The Rediscovery of *H. pylori* Bacteria in the Gastric Mucosa by Robin Warren, and Implications of this Finding for Human Biology and Disease

Steven F. Moss

Published online: 12 October 2013
© Springer Science+Business Media New York 2013

Robin Warren in his lab. Perth, Western Australia, 1986

Introduction

Every current medical student has learned the story of the discovery of the bacteria now known as *Helicobacter pylori*. Robin Warren, a clinical pathologist in Perth, Western Australia, observed gastric bacteria under the microscope that no one else believed existed, that is until a young medical resident, Barry Marshall, drank a home-brewed culture to prove that the bacteria cause gastritis. Fast forward 25 years and they are awarded the Nobel Prize for their discovery.

Gastroenterologists are familiar with Marshall's side of the story, since he is one of our own. Warren's part in the initiation of the *H. pylori* saga is less well known in popular mythology, but it is well worth retelling. To do so, I have leaned heavily on Warren's compelling 2005 address to the Nobel Committee [1] when he and Marshall were awarded the prize in medicine or physiology for their discovery of *H. pylori* and its role in gastritis and peptic ulcer disease. The chapter Warren wrote in the fascinating book *Helicobacter Pioneers* edited by Barry Marshall, provides further details [2]. I also had the pleasure of speaking with Dr. Warren in June 2013, some 34 years almost to the day since his first written description of the gastric bacteria he had recognized in a patient's routine pathology report, containing his remarkably prescient conclusions regarding their possible importance:

S. F. Moss (✉)
Department of Medicine, Rhode Island Hospital, Brown
University, 593 Eddy St, APC 414, Providence, RI 02903, USA
e-mail: Steven_Moss@brown.edu

Warren's first written description of gastric bacteria was in his clinical pathology report of an endoscopic gastric biopsy

"Surface mucosa...contains numerous coiled or curved bacilli up to 3 μ m in length....superficial erosion with some fibrinous exudate mixed with the mucus and containing occasional polymorphs. The lamina propria shows a moderate increase in small round cells with scattered plasma cells and occasional polymorphswith some evidence of atrophy."

Conclusion:..... "The bacteria have the morphology of *Campylobacter*. They appear to be actively growing and not a contaminant. I am not sure of the significance of these unusual findings, but further investigation of the patient's eating habits, gastro-intestinal function and microbiology may be worthwhile"

J.R. Warren, pathologist, June 12 1979

Photomicrograph of Warren's index case, with numerous *H. pylori* bacteria evident on silver staining

Warren's Story

John Robin Warren was born in Adelaide, South Australia. He attended medical school at Adelaide University and then spent his entire career as a pathologist at the Royal Perth Hospital in Western Australia.

In his Nobel acceptance speech, he modestly attributes his discovery of gastric bacteria to serendipity—"I was in the right place at the right time and I had the right interests and skills to do more than just pass it by." In conversation, he explains what he meant by this:

When I started as a pathologist, gastric histology was just coming in. The flexible endoscope was becoming quite common and the gastroenterologists were taking numerous biopsies from the stomach and the intestine, which they hadn't done before. The diagnosis of gastritis was very poorly understood at that time because it was rarely well seen. The specimens were usually whole stomach surgical specimens which arrived in the pathology department already autolyzed. With endoscopy, these new biopsies started appearing and they were easy to see—quite well fixed small pieces of

tissue that Whitehead described very nicely in his articles at the beginning of the 1970s.

I had some experience in microbiology as well so I was interested in bacteria, though it wasn't my main focus. I liked to stain Gram-negative bacteria and it just so happened that the silver stain I was using picked up *Helicobacter*. Otherwise, I probably would never have been able to get started because they were very hard to see with the ordinary H&E stain, but with the silver stain I could at least prove to my colleagues that they were there.

Convincing his pathology colleagues that the bacteria he was seeing might be the cause of the gastritis, and therefore of clinical significance, was quite a challenge. Fortunately, he persuaded his laboratory technicians to silver stain all gastric biopsies submitted to the department, despite their initial reluctance.

