

Chapter 2

Epidemiology of Gastric Cancer and *Helicobacter pylori*

Jonathan Volk and Julie Parsonnet

Introduction

In 1994, the International Agency for Research on Cancer (IARC) declared *Helicobacter pylori* to be a type I carcinogen, or a definite cause of cancer in humans (Humans 1994). This landmark decision—based almost exclusively on epidemiologic evidence—was immediately controversial. Some argued that *H. pylori* could not be considered a “cause” of cancer but only a “risk factor” or “cofactor” (although the difference between these two is largely semantic). Others maintained that the absence of experimental evidence in animals was a critical flaw in the IARC’s arguments and left the possibility of residual confounding. Others straddled the fence in anticipation of randomized clinical trials looking at whether *H. pylori* eradication prevented cancer.

Now, almost 15 years after the IARC’s declaration, there is broad consensus that *H. pylori* causes gastric adenocarcinoma and lymphoma despite the failure of the only completed randomized treatment trial to demonstrate adenocarcinoma prevention (Wong et al. 2004). Although the biology presented in this book—including animal models—provides plausibility for this acausal association between *H. pylori* and cancer (Pritchard and Przemeck 2004), it is the depth and breadth of epidemiologic evidence that remains the foundation for the scientific conviction. Herein, we present these epidemiologic findings.

Gastric Cancer Epidemiology

Gastric cancers remain a leading cause of cancer morbidity and mortality worldwide, with adenocarcinomas arising from gastric glands accounting for 90% of incident cases (Aaltonen et al. 2000; Coleman et al. 1993). Other less-common epithelial stomach cancers include squamous cell carcinoma, adenosquamous carcinoma, small cell, and carcinoid tumors. Nonepithelial stomach cancers such as leiomyomas, stromal tumors, and malignant lymphomas can also be found in the stomach (Aaltonen et al. 2000). For this chapter, we limit discussion to adenocarcinomas.

Classifications of Adenocarcinomas of the Stomach

Adenocarcinomas—malignant tumors of glandular epithelium—can be classified as proximal tumors, which originate in the stomach cardia and gastroesophageal junction, or distal tumors, which originate in the fundus, body, or antrum of the stomach (Brown and Devesa 2002). The location of the tumor is important, because incidence, trends over time, risk factors, and mortality rates differ between distal and proximal adenocarcinomas.

In 1965, gastric adenocarcinomas were further subdivided into two distinct histologic subtypes, intestinal and diffuse (Lauren 1965), known as the Lauren classification. Intestinal-type adenocarcinomas form recognizable glands whereas diffuse adenocarcinomas consist of poorly cohesive cells that diffusely infiltrate the gastric wall and form no recognizable glands (Aaltonen et al. 2000). The Lauren classification has proven useful for observing the natural history and epidemiology of gastric cancer. Even as early as 1965, Lauren observed a male predominance and older age at diagnosis for patients with intestinal-type compared with diffuse-type gastric cancer (Lauren 1965).

Importantly, preneoplastic lesions are only associated with the later development of intestinal-type adenocarcinoma. In a model proposed by Correa (Correa 1992; Correa et al. 1975), this multistep process for progression of normal gastric cells to adenocarcinomas starts with chronic gastritis. Chronic gastritis later develops into intestinal metaplasia and dysplasia, with the partial or complete loss of cell differentiation (Aaltonen et al. 2000; Correa 2002). Ultimately, these areas of dysplasia are thought to progress to adenocarcinoma. However, because individual lesions are not followed over time without intervention, it is impossible to prove that a specific preneoplastic lesion has progressed to gastric adenocarcinoma. Others have suggested that intestinal metaplasia does not progress to carcinoma but is instead an alternate endpoint from a shared cause (Tatematsu et al. 2003). In contrast to intestinal-type adenocarcinoma, there are no clearly defined precursors for diffuse-type adenocarcinoma.

Incidence of Gastric Cancer

Based on information from the United States National Cancer Institute's Surveillance Epidemiology and End Results Program (SEER), which collected data from 17 sites between 2002–2004, 0.90% (1/111) of men and women born today in the United States will be diagnosed with stomach cancer during their lifetime. SEER data from 2000–2004 indicate current age-adjusted gastric cancer incidence rates of 11.4 per 100,000 men and 5.6 per 100,000 women annually. The median age of diagnosis is 71 years, and 70% of cases are diagnosed between ages 55–84. As of January 2004, 34,708 men and 25,592 women with gastric cancer were living in the United States (Ries et al. 2007, based on November 2006 SEER data submission, posted to the SEER Web site, 2007 #2571).

Geographical Distribution

Gastric cancer incidence rates vary significantly in different countries and regions of the world. Japan has the highest rates of stomach cancer with 77.9 cases per 100,000 males and 33.3 per 100,000 females annually. Other countries in eastern Asia (including China and Korea), eastern Europe, and tropical South America also have high gastric cancer incidence rates (Ferlay et al. 2004). In contrast, lower incidence rates of gastric cancer have been observed in eastern and northern Africa, North America, and south and southeast Asia, with average age-standardized incidence rates of 5.9–9.0 per 100,000 men and 2.6–5.3 per 100,000 women. Diagnostic and surveillance deficiencies may account for some of the reported low rates in some of these countries. Although incidence differs throughout the world, men consistently manifest incidence higher than women (Parkin et al. 1999b).

Data from England and Wales demonstrate that country of birth is a stronger predictor of stomach cancer risk than the country of current residence (Coggon et al. 1990). Immigrants who migrate from regions at high risk for gastric cancer to regions at lower risk have an intermediate risk level. A study of immigrants from Japan to Hawaii found a lower age-adjusted rate of stomach cancer among the immigrants compared with the remainder of the Japanese population still living in Japan. An even lower rate was observed among second-generation immigrants (Kolonel et al. 1981). A similar study of people from higher-risk populations in England, Scotland, Ireland, Poland, the former Yugoslavia, Greece, and Italy who moved to Australia—a low-risk population for gastric cancer—found a risk reduction that increased with time spent in Australia (McMichael et al. 1980).

Gastric cancer incidence rates also differ by ethnicity. In the United States between 2000–2004, the highest annual incidence rates were observed among Asian/Pacific Islanders (18.9 per 100,000 men and 10.8 per 100,000 women), followed by blacks (17.5 per 100,000 men and 9.1 per 100,000 women), Hispanics (16.0 per 100,000 men and 9.6 per 100,000 women), American Indians and Alaska Natives (16.3 per 100,000 men and 7.9 per 100,000 women), and whites (10.2 per 100,000 men and 4.7 per 100,000 women) (Ries et al. 2007). Interestingly, the trends observed among ethnic groups are observed for both men and women.

Trends Over Time

The incidence of gastric cancer has decreased over time. In the United States from 1975 to 2004, there was a statistically significant decrease in gastric cancer observed for both men and women (Ries et al. 2007). Outside of the United States, the incidence of stomach cancer is also decreasing (Coleman et al. 1993; Parkin et al. 1999b), even in higher-risk countries (Parsonnet 1995). In 1990, there were only 6% more gastric cancer cases compared with 1985 despite an aging population and an increase in total number of people in the world (Parkin et al. 1999a).

Differences in Epidemiology of Various Tumor Types

Changes in incidence rate described above do not apply to all types of gastric cancer. Distal (fundus, body, and antrum), intestinal-type gastric cancer incidence has declined, whereas the incidence of proximal (cardia and gastroesophageal junction) adenocarcinomas has increased. This decrease in intestinal-type tumors accounts for the overall declining trend in gastric cancer incidence (Correa and Chen 1994; Howson et al. 1986).

In contrast to more distal tumors, the incidence of proximal tumors of the gastric cardia has risen steadily from 1974 to 1994 among men, and to a lesser extent, among women. The age-standardized incidence rates increased from 2.1 to 3.3 per 100,000 among whites and 1.0 to 1.9 per 100,000 among blacks (Devesa et al. 1998). These proximal tumors are more common in developed countries, especially among whites and those of higher socioeconomic status. Obesity and gastroesophageal reflux disease (GERD) both have important pathogenic roles for this gastric cancer subtype (Crew and Neugut 2006).

Mortality and Case Fatality

Worldwide, an estimated 850,000 people died from gastric cancer in 2001 (522,000 men and 328,000 women), making gastric cancer the second leading cause of cancer death after lung cancer (Parkin et al. 1999a). As of 1990, the 5-year mortality rate for stomach cancer remained poor, only better than lung and pancreatic cancer in most regions of the world (Parkin et al. 1999a). A notable exception to this dismal prognosis is in Japan, where intensive screening efforts have resulted in the earlier diagnosis of gastric cancer and a much higher 5-year survival rate (57%). In the United States between 1992 and 1998, the overall 5-year survival for gastric cancer for all disease stages was 22% (Jemal et al. 2003); localized disease had much higher 5-year survival rates (59%) than metastatic disease (2%).

According to SEER data collected between 2000 and 2004, the median age of death from gastric cancer was 74 years, with an age-adjusted death rate of 4.2 per 100,000 people (5.9 per 100,000 men and 3.0 per 100,000 women) (Ries et al. 2007). Age-adjusted mortality rates increase dramatically with age. The mortality rate for individuals older than age 85 is 46.1 per 100,000 people, compared with 12.9 per 100,000 for people aged 65–69 and 1.3 per 100,000 for those aged 40–44. Notably, deaths from gastric cancer differed significantly among different ethnic groups and paralleled the trends observed for gastric cancer incidence. Rates were highest among black Americans (11.9 per 100,000 men and 5.8 per 100,000 women), followed by Asian/Pacific Islanders (10.5 per 100,000 men and 6.2 per 100,000 women), American Indian/Alaska native (9.6 per 100,000 men and 5.5 per 100,000 women), Hispanic (9.1 per 100,000 men and 5.1 per 100,000 women), and white Americans (5.2 per 100,000 men and 2.6 per 100,000 women) (Ries et al. 2007).

