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Abstract: We describe how a chance discovery of bacteria that infect stomach linings completely changed how physicians treat ulcers. Specifically, we chronicle how: 1) two Australian physicians brought the bacterial infection to the world's attention and challenged the conventional view that stomach acidity caused ulcers; 2) a global community of researchers helped corroborate the Australians' findings and developed convenient tests and effective treatments; and 3) these tests and treatments were gradually, but not immediately, adopted.

Note: This case history, like the others in this series, is included in a list compiled by Victor Fuchs and Harold Sox (2001) of technologies produced (or significantly advanced) between 1975 and 2000 that internists in the United States said had had a major impact on patient care. The case histories focus on advances in the 20th century (i.e. before this millennium) in the United States, Europe, and Japan -- to the degree information was available to the researchers. Limitations of space and information severely limit coverage of developments in emerging economies.

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Eradicating *Helicobacter Pylori* Infections to Treat Ulcers

Helicobacter pylori (H. pylori) bacteria are tiny, spiral-shaped organisms that burrow into the stomach lining, causing the irritation and inflammation commonly known as "gastritis." This irritation and inflammation can eventually lead *t*o ulcers.[1] Ulcers produce many debilitating symptoms, some of which have been recorded since Hippocrates' time. These symptoms range from burning pain and perforations in the stomach to bloody vomit, bloody diarrhea, and severe inflammation that blocks digestion, causing malnutrition. *H. pylori* infections can also significantly increase a person's risk of developing stomach cancer—which leads to death within five years in over three-quarters of cases.[2]

DNA evidence suggests humans have suffered *H. pylori* infections for more than 58,000 years – and according to some estimates, nearly ninety-percent of the population of some countries continues to be infected (although most developed countries have a much lower rate).[3] However, it was only in the 1980s that two physicians in Perth, Australia, brought the bacterial infection, believed to cause up to ninety-five percent of ulcers in the stomach and small intestine,[4] to the world's attention. Although the two Australians would win the Nobel Prize in medicine in 2005, their research findings initially produced both excitement and skepticism. Gradually, skeptics were won over and eradication of the infection became a standard treatment by the end of the 1990s, as we will see in this case history.

The three main sections of this case describe how: 1) these two physicians challenged the conventional view that stomach acidity caused ulcers; 2) a global community of researchers helped corroborate the Australians' findings and developed convenient tests and effective treatments; and 3) these tests and treatments came to be gradually, but not immediately, adopted.

1. Challenging Conventional Views (1976-1985)

Early understanding of ulcers

In 1910, Croatian physician, Karl Schwartz, published research suggesting that the excess release of acid could corrode the linings of the stomach and small intestine, causing ulcers. For decades after, researchers and clinicians followed what became known as "Schwartz's dictum": "no acid, no ulcers." Physicians further believed that stress and certain foods increased acid production, inducing ulcers.[5]

Even before Schwartz proposed his theory, physicians had prescribed "antacids" -- naturally-occurring minerals and metals that neutralize stomach acid – to alleviate ulcer symptoms. These antacids included:

- *Calcium carbonate*--chewed to relieve stomach pain since ancient times;[6]
- *Magnesium hydroxide*--used in Milk of Magnesia since 1872; and
- *Bismuth*--taken in salts since the eighteenth century and in liquid Pepto-Bismol since 1901.

However, antacids provided only temporary relief. When treatments stopped, symptoms returned. In addition, the dietary and lifestyle changes that many physicians suggested to patients to reduce stomach acidity were usually ineffective.[7]

Alternatives to antacids

In 1976, Smith, Kline & French, a one-hundred-and-forty-year-old American pharmaceutical company, introduced a drug to reduce acid production, rather than neutralize the already-produced acid (as antacids

did). Many decades of research into the mechanism of acid production enabled development of the drug. In the early 1900s, the Nobel-Prize-winning Russian physiologist Ivan Pavlov had found that signals from the brain prompted acid production, but he had not shown how. Researchers then discovered that the brain's signals triggered the production of hormones, which in turn stimulated acid production by the stomach glands. In the mid-1960s, James W. Black, a Scottish pharmacologist working in Smith, Kline's British laboratory identified the specific hormone responsible: a histamine, dubbed "H2." Black and fellow researchers at Smith, Kline then systematically synthesized and screened compounds that stopped H2 from stimulating acid production. Black had already used this relatively new approach of targeting the action of hormones at ICI Pharmaceuticals, one of the largest companies in Britain; at ICI, Black and his colleagues developed a drug that lowered blood pressure by blocking the hormones that stimulate the heart to pump harder.[1] Similarly, the "H2 blockers," developed by Black's Smith, Kline team, chemically bonded with the histamine to prevent it from stimulating acid production by stomach glands.[8]

Smith, Kline & French sought approval for its most promising H2 blocker from British regulators in 1973. The approval process required developers of new drugs to demonstrate their safety in clinical trials, but, as it happened, the blocker was too toxic to pass. The company's second blocker also failed, but a third was able to demonstrate safety in three years. This H2 blocker was so effective that ulcers healed in about six weeks, although British regulators did not at the time require evidence of effectiveness. After receiving regulatory approval, Smith, Kline started marketing the H2 blocker, named "Tagamet," in the UK in November 1976, and, seven months later, in Canada (where regulators followed the lead of their British counterparts).[9]

In October 1976 Smith, Kline & French sought approval to market Tagamet from U.S. Food & Drug Administration (FDA). The FDA approved the application in an exceptionally brief ten months. Normally, American regulators would have required Smith, Kline to demonstrate both the safety and effectiveness of its drug through clinical trials in the United States. However, the FDA made an exception for Tagamet because there were no effective alternative treatments: it accepted Smith, Kline's data from its British trials even though these trials had only shown safety and had been conducted outside the United States. Because the effects of long-term use had not been established, however, the FDA took a cautious approach: it approved Tagamet as an eight-week treatment for ulcers in the small intestine. Then, in 1979, after Smith, Kline & French submitted additional trial results, the FDA broadened its approval to include treatment of stomach ulcers. Tagamet went on to become the best-selling drug in the world at the time, posting global sales of USD$1 billion in 1986. Two years later, Dr. James Black would share in the 1988 Nobel Prize for Physiology and Medicine for his work on the targeted development of H2 blockers and blood-pressure drugs.[10]

Even though H2 blockers (which often were prescribed in treatment regimens that included antacids) rapidly healed ulcers, they did not cure the underlying disease. By the mid-1980s, several studies suggested ulcers could recur in as many as a quarter of cases after treatments ended.[11]

Foundations of a lasting cure

The first step toward a lasting cure for ulcers was taken in 1979 by J. Robin Warren, a pathologist working at the Royal Perth Hospital in Perth, Australia. Although Warren later recalled Perth was a "small, isolated community,"[12] physicians at Warren's hospital had begun using newly-available endoscopes to diagnose stomach diseases in the 1970s. Earlier endoscopes -- narrow tubes inserted through patients' mouths -- had only allowed physicians to see the insides of stomachs (to, for instance, observe inflammation). The endoscopes that became available in the 1970s enabled physicians to extract stomach tissue samples through the inserted tubes. When Warren was examining one of these tissue samples (taken from a patient with a stomach disorder) through a microscope he saw an unusual and hitherto-unnamed spiral-shaped bacteria.

[1] This approach is referred to as "rational drug design."

Over the next two years, he found the same spiral-shaped bacteria in tissue samples taken from thirty-five patients with gastritis and other stomach complaints.[13]

In fact, physicians had observed the bacteria, named *Helicobacter pylori*[2] in 1989, as early as the mid-nineteenth century. Some researchers even speculated the bacterium might cause ulcers, but they lacked the tools to isolate and study it. By the time better tools were available, researchers had lost interest and improved personal hygiene (for instance, frequent washing with soap and regular cleaning of teeth) had reduced *H. pylori* infections in much of the developed world. Throughout the twentieth century, physicians sometimes observed the bacterial infections, but they viewed them as curious byproduct rather than a cause of disease. Others assumed that stomach acid would not allow bacteria to survive and – unlike Warren – ignored the possibility of bacterial infections.[14]

In 1981, Warren recruited Barry Marshall to help study the stomach-dwelling bacterium he had recently discovered. Marshall, who had just completed his basic medical training, had joined Royal Perth Hospital intending to specialize in cardiology. However, he first had to complete a rotation in gastroenterology and participate in a research project in order to qualify as a cardiologist. Working with Warren would satisfy his research requirement.[15]

Initially, Marshall's assignment was routine: to extract tissue samples for Warren's analysis and match the analysis with patient symptoms and diagnoses. But Marshall's role then extended far beyond what was necessary to meet his research requirement; he stayed with Warren's project and never went back to cardiology. For two years, he learned to search the U.S. National Library of Medicine's online database, at a time when tools that made searching easy were unavailable.[3] Through these searches he found previous reports of spiral stomach bacteria, the significance of which had been overlooked. Working with Warren, he studied another hundred stomach tissue samples. Analysis of those samples showed that over half the patients with gastritis had bacterial infections. In addition, Marshall found that bacterial infections were present in over three quarters of patients with stomach ulcers and all of the patients with small intestine ulcers.[16]

Skeptical reactions

Warren and Marshall reported their findings at conferences in Australia and Europe in 1982. Each also wrote a "letter" (typically, brief reports of preliminary findings) to *The Lancet,* a prestigious British medical journal, in 1983.[17] Their letters immediately stirred controversy. Physicians could not believe that bacteria could survive in stomach acid, particularly in patients with ulcers thought to be caused by excess acid. In fact, Warren himself had expressed surprise at the bacteria's ability to withstand the stomach's acidity in his *Lancet* letter.[18]

In 1984, Warren and Marshall published an article in *The Lancet* suggesting that the infections were causing the ulcers in the stomach and small intestine. However, this publication further increased skepticism, because physicians considered stomach ulcers and small intestine ulcers to be separate, unrelated conditions. Moreover, Warren and Marshall could not test their hypothesis by reproducing *H. pylori* infections in lab animals.[19]

In June 1984, Barry Marshall tried – and succeeded – in infecting himself. First, colleagues extracted tissue samples showing Marshall's stomach was infection-free. Marshall then drank a broth containing *H. pylori*

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[2] Warren and Marshall had initially named the bacteria *Campylobacter pylori,* but subsequent research determined that it was unlike other *Campylobacter bacteria,* and the name and categorization was changed in 1989.

[3] The U.S. National Library of Medicine, part of the U.S. Public Health Service, is located on the campus of the U.S. National Institutes of Health. The catalog, known as MEDLINE, went online in 1971, but users had to program their own searches. It was updated to include a search engine in 1996.

taken from one of his patients. In a week, he experienced fatigue and vomiting. Four days after that, Marshall's colleagues extracted additional samples that showed inflammation and an *H. pylori* infection. The experiment became famous shortly after it was completed, because Robin Warren told the story of what his collaborator had done to himself to a journalist from U.S. tabloid newspaper, *The Star.* The tabloid's story -- "'Guinea Pig' Doctor Discovers New Cure for Ulcers … and the Cause" – was picked up by other newspapers and magazines, including *The New York Times,* and was retold in popular accounts of the discovery for years thereafter. Marshall and his colleagues published their experiment in an Australian medical journal in April 1985. (Contrary to popular belief, however, Marshall did not require antibiotics to cure himself; his immune system was able to clear the infection in two weeks.)[20]

2. Developing Tests and Treatments (1984-1993)

Skepticism persists

Marshall's dramatic experiment did not immediately change medical beliefs or practice. Many physicians continued to question the causal connection between the bacteria and ulcers, because not everyone who had an *H. pylori* infection developed stomach inflammation or ulcers. And, diagnosis and treatment was difficult. Lab analyses of the stomach tissue samples could take up to a week to complete due to the time required to grow the bacteria in a lab dish, and standard antibiotic treatments failed to eradicate *H. pylori* infections in three quarters of patients.[21] However, researchers – some sympathetic, some skeptical – continued to investigate *H. pylori* and provided the groundwork for better tests and treatments.