The technologists didn't like that because silver staining is laborious, time-consuming, and finicky. But by silver staining multiple biopsies, my fellow pathologists did diagnose *Helicobacter* so I developed quite a decent collection of gastric biopsies with bacteria on them. No one else was interested, however, and the clinicians thought it was a lot of rubbish. The best I could convince them was that it was a contaminant secondary to the gastritis, whereas as far as I was concerned it was pretty obviously the *cause* of the gastritis, which was always present when the bacteria were there. But I couldn't really go much further than that because I couldn't convince any clinicians to collaborate and all I could contribute was the pathology. It was very difficult. As it turned out later on, the bacteria were related to peptic ulcers, particularly duodenal ulcers, but I was never told who had a duodenal ulcer. As far as the clinicians were concerned, it was a separate disease, no more relevant than a sore toe, so they never mentioned it. Unlike gastric ulcers which could be malignant, duodenal ulcers were almost never biopsied.

In 1981, Barry Marshall was a young registrar in general medicine rotating through the gastroenterology service at Royal Perth Hospital, where he was expected to undertake a small research project. His gastroenterology consultant suggested a couple of ideas, including seeing Dr. Warren who, he was told, had been looking for a clinician collaborator for a year or so. Despite this inauspicious introduction, their collaboration rapidly led to the recognition of the association of these unknown bacteria with peptic ulcer disease, and the initial culture of *H. pylori* in the microbiology department after a fortuitously long Easter weekend—which allowed for their slow growth in vitro.

The critical initial reports describing the histology and bacterial cultures were published as two independently authored letters to *The Lancet* in 1983 under the same heading [3, 4]—an unusual scenario, as Warren explains:

That was because the letter that I sent was the summary of the article I was writing when I met Barry. But I just put it aside because we were undertaking a much wider clinico-pathological study. Since I had that paper almost ready for publication at the time, I sent a synopsis of it as my letter to *The Lancet*. Barry wrote an accompanying letter which described our clinical findings, whereas my letter describes just my own, from before I met Barry.

Even as these initial letters were in press, Warren and Marshall continued to face skepticism as they challenged the prevailing dogma that the acidic environment of the stomach was too hostile for bacterial survival, and that ulcers were related to stress and hyperacidity. An abstract submitted to the annual Gastroenterology Society of Australia meeting that was to be held in Perth in May 1983 was one of only 12 rejected (whereas 56 were accepted). Their joint publication linking the “unidentified curved bacilli” to peptic ulcer disease then underwent extensive delays at *The Lancet* ostensibly due to difficulties with finding reviewers, before finally appearing in June 1984 [5].

But the tide was turning as other investigators around the world were reporting similar findings and Marshall went on to swallow live *H. pylori* in an attempt to fulfill Koch’s postulates [6]. Warren’s continuing involvement with Marshall over the next few years led to a series of important manuscripts including the first description of a rapid urease test [7], a ^{14}C urea breath test [8] and of an enzyme-linked immunosorbent assay (ELISA) [9] for *H. pylori* diagnosis. A prospective randomized treatment trial reported that eradication therapy reduced duodenal ulcer relapse [10] and marked the tipping point after which widespread clinical adoption occurred.

Implications of the Finding

Warren and Marshall rapidly recognized the role of *H. pylori* in gastritis and peptic ulcers and Marshall even speculated in his 1983 letter to *The Lancet* that the bacteria “may have a part to play in other poorly understood, gastritis associated diseases (i.e. peptic ulcer and gastric cancer).” The growth of knowledge about this bacterium has spawned an exuberant literature (Fig. 1), even including its own dedicated journal, *Helicobacter* [11]. The impact of the discovery of *H. pylori* on the biomedical community has been enormous, influencing routine clinical management and research in

Fig. 1 The growth of scientific knowledge of *H. pylori*, 1983–2012. PubMed was searched for publications citing *Helicobacter pylori*, *Campylobacter pylori* or *Campylobacter pyloridis* in the title or abstract

numerous fields, including the basic sciences, public health and even human evolution. Research on *H. pylori* has been notable for its cross-disciplinary nature, fostering many atypical scientific collaborations—for example, between gastroenterologists and infectious disease physicians, microbiologists, immunologists, epidemiologists, pediatricians, basic and genome scientists and evolutionary biologists, to name but a few interested parties.