Until the 1940s, gastric cancer was the most common cause of cancer death among men (Howson et al. 1986). Decreases in stomach cancer mortality started as early as 1926. Joint point analysis from the SEER database reveals statistically significant decreases in gastric cancer mortality in the United States. Between 1990 and 2004, there was a -3% annual percentage change in gastric cancer mortality, with a -3.5% decrease observed for men between the years 1991 and 2004 and a -2.6% decrease observed among women during the same time period (Ries et al. 2007). A statistically significant decrease in gastric cancer mortality rates was also noted between 1975 and 1987 and a nonsignificant decrease between 1987 and 1990 (Ries et al. 2007). According to estimates from the National Center for Health Statistics (American Cancer Society), an estimated 21,260 Americans (13,000 men and 8,260 women) will be diagnosed with stomach cancer in 2007, with 11,210 deaths. This number represents a decrease from the 12,100 deaths seen in 2003.

The decrease in mortality rates seen in the last several decades likely reflects a decreasing incidence of gastric cancer, because the case-fatality rates have changed little. An exception to this, however, may be evident in regions where gastric cancer screening has been undertaken. By identifying early cancers, surgical intervention can be applied when it has the highest probability of benefit. Motivated by high rates of gastric cancer incidence and mortality, Japan introduced a mass screening program in the 1960s (Fukao et al. 1995). Double-contrast barium x-rays were offered in all municipalities of Japan by 1975, and more recently, people have been screened with endoscopy, serum pepsinogen concentrations, and anti-*H. pylori* antibody tests. Using observational data, including cohort studies, case-control studies, and ecologic analyses from different municipalities with varying levels of screening participation, these screening efforts are thought to have caused a decrease in stomach cancer mortality in Japan (Fukao et al. 1995; Miyamoto et al. 2007). No randomized trials of screening have been conducted and it is not clear whether similar screening efforts would yield a benefit in populations with lower rates of gastric cancer. Currently, neither the American Cancer Society (Smith et al. 2003) nor the National Cancer Institute (National Cancer Institute 2007) recommends stomach cancer screening in the United States.

Risk Factors for Gastric Cancer, Excluding *Helicobacter pylori*

Risk factors for gastric cancer that have undergone extensive investigation include genetic susceptibility, use of cigarettes, poor nutrition, alcohol abuse, obesity, gastroesophageal reflux, pernicious anemia, radiation exposure, and partial gastrectomies. When examining the relationships among these risk factors and the subsequent development of gastric cancer, it is important to control for *H. pylori*, an important confounding variable that is discussed in detail in its own section. Unfortunately, many studies of gastric cancer risk factors do not adequately control for *H. pylori* and other potential confounders. For example, although higher stomach cancer rates are seen among individuals with low socioeconomic status (Neugut et al.

1996), this depressed socioeconomic status is confounded by increased usage of tobacco, decreased intake of fruits and vegetables, poorer sanitary conditions that may and probable increased *H. pylori* transmission.

Genetic Factors

Although most familial gastric cancers results from concordant *H. pylori* infection within families (Lugli et al. 2007), there are some families with extraordinarily high rates of diffuse-type gastric cancer occurring at unusually young ages. Genetic susceptibility has proved to have a role in these families. The most well-studied familial genetic defect is a germline mutation in a cell-adhesion protein, E-cadherin. First observed in a kindred group of Maori ethnicity (Guilford et al. 1998), germline mutations of *e-cadherin* have been identified in familial cancers in Europe (Gayther et al. 1998; Guilford et al. 1999), Japan (Shinmura et al. 1999; Yabuta et al. 2002), the United States (Oliveira et al. 2002), and Korea (Yoon et al. 1999). An individual who possesses one of the germline *e-cadherin* gene mutations listed in the International Gastric Cancer Linkage Consortium has a cumulative risk of gastric cancer before 80 years of age of 67% [95% confidence interval (CI), 33%–99%] for men and 83% (95% CI, 58%–99%) for women (Pharoah et al. 2001). Fortunately, *e-cadherin* mutations are rare and are thought to account for less than 3% of gastric tumors (Stone et al. 1999).

Other genetic factors besides *e-cadherin* have been linked to malignancy. Gastric tumors are sometimes observed in hereditary cancer syndromes such as hereditary nonpolyposis colorectal cancer, Li-Fraumeni syndrome, familial adenomatous polyposis, and Peutz-Jeghers syndrome (Caldas et al. 1999). Since the first report in 1953, numerous studies have demonstrated that individuals with blood type A (El Hajj et al. 2007) have higher rates of intestinal-type gastric cancer, chronic atrophic gastritis, intestinal metaplasia, and dysplasia (El Hajj et al. 2007; Kneller et al. 1992). It is postulated that *H. pylori* expressing the BabA adhesin are better able to adhere to the gastric epithelium on individuals expressing blood type A antigens (Gerhard et al. 1999; Ilver et al. 1998), enhancing the persistence of *H. pylori* infection and subsequent gastric cancer development.

Environmental Factors

Familial clusters of cancer do not always indicate inherited genes, because smoking, environmental exposures, alcohol, and especially *H. pylori* also aggregate in families. Cigarette smoking increases the risk of proximal and distal stomach cancers independent of *H. pylori* infection. Although smoking and *H. pylori* often go hand-in-hand, an IARC working group on Tobacco Smoke and Involuntary Smoking concluded that smoking tobacco independently increased gastric cancer risk (IARC 2004) and that confounding by *H. pylori* could be “reasonably ruled out.” They also noted a dose-response relationship with tobacco exposure and

cancer risk, with decreased risk observed with increased duration of tobacco cessation. A large study by Chao et al. that followed 467,788 men and 588,053 women for 14 years concluded that 28% of gastric cancers in men and 14% in women could be attributed to smoking (Chao et al. 2002); unfortunately, *H. pylori* was not directly evaluated as a confounder in this study.

In 1997, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) conducted a thorough review exploring the relationship between food and nutrition and cancer risk (World Cancer Research Fund and American Institute for Cancer Research 1997). Using data from case-control and cohort studies, the panel concluded that diets high in fruits and vegetables conferred a protective benefit for stomach cancer. In the European Prospective Investigation into Cancer and Nutrition cohort (EPIC), a large study of 521,457 men and women aged 35–70 years, increased intake of total meat, red meat, and processed meat was associated with distal gastric cancers, although not with proximal cancers. The relationship between diet and distal cancers was particularly significant striking among individuals also infected with *H. pylori* (Gonzalez et al. 2006). This study also demonstrated an inverse relationship between gastric cancer risk and high levels of plasma vitamin C, particularly among individuals with high intakes of red meat and other processed meats.

Salt was found to be a risk factor for gastric tumors by the WCRF/AICR panel (World Cancer Research Fund and American Institute for Cancer Research 1997). One proposed mechanism for this deleterious effect is that salt results in mucosal damage in the stomach, and consequently, an inflammatory regenerative response with increased DNA synthesis and cell proliferation (Bergin et al. 2003). This increased cell proliferation in turn increases the risk for tumorigenesis. The use of refrigeration has been found to decrease stomach cancer risk, likely the result of less salt being used in refrigerated food, as well as the decreased risk of food contamination with carcinogenic compounds.

Proximal gastric cancers have a different pathogenesis and different risk factors than from tumors of the distal stomach. For example, although alcohol does not affect overall gastric cancer rates, heavy drinking may increase rates of proximal tumors (Terry et al. 2002). A significant association between body mass index and proximal tumors—but not distal tumors—has been observed (Chow et al. 1999; Ji et al. 1997; Terry et al. 2002). Although GERD is a clear risk factor for the development of adenocarcinoma of the esophagus (Farrow et al. 2000), the evidence in support of GERD as a risk factor for gastric tumors is mixed. Some studies have concluded that reflux is only weakly associated with proximal adenocarcinomas of the gastric cardia (Mayne and Navarro 2002). Other studies demonstrated increased proximal stomach cancers with increased GERD symptom severity (Lagergren et al. 1999). However, other studies have found no relationship between GERD and proximal gastric cancers (Farrow et al. 2000).

Other risk factors for gastric cancer are rarely encountered. Pernicious anemia, which may result in severe atrophic gastritis and intrinsic factor deficiency, increases risk for both gastric cancer and carcinoid tumors (Hsing et al. 1993; Kokkola et al. 1998). Exposure to radiation also increases gastric cancer risk. After the bombing

of Hiroshima and Nagasaki, a greater than expected number of gastric tumors occurred to those exposed in childhood (Kai et al. 1997).

Partial gastrectomy is a long-recognized predisposing factor for cancer. Although peptic ulcer disease and its surgical treatment have become increasingly rare in the modern era of acid inhibition, *H. pylori* eradication, and aggressive endoscopy (Higham et al. 2002; Targownik and Nabalamba 2006), some patients still undergo partial gastrectomy for gastrointestinal bleeding. A review of 58 studies showed that individuals who had partial gastrectomies and survived more than 15 years after surgery had a two- to fourfold increase in stomach cancer risk (Stalnikowicz and Benbassat 1990). A metaanalysis also done in 1990 (Tersmette et al. 1990) concluded that this increased cancer risk was limited to a subset of patients who had partial gastrectomies for gastric ulcers (relative risk = 2.12; 95% CI, 1.73–2.59) as compared with duodenal ulcers (relative risk = 0.84; 95% CI, 0.66–1.05). In support of this finding, individuals with a history of duodenal ulcer seem to be at lower risk for gastric malignancy than those without (Hansson et al. 1996).