Convenient tests developed and introduced

Research supporting the development of diagnostic tests advanced first. In 1984, microbiologists at the University of Amsterdam's Academic Medical Center reported abnormal amounts of the digestive stomach enzyme, "urease," in *H. pylori*-infected tissue samples. Urease could be easily detected because it changes the color of urea (excreted in urine) from bright yellow to pink, just as acid turns blue litmus paper red.[22] Thus, inferring an *H. pylori* infection from a urease test was potentially quicker and cheaper than testing for the bacterium itself (although it still required extracting tissue samples).[23]

Marshall led the effort to develop such a urease test. He worked with an Australian diagnostics company, Delta West, although he had by then joined the University of Virginia's medical school, in the United States. Delta West introduced its first a urease test kit in Australia in 1987.[24]

In May 1988, Delta West applied to the FDA for permission to market the test kits in the United States. This application was quickly approved – without a clinical trial – under the so-called "510(k)" exemption. (The FDA grants such exemptions to new devices and tests that it decides are "substantially equivalent" to existing devices and tests). Once approved, the test kits could be used by physicians to rapidly identify H. pylori-infected tissue samples in their offices, clinics, and hospitals, rather than sending the samples to a lab.[25]

Blood tests then made diagnoses even more convenient. The tests were based on the discovery, made by German researchers in 1988, of antibodies produced by the immune systems of patients with *H. pylori* infections. Unlike urease testing, which required extracting stomach tissue, detecting the antibodies only required drawing blood.[26] Quidel, a California diagnostics company, was the first to develop blood tests for the *H. pylori* antibodies, securing approval from the FDA in 1991, also under the 510(k) exemption. The next year, the FDA approved Quidel's second, so-called "finger-stick" blood test for use in doctors' offices; that test required just a drop of blood, rather than a vial that had to be sent out to a lab.[27] (For a summary table of *H. pylori* tests, see **Exhibit 1.**)

Effective treatments developed

Advances in treatments followed soon after advances in tests. In 1985, microbiologists who worked in a pathology (rather than research) lab in a major regional hospital in Birmingham, England, reported that *H. pylori* had developed resistance to some antibiotics; this explained why some of the early eradication attempts had been ineffective.[28] In 1988, Marshall and his University of Virginia colleagues found that the potency of other antibiotics that had been only moderately effective when taken alone increased when taken with an antacid.[29]

Over the next few years, researchers at academic medical centers in Sweden, The Netherlands, and Australia developed even more effective treatments that combined antibiotics with acid-reducers.[4] These combinations healed ulcers in ninety-five percent or more cases—whereas previous treatments had done so in seventy percent or fewer cases. Remarkably, after treatments ended, patients in one study had been tracked for four years--and their ulcers had not returned.[30]

Some of these combination treatments included a newly-available class of acid-reducers—"proton pump inhibitors" (PPIs) developed by Astra, a longtime Swedish pharmaceutical company. Astra researchers in Gothenburg, Sweden, began synthesizing compounds to reduce acidity around the same time that Smith, Kline had started H2 blocker research in England. Unlike Smith, Kline however, Astra did not "target" a specific acid-producing molecule or mechanism. In 1974, Astra's researchers did synthesize an acid-reducing compound, but it turned out to also suppress hormone production in the thyroid and cause cancer in the thymus gland.[31] The Swedish researchers tried to synthesize a less toxic acid-reducing compound, but failed.[32]

Researchers from the University of Alabama helped Astra's Swedish researchers overcome these problems.[33] The Alabama researchers, who had studied the stomach's acid secretion for ten years, discovered that while the H2 histamine stimulated acid production by the stomach gland, an enzyme (colloquially known as a "proton pump") pumped out the acid that the gland had produced. A chance meeting of the Alabama and Astra researchers at a 1977 conference in Sweden led them to speculate that Astra's compound worked by disrupting the action of the proton pump enzyme.[34]

The researchers collaborated to systematically synthesize and tested less toxic compounds that targeted the proton pump enzyme.[35] By 1980, their collaboration had produced a safe proton pump inhibitor (or PPI). Clinical trials in two Swedish university hospitals showed that the PPI healed ulcers faster than H2 blockers, and fewer ulcers recurred after treatment ended. On the basis of these results, European regulators approved Astra's PPI in 1988, and American regulators followed in 1990.[36][5] By 1993, Swedish and Australian researchers had shown that a PPI combined with antibiotics healed ulcers and eradicated H. pylori infections faster than other combinations, with the lowest rates of ulcer recurrence.[37]

Research on drug combinations in the U.S. benefited from the FDA's loose enforcement of rules for testing new uses for already approved drugs. Although in principle the FDA requires pre-approval of such tests, in practice it often does not penalize researchers who do not seek pre-approval. The drugs tested for *H. pylori* treatments--antibiotics, antacids, H2 blockers, and PPIs—had already been approved. Therefore, researchers could—and did--run trials combining these drugs without seeking FDA pre-approval.[38] (For a summary table of *H. pylori* treatments, see **Exhibit 2.**)

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[4] Combinations of antibiotics had also been used to eradicate infections in the 1950s. However, studies conducted by the FDA in the 1960s found those combinations to be significantly less effective than producers had previously claimed. The FDA then required drug companies to stop marketing these combinations and instituted strict standards for approving new combinations.

[5] Astra marketed the drug in Europe under the name "Lo-Sec" and in the U.S. under the name "Prilosec." Astra would go on to develop and introduce an improved PPI ("Nexium") in 2000.

Skepticism reduced

Researchers in Australia, Europe, and the United States—including a few who had started out as critics of Marshall and Warren[39]--achieved the advances described above, such as identification of the *H. pylori* antibody and development of antibiotic combinations capable of eradicating *H. pylori* infections. They included gastroenterologists and pathologists, like Marshall and Warren, who did clinical research, as well as many microbiologists. Many of these researchers worked in academic centers, such as the University of Alabama program. However, their research was supplemented by research conducted by practicing physicians who did not normally publish research. These physicians treated patients in hospitals and clinics in over fifty countries, including: Brazil, Chile, China, Czechoslovakia, Fiji, Greece, Hungary, India, Japan, Kenya, Kuwait, Malaysia, Mexico, Pakistan, Panama, Poland, Romania, Rwanda, Saudi Arabia, Senegal, South Africa, Spain, Tonga, Tunisia, and Yugoslavia. Although these practicing physicians' studies ran for short periods and had small sample sizes, their findings swayed skeptical physicians' opinions.[40]

Results of larger controlled trials, published in 1992 and 1993, then corroborated the results of these many small studies. The results showed that ulcers did not return for at least two years after patients' *H. pylori* infections had been eradicated with combination regimens.[41]

In 1994, the National Institutes of Health, a U.S. government agency that funds medical research, organized a consensus conference on *H. pylori.* The American College of Gastroenterology, a professional organization that supports research and education, followed in 1996. That same year, European researchers and public health officials also organized a consensus conference in Maastricht, Netherlands. Experts at all three conferences declared *H. pylori* the cause of almost all ulcers[6] and recommended widespread testing and treatment of ulcer patients.[42]

In 1994, the same year of the first consensus conference in the U.S., the World Health Organization designated *H. pylori* a cancer-causing agent.[43] The designation had been prompted by studies that tested over 5,000 patients across Europe, the United States, Japan, and China. The results revealed that those with *H. pylori* infections were up to six times more likely to develop stomach cancer.[44]

3. Gradual adoption (1994-2005)

Publicity helps increase testing

By the mid-1990s, nearly all gastroenterologists and about two-thirds of general physicians in the United States reported testing for *H. pylori.* Increased testing had been spurred in part by wide media coverage. For instance, reporters at national newspapers (e.g. *The New York Times, The Wall Street Journal,* and *USA Today),* regional newspapers (e.g. the *St. Petersburg Times),* general interest magazines (e.g. *The New Yorker, Reader's Digest,* and *Fortune),* and on television *(NBC Nightly News)* interviewed pioneer Barry Marshall (who was already well-known for his 1984 self-experiment) and other researchers.[45]

FDA approval of urease breath tests in 1996 further encouraged testing. Previous urease tests required trained gastroenterologists to extract stomach tissue. The breath tests, which could be administered by general physicians, simply required patients to swallow tablets. The tablets released traceable particles when they encountered urease in the stomach. Then the patients breathed into balloons that were sealed and sent to a lab that would test for the urease-released particles.[46]

Barry Marshall had collaborated with Tri-Med, an American startup, to develop a urease breath test in the late 1980s. A test had also been concurrently developed by physicians at Baylor College of Medicine, in

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[6] Experts acknowledged that in a small percentage of cases stomach ulcers could instead be caused by long-term use of certain pain medications.

Houston, Texas, for Meretek, an American diagnostics company. However, an FDA ruling that breath tests were not substantially equivalent to tests that had already been approved slowed their introduction, because Tri-Med and Meretek had to conduct clinical trials to demonstrate the safety and effectiveness of their tests. The FDA also required two applications for the tests – one for a new drug (the tablet) and one for a new device (the balloon). In 1996, the FDA approved Meretek's test but rejected Tri-Med's applications on the grounds that they had not shown effectiveness. Tri-Med conducted more trials and submitted the results to the FDA the next year, after which its test, too, received approval.[47]

Blood tests for *H. pylori* antibodies also became more widely available. As mentioned, Quidel had offered the first *H. pylori* blood test in 1991. In the next seven years, over twenty-five diagnostics companies added blood tests to their offerings.[48] (See **Exhibit 3** for a list of producers.)

The wider availability of improved tests helped broaden testing: in a 1998 a survey of US physicians nearly all said they routinely tested patients with ulcer symptoms for *H. pylori.*[49]

Treatments lag tests

Physicians did not immediately follow the treatment guidelines set in 1994 by government agencies and professional organizations.[50] Studies from the mid-1990s suggested physicians prescribed the recommended combinations of antibiotics and acid-reducers only about three to fifteen percent of the time. Instead, they prescribed H2 blockers or PPIs, which patients usually had to continue to take because H2 blockers and PPIs alone did not eradicate *H. pylori* infections. Observers speculated that one reason why physicians stayed with H2 blockers and PPIs was that pharmaceutical companies, whose representatives play an important role in disseminating information about new treatments, did not market the eradication combinations specified by the treatment guidelines. And, indeed FDA rules prevented such marketing: physicians could prescribe combinations containing antibiotics that the FDA has already approved for other diseases to ulcer patients. However, pharmaceutical companies could not market the antibiotics and antibiotic-containing combinations recommended by guidelines as treatments for ulcers without obtaining additional FDA approvals. And, concerns about antibiotic resistance (which many physicians also shared) made the FDA reluctant to approve the marketing of antibiotics for new uses.[51]

Patients who were prescribed the recommended combinations also often had difficulty following them, because they required taking up to sixteen pills per day for ten to fourteen days. With H2 blockers or PPIs treatments, patients had to take just two to four pills per day.[52]

In 1996, the FDA allowed pharmaceutical companies to market individual antibiotics as well as three combinations containing antibiotics as treatments for ulcers.[7] The approvals of the combination treatments were considered "highly unusual" by observers because the applications had been supported by studies that had measured different outcomes. For instance, some studies measured ulcer healing rates, others eradication rates, and still others rates of ulcer recurrence. To avoid such inconsistencies in the future, the FDA also standardized the clinical trial requirements for *H. pylori* combinations that would be used to guide pharmaceutical companies as they ran trials and submitted applications. The FDA approvals encouraged the multinational pharmaceutical companies (who produced the individual drugs) to actively market the drugs and combinations that eradicated *H. pylori* infections to physicians.[53] (See **Exhibit 3** for a list of producers).