Some of the highlights of most interest to gastroenterologists are listed in Table 1 and discussed below.

Gastric Acid Secretion

Prior to Warren and Marshall’s discovery, the pathogenesis of “peptic” gastroduodenal ulcer disease was thought to be entirely due to abnormalities in gastrin and acid secretion. Human gastric acid secretion had been studied by increasingly sophisticated methods for at least a century. The “acid Mafia,” a well-funded, influential cadre of established investigators had described excessive basal, peak and meal-stimulated acid secretion in sporadic duodenal ulcer patients. Although it was then known that luminal acidity suppressed release of the prosecretory hormone gastrin from antral G cells, the pathophysiology of its escape from this negative feedback control in peptic ulcer subjects was unknown. Gastric ulcers, which are associated with normal or low rates of acid secretion, were instead considered to be related to a failure of host defenses. Within a few years, this thinking was turned on its head by the discovery that *H. pylori* was responsible for the gastric acid hypersecretion in duodenal ulcer disease via impaired antral somatostatin secretion and exaggerated gastrin release [12, 13]. Gastric acid hyposecretion may also result from *H. pylori* infection [14], with the net effect on acid secretion depending upon

Table 1 Implications of the discovery of *H. pylori**H. pylori* as a gastric pathogen

The dominant cause of chronic gastritis, gastroduodenal ulcers, gastric MALT lymphoma and gastric adenocarcinoma [15, 33]

H. pylori as a bacterial carcinogen

The first (and, thus far, only) bacterial carcinogen. Identification of a putative human bacterial oncoprotein (CagA). Reinvigoration of Virchow's views on the inflammatory origins of cancer. Eradication of *H. pylori* cures most gastric MALT lymphoma [16, 17, 34]

Other adverse effects of *H. pylori*

A cause of idiopathic thrombocytopenic purpura and (especially in children), obscure iron-deficiency anemia [35, 36]. Associated with stunted growth and low IQ in the developing world [37]

Whole genome sequencing

One of the first genomes to be completely sequenced, enhancing knowledge of *H. pylori* biology and pathogenesis, with implications for drug and vaccine development [38]

Gastric physiology, function and cell turnover

Examining the effects of *H. pylori* eradication improved our understanding of somatostatin/gastrin/gastric acid secretion and regulation [12–14] among other aspects of gastric biology, including physiology, microscopic histopathology, cell biology and immunology [21, 39]

Human evolution

Probing the genomic diversity of *H. pylori* among human populations has informed knowledge of human evolutionary history and migration patterns [40]. The coexistence of mammals with *Helicobacter* species is widespread, demonstrating an ancient and probably mutually beneficial, relationship

H. pylori as a beneficial commensal species?

An inverse relationship of *H. pylori* with esophageal adenocarcinoma, eosinophilic esophagitis, asthma and inflammatory bowel disease highlights the possible adverse consequences of *H. pylori*'s rapid disappearance from the human stomach for the first time, [24, 25, 28] prompting numerous other investigations of the gastrointestinal microbiota

Fig. 2 Gastric evolution. Changes in gastric physiology and function associated with *H. pylori* eradication in the developing world reveal profound effects of *H. pylori* on gastric function. Modified from Blaser MJ et al. Gut 2008;57:561–567, with permission of author and publisher

the localization of *H. pylori*-related inflammation: antral predominant inflammation is associated with hypergastrinemia whereas corpus predominant inflammation associates with parietal cell hypofunction. The effects of *H. pylori* eradication on acid secretion and some other aspects of

gastric physiology are shown in Fig. 2, illustrating how the discovery of *H. pylori* has changed our understanding of human gastric biology.