The impact of proton pump inhibitors and histamine-2 antagonists in gastric carcinogenesis is unclear. In animals, these medications have been linked to gastric carcinoid tumors (Gillen and McColl 2001). Although there have been no longitudinal studies exploring whether proton pump inhibitors and histamine antagonists increase gastric cancer risk in humans, a postmarketing surveillance report of cimetidine indicated no increase in gastric cancer incidence with its use (Colin-Jones et al. 1992). Despite this, some researchers suggest eradicating *H. pylori* before the initiation of these medications because hypochlorhydria promotes extension of *H. pylori* throughout the stomach and development of atrophic gastritis (Kuipers et al. 1996).

Epstein-Barr Virus–Related Tumors

Fewer than 1% of gastric cancers are lymphoepithelioma-like carcinomas (LELCs) — epithelial tumors with extensive lymphoid infiltration into the stroma. These tumors are histopathologically similar to nasopharyngeal carcinomas and contain monoclonally integrated Epstein-Barr virus (EBV) (Herrmann and Niedobitek 2003; Wu et al. 2000). LELC gastric tumors have distinctive oncogene expression, such as p53 overexpression and underexpression of c-erb2 and E-cadherin that likely have causal roles for this gastric cancer subtype (Wu et al. 2000). EBV-associated tumors occur more frequently in males and in younger patients. They are also more often located in the gastric body or cardia rather than in the antrum (Takada 2000). EBV may also have a role in non-LELC gastric tumors, although the evidence remains inconclusive.

***Helicobacter pylori* Epidemiology**

Spiral-shaped bacteria were first observed in the stomachs of humans well over a century ago (Weisse 1996). Although early research linked these spiral-shaped bacteria to gastric inflammation and other upper gastrointestinal disorders (Doenges

1938; Kreinitz 1906), later studies would deem these bacteria contaminants (Palmer 1954) and the field stagnated.

The subsequent history of *H. pylori*'s "discovery" and the ultimate Nobel prize to Marshall and Warren is now widely known. Together, Marshall and Warren showed that "unidentified curved bacilli" in gastric biopsies were associated with "active, chronic gastritis" and with ulcers (Marshall and Warren 1984; Marshall et al. 1985b). In the face of the world's skepticism, Marshall ultimately swallowed an inoculum of *H. pylori* to prove its pathogenicity (Marshall et al. 1985a). Although they were barraged with criticism, Marshall and Warren persisted in their insistence that the organism caused gastritis and ulcer disease and finally a cascade of data from investigators around the world proved their theory correct.

Research reveals that humans have been infected with *H. pylori* for at least 58,000 years, before human migration from Africa (Linz et al., Nature, 2007). The investigators, using a large data set of *H. pylori* strains, found a decrease in bacterial genetic diversity with increasing distance from east Africa. In fact, human migration in modern times can be predicted from phylogenetic bacterial models (Falush et al. 2003; Kersulyte et al. 2000).

Prevalence and Incidence by Region

Approximately half of the world's population is infected with *H. pylori*, although prevalence rates differ tremendously in different regions of the world. Prevalence of *H. pylori* infection increases with age, and is higher in developing than in developed countries (Brown 2000). An exception to this increasing *H. pylori* prevalence with age is the lower prevalence often seen in the very elderly (Taylor et al. 1995). It is likely that advancing gastric atrophy and intestinal metaplasia with age sometimes causes loss of infection with advancing age in the elderly (Ohata et al. 2004).

In developing countries, infection can be so common as to be almost universal in adults, although there are some notable exceptions. For example, Indonesia and Papua New Guinea have reported disproportionately low prevalences of *H. pylori* in some regions (Mitchell et al. 1988; Tokudome et al. 2005). The pattern of higher prevalence in developing countries is also seen among children, with prevalence rates estimated as low as 1.2% in a sample of 2–4 year-old children from the Netherlands to as high as 70–80% in some developing countries (Magalhaes Queiroz and Luzzza 2006; Mourad-Baars et al. 2007).

H. pylori incidence is more difficult to determine than prevalence because the initial infection invariably goes unnoticed and undiagnosed. Based on changes in prevalence with age, the incidence of *H. pylori* has been estimated to be 1% per year among white Americans and as high as 3% per year among African Americans (Graham et al. 1991; Parsonnet 1995). The incidence of *H. pylori* in developing countries is much higher, with yearly incidence rates as high as 3%–10% (Parsonnet

1995). Incidence of infection is highest in early childhood; the majority of infections in high prevalence areas occur before age 5 (Granstrom et al. 1997; Malaty et al. 2002; Rothenbacher et al. 2002; Rowland et al. 2006). In studies of children younger than 2 years, there have been reports of children who initially test positive for *H. pylori* but on repeat breath test are seronegative negative (Goodman et al. 2005; Klein et al. 1994; Rothenbacher et al. 2002; Thomas et al. 1999). It has not yet been determined whether the conversion reversion from *H. pylori* seropositive positive to seronegative negative in children reflects transient infections or, rather, false positives in a population with low seroprevalence infection prevalence (Nurgalieva et al. 2006; Perry and Parsonnet 2005; Rosenstock et al. 2000). For adults in developed countries throughout the world, the incidence is low, estimated at 0.5% of susceptible adults becoming infected yearly.

In recent years, there has been a decrease in *H. pylori* prevalence worldwide that has coincided with improved hygiene and socioeconomic status. For example, a study of healthy adults from southern China showed a significant decrease in *H. pylori* seroprevalence (62.5% to 49.3%) from 1993 to 2003 (Chen et al. 2007). Because *H. pylori* infection typically remains in the stomach for life, a decrease in incidence over time is eventually manifest by disproportionately higher rates of *H. pylori* in the elderly than in the young (a birth cohort effect). This birth cohort effect has been documented in Europe and the United States, with a 10% decrease in incidence per decade (Banatvala et al. 1993; Parsonnet et al. 1992; Roosendaal et al. 1997).

Risk Factors for Infection

Lower socioeconomic status, often measured indirectly using level of education, household crowding, sharing of beds, plumbing, and water sanitation, has been consistently identified as a risk factor for *H. pylori* infection (Brown 2000). A large study of 3,194 people from 17 countries showed an inverse relationship between education and *H. pylori* seroprevalence in 11 of 17 populations studied; the remaining 6 populations also showed this relationship, but without reaching clinical significance (Eurogast Study 1993). Similarly, a study of children from northeastern Brazil found that children from lower socioeconomic status had much higher *H. pylori* seroprevalence rates (55%) compared with the wealthier children (16.4%) (Parente et al. 2006). Socioeconomic status in childhood, rather than later in life, is most important in determining *H. pylori* infection (Torres et al. 1998; Ueda et al. 2003). This finding is substantiated by studies of immigrants. Adult immigrants from countries with high prevalence of *H. pylori* infection have prevalence that parallels their country of origin (Perez-Perez et al. 2005; Tsai et al. 2005). Children of immigrants have a prevalence closer to that of the new country, especially after controlling for such variables as household crowding and parents' level of education (O'Rourke et al. 2003; Tsai et al. 2005).

Large differences in *H. pylori* seroprevalence also exist among ethnic groups even within the same country or region. These differences are likely the result, at

least in part, of socioeconomic differences. In the United States, non-Hispanic whites have lower *H. pylori* infection rates than African Americans and Hispanic populations (Graham et al. 1991; Hopkins et al. 1990). In a large cross-sectional study of adult Americans from 1988 to 1991, the overall *H. pylori* seroprevalence was 33%, with the highest rates seen in Mexican Americans (62%) followed by African Americans (53%) and non-Hispanic whites (26%) (Everhart et al. 2000).

Similar differences between ethnic groups have been observed outside of the Americas. In a study done in New Zealand, indigenous Maori have significantly higher rates of infection (39%–70%) than white New Zealanders (15%) (Morris et al. 1986). Similarly, Aborigines from western Australia have 2–3 times higher rates of *H. pylori* infection than nonindigenous Australians (Windsor et al. 2005). Other studies have also found ethnic differences in Belgium (Blecker et al. 1993) and Malaysia (Goh and Parasakthi 2001).

Higher *H. pylori* infection rates have been documented in communities where hygiene is poor, such as institutions for the disabled and in orphanages (Brown 2000). Other risks include bed sharing among children, which is strongly correlated with transmission (Mendall et al. 1992; Perry et al. 2005). In contrast, attending daycare (Wizla-Derambure et al. 2001) and school (Tindberg et al. 2001) with infected classmates was not found to increase risk of infection.

Mechanisms of Transmission

New *H. pylori* infections go undetected unless they are iatrogenic or induced experimentally. As a result, the mechanism of *H. pylori* transmission has been difficult to determine definitively, and the preponderance of evidence is circumstantial. Nevertheless, these data suggest that person-to-person transmission is the most important or perhaps only means of *H. pylori* transmission.

The primary source of evidence to support person-to-person transmission comes from cross-sectional data from families. Numerous studies have found clustering of *H. pylori* infections within families, with infection rates highest among first-degree relatives of infected individuals (Drumm et al. 1990; Kivi et al. 2005; Nguyen et al. 2006). Mothers seem to be more important sources for *H. pylori* transmission than fathers. Studies in Japan and Germany found that children with *H. pylori*-infected mothers were significantly more likely to be infected than children with *H. pylori*-seronegative mothers; no associations were found between *H. pylori* infection in fathers and their children (Fujimoto et al. 2007; Weyermann et al. 2006). A prospective study done in Japan with 9 years of follow-up supports these findings with *H. pylori* seroconversion occurring only in children with *H. pylori*-infected mothers (Malaty et al. 2000).