After companies started marketing *H. pylori* eradication treatments, their use rapidly increased. In a 1998 survey, about seventy percent of American gastroenterologists and general practitioners surveyed reported

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[7] The following year (in October 1997) the FDA approved the marketing of an antiviral combination that would dramatically reduce AIDs-related deaths.

routinely prescribing eradication regimens according to guidelines (up from fewer than fifteen percent in 1995 surveys).[54]

In the late 1990s, Glaxo Welcome (UK), makers of an H2 blocker, and Pepto-Bismol (U.S.), makers of bismuth, introduced FDA-approved combinations in convenient pill "packs." The new packs increased patient compliance by reducing the number of pills taken by half (to eight per day, down from sixteen). Within a few years, Astra (Sweden) and TAP (U.S./Japan), both makers of PPIs, also offered combinations in packs.[55]

Testing and Treatment in Europe and Japan

As in the U. S., publicity in Europe – for instance, the 1994 BBC documentary "Ulcer Wars" – helped promote testing but did not immediately increase the prescription of recommended treatments.[56] In the mid-1990s, European physicians tested ulcer patients for *H. pylori* over three-quarters of the time. However, they prescribed the recommended eradication treatments only about four percent of the time. A few years later, after better tests and treatments became available in Europe, surveys showed physicians tested almost all ulcer patients. And, doctors in some parts of Europe had switched to prescribing the recommended treatments in over ninety percent of patients who had been found to have *H. pylori* infections.[57]

Adoption of both testing and treatment lagged in Japan. An estimated sixty percent of adults –relatively high for a developed country – had infections. And, about 50,000 people died of stomach cancer each year, leading many Japanese researchers to study *H. pylori*'s links to stomach cancer. However, Japanese officials did not approve insurance payments (under the country's insurance programs[8]) for eradication treatments until 2000. In addition, for ten years the Japanese government allowed insurance reimbursement of *H. pylori* testing and treatment for only patients with ulcers – but not those with stomach cancer. Government officials expanded coverage in 2010, after a large-scale, controlled trial conducted at medical centers throughout Japan had shown eradication of infections reduced stomach cancer rates among those treated.[58]

4. Epilogue

Studies conducted worldwide in the 2000s suggested eradication of *H. pylori* infections could prevent over seventy-five percent of stomach cancer cases. Studies conducted in China, Japan, and the UK also suggested that mass *H. pylori* screening of adults (including people who had no symptoms) and eradication of any infections found would be cost effective in combating stomach cancer. However, some researchers questioned the wisdom of mass screening and treatment.[59] Advocates of treating infected patients before they had ulcers organized a conference in 2014 in Kyoto, Japan, to set new global guidelines for screening and treatment.[60]

[8] The Japanese government required all residents to buy health insurance (either through an employer or government-run program). The government also set the fee schedule for all health care providers.

Exhibits

Exhibit 1 Overview of *H. pylori* Tests, 1980s-1990s

Date available	Test	Accuracy		Advantages	Disadvantages
		Sensitivity	Specificity		
1983	Tissue sample collected in gastroenterologist's office and analyzed in lab using traditional lab methods	80-95%	98-100%	Direct measure of presence of *H. pylori* bacteria	Requires expertise, time-consuming (3-7 days), expensive (~USD$1,200/test)
1987	Tissue sample collected and analyzed in gastroenterologist's office for evidence of excess urease using rapid test kit	90-95%	98%	Fast (15 minutes for results), inexpensive (~USD$10/test plus cost of collecting tissue sample)	Indirect measure of presence of *H. pylori* infection
1991	Blood sample collected and analyzed in lab for evidence of antibodies to *H. pylori* infection using test kit	91%*	79%*	Convenient, inexpensive	Indirect measure of history of infection, not presence of infection; cannot detect infection until six weeks after initial exposure; antibodies remain in system for up to six months after bacteria eradicated with treatments; often cannot detect evidence of *H. pylori* infection once pre-cancerous conditions develop in stomach
1992	Blood drops from finger stick analyzed for evidence of antibodies to *H. pylori* infection in physician's office using test kit	86-90%	79-88%	Fast (5-10 minutes for results), convenient, inexpensive (USD$8/test)	Indirect measure of history of infection, not presence of infection; cannot detect infection until six weeks after initial exposure; antibodies remain in system for up to six months after bacteria eradicated with treatments
1996	Breath sample taken in physician's office and analyzed at lab for evidence of excess urease	95-100%	95-100%	Fast (30 minutes to administer, longer for results), convenient, non-invasive	Indirect measure of *H. pylori* infection, more expensive than other tests administered in office setting (USD$60-300/test), some versions of test require exposure to radioactive particles
1998	Stool sample collected by physician and analyzed in lab for evidence of molecules produced by *H. pylori*	80%	98%	Direct measure of presence of *H. pylori* infection, non-invasive	Time-consuming

Note: Later blood tests to detect *H. pylori* antibodies achieved accuracy rates of 98% sensitivity and 94% specificity.

Sources: *Medical World News* (1987) and Frost & Sullivan (1998).

Exhibit 2 Overview of Selected Recommended *H. pylori* Treatment Combinations, 2007-2014

Region	First-line therapy	Second-line (salvage) therapy
USA (2007)	Clarithromycin-containing triple therapy for 14 days	Bismuth-containing quadruple therapy for 7–10 days
	Bismuth-containing quadruple therapy for 10–14 days	Levofloxacin-containing triple therapy for 10 days
	Sequential therapy for 10 days	
European Union (2012)	In areas of <20 % clarithromycin resistance:	
	Clarithromycin-containing triple therapy for 10–14 days	Bismuth-containing quadruple therapy for 10–14 days
	Bismuth-containing quadruple therapy for 10–14 days	Levofloxacin-containing triple therapy for 10 days
	In areas of >20 % clarithromycin resistance:	
	Sequential therapy for 10 days	Levofloxacin-containing therapy for 10 days
	Bismuth-containing quadruple therapy for 10–14 days	
	Non-bismuth quadruple therapy for 3–10 days	
Japan (2010)	Clarithromycin-containing triple therapy for 7 days	Metronidazole-containing triple therapy for 7 days
Korea (2014)	Clarithromycin-containing triple therapy for 10–14 days	Bismuth-containing quadruple therapy for 7–14 days
	Bismuth-containing quadruple therapy for 7–14 days	Regimen including ≥2 other antibiotics
China (2013)	Bismuth-containing quadruple therapy for 10–14 days	Bismuth-containing quadruple therapy for 10–14 days

Sources: Suzuki et al (2016).

Exhibit 3: Companies offering *H. pylori* Tests and Treatments, 1988-2006

Year	Company (Domicile)	Originating Industry	Offered Tests	Offered Treatments
1988*	Procter & Gamble (USA)	Consumer goods and health care products		X
1988*	Glaxo Wellcome (UK)	Pharmaceuticals		X
1988*	Eli Lilly (USA)	Pharmaceuticals		X
1988*	Merck & Company (USA)	Pharmaceuticals		X
1988*	Pfizer (USA)	Pharmaceuticals		X
1988*	Searle (USA)	Pharmaceuticals and diagnostic devices		X
1988*	SmithKline Beecham (UK)	Pharmaceuticals		X
1988	Auspharm International (Australia)	Pharmaceuticals	X	
1988	Astra Pharmaceuticals (Sweden)	Pharmaceuticals		X
1989	Remel Co. (USA)	Diagnostic devices and agents	X	
1991	Quidel Corp. (USA)	Diagnostic devices	X	
1991	Bainbridge Laboratories (USA)	Diagnostic devices	X	
1991	Biomerica Inc. (USA)	Diagnostic devices	X	
1991	E-Z-EM Inc. (USA)	Diagnostic devices and agents	X	

1991	Hycor Biomedical Inc. (USA)	Diagnostic devices	X	
1991	Whittaker Bioproducts Inc. (USA)	Diagnostic devices	X	
1991	Taisho Pharmaceuticals (Japan) (marketed in U.S. by Abbott)	Pharmaceuticals		X
1992	**Amrad (Australia)**	**Pharmaceuticals and diagnostic devices**	**X**	
1992	TAP (USA/Japan)	Pharmaceuticals		X
1993	New Horizons Diagnostics Co. (USA)	Diagnostic devices	X	
1993	**United Biotech Inc. (USA)**	**Diagnostic devices**	**X**	
1993	Daiichi Seiyaku (Japan, marketed outside of Japan by Sanofi)	Pharmaceuticals		X
1994	SmithKline Diagnostics Inc. (USA, marketed by Abbott)	Diagnostic devices	X	
1995	GI Supply (USA)	Diagnostic devices	X	
1995	Orion Diagnostica (Finland)	Diagnostic devices	X	
1995	Schiff & Co. (USA)	Pharmaceutical, biomedical, and medical device consultants	X	
1995	Serim Research Corp (USA)	Diagnostic devices and agents	X	
1995	Washington Biotechnology (USA)	Diagnostic devices and vaccine testing	X	
1996	Armkel LLC (USA)	Consumer good, health care products, and diagnostic devices	X	
1996	Chemtrak Inc.(USA)	Diagnostic devices	X	
1996	Cortecs LTD (UK)	Pharmaceuticals	X	
1996	**Elias USA Inc. (USA)**	**Diagnostic devices**	**X**	
1996	Meretek (USA)	Diagnostic devices	X	
1996	Johnson & Johnson (USA)	Pharmaceuticals and diagnostic devices		X
1997	Consolidated Technologies (USA)	Diagnostic devices	X	
1997	Kenlor Industries (USA)	Diagnostic devices and agents	X	
1997	Pyramid Biological Corp. (USA)	Blood products and diagnostic devices	X	
1997	**Tri-Med Specialties (USA)**	**Diagnostic devices**	**X**	
1998	Abbott Laboratories (USA)	Pharmaceuticals and diagnostic devices	X	
1998	AMDL Inc. (USA)	Diagnostic devices	X	
1998	Boehringer Mannheim Corp. (Germany)	Pharmaceuticals and diagnostics devices	X	
1998	Inova Diagnostics Inc. (USA)	Diagnostic devices	X	
1998	**Micro Detect Inc. (USA)**	**Diagnostic devices**	**X**	
1998	Princeton Biomedical (USA)	Diagnostic devices	X	
1998	Saliva Diagnostic Systems Inc. (USA)	Diagnostic devices	X	
1998	Shield Diagnostics LTD (USA)	Laboratory services	X	
1998	Zeus Scientific Inc. (USA)	Diagnostic devices	X	
1999	Columbia Bioscience (USA)	Diagnostic devices	X	
1999	Enteric Products Inc. (USA)	Diagnostic devices	X	
1999	Medical Instruments Corporation of America (division of MIC AG, Switzerland)	Diagnostic devices	X	
1999	Trinity Biotech (USA)	Diagnostic devices	X	

2000	Biomerieux Inc. (France)	Diagnostic devices and agents	X	
2000	Diagnostic Products Corp. (USA)	Diagnostic devices	X	
2000	Medmira Laboratories (Canada)	Diagnostic devices	X	
2001	Oridion Medical (Israel)	Diagnostic devices	X	
2001	Oxoid LTD (UK)	Diagnostic devices and agents	X	
2002	Nichols Institute Diagnostics (USA)	Laboratory services	X	
2003	Acon Laboratories (USA)	Diagnostic devices	X	
2003	Alfa Scientific Designs (USA)	Diagnostic devices	X	
2003	Meridian Bioscience Inc. (USA)	Diagnostic devices	X	
2004	Biohit (Finland)	Diagnostic devices	X	
2004	Presutti Laboratories (USA)	Pharmaceuticals		X
2006	**ARJ Medical Inc. (USA/Egypt)**	**Diagnostic devices**	**X**	
2006	Otsuka Pharmaceutical (Japan)	Pharmaceuticals	X	

Note: Companies marked with an asterisk (*) already had treatments approved for marketing for other indications as of 1988. Startups are listed in **bold** type.

