 70-74. Lippencott-Raven Publishers, Hagerstown, MD 21740.
3. “The future of *H. pylori* eradication: a personal perspective,” by Barry J. Marshall in *Alimentary Pharmacology and Therapeutics* (1997) Vol. 11, Suppl. 1, pp. 109-15.

The complete genomic sequence of *H. pylori* was published in *Nature* (August 7, 1997) Vol. 388, pp. 539-547. www.tigr.org/tdb/mdb/hpdb/hpdb.html.

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