DNA fingerprinting studies also support person-to-person transmission within the family unit. *H. pylori* strains are more similar within families than among unrelated individuals (Bamford et al. 1993; Raymond et al. 2004). Similar fingerprints are particularly common among siblings (Wang et al. 1993); in one study, 81% of

siblings shared the same strain of *H. pylori*, compared with 56% of mothers and their children and 0% of fathers and their children (Kivi et al. 2003).

Three possible mechanisms for person-to-person transmission of *H. pylori* have been proposed: fecal–oral, oral–oral, and gastro–oral (defined here as either transmission by vomitus, or the iatrogenic introduction of *H. pylori* into the stomach through the use of infected instruments). The data in support of fecal–oral transmission are inconclusive. Although viable *H. pylori* have been detected in feces of both children and adults (Kelly et al. 1994), some studies only report culturing *H. pylori* from cathartic rather than normal stools (Parsonnet et al. 1999). In support of fecal–oral transmission, a study of 671 healthcare workers concluded that contact with fecal matter was a significant risk factor for *H. pylori* infection (De Schryver et al. 2006). Additionally, a prospective study found that gastroenteritis in an *H. pylori*-infected household member was associated with a fourfold increased risk of new infection in another household member (Perry et al. 2006). In this study, however, diarrhea was not an independent risk factor for infection if vomiting was not also present. In opposition to the fecal–oral hypothesis, no excess risk for *H. pylori* infection has been observed in sewage workers (Friis et al. 1996; Jeggli et al. 2004).

Fewer data support oral–oral transmission. Although *H. pylori* has been detected by polymerase chain reaction from saliva and dental plaques (Krajden et al. 1989; Mapstone et al. 1993), it has rarely been cultured from the mouth (Ferguson et al. 1993; Krajden et al. 1989; Parsonnet et al. 1999). Dental workers do not have an increased risk for *H. pylori* (Malaty et al. 1992). One would anticipate high rates of transmission of *H. pylori* between married couples if saliva were the source, and this is not consistently observed. Some investigators report little *H. pylori* concordance among married couples (Miyaji et al. 2000; Perez-Perez et al. 1991), whereas others find a high correlation among couples even after controlling for confounding factors (Brown et al. 2002; Singh et al. 1999; Stone et al. 2000). The strongest studies, which examined the genotype of infecting strains within couples, have not found strong evidence of concordance; the great majority of spouses are infected with different strains (Kuo et al. 1999; Luman et al. 2002; Suzuki et al. 1999).

The strongest data support gastric–oral transmission, especially in the setting of gastric intubation. The majority of these iatrogenic cases result from direct inoculation of contaminated gastric contents into the stomach via incompletely cleaned endoscopic equipment (Langenberg et al. 1990). Iatrogenic outbreaks have been documented (Graham et al. 1988; Pardo-Mindan et al. 1989; Ramsey et al. 1979; Tytgat 1995), and the strains of *H. pylori* isolated from patients using the same endoscopy equipment have been identical. Endoscopists and endoscopy nurses are also at increased risk for *H. pylori* infection (Chong et al. 1994; Lin et al. 1994).

Given the ubiquity of *H. pylori* infection throughout the world and the infrequency of endoscopic examinations, direct gastric–oral inoculation cannot be the primary route of transmission. However, indirect gastric–oral transmission seems plausibly important. *H. pylori* has consistently been cultured in large quantities from vomitus (Brown 2000; Leung et al. 1998; Parsonnet et al. 1999). In addition, in a prospective study, exposure to an *H. pylori*-infected individual with vomiting conferred a sixfold

increased risk for new infection (Perry et al. 2006). Additional data from observational studies concluded that children exposed to emesis were significantly more likely to be infected than children not exposed to emesis (Ito et al. 2006; Luzzza et al. 2000). Vomitus has also been implicated in transmission of *H. pylori* among monkeys (Solnick et al. 2006).

Frequently, infections that are transmitted from person to person can also be transmitted via water or other environmental vectors. Evidence for contaminated water as a source of *H. pylori* transmission, however, is weak. Some studies in developing countries have found increased risk for *H. pylori* infection in individuals using, irrigating with, or swimming in, unclean water (Glynn et al. 2002; Goodman et al. 1996; Hopkins et al. 1993; Hulten et al. 1996; Karita et al. 2003; Klein et al. 1991; Nurgalieva et al. 2002). However, the household-based clustering of *H. pylori* infection in populations with municipal water sources, and the lack of concordance of *H. pylori* with other waterborne diseases raises doubt about the importance of these findings (Egemen et al. 2006; Lin et al. 2005). Although *H. pylori* DNA has often been amplified from untreated water, it has been cultured only once using immunomagnetic separation on raw sewage (Lu et al. 2002). Moreover, when *H. pylori* is exposed to water or when it is under other forms of stress, it loses its classic spiral morphology and becomes coccoid. The coccoid form of *H. pylori* cannot be cultured, and it is still debated in the literature whether it is viable and able to infect (Chen 2004; Delpont and van der Merwe 2007; Sorberg et al. 1996).

Food and animal exposure have also been implicated as possible routes of transmission, although none consistently (Brown 2000; Hopkins et al. 1993). *H. pylori* naturally infects monkeys (Drazek et al. 1994; Dubois et al. 1994) and cats (Handt et al. 1995), and has also been found in sheep and their milk (Dore et al. 2001), and on houseflies (Grubel et al. 1997; Osato et al. 1998). Pet ownership, however, is not linked to infection (indeed, it has been found to be protective) (Graham et al. 1991; Webb et al. 1994), and animal exposure more generally is unlikely to explain the extremely high rates of infection worldwide.

Links Between *Helicobacter pylori* and Cancer

Interest in *H. pylori* as a potential cancer-causing agent began soon after the pioneering discoveries of Marshall and Warren in the 1980s. It had been known for many years that gastric adenocarcinomas often arose in areas of gastritis. Because of its induction of chronic gastritis, investigators began almost immediately to take interest in *H. pylori*'s causal role in malignancy.

The first studies to examine this association were ecologic and compared regional *H. pylori* incidence with regional cancer incidence (Eurogast Study 1993; Forman et al. 1990). Many subsequent case-control studies examined the prevalence of *H. pylori* in persons with and without cancer. Now, in retrospect, it is understood that these studies—which in a metaanalysis indicated a 1.8-fold increased risk of

cancer (Huang et al. 1998)—underestimated the true risk. The underestimate resulted from the loss of *H. pylori* infection and its serologic response as the stomach progresses toward malignancy (Genta and Graham 1993; Masci et al. 1996; Osawa et al. 1996). Stronger support for a role in cancer comes from nested case-control studies. These studies examine *H. pylori* prevalence in stored sera obtained from cases and matched controls years before the development of cancer. Together, these demonstrate a stronger risk of cancer [odds ratio (OR) = 3.0; 95% CI, 2.3–3.8 (Helicobacter and Cancer Collaborative Group 2001)]. The risk was particularly high when sera were drawn more than 10 years before the development of cancer in the case (OR = 5.9; 95% CI, 3.9–10.3), again suggesting that diagnostic artifact occurs when sera are obtained close to the time of cancer diagnosis. Even more compelling data for an association between *H. pylori* and cancer come from longitudinal cohort studies. In a large prospective trial conducted in Japan, only those infected with *H. pylori* later developed gastric cancer; 36 of 1,246 infected individuals developed gastric cancer compared with none of the 280 uninfected participants (infinite OR) (Uemura et al. 2001). A prospective study of 1,225 Taiwanese patients confirmed this “infinite” OR ($p = 0.015$) (Hsu et al. 2007). The broad spectrum of strongly supportive studies have led some to speculate that *H. pylori* is a necessary factor in the development of gastric cancer of the distal stomach (Brenner et al. 2004).

As a single agent, *H. pylori* may be responsible for as many as 5.5% of all cancers (Parkin 2006), making it the leading infectious cause of cancer worldwide. This figure, however, derives only from tumors of the gastric antrum and body. The role of *H. pylori* in proximal tumors is more debated, in large part because of the difficulties differentiating adenocarcinomas of the proximal stomach from those of the gastroesophageal junction (Odze 2005; Richter 2007). Overall, *H. pylori* infection seems to be important for inflammation in the proximal stomach but remains inversely related to proximal cancers of the gastric cardia and gastroesophageal junction (Yang and Davis 1988). In a large prospective nested case-control study of 29,133 participants aged 50–69 years, *H. pylori* was strongly associated with distal gastric cancer (OR = 7.9; 95% CI, 3.0–20.9) but inversely proportional to proximal gastric cancers (adjusted OR = 0.31; 95% CI, 0.11–0.89) (Kamangar et al. 2006). This finding confirmed the results of a metaanalysis of previous nested case-control studies that showed no increased risk for the development of proximal gastric cancers among those infected with *H. pylori* (Helicobacter and Cancer Collaborative Group 2001).

Proximal tumors often occur in the setting of GERD, and *H. pylori* infection is less common in patients with these symptoms (OR = 0.60; 95% CI, 0.47–0.78) (Raghunath et al. 2003). Pathophysiologically, *H. pylori* may prevent GERD by decreasing gastric pH. Given the strong causal relationship between GERD and adenocarcinoma of the esophagus (Lagergren et al. 1999), *H. pylori* may confer a protective benefit for cardia tumors as well. Although incidence rates of distal gastric adenocarcinoma have declined with decreased *H. pylori* infection rates, it is likely that these decreasing *H. pylori* infection rates observed in western countries explain the simultaneous increase in proximal adenocarcinomas.