Sources: Frost & Sullivan (1998), and the FDA PMA and 510(k) online databases.

Endnotes

[1] Julia Fashner and Alfred C. Gitu, "Diagnosis and Treatment of Peptic Ulcer Disease and *H. Pylori* Infection," *American Family Physician* 91, no. 4 (February 15, 2015): 236–42; Sheila Crowe, *Acid-Peptic Diseases of the Stomach and Duodenum Including* Helicobacter Pylori *and* NSAIDs (London: Henry Stewart Talks, 2014), http://nrs.harvard.edu/urn-3:hul.ebookbatch.HSTLK_batch:20170425HST3707.

[2] Recent research suggests *H. pylori* infections may play a role in many other diseases such as coronary heart disease, liver disease, diabetes, glaucoma, anemia, Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis. Julia Fashner and Alfred C. Gitu, "Diagnosis and Treatment of Peptic Ulcer Disease and *H. Pylori* Infection," *American Family Physician* 91, no. 4 (February 15, 2015): 236–42; E. J. Kuipers, J. C. Thijs, and H. P. Festen, "The Prevalence of *Helicobacter Pylori* in Peptic Ulcer Disease," *Alimentary Pharmacology & Therapeutics* 9 Suppl 2 (1995): 59–69; Sheila Crowe, *Acid-Peptic Diseases of the Stomach and Duodenum Including* Helicobacter Pylori *and* NSAIDs (London: Henry Stewart Talks, 2014), http://nrs.harvard.edu/urn-3:hul.ebookbatch.HSTLK_batch:20170425HST3707; Sebastian Suerbaum and Pierre Michetti, "*Helicobacter Pylori* Infection," *New England Journal of Medicine* 347, no. 15 (October 10, 2002): 1175–86, https://doi.org/10.1056/NEJMra020542; Dino Vaira et al., "Screening for *Helicobacter Pylori," The Lancet,* Originally published as Volume 2, Issue 8775, 338, no. 8775 (November 2, 1991): 1149, https://doi.org/10.1016/0140-6736(91)92009-Q; Francesco Franceschi et al., "Extragastric Diseases and *Helicobacter Pylori," Helicobacter* 20, no. S1 (2015): 40–46, https://doi.org/10.1111/hel.12256; M. J. Blaser, "The Role of *Helicobacter Pylori* in Gastritis and Its Progression to Peptic Ulcer Disease," *Alimentary Pharmacology & Therapeutics* 9 (April 1, 1995): 27–30, https://doi.org/10.1111/j.1365-2036.1995.tb00780.x.

[3] Infection rates are affected by several factors, including: industrialization, urbanization, access to clean drinking water, and socioeconomic status. Ann GibbonsFeb. 7, 2007, and 12:00 Am, "Out of Africa, in the Gut," *Science* | AAAS, February 7, 2007, https://www.sciencemag.org/news/2007/02/out-africa-gut; Daniel Falush et al., "Traces of Human Migrations in *Helicobacter Pylori* Populations," *Science* (New York, N.Y.) 299, no. 5612 (March 7, 2003): 1582–85, https://doi.org/10.1126/science.1080857; John C. Atherton and Martin J. Blaser, "Coadaptation of *Helicobacter Pylori* and Humans: Ancient History, Modern Implications," *The Journal of Clinical Investigation* 119, no. 9 (September 2009): 2475–87, https://doi.org/10.1172/JCI38605; David Y Graham, "History of *Helicobacter Pylori,* Duodenal Ulcer, Gastric Ulcer and Gastric Cancer," *World Journal of Gastroenterology*: WJG 20, no. 18 (May 14, 2014): 5191–5204, https://doi.org/10.3748/wjg.v20.i18.5191; Shamshul Ansari and Yoshio Yamaoka, "Current Understanding and Management of *Helicobacter Pylori* Infection: An Updated Appraisal," F1000Research 7 (2018), https://doi.org/10.12688/f1000research.14149.1; James K. Y. Hooi et al., "Global Prevalence of *Helicobacter Pylori* Infection: Systematic Review and Meta-Analysis," *Gastroenterology* 153, no. 2 (August 1, 2017): 420–29, https://doi.org/10.1053/j.gastro.2017.04.022.

[4] Estimates vary, but approximately 70% or more of ulcers in the stomach are now thought to be caused by *H. pylori* infections. (The remaining 30% of stomach ulcers are attributed to frequent use of certain pain relievers and other medications.) *H. pylori* infections are thought to cause 95-100% of ulcers in the top section of the small intestine, where it exits the bottom of the stomach. (This part of the small intestine is known as the *duodenum).* See Julia Fashner and Alfred C. Gitu, "Diagnosis and Treatment of Peptic Ulcer Disease and *H. Pylori* Infection," *American Family Physician* 91, no. 4 (February 15, 2015): 236–42; Sheila Crowe, *Acid-Peptic Diseases of the Stomach and Duodenum Including* Helicobacter Pylori *and* NSAIDs (London: Henry Stewart Talks, 2014), http://nrs.harvard.edu/urn-3:hul.ebookbatch.HSTLK_batch:20170425HST3707.

[5] Ivan Pavlov conducted much of the groundbreaking research on the digestive process, for which he won the 1904 Nobel Prize for Medicine and Physiology. Karl Schwartz built his famous theory on a series of case studies of only 14 patients, but his contemporaries conducted additional research that seemed to support Schwartz's findings. Many, such as Bertram W. Sippy, advocated for not only the use of antacids to control stomach acidity and treat ulcers, but also dramatic changes in diet, such as restricting patients to small hourly feedings of milk and cream under supervision in a hospital, which was gradually expanded into a bland diet when a patient returned home. Schwartz developed surgeries to remove and repair ulcers in addition to promoting the use of antacids. Later surgeons developed more extreme interventions for chronic ulcer patients based on Pavlov's findings: they severed the nerves that transmitted the brain signals that initiated the digestive process. Mark Kidd and Irvin M. Modlin, "A Century of *Helicobacter Pylori,*" *Digestion* 59, no. 1 (1998): 1–15, https://doi.org/10.1159/000007461; "The Nobel Prize in Physiology or Medicine 1904," NobelPrize.org, accessed April 26, 2019, https://www.nobelprize.org/prizes/medicine/1904/pavlov/facts/; Joshua Gustafson and David Welling, "'No Acid, No Ulcer'—100 Years Later: A Review of the History of Peptic Ulcer Disease," *Journal of the American College of Surgeons* 210, no. 1 (January 1, 2010): 110–16, https://doi.org/10.1016/j.jamcollsurg.2009.08.014; Michael Specter, "Drool," November 17, 2014, https://www.newyorker.com/magazine/2014/11/24/drool; Stella Fatovi-Fereni and Marko Bani, "No Acid, No Ulcer: Dragutin (Carl) Schwarz (1868–1917), the Man Ahead of His Time," *Digestive Diseases* 29, no. 5 (2011): 507–10, https://doi.org/10.1159/000334384; Graham, "History of *Helicobacter Pylori,* Duodenal Ulcer, Gastric Ulcer and Gastric Cancer"; Barry Marshall J, Helicobacter *Pioneers: Firsthand Accounts from the Scientists Who Discovered* Helicobacters, *1892-1982* (Carlton, Vic.; Oxford: Blackwell Science Asia, 2003).

[6] Calcium carbonate has been used in TUMS since 1928.

[7] A. Bettarello, "Anti-Ulcer Therapy. Past to Present," *Digestive Diseases and Sciences* 30, no. 11 Suppl (November 1985): 36S-42S; H. Abrahamsson and G. Dotevall, "Pharmacological and Clinical Aspects of Some Drugs Used in Peptic Ulcer Treatment," *Scandinavian Journal of Gastroenterology.* Supplement 55 (1979): 117–20; Gustafson and Welling, "'No Acid, No Ulcer'—100 Years Later." https://www.tums.ca/about/;"Digestive Health FAQs | Phillips'®;" Accessed March 8, 2019.

https://www.phillipsdigestive.com/frequently-asked-question/;"Rorer Group | Encyclopedia.Com." Accessed March 8, 2019. https://www.encyclopedia.com/books/politics-and-business-magazines/rorer-group; "Maalox Antacid (Liquid) Physicians Total Care, Inc." Drugs.com. Accessed March 8, 2019. https://www.drugs.com/otc/113258/maalox-antacid.html; "History of Pepto-Bismol." Accessed March 4, 2019. https://www.pepto-bismol.com/en-us/about/history.

[8] *The Pharmaceutical Journal*2 JUL 2009, "Rational Drug Design — Identifying and Characterising a Target," *Pharmaceutical Journal,* accessed March 8, 2019, https://www.pharmaceutical-journal.com/opinion/comment/rational-drug-design-identifying-and-characterising-a-target/10969751.article; "Tagamet Discovery of Histamine H2-Receptor Antagonists - Landmark," *American Chemical Society,* accessed May 22, 2017, https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/cimetidinetagamet.html; Kidd and Modlin, "A Century of *Helicobacter Pylori*"; Gustafson and Welling, "'No Acid, No Ulcer'—100 Years Later"; Bettarello, "Anti-Ulcer Therapy. Past to Present"; Abrahamsson and Dotevall, "Pharmacological and Clinical Aspects of Some Drugs Used in Peptic Ulcer Treatment"; R. E. Pounder et al., "Healing of Gastric Ulcer during Treatment with Cimetidine," *Lancet* (London, England) 1, no. 7955 (February 14, 1976): 337–38; S. J. Haggie, D. C. Fermont, and J. H. Wyllie, "Treatment of Duodenal Ulcer with Cimetidine," *Lancet* (London, England) 1, no. 7967 (May 8, 1976): 983–84; Phillip H. Wiggins, "Tagamet: SmithKline's Aid For Earnin s," *The New York Times,* July 24, 1978, sec. Archives, https://www.nytimes.com/1978/07/24/archives/tagamet-smithklines-aid-for-earnings-other-drugs-in-field.html; Jean L. Marx, "The 1988 Nobel Prize for Physiology or Medicine," *Science;* Washington 242, no. 4878 (October 28, 1988): 516; "The Nobel Prize in Physiology or Medicine 1988," NobelPrize.org, accessed May 3, 2019, https://www.nobelprize.org/prizes/medicine/1988/black/facts/; "The Nobel Prize in Physiology or Medicine 1904."