Peptic Ulcer Management

The year 1994 was a bumper one for *H. pylori*, finally bringing this bacterium to the attention of most clinicians when the NIH consensus conference report was published in the *Journal of the American Medical Association*, mandating testing for and treating *H. pylori* in ulcer disease [15]. Clinicians in the United States were finally catching up with many of their foreign colleagues who had been quicker to adopt evolving knowledge about *H. pylori*; even the “acid Mafia” finally accepted the new paradigm.

Gastric Cancer

That same year led to a landmark declaration of *H. pylori* as a definite (class 1) carcinogen by the World Health Organization's (WHO) International Agency for Research on Cancer [16] based at that time on what was fairly limited epidemiology and little experimental evidence. A wealth of research since has confirmed that link, with a surfeit of mechanistic data (including the discovery of the *H. pylori* gene product CagA, a unique bacterial oncoprotein), the development of animal models of *H. pylori*-induced cancer, and even some, albeit underpowered,

randomized trials [17] that have cemented the role of *H. pylori* as the dominant gastric carcinogen. The designation of *H. pylori* as a definite carcinogen in 1994 did, however, prevent the conduct of the large-randomized clinical trials that normally would have been required to support this hypothesis, due to ethical concerns regarding untreated controls.

Knowledge of *H. pylori*'s role in distal gastric carcinogenesis now explains much of the geographic variation in gastric cancer prevalence and the reduction of gastric cancer incidence in immigrants from the Far East to the United States, which had previously been attributed to a diminution of dietary salt and nitrates [18]. *H. pylori* infection carries the greatest weight in the tripartite etiology of gastric cancer, the other factors being diet and host genetics [19].

Gastric MALT Lymphoma

The association of a chronic bacterial infection with gastric carcinogenesis has vindicated Virchow's view of cancer as a chronic wound that fails to heal [20], and further exploration of the link between inflammatory cells and gastric cancer has led to investigating whether bone marrow-derived cells might even be the origins of *Helicobacter*-associated carcinoma [21]. The chronic antigenic drive of *H. pylori* promotes an acute and chronic cellular infiltrate. Occasionally, recruited gastric T lymphocytes undergo a neoplastic clonal evolution to a mucosal-associated lymphoid tissue (MALT) lymphoma. The discovery that *H. pylori* is responsible for the maintenance of this T cell neoplasm [22] was followed by the rapid adoption of therapeutic *H. pylori* eradication, a form of cancer chemotherapy so novel, effective (sustained cure rate of ~80 % [23]), and safe that randomized trials were never even considered. Though *H. pylori* eradication is most helpful for early-stage low-grade MALT lymphomas, it is now being extended in trials to some higher grade lesions.

Effects and Benefits Outside the Stomach

In the last decade, there has been considerable interest in exploring conditions outside the stomach that have a relationship with *H. pylori*, and in evaluating possibly beneficial consequences of the gastric carriage of *H. pylori* to humankind. *H. pylori*'s disappearance from many human populations in the developed world has coincided with the emergence of certain conditions of increasing prevalence in fully industrialized nations, including some characterized by unrestrained extragastric inflammation such as childhood-onset asthma, inflammatory bowel disease, eosinophilic esophagitis, and even esophageal adenocarcinoma [24–26]. Although the mechanisms underlying these

inverse relationships remain obscure in humans, recent studies of animal models have demonstrated that the acquisition of *H. pylori* infection early in life may enhance mucosal and systemic regulatory T cell function while suppressing auto-reactivity [27, 28]. Given these findings, it has even been proposed to intentionally introduce *H. pylori* in early childhood if it is not naturally acquired [29], with the intention of eradicating it later in adulthood before gastric disease progresses beyond the “point of no return” in gastric carcinogenesis.

While this concept is controversial, the inverse relationship of *H. pylori* and esophageal adenocarcinoma is consistent and significant—so much so that the WHO has granted *H. pylori* the dubious distinction of being the only microbe designated as a definite cause of one form of cancer (distal gastric), while being definitely *inversely* related (“protective”) against another (esophageal adenocarcinoma) [30].