Effect Modifiers for Helicobacter pylori and Malignancy

Most people infected with *H. pylori* will remain free of symptoms and will never develop gastric cancer in their lifetimes. Host genetic factors, bacterial variation, and diet and environmental cofactors all have significant roles in the variable evolution and presentation of *H. pylori* infection.

Genetic Factors

Approximately 10% of gastric cancers cluster in families but only a small portion of these cancers result from known hereditary cancer syndromes. Other genetic factors have been investigated that might influence the consequences.

Notably, the intensity and type of immune response to infection with *H. pylori* is determined by host genetics. In 2000, El-Omar demonstrated that specific polymorphisms of interleukin (IL)-1 β , an important inflammatory cytokine and potent inhibitor of gastric acid secretion, contribute to intestinal-type stomach cancer progression (El-Omar et al. 2000). These findings have now been extensively replicated worldwide. Polymorphisms in tumor necrosis factor (TNF)- α (Machado et al. 2003), IL-1 receptor antagonist (El-Omar et al. 2000), and IL-10 (El-Omar et al. 2003) also influence intestinal-type gastric cancer evolution whereas polymorphisms in the IL-8 promotor have been linked to diffuse-type cancer (Lee et al. 2005). Individuals unfortunate enough to possess polymorphisms in IL-1 β , TNF- α , and IL-10 have a 27-fold increased risk for the development of gastric cancer (El-Omar et al. 2003).

Human leukocyte antigen (HLA) genotypes have been variably linked to gastric cancer, with different HLA types associated with cancer or cancer protection in different regions of the world (Garza-Gonzalez et al. 2004; Hirata et al. 2007; Li et al. 2005; Perri et al. 2002; Quintero et al. 2005; Watanabe et al. 2006).

Bacterial Factors

Variations in *H. pylori* genes confer different risks of cancer development. *H. pylori* can undergo point mutations and chromosomal rearrangements (Blaser and Berg 2001) and, consequently, there is an impressive degree of genetic diversity, even within a single host (Cooke et al. 2005; Israel et al. 2001; Kim et al. 2004). Approximately half of all strains of *H. pylori* contain a 40-kb DNA virulence cassette known as the pathogenicity island (PAI) (Stein et al. 2002; Yamazaki et al. 2003). This cassette, which is discussed in detail elsewhere in this book, encodes a Type IV secretion system that injects the CagA protein into the host epithelial cell. *H. pylori* possessing this cassette produce greater gastric inflammation and a higher risk of intestinal-type malignancies than strains that do not contain this gene (Chow et al. 1998; Parsonnet et al. 1997). A metaanalysis published in 2003 showed that

CagA is an independent risk factor for distal gastric cancers (OR = 1.64; 95% CI, 1.21–2.24) (Huang et al. 2003).

Certain genotypes (the s1 and m1 genotypes) of the *vacA* gene, a gene that encodes a vacuolating cytotoxin, are associated both with the presence of a viable pathogenicity island and with the development of cancer (Con et al. 2007). Other polymorphic bacterial factors linked to cancer contribute to *H. pylori* adherence to gastric epithelial cells (*babA*), bacterial invasion into the gastric glands, and persistence of infection within the gastric lumen.

From an epidemiologic perspective, global distribution of the more pathogenic genotypes might help to explain disease distribution (Bravo et al. 2002; Kersulyte et al. 2000). For example, in Asia, a region with high gastric cancer incidence, nearly all strains of *H. pylori* possess the PAI, whereas the rates are closer to 50% in the United States and Europe (Covacci et al. 1999). In addition to regional differences in the presence of the PAI, polymorphisms within the PAI vary geographically and may relate to disease pathogenesis (Yamaoka et al. 2000). Also being mapped to determine population effects are the *vacA* genotypes; less virulent strains with *vacA* s2 genotype are extremely rare in Asia, whereas they comprise 20%–40% of strains in North America, northern Europe, and Australia (Van Doorn et al. 1999). Recently, an *H. pylori* genotype database has been developed to assess the breadth of gene sequences in isolates entered worldwide (Ahmed et al. 2007); this database will enable a broader understanding of the genetics of virulence and disease. Such an understanding will be complicated, however, by the existence of multiple genotypes of varying pathogenicity within individual hosts (Matteo et al. 2007).

Environmental Factors

Although diet has been extensively studied in gastric carcinogenesis, it is not well studied in the setting of *H. pylori* infection. A prospective cohort study in Scandinavia demonstrated a protective effect of vitamin C and beta-carotene in individuals infected with *H. pylori* (Ekstrom et al. 2000). This finding was initially supported in a prospective study from Colombia that demonstrated that *H. pylori* eradication and increased dietary vitamin C and beta-carotene independently prevented progression of preneoplastic lesions to cancer (Correa et al. 2000). Long-term follow-up from this trial, however, showed that the benefits of vitamin C and beta-carotene—but not of *H. pylori* eradication—disappeared when participants were followed up for a longer period of time (Mera et al. 2005).

Increased dietary salt may also increase gastric cancer risk. As mentioned above, before the discovery of *H. pylori*, salt was linked to gastric cancer in humans. In animal models, increased dietary salt in the setting of *H. pylori* augments gastric carcinogenesis (Fox et al. 2003). In humans, a study of 2,476 participants followed prospectively for 14 years, the years yielded a significant relationship between increased salt consumption and the development of gastric cancer, but only in subjects who were both infected with *H. pylori* and had atrophic gastritis (Shikata et al. 2006).

Another area of increasing interest is the possibility of coinfection with other organisms influencing the outcome of *H. pylori* in humans. By mitigating the Th1 inflammatory response, helminths could theoretically reduce gastric inflammation and cancer incidence. This reduction of inflammation has been observed in animals coinfecting with *H. pylori* felis and helminths (Fox et al. 2000) and has also been suggested in small ecologic studies of humans (Mitchell et al. 2002; Whary et al. 2005). The clinical significance of these findings is now an intense area of investigation.

Unanswered Epidemiologic Questions

Although much has been learned about *H. pylori* and its relationship to gastric cancer since 1982, some critical questions remain unresolved and additional research is needed.

Why Do Males Have Higher Risk for Cancer?

More men than women develop gastric cancer. In fact, distal, noncardia gastric cancers is on average twice as common among men compared with women (Crew and Neugut 2006). This higher incidence of gastric cancer observed among men is partially explained by higher *H. pylori* infection rates. A metaanalysis of large, population-based studies found that male gender was significantly associated with *H. pylori* infection (OR = 1.16; 95% CI, 1.11–1.22), although this difference was not observed in studies of children sufficient to explain the differences in cancer incidence (De Martel and Parsonnet 2006). Other cofactors beyond *H. pylori* infection such as smoking, alcohol, increased dietary salt, or even a protective effect of female hormones have not been demonstrated to explain the differences observed (Ferreccio et al. 2007; Lindblad et al. 2005). Understanding gender differences in gastric cancer would provide insights into carcinogenesis more generally.

Is There an African Enigma?

Although *H. pylori* infection has a significant role in gastric cancer development, higher *H. pylori* infection rates are not always associated with higher gastric cancer rates. As early as 1992, Holcombe noted that despite high rates of *H. pylori* infection and *H. pylori*-associated gastritis in Nigeria, gastric cancer was uncommon; they termed this “the Africa enigma” (Holcombe 1992). Additional research has noted a similar pattern of high *H. pylori* infection rates and low gastric cancer incidence in India, Bangladesh, Pakistan, and Thailand (Miwa et al. 2002; Singh and

Ghoshal 2006). Some have maintained that microbial coinfection with helminths explains these paradoxical *H. pylori* responses (Whary et al. 2005). For example, several human studies have found shifts in *H. pylori* immunoglobulin (Ig)G antibodies in helminth-infected populations to IgG1 rather than IgG2 (Mitchell et al. 2002; Whary et al. 2005), indicating different—and possibly less inflammatory—immunologic response to gastric infection. Others maintain that dietary factors, host genetics, or bacterial factors explain these observations (Ghoshal et al. 2007; Louw et al. 2001; Singh and Ghoshal 2006). Still others aver there is no “African enigma,” only low life expectancy among the poorest individuals, deficient cancer reporting, and *H. pylori* diagnostic artifact (Agha and Graham 2005). It is unlikely, however, that anyone would argue that host response to infection does not vary from individual to individual. Understanding this variability across populations could be the key to identifying attainable cancer intervention strategies.

Can Treatment of Helicobacter pylori Prevent Cancer?

Treatment of *H. pylori* infection to prevent gastric cancer is an appealing prevention strategy and numerous studies have indicated it is also likely to be cost effective (Fendrick et al. 1999; Mason et al. 2002; Parsonnet et al. 1996; Roderick et al. 2003). Yet, to date, no randomized, prospective trials have shown that eradication of existing infection prevents cancer. Several studies, however, show tantalizing evidence that such treatment might work. A nonrandomized, nonblinded trial of *H. pylori* eradication in Japanese patients with early gastric cancer showed significantly lower rates of cancer relapse in patients who received eradication therapy than those who did not (Uemura et al. 1997); this finding has been supported by larger retrospective analyses (Nakagawa et al. 2006) but has yet to be supported by a randomized clinical trial. Randomized trials of preneoplastic conditions indicate that *H. pylori* therapy may improve the overall pathology of the stomach, decreasing atrophic gastritis and intestinal metaplasia (Correa et al. 2000; Ley et al. 2004; Sung et al. 2000). Although an improvement in histopathology has been reported in only a minority of subjects, the study with longest follow-up indicates that the differences between treated and untreated subjects may become increasingly evident as years pass (Mera et al. 2005).