[9] Gilbert Cant, "WORRYING ABOUT ULCERS: Most 'remedies' for Stomach Ulcers Have Not Worked. The Patient's Only Consolation--Which Does Little for the Pain-- Is That His Physician Did Not Know Any Better.," *New York Times,* 1977, sec. *The New York Times Magazine;* CHARLES J. ELIA, "SmithKline Stock Is Buffeted by Suggestion Its New Ulcer Drug May Cause Side Effects," *Wall Street Journal* (1923 - Current File); New York, N.Y., June 2, 1977, sec. 1; P R Lee and J Herzstein, "International Drug Regulation," Annual Review of Public Health 7, no. 1 (1986): 217–35, https://doi.org/10.1146/annurev.pu.07.050186.001245; Kathryn M. Welling, "Tomorrow's Medicine Chest: Will Contain More Effective Remedies Than Today's," *Barron's National Business and Financial Weekly* (1942-Current File); Boston, Mass., June 28, 1976; JUL 2009, "Rational Drug Design — Identifying and Characterising a Target"; "Tagamet Discovery of Histamine H2-Receptor Antagonists - Landmark"; Kidd and Modlin, "A Century of *Helicobacter Pylori*"; Gustafson and Welling, "'No Acid, No Ulcer'—100 Years Later"; Bettarello, "Anti-Ulcer Therapy. Past to Present"; Abrahamsson and Dotevall, "Pharmacological and Clinical Aspects of Some Drugs Used in Peptic Ulcer Treatment"; Pounder et al., "Healing of Gastric Ulcer during Treatment with Cimetidine"; Haggie, Fermont, and Wyllie, "Treatment of Duodenal Ulcer with Cimetidine"; Wiggins, "Tagamet"; Marx, "The 1988 Nobel Prize for Physiology or Medicine"; "The Nobel Prize in Physiology or Medicine 1988"; "The Nobel Prize in Physiology or Medicine 1904."

[10]Reports from studies conducted in the late 1970s suggested Tagamet might induce cancers in rats and lower sperm counts in human males. JUL 2009, "Rational Drug Design — Identifying and Characterising a Target"; D. J. Shearman, "A New Form of Antihistamine--the H2-Receptor Antagonist," *The Medical Journal of Australia* 1, no. 26 (June 26, 1976): 1005–9; "Tagamet Discovery of Histamine H2-Receptor Antagonists - Landmark"; Wiggins, "Tagamet"; "The Nobel Prize in Physiology or Medicine 1988"; Lee and Herzstein, "International Drug Regulation"; Cant, "WORRYING ABOUT ULCERS"; ELIA, "SmithKline Stock Is Buffeted by Suggestion Its New Ulcer Drug May Cause Side Effects"; STEVEN S. ANREDER, "Up & down Wall Street," *Barron's National Business and Financial Weekly* (1942-Current File); Boston, Mass., March 28, 1977; Welling, "Tomorrow's Medicine Chest"; GAIL BRONSON Staff Reporter of THE WALL STREET JOURNAL, "SmithKline Receives Approval to Market New Ulcer Medicine: Tagamet Should Be Available For Physicians to Prescribe Within One or Two Weeks," *Wall Street Journal* (1923 - Current File); New York, N.Y., August 18, 1977; "F.D.A. Unit Backs SmithKline Ulcer Drug," *New York Times,* 1977, sec. Business & Finance; "SmithKline Antiulcer Drug Cleared by FDA Panel for Extended Use," *Wall Street Journal* (1923 - Current File); New York, N.Y., June 1, 1979, sec. 1; A. WALL STREET JOURNAL Staff Reporter, "SmithKline Ulcer Drug Gets Broader Approval," *Wall Street Journal* (1923 - Current File); New York, N.Y., April 25, 1980; Richard Wright, "How Zantac Became the Best-Selling Drug in History," *Journal of Health Care Marketing* 16, no. 4 (Winter 1996): 24–29; Gina Kolata, "Companies Search for Next $1 Billion Drug," *The New York Times,* November 28, 1988, sec. Business, http://www.nytimes.com/1988/11/28/business/companies-search-for-next-1-billion-drug.html.

[11] For instance, one study showed about twenty-five percent of small intestine ulcers recurred within three months after being healed with Tagamet. Another study showed about twenty percent of stomach ulcers recurred within two years of being healed with Tagamet and antacids. However, both of these studies had small sample sizes and ran for a limited amount of time. W. Haddad, D. J. Kestenbaum, and H. S. Wang, "Effect of Cimetidine on Healing and Surgical Treatment of Gastric Ulcers," *American Journal of Surgery* 149, no. 5 (May 1985): 665–67; G. Vantrappen et al., "A Comparative Study of Colloidal Bismuth Subcitrate and Cimetidine on the Healing and Recurrence of Duodenal Ulcer," *Scandinavian Journal of Gastroenterology.* Supplement 80 (1982): 23–30; G. Vantrappen et al., "Randomised Open Controlled Trial of Colloidal Bismuth Subcitrate Tablets and Cimetidine in the Treatment of Duodenal Ulcer," *Gut* 21, no. 4 (April 1980): 329–33; See also: M. Tatsuta, H. Iishi, and S. Okuda, "Effects of Cimetidine on the Healing and Recurrence of Duodenal Ulcers and Gastric Ulcers," *Gut* 27, no. 10 (October 1986): 1213–18; Later studies suggested recurrence rates were even higher. See: G. Lindell et al., "On the Natural History of Peptic Ulcer," *Scandinavian Journal of Gastroenterology* 29, no. 11 (November 1994): 979–82.

[12] "The Nobel Prize in Physiology or Medicine 2005," NobelPrize.org, accessed March 11, 2019, https://www.nobelprize.org/prizes/medicine/2005/warren/facts/; Warren grew up in South Australia and was the son of a vintner and a nurse. Despite the onset of epilepsy in his teen years, he had gone on to attend the only medical school in the region.

[13] "The Nobel Prize in Physiology or Medicine 2005," NobelPrize.org, accessed March 11, 2019, https://www.nobelprize.org/prizes/medicine/2005/warren/facts/; Marshall, Helicobacter *Pioneers;* Richard Heatley, *The* Helicobacter Pylori *Handbook,* 2nd ed. (Oxford, England?; Malden, Mass: Blackwell Science, 1998); Julie Parsonnet, "Clinician-Discoverers — Marshall, Warren, and H. Pylori," *New England Journal of Medicine* 353, no. 23 (December 8, 2005): 2421–23, https://doi.org/10.1056/NEJMp058270; Barry J. Marshall, "One Hundred Years of Discovery and Rediscovery of *Helicobacter Pylori* and Its Association with Peptic Ulcer Disease," in Helicobacter Pylori: *Physiology and Genetics,* ed. Harry LT Mobley, George L. Mendz, and Stuart L. Hazell (Washington (DC): ASM Press, 2001), http://www.ncbi.nlm.nih.gov/books/NBK2432/; Barry Marshall, "A Brief History of the Discovery of *Helicobacter Pylori,*" 2016.

[14] John S. Edkins, who identified the digestive hormone gastrin, studied the effects of bacteria in cats' stomachs, but he never made the leap to analyzing bacteria found in human stomach tissues. Marshall and other researchers would later compile some of these accounts into histories. See for example: Marshall, Helicobacter *Pioneers;* Marshall, "One Hundred Years of Discovery and Rediscovery of *Helicobacter Pylori";* Gustafson and Welling, "'No Acid, No Ulcer'—100 Years Later." Kidd and Modlin, "A Century of Helicobacter Pylori"; Crowe, *Acid-Peptic Diseases of the Stomach and Duodenum Including* Helicobacter Pylori *and* NSAID.

[15] Marshall was the son of a miner and a nurse, and had grown up in and around Perth, where he also attended medical school. "The Nobel Prize in Physiology or Medicine 2005," NobelPrize.org, accessed May 3, 2019, https://www.nobelprize.org/prizes/medicine/2005/marshall/biographical/

[16] Gustafson and Welling, "'No Acid, No Ulcer'—100 Years Later." "The Nobel Prize in Physiology or Medicine 2005," NobelPrize.org, accessed May 3, 2019, https://www.nobelprize.org/prizes/medicine/2005/marshall/biographical/; Parsonnet, "Clinician-Discoverers — Marshall, Warren, and H. Pylori"; Marshall, Helicobacter *Pioneers;* Marshall, "A Brief History of the Discovery of *Helicobacter Pylori";* Marshall, "One Hundred Years of Discovery and Rediscovery of *Helicobacter Pylori* and Its Association with Peptic Ulcer Disease"; Barry J. Marshall, "*Campylobacter Pyloridis* and Gastritis," *The Journal of Infectious Diseases* 153, no. 4 (1986): 650–57; BarryJ Marshall and J. Robin Warren, "UNIDENTIFIED CURVED BACILLI IN THE STOMACH OF PATIENTS WITH GASTRITIS AND PEPTIC ULCERATION," *The Lancet,* Originally published as Volume 1, Issue 8390, 323, no. 8390 (June 16, 1984): 1311–15, https://doi.org/10.1016/S0140-6736(84)91816-6.

[17] Warren's letter described the lab agent he used to identify the bacteria, as well as the conditions that accompanied the infections; Marshall's letter summarized past reports of similar bacteria in humans, explained that animals apparently harbored different stomach bacteria, and described how he and Warren had grown the bacteria in the lab.

[18] Kidd and Modlin, "A Century of *Helicobacter Pylori*"; "NEW FACES AMONG THE *CAMPYLOBACTERS," The Lancet,* Originally published as Volume 2, Issue 8351, 322, no. 8351 (September 17, 1983): 662, https://doi.org/10.1016/S0140-6736(83)92538-2; J. Robin Warren and Barry Marshall, "UNIDENTIFIED CURVED BACILLI ON GASTRIC EPITHELIUM IN ACTIVE CHRONIC GASTRITIS," *The Lancet* 321, no. 8336 (1983): 1273–1275, https://doi.org/10.1016/S0140-6736(83)92719-8; Marshall, Helicobacter *Pioneers;* "SPIRALS AND ULCERS," *The Lancet,* Originally published as Volume 1, Issue 8390, 323, no. 8390 (June 16, 1984): 1336–37, https://doi.org/10.1016/S0140-6736(84)91827-0; "The Nobel Prize in Physiology or Medicine 2005"; "The Nobel Prize in Physiology or Medicine 2005"; Heatley, *The* Helicobacter Pylori *Handbook;* Parsonnet, "Clinician-Discoverers — Marshall, Warren, and *H. Pylori*"; Steffen Backert and Yoshio Yamaoka, Helicobacter Pylori *Research: From Bench to Bedside* (Tokyo, JAPAN: Springer, 2016), http://ebookcentral.proquest.com/lib/harvard-ebooks/detail.action?docID=4526263; Crowe, *Acid-Peptic Diseases of the Stomach and Duodenum Including* Helicobacter Pylori *and* NSAIDs; Blaser, "Hypothesis"; Michael Specter, "GERMS ARE US: Annals of Science," *The New Yorker;* New York, October 22, 2012.

[19] Following the model established by German physician Robert Koch in 1890, researchers sought to prove connections between bacteria and disease by showing that the bacteria was present in all cases of the disease. Then researchers would isolate the bacteria from a host, grow it in a lab, use the lab-grown bacteria to infect a new host, and, finally, isolate the bacteria from the newly-infected host. Frequently this research was undertaken by infecting and testing animals, however, *H. pylori* did not grow in the animals typically used for research, such as pigs, dogs, cats, rats, or mice. In addition, the bacteria took a comparatively long time (several days) to grow in a lab dish. These factors would slow research for years to come. Kidd and Modlin, "A Century of *Helicobacter Pylori*"; "NEW FACES AMONG THE *CAMPYLOBACTERS*"; Robin Warren and Marshall, "UNIDENTIFIED CURVED BACILLI ON GASTRIC EPITHELIUM IN ACTIVE CHRONIC GASTRITIS"; Marshall, Helicobacter *Pioneers;* "SPIRALS AND ULCERS"; "The Nobel Prize in Physiology or Medicine 2005"; "The Nobel Prize in Physiology or Medicine 2005"; Heatley, *The* Helicobacter Pylori *Handbook;* Parsonnet, "Clinician-Discoverers — Marshall, Warren, and *H. Pylori*"; Backert and Yamaoka, Helicobacter Pylori *Research;* Crowe, *Acid-Peptic Diseases of the Stomach and Duodenum Including* Helicobacter Pylori *and* NSAIDs; Blaser, "Hypothesis"; Specter, "GERMS ARE US."