Conclusions

The careful observations of a lone surgical pathologist made during his routine clinical work abruptly changed the clinical management of gastroduodenal disease worldwide, highlighting the relationship of the intestinal microbiota with gastrointestinal health and disease. But how did Warren focus on what many other pathologists using similar tools must have seen, but previously ignored?

The fact that I was interested in visual art, photography and drawing helped me. Most people point the camera at someone's face and snap it; they don't care what's around them or where the head fits in the picture. But if you want a decent picture you don't do that, you've got to look fairly carefully at what you are photographing, including everything around the subject, and not just the actual item you are interested in. And so that helped me to see something unusual, or at least have a second look when I saw it.

Though Warren did not realize it at the time, in that pre-PubMed, pre-Google era, others had previously observed and published on spiral-shaped bacteria in the stomachs of humans and other mammals over the previous century [2, 31]. An antibacterial cure for dyspepsia and ulcers had even been promoted in the 1950s [32]. Nevertheless, unlike his predecessors, Warren's insistence that there must be a clinical consequence of the severe gastritis he saw in association with *H. pylori* infection pushed him to explore his observations further by pursuing a possible association between gastric histopathology and disease. After recruiting Marshall for this purpose, as the saying goes, “the rest is history,” ultimately leading to a paradigm shift in the

way that the gastric and even the intestinal microbiota are viewed today.

Acknowledgments I greatly appreciate Professor Robin Warren agreeing to our telephone conversation; it was a great privilege for me to speak with him. I also thank Jose Aponte-Pieras for help with preparing Fig. 1.