The one randomized trial of cancer prevention completed to date—a study conducted in China—was underpowered for the final endpoint of gastric cancer (Parsonnet and Forman 2004). Among a subset of participants, however, eradication did show a benefit; i.e., among participants who had no preneoplastic lesions in their first endoscopy, there was a decreased incidence of gastric cancer after active treatment (Wong et al. 2004). Further randomized trials are underway. Given the difficulties of conducting these trials and the decreasing incidence of gastric cancer worldwide, however, it is possible none will ever be completed successfully. In the absence of clinical trial support, there is yet no policy in place in any country to screen populations for infection and treat all infected individuals. Instead, consensus

groups have recommended screening and treating those at highest risk: i.e., those with a family history of cancer, with prior gastric surgery, or with documented atrophic gastritis (Malfertheiner et al. 2007).

What Is the Best Approach to Helicobacter pylori Prevention?

H. pylori and its related diseases are disappearing spontaneously worldwide. Acceleration of the organism's disappearance through primary prevention, however, could save myriad lives. Because the preponderance of evidence supports person-to-person transmission of *H. pylori*, efforts to improve hygiene and handwashing may be effective strategies for gastric cancer prevention. These methods have the added advantage of preventing other enteric infections, and of proven feasibility. Consuming a diet high in vegetables and fruit and low in salt may also be an effective way to reduce stomach cancer rates (World Cancer Research Fund and American Institute for Cancer Research 1997), but effectuating dietary change can be an onerous challenge.

A vaccine for *H. pylori* is another appealing primary prevention strategy for gastric cancer. The precedent for a vaccine to prevent cancer has already been established with the hepatitis B vaccine to prevent hepatomas and HPV vaccine to prevent cervical cancer. Unfortunately, the development of an *H. pylori* vaccine has proved to be more difficult than the hepatitis B and HPV vaccines. Although an enormous amount has been learned about the immune response to *H. pylori* infection (Suerbaum and Michetti 2002), there are as yet no known correlates of protective immunity for infection or reinfection in humans. In mouse models, infection can be prevented with a variety of vaccines (Arora and Czinn 2005). The human response to *H. pylori* is more complicated, however, and no vaccine has yet reached efficacy trials in humans (Kabir 2007). Should a vaccine appear, it is likely to be a cost-effective approach to cancer prevention (Rupnow et al. 1999; Rupnow et al. 2001).

In considering *H. pylori* prevention, however, it is also important to assess whether there may be downsides to the strategy. Recent observational data suggest that *H. pylori* might provide some protection against acute diseases of childhood. Theoretically, by upregulating the systemic Th1 immune response, infection might assist in combating common childhood infections. A small amount of evidence supports this; *H. pylori* infection has been linked to protection from both diarrheal disease (Perry et al. 2004)—a leading cause of death in children worldwide—and tuberculosis (Perry et al. 2007). In addition, some argue that absence of *H. pylori*'s Th1 stimulation in young children has fostered increases in asthma and other allergic diseases (Chen and Blaser 2007; Kosunen et al. 2002; Pessi et al. 2005). Finally, in adults, an ever-increasing amount of data indicates that the absence of *H. pylori* promotes both GERD and its long-term consequence—adenocarcinoma of the esophagus (Cremonini et al. 2003; de Martel et al. 2005).

Although there is no doubt that the areas of the world that have spontaneously lost *H. pylori* from their resident flora experience greater life expectancy and

decreased morbidity than those in which it persists, we have, in the past, always “let nature take its course.” With a vaccine, we would be in a position to precipitate the loss of *H. pylori* even from regions of the world where acute infectious diseases run rampant. One would be prudent, then, to ask whether the survival of *H. pylori* in these microbial ecologies provides a survival advantage to children that counterbalances the risks of gastric adenocarcinoma later in life.

References

- Aaltonen, L.A., Hamilton, S.R., World Health Organization., and International Agency for Research on Cancer. (2000). Pathology and genetics of tumours of the digestive system. Lyon: IARC Press.
- Agha, A., and Graham, D.Y. (2005). Evidence-based examination of the African enigma in relation to *Helicobacter pylori* infection. *Scand J Gastroenterol.* 40:523–9.
- Ahmed, N., Majeed, A.A., Ahmed, I., Hussain, M.A., Alvi, A., Devi, S.M., Rizwan, M., Ranjan, A., Sechi, L.A., and Megraud, F. (2007). genoBASE pylori: a genotype search tool and database of the human gastric pathogen *Helicobacter pylori*. *Infect Genet Evol.* 7:463–8.
- American Cancer Society, Atlanta, GA. (2007). http://www.cancer.org/docroot/MED/content/downloads/MED_1_1x_CFF2007_Estimated_Deaths_Sites_by_State.asp.
- Arora, S., and Czinn, S.J. (2005). Vaccination as a method of preventing *Helicobacter pylori*-associated gastric cancer. *Cancer Epidemiol Biomarkers Prev.* 14:1890–1.
- Bamford, K.B., Bickley, J., Collins, J.S., Johnston, B.T., Potts, S., Boston, V., Owen, R.J., and Sloan, J.M. (1993). *Helicobacter pylori*: comparison of DNA fingerprints provides evidence for intrafamilial infection. *Gut.* 34:1348.
- Banatvala, N., Mayo, K., Megraud, F., Jennings, R., Deeks, J.J., and Feldman, R.A. (1993). The cohort effect and *Helicobacter pylori*. *J Infect Dis.* 168:219.
- Bergin, I.L., Sheppard, B.J., and Fox, J.G. (2003). *Helicobacter pylori* infection and high dietary salt independently induce atrophic gastritis and intestinal metaplasia in commercially available outbred Mongolian gerbils. *Dig Dis Sci.* 48:475–85.
- Blaser, M.J., and Berg, D.E. (2001). *Helicobacter pylori* genetic diversity and risk of human disease. *J Clin Invest.* 107:767–73.
- Blecker, U., Hauser, B., Lanciers, S., Peeters, S., Suys, B., and Vandenplas, Y. (1993). The prevalence of *Helicobacter pylori*-positive serology in asymptomatic children. *J Pediatr Gastroenterol Nutr.* 16:252.
- Bravo, L.E., van Doorn, L.J., Realpe, J.L., and Correa, P. (2002). Virulence-associated genotypes of *Helicobacter pylori*: do they explain the African enigma? *Am J Gastroenterol.* 97:2839–42.
- Brenner, H., Arndt, V., Stegmaier, C., Ziegler, H., and Rothenbacher, D. (2004). Is *Helicobacter pylori* infection a necessary condition for noncardia gastric cancer? *Am J Epidemiol.* 159:252–8.
- Brown, L.M. (2000). *Helicobacter pylori*: epidemiology and routes of transmission. *Epidemiol Rev.* 22:283–97.
- Brown, L.M., and Devesa, S.S. (2002). Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin North Am.* 11:235–56.
- Brown, L.M., Thomas, T.L., Ma, J.L., Chang, Y.S., You, W.C., Liu, W.D., Zhang, L., Pee, D., and Gail, M.H. (2002). *Helicobacter pylori* infection in rural China: demographic, lifestyle and environmental factors. *Int J Epidemiol.* 31:638–45.
- Caldas, C., Carneiro, F., Lynch, H.T., Yokota, J., Wiesner, G.L., Powell, S.M., Lewis, F.R., Huntsman, D.G., Pharoah, P.D., Jankowski, J.A., MacLeod, P., Vogelsang, H., Keller, G., Park, K.G., Richards, F.M., Maher, E.R., Gayther, S.A., Oliveira, C., Grehan, N., Wight, D., Seruca, R.,