[20] Barry Marshall and Paul C Adams, "*Helicobacter Pylori:* A Nobel Pursuit?," *Canadian Journal of Gastroenterology* 22, no. 11 (November 2008): 895–96; B. J. Marshall et al., "Attempt to Fulfil Koch's Postulates for Pyloric *Campylobacter," The Medical Journal of Australia* 142, no. 8 (1985): 436–39, https://doi.org/10.5694/j.1326-5377.1985.tb113443.x; "The Nobel Prize in Physiology or Medicine 2005"; Marshall, Helicobacter *Pioneers;* "The Doctor Who Drank Infectious Broth, Gave Himself an Ulcer, and Solved a Medical Mystery | DiscoverMagazine.Com," accessed March 27, 2019, http://discovermagazine.com/2010/mar/07-dr-drank-broth-gave-ulcer-solved-medical-mystery; Claudia Cornwall, *Catching Cancer: The Quest for Its Viral and Bacterial Causes* (Rowman & Littlefield Publishers, 2013); Alison George, "Hard to Swallow: As a Junior Doctor, Barry Marshall Was so Sure the Medical Establishment Was Wrong about the

Cause of Stomach Ulcers That He Swallowed the Bacteria He Believed Were to Blame. It Still Took Years to Convince Everyone--but It Was to Win Him a Share in a Nobel Prize. Alison George Asked Him How He Did It.(Interview)," *New Scientist* 192, no. 2581 (2006): 53.

[21]"The Doctor Who Drank Infectious Broth, Gave Himself an Ulcer, and Solved a Medical Mystery | DiscoverMagazine.Com"; "The Nobel Prize in Physiology or Medicine 2005"; "Barry J. Marshall - Nobel Lecture: *Helicobacter* Connections," accessed July 25, 2017, https://www.nobelprize.org/nobel_prizes/medicine/laureates/2005/marshall-lecture.html; Marshall, Helicobacter *Pioneers;* Marshall, "One Hundred Years of Discovery and Rediscovery of *Helicobacter Pylori* and Its Association with Peptic Ulcer Disease."

[22] The urea turns bright yellow when concentrated in gel, and the color change to pink is due to the production of ammonia. See B. Marshall et al., "Rapid Urease Test in the Management of *Campylobacter Pyloridis* -Associated Gastritis.," *American Journal of Gastroenterology* 82, no. 3 (1987): 200–210, https://doi.org/10.1111/j.1572-0241.1987.tb05292.x

[23] -M. -L. Langenberg et al., "*CAMPYLOBACTER*-UKE ORGANISMS IN THE STOMACH OF PATIENTS AND HEALTHY INDIVIDUALS," *The Lancet,* Originally published as Volume 1, Issue 8390, 323, no. 8390 (June 16, 1984): 1348–49, https://doi.org/10.1016/S0140-6736(84)91836-1.

[24] Langenberg et al.

[25] B. Marshall et al., "Rapid Urease Test in the Management of *Campylobacter Pyloridis* -Associated Gastritis.," *American Journal of Gastroenterology* 82, no. 3 (1987): 200–210, https://doi.org/10.1111/j.1572-0241.1987.tb05292.x; G. Oderda et al., "Rapid Urease Test (CLO-Test) for Early Detection of *Campylobacter Pylori* Infection in Children," *The American Journal of Gastroenterology* 83, no. 7 (July 1988): 792; P. E. Coudron and D. F. Kirby, "Comparison of Rapid Urease Tests, Staining Techniques, and Growth on Different Solid Media for Detection of *Campylobacter Pylori," Journal of Clinical Microbiology* 27, no. 7 (July 1989): 1527–30; Linda C. Higgins. "Ulcers and Gastritis: The *Campylobacter* Controversy." *Medical World News.* December 28, 1987 (Cover Story), pages 44-56; Frost & Sullivan. (1998) U.S. Peptic Ulcer Therapeutics and *H. pylori* Diagnostics Markets.

[26] Isolde Apel et al., "Antibody Response of Patients against a 120 KDa Surface Protein of *Campylobacter Pylori," Zentralblatt Für Bakteriologie, Mikrobiologie Und Hygiene.* Series A: Medical Microbiology, Infectious Diseases, Virology, Parasitology 268, no. 2 (April 1, 1988): 271–76, https://doi.org/10.1016/S0176-6724(88)80012-9.

[27] Frost & Sullivan. (1998) U.S. Peptic Ulcer Therapeutics and *H. pylori* Diagnostics Markets.

[28] C. A. McNulty, J. Dent, and R. Wise, "Susceptibility of Clinical Isolates of *Campylobacter Pyloridis* to 11 Antimicrobial Agents.," *Antimicrobial Agents and Chemotherapy* 28, no. 6 (December 1, 1985): 837–38, https://doi.org/10.1128/AAC.28.6.837; C. A. McNulty and J. C. Dent, "Susceptibility of Clinical Isolates of *Campylobacter Pylori* to Twenty-One Antimicrobial Agents," *European Journal of Clinical Microbiology & Infectious Diseases: Official Publication of the European Society of Clinical Microbiology* 7, no. 4 (August 1988): 566–69.

[29] Barry Marshall et al., "Prospective Double-Blind Trial of Duodenal Ulcer Relapse after Eradication of *Campylobacter Pylori," The Lancet* 2, no. 8626 (1988): 1437–42, https://doi.org/10.1016/S0140-6736(88)90929-4; Soon after, researchers in Sweden corroborated Marshall's results. See: P. Unge et al., "Does Omeprazole Improve Antimicrobial Therapy Directed towards Gastric *Campylobacter Pylori* in Patients with Antral Gastritis? A Pilot Study," *Scandinavian Journal of Gastroenterology.* Supplement 167 (1989): 49–54.

[30] Unge et al., "Does *Omeprazole* Improve Antimicrobial Therapy Directed towards Gastric *Campylobacter Pylori* in Patients with Antral Gastritis?"; T. J. Borody et al., "Recurrence of Duodenal Ulcer and *Campylobacter Pylori* Infection after Eradication," *The Medical Journal of Australia* 151, no. 8 (October 16, 1989): 431–35; L. L. George et al., "Cure of Duodenal Ulcer after Eradication of *Helicobacter Pylori," The Medical Journal of Australia* 153, no. 3 (August 6, 1990): 145–49; E. A. J. Rauws and G. N. J. Tytgat, "Cure of Duodenal Ulcer Associated with Eradication of *Helicobacter Pylori," The Lancet,* Originally published as Volume 1, Issue 8700, 335, no. 8700 (May 26, 1990): 1233–35, https://doi.org/10.1016/0140-6736(90)91301-P; On the history of combination drugs, see: Scott H. Podolsky and Jeremy A. Greene, "Combination Drugs — Hype, Harm, and Hope," *New England Journal of Medicine* 365, no. 6 (August 11, 2011): 488–91, https://doi.org/10.1056/NEJMp1106161.

[31]The compound interfered with the thyroid's ability to use iodine for hormone production, and iodine collected in the thymus (below the thyroid), eventually inducing malignant growths.

[32] Jie Jack Li, *Blockbuster Drugs: The Rise and Fall of the Pharmaceutical Industry* (OUP USA, 2014).

[33]In 1960, the inventor of modern endoscopes, a London-trained South African, had founded an exceptionally strong gastroenterology research program at the University of Alabama.

[34] Li.

[35] The history of H2 blockers and PPIs thus demonstrates two contrasting approaches to drug discovery. As mentioned, Astra and Smith Kline started research around the same time in the 1960s. Astra took the traditional approach of synthesizing and testing many compounds until it found one that had the desired effect--the reduction of acid in the stomach. A decade later, Astra had an effective – but toxic – drug, and research had stalled. By contrast, Smith, Kline used the new "rational" approach to drug design. Their researchers identified a target molecule crucial to the production of acid and synthesized and tested compounds that disrupted the functioning of that molecule. A decade later, Smith, Kline launched Tagamet. Astra abandoned their traditional approach after meeting the Alabama researchers; thereafter, they designed and tested drugs that targeted the proton pump in the stomach gland.

[36] Astra marketed the drug in Europe under the name "Lo-Sec" and in the U.S. under the name "Prilosec." Astra would go on to develop and introduce an improved PPI ("Nexium") in 2000.

[37] Marshall, Helicobacter *Pioneers;* Erik Fellenius et al., "Substituted Benzimidazoles Inhibit Gastric Acid Secretion by Blocking (H + + K +) ATPase," Nature 290, no. 5802 (March 1981): 159, https://doi.org/10.1038/290159a0; P. Unge, "Antibiotic Treatment of *Helicobacter Pylori* Infection," *Current Topics in Microbiology and Immunology* 241 (1999): 261–300; F. Bazzoli et al., "EFFICACY AND TOLERABILITY OF A SHORT-TERM, LOW-DOSE TRIPLE THERAPY FOR ERADICATION OF *HELICOBACTER-PYLORI," Gastroenterology* 104, no. 4 (1993): A40–A40; F. Bazzoli et al., "SHORT-TERM LOW-DOSE TRIPLE THERAPY FOR THE ERADICATION OF *HELICOBACTER-PYLORI," European Journal Of Gastroenterology & Hepatology* 6, no. 9 (1994): 773–777, https://doi.org/10.1097/00042737-199409000-00004; Lars Olbe, Enar Carlsson, and Per Lindberg, "A Proton-Pump Inhibitor Expedition: The Case Histories of *Omeprazole* and *Esomeprazole," Nature Reviews Drug Discovery* 2, no. 2 (February 2003): 132–39, https://doi.org/10.1038/nrd1010; Fellenius et al., "Substituted Benzimidazoles Inhibit Gastric Acid Secretion by Blocking (H + + K +) ATPase"; R. Huber et al., "The Continuing Development of Proton Pump Inhibitors with Particular Reference to Pantoprazole," *Alimentary Pharmacology & Therapeutics* 9, no. 4 (August 1, 1995): 363–78, https://doi.org/10.1111/j.1365-2036.1995.tb00394.x; Per Lindberg et al., "Omeprazole: The First Proton Pump Inhibitor," *Medicinal Research Reviews* 10, no. 1 (1990): 1–54, https://doi.org/10.1002/med.2610100102; Li, *Blockbuster Drugs.*

[38] Marshall, Helicobacter *Pioneers*; Christopher M. Wittich, Christopher M. Burkle, and William L. Lanier, "Ten Common Questions (and Their Answers) About Off-Label Drug Use," Mayo Clinic Proceedings 87, no. 10 (October 2012): 982–90, https://doi.org/10.1016/j.mayocp.2012.04.017; Crowe, *Acid-Peptic Diseases of the Stomach and Duodenum Including* Helicobacter Pylori *and* NSAIDs.

[39] As Marshall notes in his Nobel biography, "In the USA David Graham, Pete Peterson and Martin Blaser began as critics." Each went on to make major contributions to *H. pylori* research. "The Nobel Prize in Physiology or Medicine 2005."