References

1. *Helicobacter: The Ease and Difficulty of a New Discovery*. Available at: http://www.nobelprize.org/nobel_prizes/medicine/laureates/2005/warren-lecture.html. Accessed June 21, 2013.
2. Warren JR. The discovery of *Helicobacter pylori* in Perth, Western Australia. In: Marshall BJ, ed. *Helicobacter Pioneers: Firsthand Accounts from the Scientists who Discovered Helicobacters 1892–1982*. Carlton South: Blackwell; 2002:151–164.
3. Warren JR. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet*. 1983;1:1273.
4. Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet*. 1983;1:1273–1275.
5. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984;1:1311–1315.
6. Marshall BJ, Armstrong JA, McGeachie DB, Glancy RJ. Attempt to fulfill Koch's postulates for pyloric *Campylobacter*. *Med J Aust*. 1985;142:436–439.
7. Marshall BJ, Warren JR, Francis GJ, Langton SR, Goodwin CS, Blincow ED. Rapid urease test in the management of *Campylobacter pyloridis*-associated gastritis. *Am J Gastroenterol*. 1987;82:200–210.
8. Surveyor I, Goodwin CS, Mullan BP, et al. The ¹⁴C-urea breath-test for the detection of gastric *Campylobacter pylori* infection. *Med J Aust*. 1989;151:435–439.
9. Goodwin CS, Blincow E, Peterson G, et al. Enzyme-linked immunosorbent assay for *Campylobacter pyloridis*: correlation with presence of *C. pyloridis* in the gastric mucosa. *J Infect Dis*. 1987;155:488–494.
10. Marshall BJ, Goodwin CS, Warren JR, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. *Lancet*. 1988;2:1437–1442.
11. Graham DY ed. *Helicobacter*. Wiley-Blackwell. Available at [http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1523-5378/homepage/ProductInformation.html](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1523-5378/homepage/ProductInformation.html). Accessed June 21, 2013.
12. Levi S, Beardshall K, Haddad G, Playford R, Ghosh P, Calam J. *Campylobacter pylori* and duodenal ulcers: the gastrin link. *Lancet*. 1989;1:1167–1168.
13. Moss SF, Legon S, Bishop AE, Polak JM, Calam J. Effect of *Helicobacter pylori* on gastric somatostatin in duodenal ulcer disease. *Lancet*. 1992;340:930–932.
14. El-Omar EM, Oien K, El-Nujumi A, et al. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. *Gastroenterology*. 1997;113:15–24.
15. NIH Consensus Conference. *Helicobacter pylori* in peptic ulcer disease. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *JAMA*. 1994;272:65–69.
16. *Schistosomes, Liver Flukes and Helicobacter pylori*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7–14 June 1994. *IARC Monogr Eval Carcinog Risks Hum*. 1994;61:1–241.
17. Fuccio L, Zagari RM, Eusebi LH, et al. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? *Ann Intern Med*. 2009;151:121–128.
18. Haenszel W. Report of the working group on studies of cancer and related diseases in migrant populations. *Int J Cancer*. 1969;4:364–371.
19. El-Omar EM, Carrington M, Chow W, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature*. 2000;404:398–402.
20. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet*. 2001;357:539–545.
21. Houghton J, Stoicov C, Nomura S, et al. Gastric cancer originating from bone marrow-derived cells. *Science*. 2004;306:1568–1571.
22. Wotherspoon AC, Doglioni C, Diss TC, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. *Lancet*. 1993;342:575–577.
23. Zullo A, Hassan C, Cristofari F, et al. Effects of *Helicobacter pylori* eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. *Clin Gastroenterol Hepatol*. 2010;8:105–110.
24. Owyang SY, Luther J, Kao JY. *Helicobacter pylori*: beneficial for most? *Expert Rev Gastroenterol Hepatol*. 2011;5:649–651.
25. Islami F, Kamangar F. *Helicobacter pylori* and esophageal cancer risk: a meta-analysis. *Cancer Prev Res (Phila)*. 2008;1:329–338.
26. Dellon ES, Peery AF, Shaheen NJ, et al. Inverse association of esophageal eosinophilia with *Helicobacter pylori* based on analysis of a US pathology database. *Gastroenterology*. 2011;141:1586–1592.
27. Oertli M, Muller A. *Helicobacter pylori* targets dendritic cells to induce immune tolerance, promote persistence and confer protection against allergic asthma. *Gut Microbes*. 2012;3:566–571.
28. Arnold IC, Dehzad N, Reuter S, et al. *Helicobacter pylori* infection prevents allergic asthma in mouse models through the induction of regulatory T cells. *J Clin Invest*. 2011;121:3088–3093.
29. Blaser MJ. An endangered species in the stomach. *Sci Am*. 2005;292:38–45.
30. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens—part B: biological agents. *Lancet Oncol*. 2009;10:321–322.
31. Bizozzero G. Ueber die schlauchförmigen Drüsen des Magendarmkanals und die Beziehungen ihres Epithels zu dem Oberflächenepithel der Schleimhaut. *Archiv für mikroskopische Anatomie*. 1893;42:82–152.
32. Rigas B, Papyassiliou ED, John Lykoudis: The general practitioner in Greece who in 1958 discovered the etiology of, and a treatment for, peptic ulcer disease. In: Marshall BJ, ed. *Helicobacter Pioneers: Firsthand Accounts from the Scientists who Discovered Helicobacters 1892–1982*. Carlton South: Blackwell; 2002:75–88.
33. McColl KEL. *Helicobacter pylori* infection. *N Engl J Med*. 2010;362:1597–1604.
34. Wroblewski LE, Peek RM Jr. *Helicobacter pylori* in gastric carcinogenesis: mechanisms. *Gastroenterol Clin North Am*. 2013;42:285–298.
35. Qu XH, Huang XL, Xiong P, et al. Does *Helicobacter pylori* infection play a role in iron deficiency anemia? A meta-analysis. *World J Gastroenterol*. 2010;16:886–896.
36. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117:4190–4207.
37. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection—the Maastricht IV/Florence consensus report. *Gut*. 2012;61:646–664.
38. Tomb JF, White O, Kerlavage AR, et al. The complete genome sequence of the gastric pathogen *Helicobacter pylori*. *Nature*. 1997;388:539–547.

39. Ernst PB, Peura DA, Crowe SE. The translation of *Helicobacter pylori* basic research to patient care. *Gastroenterology*. 2006;130:188–206.
40. Linz B, Balloux F, Moodley Y, et al. An African origin for the intimate association between humans and *Helicobacter pylori*. *Nature*. 2007;445:915–918.