- Roviello, F., Ponder, B.A., and Jackson, C.E. (1999). Familial gastric cancer: overview and guidelines for management. *J Med Genet.* 36:873–80.
- Chao, A., Thun, M.J., Henley, S.J., Jacobs, E.J., McCullough, M.L., and Calle, E.E. (2002). Cigarette smoking, use of other tobacco products and stomach cancer mortality in US adults: The Cancer Prevention Study II. *Int J Cancer.* 101, 380–9.
- Chen, T.S. (2004). Is the coccoid form of *Helicobacter pylori* viable and transmissible? *J Chin Med Assoc.* 67:547–8.
- Chen, Y., and Blaser, M.J. (2007). Inverse associations of *Helicobacter pylori* with asthma and allergy. *Arch Intern Med.* 167:821–7.
- Chen, J., Bu, X.L., Wang, Q.Y., Hu, P.J., and Chen, M.H. (2007). Decreasing seroprevalence of *Helicobacter pylori* infection during 1993–2003 in Guangzhou, southern China. *Helicobacter.* 12:164–9.
- Chong, J., Marshall, B.J., Barkin, J.S., McCallum, R.W., Reiner, D.K., Hoffman, S.R., and O’Phelan, C. (1994). Occupational exposure to *Helicobacter pylori* for the endoscopy professional: a sera epidemiological study. *Am J Gastroenterol.* 89:1987.
- Chow, W.H., Blaser, M.J., Blot, W.J., Gammon, M.D., Vaughan, T.L., Risch, R.A., Perez-Perez, G.I., Schoenberg, J.B., Stanford, J.L., Rotterdam, H., West, A.B., and Fraumeni, J.F. (1998). An inverse relation between *cagA*+ strains of *Helicobacter pylori* infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res.* 58:588.
- Chow, W.H., Swanson, C.A., Lissowska, J., Groves, F.D., Sobin, L.H., Nasierowska-Guttmejer, A., Radziszewski, J., Regula, J., Hsing, A.W., Jagannatha, S., Zatonski, W., and Blot, W.J. (1999). Risk of stomach cancer in relation to consumption of cigarettes, alcohol, tea and coffee in Warsaw, Poland. *Int J Cancer.* 81:871–6.
- Coggon, D., Osmond, C., and Barker, D.J. (1990). Stomach cancer and migration within England and Wales. *Br J Cancer.* 61:573–4.
- Coleman, M.P., Esteve, J., Damiecki, P., Arslan, A., and Renard, H. (1993). Trends in Cancer incidence and mortality. Lyon: International Agency for Research on Cancer.
- Colin-Jones, D.G., Langman, M.J., Lawson, D.H., Logan, R.F., Paterson, K.R., and Vessey, M.P. (1992). Postmarketing surveillance of the safety of cimetidine: 10 year mortality report. *Gut.* 33:1280.
- Con, S.A., Takeuchi, H., Valerin, A.L., Con-Wong, R., Con-Chin, G.R., Con-Chin, V.G., Nishioka, M., Mena, F., Brenes, F., Yasuda, N., Araki, K., and Sugiura, T. (2007). Diversity of *Helicobacter pylori* *cagA* and *vacA* genes in Costa Rica: its relationship with atrophic gastritis and gastric cancer. *Helicobacter* 12:547–52.
- Cooke, C.L., Huff, J.L., and Solnick, J.V. (2005). The role of genome diversity and immune evasion in persistent infection with *Helicobacter pylori*. *FEMS Immunol Med Microbiol.* 45:11–23.
- Correa, P. (1992). Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award lecture on cancer epidemiology and prevention. *Cancer Res.* 52:6735.
- Correa, P. (2002). Gastric neoplasia. *Curr Gastroenterol Rep* 4:463–70.
- Correa, P., and Chen, V.W. (1994). Gastric cancer. *Cancer Surv.* 19–20:55–76.
- Correa, P., Fontham, E.T., Bravo, J.C., Bravo, L.E., Ruiz, B., Zarama, G., Realpe, J.L., Malcom, G.T., Li, D., Johnson, W.D., and Mera, R. (2000). Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-*Helicobacter pylori* therapy. *J Natl Cancer Inst.* 92:1881.
- Correa, P., Haenszel, W., Cuello, C., Tannenbaum, S., and Archer, M. (1975). A model for gastric cancer epidemiology. *Lancet.* 2:58.
- Covacci, A., Telford, J.L., Del Giudice, G., Parsonnet, J., and Rappuoli, R. (1999). *Helicobacter pylori* virulence and genetic geography. *Science.* 284:1328–33.
- Cremonini, F., Di Caro, S., Delgado-Aros, S., Sepulveda, A., Gasbarrini, G., Gasbarrini, A., and Camilleri, M. (2003). Meta-analysis: the relationship between *Helicobacter pylori* infection and gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 18:279–89.
- Crew, K.D., and Neugut, A.I. (2006). Epidemiology of gastric cancer. *World J Gastroenterol.* 12:354–62.

- Delport, W., and van der Merwe, S.W. (2007). The transmission of *Helicobacter pylori*: the effects of analysis method and study population on inference. *Best Pract Res Clin Gastroenterol.* 21:215–36.
- de Martel, C., Llosa, A.E., Farr, S.M., Friedman, G.D., Vogelstein, J.H., Orentreich, N., Corley, D.A., and Parsonnet, J. (2005). *Helicobacter pylori* infection and the risk of development of esophageal adenocarcinoma. *J Infect Dis.* 191:761–7.
- De Martel, C., and Parsonnet, J. (2006). *Helicobacter pylori* infection and gender: a meta-analysis of population-based prevalence surveys. *Dig Dis Sci.* 51.
- De Schryver, A., Van Winckel, M., Cornelis, K., Moens, G., Devlies, G., and De Backer, G. (2006). *Helicobacter pylori* infection: further evidence for the role of feco-oral transmission. *Helicobacter.* 11:523–8.
- Devesa, S.S., Blot, W.J., and Fraumeni, J.F., Jr. (1998). Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer.* 83:2049–53.
- Doenges, J.L. (1938). Spirochaetes in gastric glands of macacus rhesus and humans without defined history of related disease. *Proc Soc Exp Biol Med.* 38:536.
- Dore, M.P., Sepulveda, A.R., El-Zimaity, H., Yamaoka, Y., Osato, M.S., Mototsugu, K., Nieddu, A.M., Realdi, G., and Graham, D.Y. (2001). Isolation of *Helicobacter pylori* from sheep-implantations for transmission to humans. *Am J Gastroenterol.* 96:1396–401.
- Drazek, E.S., Dubois, A., and Holmes, R.K. (1994). Characterization and presumptive identification of *Helicobacter pylori* isolates from rhesus monkeys. *J Clin Microbiol.* 32:1799.
- Drumm, B., Perez-Perez, G.I., Blaser, M.J., and Sherman, P.M. (1990). Intrafamilial clustering of *Helicobacter pylori* infection. *N Engl J Med.* 322:359.
- Dubois, A., Fiala, N., Heman-Ackah, L.M., Drazek, E.S., Tarnawski, A., Fishbein, W.N., Perez-Perez, G.I., and Blaser, M.J. (1994). Natural gastric infection with *Helicobacter pylori* in monkeys: a model for spiral bacteria infection in humans. *Gastroenterology.* 106:1405.
- Egemen, A., Yilmaz, O., Akil, I., and Altuglu, I. (2006). Evaluation of association between hepatitis A and *Helicobacter pylori* infections and routes of transmission. *Turk J Pediatr.* 48:135–9.
- Ekstrom, A.M., Serafini, M., Nyren, O., Hansson, L.E., Ye, W., and Wolk, A. (2000). Dietary antioxidant intake and the risk of cardia cancer and noncardia cancer of the intestinal and diffuse types: a population-based case-control study in Sweden. *Int J Cancer.* 87:133–40.
- El Hajj, I., Hashash, J.G., Baz, E.M., Abdul-Baki, H., and Sharara, A.I. (2007). ABO blood group and gastric cancer: rekindling an old fire? *South Med J.* 100:726–7.
- El-Omar, E.M., Carrington, M., Chow, W.H., McColl, K.E., Bream, J.H., Young, H.A., Herrera, J., Lissowska, J., Yuan, C.C., Rothman, N., Lanyon, G., Martin, M., Fraumeni, J.F., Jr., and Rabkin, C.S. (2000). Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature.* 404:398–402.
- El-Omar, E.M., Rabkin, C.S., Gammon, M.D., Vaughan, T.L., Risch, H.A., Schoenberg, J.B., Stanford, J.L., Mayne, S.T., Goedert, J., Blot, W.J., Fraumeni, J.F., Jr., and Chow, W.H. (2003). Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology.* 124:1193–201.
- Eurogast Study Group. (1993). Epidemiology of, and risk factors for, *Helicobacter pylori* infection among 3194 asymptomatic subjects in 17 populations. *Gut.* 34:1672.
- Everhart, J.E., Kruszon-Moran, D., Perez-Perez, G.I., Tralka, T.S., and McQuillan, G. (2000). Seroprevalence and ethnic differences in *Helicobacter pylori* infection among adults in the United States. *J Infect Dis.* 181:1359–63.
- Falush, D., Wirth, T., Linz, B., Pritchard, J.K., Stephens, M., Kidd, M., Blaser, M.J., Graham, D.Y., Vacher, S., Perez-Perez, G.I., Yamaoka, Y., Megraud, F., Otto, K., Reichard, U., Katzowitzsch, E., Wang, X., Achtman, M., and Suerbaum, S. (2003). Traces of human migrations in *Helicobacter pylori* populations. *Science.* 299:1582–5.
- Farrow, D.C., Vaughan, T.L., Sweeney, C., Gammon, M.D., Chow, W.H., Risch, H.A., Stanford, J.L., Hansten, P.D., Mayne, S.T., Schoenberg, J.B., Rotterdam, H., Ahsan, H., West, A.B., Dubrow, R., Fraumeni, J.F., Jr., and Blot, W.J. (2000). Gastroesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. *Cancer Causes Control.* 11:231–8.