[40] V. Prado et al., "*[Campylobacter pylori* in children and adults subjected to endoscopy, correlation of endoscopic, bacteriologic and histopathologic findings]," *Revista Medica De Chile* 116, no. 6 (June 1989): 503–8; F. Beg et al., "*Campylobacter Pylori* Infection in Patients Undergoing Endoscopy in Fiji," *The New Zealand Medical Journal* 101, no. 842 (March 23, 1988): 140–41; Spires D. Ladas, Theodores Rokkas, and Sotos A. Raptis, "A Gastrointestinal Endoscopy Service in Greece," *Gastrointestinal Endoscopy* 33, no. 2 (April 1987): 131–32, https://doi.org/10.1016/S0016-5107(87)71543-0; E. Pateraki et al., "Seroepidemiology of *Helicobacter Pylori* Infection in Greece," FEMS Microbiology Immunology 2, no. 3 (October 1990): 129–36; P. Abraham and S. J. Bhatia, "*Helicobacter Pylori* in Its Lair: A Role in Ulcer Recurrence?," *Indian Journal of Gastroenterology: Official Journal of the Indian Society of Gastroenterology* 9, no. 4 (October 1990): 265–66; D. P. Britt et al., "*Helicobacter Pylori* in Dyspeptic Patients in Kuwait," *Journal of Clinical Pathology* 43, no. 12 (December 1990): 987–91; Y. M. Cheong et al., "Detection of *Helicobacter Pylori* from Endoscopic Biopsies and the Biochemical Characteristics of These Isolates," *The Malaysian Journal of Pathology* 12, no. 2 (December 1990): 97–100; M. I. Nafeeza et al., "*Campylobacter Pylori*, Non-Ulcer Dyspepsia, and Race in Malaysia," *Lancet (*London, England) 1, no. 8645 (May 6, 1989): 1018; M. Dehesa Violante, "[Clinical importance of *Campylobacter pylori*. Second part]," *Revista De Gastroenterologia De Mexico* 54, no. 4 (December 1989): 243–49; E. Ocaña Andrade et al., "[*Campylobacter pylori* in endoscopic biopsies of the gastric antrum and its association with chronic gastritis]," *Revista De Gastroenterologia De Mexico* 54, no. 4 (December 1989): 207–11; R. Baqai, "*Campylobacter Pylori* in Gastroduodenal Disease," *JPMA. The Journal of the Pakistan Medical Association* 38, no. 10 (October 1988): 253–55; J. Muszy?ski and M. Stepka, "[*Campylobacter pylori* infection--a new concept of the etiology of stomach diseases]," *Polski Tygodnik Lekarski* (Warsaw, Poland: 1960) 43, no. 35 (August 29, 1988): 1107–10; A. Regu?a and J. Dzieniszewski, "*[Campylobacter pylori* in diseases of the stomach and duodenum]," *Wiadomosci Lekarskie* (Warsaw, Poland: 1960) 42, no. 16–18 (September 15, 1989): 945–51; H. M. al-Freihi et al., "*Campylobacter Pylori* in Saudi Patients Undergoing Upper Gastrointestinal Endoscopy: Prevalence and Effect of Conventional Therapy," *Hepato-Gastroenterology* 36, no. 6 (December 1989): 516–18; M. A. al-Moagel et al., "Prevalence of *Helicobacter* (Formerly *Campylobacter) Pylori* Infection in Saudia Arabia, and Comparison of Those with and without Upper Gastrointestinal Symptoms," *The American Journal of Gastroenterology* 85, no. 8 (August 1990): 944–48; M. C. J. M. Becx et al., "Metronidazole-Resistant *Helicobacter Pylori," The Lancet,* Originally published as Volume 1, Issue 8688, 335, no. 8688 (March 3, 1990): 539–40, https://doi.org/10.1016/0140-6736(90)90772-W; K. Jaskiewicz et al., "The Association of *Campylobacter Pylori* with Mucosal Pathological Changes in a Population at Risk for Gastric Cancer," *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde* 75, no. 9 (May 6, 1989): 417–19; G. Nicholson et al., "*Campylobacter Pylori* Infection in Patients Undergoing Endoscopy in Tonga," *The New Zealand Medical Journal* 101, no. 841 (March 9, 1988): 124; C. Fendri et al., "[Diagnosis of gastritis caused by *Campylobacter pylori*. Presentation of 3 methods: bacteriology, histology and immunoblotting]," *La Tunisie Medicale* 67, no. 3 (March 1989): 151–54; S. Korbi and C. Bouzakoura, "*[Campylobacter pylori* and gastric ulcer]," *La Tunisie Medicale* 66, no. 3 (March 1988): 161–64; Y. Wang et al., "[Comparative study of *Campylobacter pyloridis* and *Campylobacter jejuni* under electron microscope]," *Hua Xi Yi Ke Da Xue Xue Bao = Journal of West China University of Medical Sciences = Huaxi Yike Daxue Xuebao* 21, no. 4 (September 1990): 390–93; Yong-Yi Feng and Ya Wang, "*CAMPYLOBACTER PYLORI* IN PATIENTS WITH GASTRITIS, PEPTIC ULCER, AND CARCINOMA OF THE STOMACH IN LANZHOU, CHINA," *The Lancet,* Originally published as Volume 1, Issue 8593, 331, no. 8593 (May 7, 1988): 1055–56, https://doi.org/10.1016/S0140-6736(88)91877-6; T. Rokkas et al., "Non-Ulcer Dyspepsia and Short Term De-Nol Therapy: A Placebo Controlled Trial with Particular Reference to the Role of *Campylobacter Pylori," Gut* 29, no. 10 (October 1988): 1386–91; D. Forman et al., "Geographic Association of *Helicobacter Pylori* Antibody Prevalence and Gastric Cancer Mortality in Rural China," *International Journal of Cancer* 46, no. 4 (October 15, 1990): 608–11; M. Asaka et al., "[Clinical significance of ELISA for *Campylobacter pylori]," Nihon Shokakibyo Gakkai Zasshi = The Japanese Journal of Gastro-Enterology* 85, no. 4 (April 1988): 950; Masahiro Asaka et al., "Relationship of *Helicobacter Pylori* to Serum Pepsinogens in an Asymptomatic Japanese Population," *Gastroenterology* 102, no. 3 (1992): 760–766, https://doi.org/10.1016/0016-5085(92)90156-S. and Ulcer Recurrence after Treatment with Colloidal Bismuth Subcitrate or Cimetidine," *Gastroenterology* 101, no. 5 (November 1991): 1187–91; G. W. Lachlan, H. M. Gilmour, and J. J. Jass, "*Campylobacter Pylori* in

Central Africa," *British Medical Journal* (Clinical Research Ed.) 296, no. 6614 (January 2, 1988): 66; J. de Portugal, M. Cordero, and J. M. de Luis, "[Clinical significance of *Helicobacter pylori],*" *Anales De Medicina Interna* (Madrid, Spain: 1984) 7, no. 12 (December 1990): 641–44; J. de Portugal, M. Cordero, and J. M. de Luis, "[Clinical significance of *Helicobacter pylori],*" *Anales De Medicina Interna* (Madrid, Spain: 1984) 7, no. 12 (December 1990): 641–44; Deb Mukhopadhyay, "A Study of Prevalence of *Helicobacter (Campylobacter) Pylori* in Non-Ulcer Dyspepsia" (ProQuest Dissertations Publishing, 1990); Wadieh Yacoub, "Immunocytochemical and Morphometric Studies of the Gastric and Duodenal G, D and EC Cells in Acid Peptic Disorders" (ProQuest Dissertations Publishing, 1988), http://search.proquest.com/docview/303600030/?pq-origsite=primo; A. S. Taha et al., "PROSTAGLANDINS AND *CAMPYLOBACTER PYLORI,*" *The Lancet,* Originally published as Volume 2, Issue 8666, 334, no. 8666 (September 30, 1989): 800–801, https://doi.org/10.1016/S0140-6736(89)90860-X See also Alfonso Calvo et al., "Results of a Population-Based Gastric Cancer Screening Program Conducted in Chile 1996-2008," *Gastroenterology,* 2011 DDW Abstract Supplement, 140, no. 5, Supplement 1 (May 1, 2011): S-419, https://doi.org/10.1016/S0016-5085(11)61720-4; Takuya Okada et al., "International Collaboration between Japan and Chile to Improve Detection Rates in Colorectal Cancer Screening," *Cancer* 122, no. 1 (January 1, 2016): 71–77, https://doi.org/10.1002/cncr.29715;.

[41] David Y. Graham, "Treatment of Peptic Ulcers Caused by Helicobacter Pylori," New England Journal of Medicine 328, no. 5 (February 4, 1993): 349–50, https://doi.org/10.1056/NEJM199302043280512; Dy Graham et al., "Effect of Treatment of Helicobacter-Pylori Infection on the Long-Term Recurrence of Gastric or Duodenal-Ulcer - a Randomized, Controlled-Study," Annals of Internal Medicine 116, no. 9 (May 1, 1992): 705–8, https://doi.org/10.7326/0003-4819-116-9-705; E. Hentschel et al., "Effect of Ranitidine and Amoxicillin Plus Metronidazole on the Eradication of Helicobacter-Pylori and the Recurrence of Duodenal-Ulcer," New England Journal of Medicine 328, no. 5 (February 4, 1993): 308–12, https://doi.org/10.1056/NEJM199302043280503; See also: S. K. Lam, "Duodenal Ulcer Relapse after Eradication of Campylobacter Pylori," Lancet (London, England) 1, no. 8634 (February 18, 1989): 384; Dy Graham et al., "Effect of Triple Therapy (Antibiotics Plus Bismuth) on Duodenal-Ulcer Healing - a Randomized Controlled Trial," Annals of Internal Medicine 115, no. 4 (August 15, 1991): 266–69, https://doi.org/10.7326/0003-4819-115-4-266.

[42] A. H. Soll, "Consensus Conference. Medical Treatment of Peptic Ulcer Disease. Practice Guidelines. Practice Parameters Committee of the American College of Gastroenterology," *JAMA* 275, no. 8 (February 28, 1996): 622–29; P. Malfertheiner et al., "Current Concepts in the Management of *Helicobacter Pylori* Infection—The Maastricht 2?2000 Consensus Report," *Alimentary Pharmacology & Therapeutics* 16, no. 2 (2002): 167–180, https://doi.org/10.1046/j.1365-2036.2002.01169.x; "The National Institutes of Health (NIH) Consensus Development Program: *Helicobacter Pylori* in Peptic Ulcer Disease," accessed June 15, 2017, https://consensus.nih.gov/1994/1994HelicobacterPyloriUlcer094html.htm; see also the summary offered in G. N. J. Tytgat, "No *Helicobacter Pylori,* No *Helicobacter Pylori*-Associated Peptic Ulcer Disease," *Alimentary Pharmacology & Therapeutics* 9 (April 1, 1995): 39–42, https://doi.org/10.1111/j.1365-2036.1995.tb00782.x.

[43]"Mono61-8.Pdf." Accessed June 1, 2018. http://monographs.iarc.fr/ENG/Monographs/vol61/mono61-8.pdf. "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans – IARC." Accessed April 8, 2019. https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-60/. "WHO | Cancer Prevention." WHO. Accessed June 1, 2018. http://www.who.int/cancer/prevention/en/.

[44] D. Forman et al., "Geographic Association of *Helicobacter Pylori* Antibody Prevalence and Gastric Cancer Mortality in Rural China," *International Journal of Cancer* 46, no. 4 (October 15, 1990): 608–11; Forman et al., "Epidemiology of, and Risk Factors for, *Helicobacter Pylori* Infection among 3194 Asymptomatic Subjects in 17 Populations. The EUROGAST Study Group.," *Gut* 34, no. 12 (1993): 1672–76, https://doi.org/10.1136/gut.34.12.1672; P. Correa et al., "*Helicobacter Pylori* and Gastric Carcinoma. Serum Antibody Prevalence in Populations with Contrasting Cancer Risks," *Cancer* 66, no. 12 (December 15, 1990): 2569–74; Abraham Nomura et al., "*Helicobacter Pylori* Infection and Gastric Carcinoma among Japanese Americans in Hawaii," *New England Journal of Medicine* 325, no. 16 (October 17, 1991): 1132–36, https://doi.org/10.1056/NEJM199110173251604.

[45] Reports on U.S. press coverage appear in "CORTECS INTERNATIONAL LIMITED: AGREEMENT WITH ASTRA RE HELISAL RAPID (Part A)" in *Australian Stock Exchange Company Announcements,* 19 January 1994; and see also: Altman, Lawrence K., "Antimicrobial Drugs Endorsed for Ulcers In a Major U.S. Shift" in *The New York Times,* 10 February 1994; Bishop, Jerry E., "Bacterium Causes Most Peptic Ulcers --- Panel Says That Antibiotics Taken for Two Weeks Can Cure Many Cases," in *The Wall Street Journal,* 10 February 1994; "Profile: Healthwatch; ulcers found to be caused by bacteria, not stress," on the *NBC News: Nightly News,* broadcast 7 February 1994; "New peptic ulcer treatment found" in *Los Angeles Times* and *St. Petersburg Times* (Tampa Bay Times), 10 February 1994; Vigoda, Arlene. "RETURN TO SENDER" in *USA Today,* 4 February 1993; Brian O'Reilly, "Why Doctors Aren't Curing Ulcers," *Fortune* 135, no. 11 (1997): 100–112. Many of these reports encouraged ulcer patients to demand *H. pylori* testing. See also: M. Thamer et al., "Influence of the NIH Consensus Conference on *Helicobacter Pylori* on Physician Prescribing among a Medicaid Population," *Medical Care* 36, no. 5 (May 1998): 646–60; Thomas Breuer et al., "How Do Clinicians Practicing in the U.S. Manage *Helicobacter Pylori*-Related Gastrointestinal Diseases?: A Comparison of Primary Care and Specialist Physicians," *The American Journal of Gastroenterology* 93, no. 4 (1998): 553–561, https://doi.org/10.1016/S0002-9270(98)00041-0.

[46] J C Atherton and R C Spiller, "The Urea Breath Test for *Helicobacter Pylori.," Gut* 35, no. 6 (June 1, 1994): 723–25, https://doi.org/10.1136/gut.35.6.723; Alicia Ault Barnett, "FDA Panel Rejects Kit for *H Pylori* Breath Test," *The Lancet* 347, no. 9001 (March 2, 1996): 604, https://doi.org/10.1016/S0140-6736(96)91289-1; "Barry J. Marshall - Nobel Lecture"; F. Mégraud, "Comparison of Different Tests for *Campylobacter Pylori," Scandinavian Journal of Gastroenterology.* Supplement 142 (1988): 64–68; "The Nobel Prize in Physiology or Medicine 2005"; G. D. Bell et al., "14C-Urea Breath Analysis, a Non-Invasive Test for *Campylobacter Pylori* in the Stomach," *Lancet* (London, England) 1, no. 8546 (June 13, 1987): 1367–68; G. D. Bell et al., "13C-Urea Breath Test for *Helicobacter Pylori*

Infection.," *Gut* 32, no. 5 (May 1, 1991): 551–52, https://doi.org/10.1136/gut.32.5.551-a; Office of the Commissioner, "Jurisdictional Updates - Jurisdictional Update: Breath Test Combination Products," WebContent, accessed April 10, 2019, https://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm103134.htm.

[47] The FDA would not streamline such approvals until 2006. Atherton and Spiller, "The Urea Breath Test for *Helicobacter Pylori.*"; Ault Barnett, "FDA Panel Rejects Kit for *H Pylori* Breath Test"; "Barry J. Marshall - Nobel Lecture"; Mégraud, "Comparison of Different Tests for *Campylobacter Pylori*"; "The Nobel Prize in Physiology or Medicine 2005"; Bell et al., "14C-Urea Breath Analysis, a Non-Invasive Test for *Campylobacter Pylori* in the Stomach"; Bell et al., "13C-Urea Breath Test for *Helicobacter Pylori* Infection."; Commissioner, "Jurisdictional Updates - Jurisdictional Update."

[48] Frost & Sullivan. (1998) U.S. Peptic Ulcer Therapeutics and *H. pylori* Diagnostics Markets. See also the companies listed in the FDA 510(k) and PMA approval databases.

[49] Breuer et al., "How Do Clinicians Practicing in the U.S. Manage *Helicobacter Pylori*-Related Gastrointestinal Diseases?"

[50] Unlike in the case of HIV/AIDS, H. pylori infections were not immediately life threatening, so the changes in treatment practices may have seemed less urgent.

[51] Thamer et al., "Influence of the NIH Consensus Conference on *Helicobacter Pylori* on Physician Prescribing among a Medicaid Population"; Robert J. Hopkins, "Current FDA-Approved Treatments for *Helicobacter Pylori* and the FDA Approval Process," *Gastroenterology* 113, no. 6 (December 1, 1997): S126–30, https://doi.org/10.1016/S0016-5085(97)80026-1. See also: Frost & Sullivan. (1998) U.S. Peptic Ulcer Therapeutics and *H. pylori* Diagnostics Markets.

[52] The estimates of adherence to treatment guidelines were based on prescription data Thamer et al., "Influence of the NIH Consensus Conference on *Helicobacter Pylori* on Physician Prescribing among a Medicaid Population." Frost & Sullivan. (1998) U.S. Peptic Ulcer Therapeutics and *H. pylori* Diagnostics Markets.

[53] Thamer et al.; Hopkins, "Current FDA-Approved Treatments for *Helicobacter Pylori* and the FDA Approval Process." See also: Frost & Sullivan. (1998) U.S. Peptic Ulcer Therapeutics and *H. pylori* Diagnostics Market.

[54] H. J. O' Connor, "*Helicobacter Pylori* and Dyspepsia: Physicians' Attitudes, Clinical Practice, and Prescribing Habits," *Alimentary Pharmacology & Therapeutics* 16, no. 3 (2002): 487–496, https://doi.org/10.1046/j.1365-2036.2002.01183.x; Breuer et al., "How Do Clinicians Practicing in the U.S. Manage *Helicobacter Pylori*-Related Gastrointestinal Diseases?"

[55] Frost & Sullivan. (1998) U.S. Peptic Ulcer Therapeutics and *H. pylori* Diagnostics Markets. See also the companies and packs listed in the FDA 510(k) and PMA approval databases.

[56] Michael Mosley, *Ulcer Wars* (London: BBC Worldwide, 1994); Peter Millson, Michael Mosley, and British Broadcasting Corporation, *Ulcer Wars: Text Adapted from the Programme Transmitted 16 May 1994, Repeated 5 December 1994* (London: BBC, 1995).

[57] O' Connor, "*Helicobacter Pylori* and Dyspepsia"; H. O'Connor and S. Sebastian, "The Burden of *Helicobacter Pylori* Infection in Europe," *Alimentary Pharmacology & Therapeutics* 18 Suppl 3 (2003): 38–44; Thomas Breuer et al., "How Do Practicing Clinicians Manage *Helicobacter Pylori*-Related Gastrointestinal Diseases in Germany? A Survey of Gastroenterologists and Family Practitioners," *Helicobacter* 3, no. 1 (1998): 1–8, https://doi.org/10.1046/j.1523-5378.1998.08027.x; For later figures, see: Doron Boltin et al., "Attitudes and Practice Related to *Helicobacter Pylori* Infection among Primary Care Physicians," *European Journal of Gastroenterology & Hepatology* 28, no. 9 (2016): 1035–1040, https://doi.org/10.1097/MEG.0000000000000659.

[58] Masahiro Asaka, "Guidelines in the management of *Helicobacter pylori* infection in Japan," *Nihon rinsho. Japanese journal of clinical medicine* 61 Suppl 2 (2003): 703–8; Masahiro Asaka, "Guidelines in the management of *H. pylori* infection in Japan," *Nihon rinsho. Japanese journal of clinical medicine* 63 Suppl 11 (2005): 12–16; Masahiro Asaka, "Guidelines in the management of *H. pylori* infection in Japan--2009 version," *Nihon rinsho. Japanese journal of clinical medicine* 67, no. 12 (2009): 2227–32; Seiji Shiota et al., "*Helicobacter Pylori* Infection in Japan," *Expert Review of Gastroenterology & Hepatology* 7, no. 1 (January 2013): 35–40, https://doi.org/10.1586/egh.12.67; Shinzo Hiroi et al., "Impact of Health Insurance Coverage for *Helicobacter Pylori* Gastritis on the Trends in Eradication Therapy in Japan: Retrospective Observational Study and Simulation Study Based on Real-World Data," *BMJ Open* 7, no. 7 (July 1, 2017): e015855, https://doi.org/10.1136/bmjopen-2017-015855; Naomi Uemura et al., "*Helicobacter Pylori* Infection and the Development of Gastric Cancer," *New England Journal of Medicine* 345, no. 11 (September 13, 2001): 784–89, https://doi.org/10.1056/NEJMoa001999; Masahiro Asaka et al., "Guidelines for the Management of *Helicobacter Pylori* Infection in Japan: 2009 Revised Edition," *Helicobacter* 15, no. 1 (2010): 1–20, https://doi.org/10.1111/j.1523-5378.2009.00738.x; M. Asaka et al., "Guidelines in the Management of *Helicobacter Pylori* Infection in Japan," *Helicobacter* 6, no. 3 (September 2001): 177–86.

[59]For instance, Dr. Martin Blaser, who helped establish the link between H. pylori and stomach cancer in the early 1990s, voiced concerns about the unintended consequences of eradication in a *New Yorker* article in 2012. Blaser and others pointed to research that suggested that H. pylori infections did not always cause ulcers and sometimes promoted good health by reducing the risks of developing obesity, asthma, and throat cancer. Other researchers noted that *H. pylori* had developed resistance to more antibiotics and poorly controlled use of antibiotics for ulcers had increased resistance among bacteria that caused other diseases. Still other researchers asked whether widespread screening and treatment would be cost effective in all nations, or only in some (for instance, in those countries with high rates of stomach cancer).

[60] Rolando Herrero, Julie Parsonnet, and Edwin Robert Greenberg, "Prevention of Gastric Cancer," *JAMA* 312, no. 12 (September 24, 2014): 1197–98, https://doi.org/10.1001/jama.2014.10498; Per-M. Hellstrom, "This Year's Nobel Prize to Gastroenterology: Robin Warren and Barry Marshall Awarded for Their Discovery of *Helicobacter Pylori* as Pathogen in the Gastrointestinal Tract," *World Journal of Gastroenterology* 12, no. 19 (2006): 3126–27; Stephen Pincock, "Nobel Prize Winners Robin Warren and Barry Marshall," *The Lancet* 366, no. 9495 (October 28, 2005): 1429, https://doi.org/10.1016/S0140-6736(05)67587-3; "The Nobel Prize in Physiology or Medicine 2005," NobelPrize.org, accessed May 10, 2019, https://www.nobelprize.org/prizes/medicine/2005/press-release/; Paul Moayyedi et al., "Effect of Population Screening and Treatment for *Helicobacter Pylori* on Dyspepsia and Quality of Life in the Community: A Randomised Controlled Trial," The Lancet 355, no. 9216 (May 13, 2000): 1665–69, https://doi.org/10.1016/S0140-6736(00)02236-4; J. Mason et al., "The Cost-Effectiveness of Population *Helicobacter Pylori* Screening and Treatment: A Markov Model Using Economic Data from a Randomized Controlled Trial," Alimentary Pharmacology & Therapeutics 16, no. 3 (March 2002): 559–68; Kentaro Sugano et al., "Kyoto Global Consensus Report on *Helicobacter Pylori* Gastritis," *Gut* 64, no. 9 (2015): 1353, https://doi.org/10.1136/gutjnl-2015-309252; Parsonnet, "Clinician-Discoverers — Marshall, Warren, and *H. Pylori.*"