- Fendrick, A.M., Chernew, M.E., Hirth, R.A., Bloom, B.S., Bandekar, R.R., and Scheiman, J.M. (1999). Clinical and economic effects of population-based *Helicobacter pylori* screening to prevent gastric cancer. *Arch Intern Med.* 159:142.
- Ferguson, D.A., Jr., Li, C., Patel, N.R., Mayberry, W.R., Chi, D.S., and Thomas, E. (1993). Isolation of *Helicobacter pylori* from saliva. *J Clin Microbiol.* 31:2802.
- Ferlay, J., Bray, F., Pisani, P., and Parkin, D.M. (2004). GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. Lyon: IARC Press.
- Ferreccio, C., Rollan, A., Harris, P.R., Serrano, C., Gederlini, A., Margozzini, P., Gonzalez, C., Aguilera, X., Venegas, A., and Jara, A. (2007). Gastric cancer is related to early *Helicobacter pylori* infection in a high-prevalence country. *Cancer Epidemiol Biomarkers Prev.* 16:662–7.
- Forman, D., Sitas, F., Newell, D.G., Stacey, A.R., Boreham, J., Peto, R., Campbell, T.C., Li, J.Y., and Chen, J. (1990). Geographic association of *Helicobacter pylori* antibody prevalence and gastric cancer mortality in rural China. *Int J Cancer.* 46:608.
- Fox, J.G., Beck, P., Dangler, C.A., Whary, M.T., Wang, T.C., Shi, H.N., and Nagler-Anderson, C. (2000). Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces *Helicobacter*-induced gastric atrophy. *Nat Med.* 6:536.
- Fox, J.G., Rogers, A.B., Ihrig, M., Taylor, N.S., Whary, M.T., Dockray, G., Varro, A., and Wang, T.C. (2003). *Helicobacter pylori*-associated gastric cancer in INS-GAS mice is gender specific. *Cancer Res.* 63:942–50.
- Friis, L., Engstrand, L., and Edling, C. (1996). Prevalence of *Helicobacter pylori* infection among sewage workers. *Scand J Work Environ Health.* 22:364–8.
- Fujimoto, Y., Furusyo, N., Toyoda, K., Takeoka, H., Sawayama, Y., and Hayashi, J. (2007). Intrafamilial transmission of *Helicobacter pylori* among the population of endemic areas in Japan. *Helicobacter.* 12:170–6.
- Fukao, A., Tsubono, Y., Tsuji, I., Hisamichi, S., Sugahara, N., and Takano, A. (1995). The evaluation of screening for gastric cancer in Miyagi Prefecture, Japan: a population-based case-control study. *Int J Cancer.* 60:45–8.
- Garza-Gonzalez, E., Bosques-Padilla, F.J., Perez-Perez, G.I., Flores-Gutierrez, J.P., and Tijerina-Menchaca, R. (2004). Association of gastric cancer, HLA-DQA1, and infection with *Helicobacter pylori* CagA+ and VacA+ in a Mexican population. *J Gastroenterol.* 39:1138–42.
- Gayther, S.A., Goringe, K.L., Ramus, S.J., Huntsman, D., Roviello, F., Grehan, N., Machado, J.C., Pinto, E., Seruca, R., Halling, K., MacLeod, P., Powell, S.M., Jackson, C.E., Ponder, B.A., and Caldas, C. (1998). Identification of germ-line E-cadherin mutations in gastric cancer families of European origin. *Cancer Res.* 58:4086–9.
- Genta, R.M., and Graham, D.Y. (1993). Intestinal metaplasia, not atrophy or achlorhydria, creates a hostile environment for *Helicobacter pylori*. *Scand J Gastroenterol.* 28:924.
- Gerhard, M., Lehn, N., Neumayer, N., Boren, T., Rad, R., Schepp, W., Miehle, S., Classen, M., and Prinz, C. (1999). Clinical relevance of the *Helicobacter pylori* gene for blood-group antigen-binding adhesin. *Proc Natl Acad Sci USA.* 96:12778.
- Ghoshal, U.C., Tripathi, S., and Ghoshal, U. (2007). The Indian enigma of frequent *H. pylori* infection but infrequent gastric cancer: is the magic key in Indian diet, host's genetic make up, or friendly bug? *Am J Gastroenterol.* 102:2113–4.
- Gillen, D., and McColl, K.E. (2001). Problems associated with the clinical use of proton pump inhibitors. *Pharmacol Toxicol.* 89:281–6.
- Glynn, M.K., Friedman, C.R., Gold, B.D., Khanna, B., Hutwagner, L., Iihoshi, N., Revollo, C., and Quick, R. (2002). Seroincidence of *Helicobacter pylori* infection in a cohort of rural Bolivian children: acquisition and analysis of possible risk factors. *Clin Infect Dis.* 35:1059–65.
- Goh, K.L., and Parasakthi, N. (2001). The racial cohort phenomenon: seroepidemiology of *Helicobacter pylori* infection in a multiracial South-East Asian country. *Eur J Gastroenterol Hepatol.* 13:177–83.
- Gonzalez, C.A., Jakszyn, P., Pera, G., Agudo, A., Bingham, S., Palli, D., Ferrari, P., Boeing, H., del Giudice, G., Plebani, M., Carneiro, F., Nesi, G., Berrino, F., Sacerdote, C., Tumino, R., Panico, S., Berglund, G., Siman, H., Nyren, O., Hallmans, G., Martinez, C., Dorronsoro, M., Barricarte, A., Navarro, C., Quiros, J.R., Allen, N., Key, T.J., Day, N.E., Linseisen, J., Nagel, G.,

- Bergmann, M.M., Overvad, K., Jensen, M.K., Tjonneland, A., Olsen, A., Bueno-de-Mesquita, H.B., Ocke, M., Peeters, P.H., Numans, M.E., Clavel-Chapelon, F., Boutron-Ruault, M.C., Trichopoulos, A., Psaltopoulou, T., Roukos, D., Lund, E., Hemon, B., Kaaks, R., Norat, T., and Riboli, E. (2006). Meat intake and risk of stomach and esophageal adenocarcinoma within the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst.* 98:345–54.
- Goodman, K.J., Correa, P., Tengana Aux, H.J., Ramirez, H., DeLany, J.P., Guerrero Pepinosa, O., Lopez Quinones, M., and Collazos Parra, T. (1996). *Helicobacter pylori* infection in the Colombian Andes: a population-based study of transmission pathways. *Am J Epidemiol.* 144:290–9.
- Goodman, K.J., O'Rourke, K., Day, R.S., Wang, C., Nurgalieva, Z., Phillips, C.V., Aragaki, C., Campos, A., and de la Rosa, J.M. (2005). Dynamics of *Helicobacter pylori* infection in a US-Mexico cohort during the first two years of life. *Int J Epidemiol.* 34:1348–55.
- Graham, D.Y., Alpert, L.C., Smith, J.L., and Yoshimura, H.H. (1988). Iatrogenic *Campylobacter pylori* infection is a cause of epidemic achlorhydria. *Am J Gastroenterol.* 83:974.
- Graham, D.Y., Malaty, H.M., Evans, D.G., Evans, D.J., Jr., Klein, P.D., and Adam, E. (1991). Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States. Effect of age, race, and socioeconomic status. *Gastroenterology.* 100:1495–501.
- Granstrom, M., Tindberg, Y., and Blennow, M. (1997). Seroepidemiology of *Helicobacter pylori* infection in a cohort of children monitored from 6 months to 11 years of age. *J Clin Microbiol.* 35:468–70.
- Grubel, P., Hoffman, J.S., Chong, F.K., Burstein, N.A., Mepani, C., and Cave, D.R. (1997). Vector potential of houseflies (*Musca domestica*) for *Helicobacter pylori*. *J Clin Microbiol.* 35:1300–3.
- Guilford, P.J., Hopkins, J.B., Grady, W.M., Markowitz, S.D., Willis, J., Lynch, H., Rajput, A., Wiesner, G.L., Lindor, N.M., Burgart, L.J., Toro, T.T., Lee, D., Limacher, J.M., Shaw, D.W., Findlay, M.P., and Reeve, A.E. (1999). E-cadherin germline mutations define an inherited cancer syndrome dominated by diffuse gastric cancer. *Hum Mutat.* 14:249–55.
- Guilford, P., Hopkins, J., Harraway, J., McLeod, M., McLeod, N., Harawira, P., Taite, H., Scoular, R., Miller, A., and Reeve, A.E. (1998). E-cadherin germline mutations in familial gastric cancer. *Nature.* 392:402–5.
- Handt, L.K., Fox, J.G., Stalis, I.H., Rufo, R., Lee, G., Linn, J., Li, X., and Kleanthous, H. (1995). Characterization of feline *Helicobacter pylori* strains and associated gastritis in a colony of domestic cats. *J Clin Microbiol.* 33:2280–9.
- Hansson, L.E., Nyren, O., Hsing, A.W., Bergstrom, R., Josefsson, S., Chow, W., Fraumeni, J.F., and Adami, H. (1996). Risk of stomach cancer in patients with gastric or duodenal ulcer disease. *New Engl J Med.* 335:242.
- Helicobacter and Cancer Collaborative Group (2001). Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut.* 49:347–53.
- Herrmann, K., and Niedobitek, G. (2003). Epstein-Barr virus-associated carcinomas: facts and fiction. *J Pathol.* 199:140–5.
- Higham, J., Kang, J.Y., and Majeed, A. (2002). Recent trends in admissions and mortality due to peptic ulcer in England: increasing frequency of haemorrhage among older subjects. *Gut.* 50:460–4.
- Hirata, I., Murano, M., Ishiguro, T., Toshina, K., Wang, F.Y., and Katsu, K. (2007). HLA genotype and development of gastric cancer in patients with *Helicobacter pylori* infection. *Hepatogastroenterology.* 54:990–4.
- Holcombe, C. (1992). *Helicobacter pylori*: the African enigma. *Gut* 33:429.
- Hopkins, R.J., Russell, R.G., O'Donnoghue, J.M., Wasserman, S.S., Lefkowitz, A., and Morris, J.G., Jr. (1990). Seroprevalence of *Helicobacter pylori* in Seventh-Day Adventists and other groups in Maryland. Lack of association with diet. *Arch Intern Med.* 150:2347.
- Hopkins, R.J., Vial, P.A., Ferreccio, C., Ovalle, J., Prado, P., Sotomayor, V., Russell, R.G., Wasserman, S.S., and Morris, J.G., Jr. (1993). Seroprevalence of *Helicobacter pylori* in Chile: vegetables may serve as one route of transmission. *J Infect Dis.* 168:222.

- Howson, C., Hiyama, T., and Wynder, E. (1986). The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidemiol Rev.* 8:1.
- Hsing, A.W., Hansson, L.E., McLaughlin, J.K., Nyren, O., Blot, W.J., Ekblom, A., and Fraumeni, J.F., Jr. (1993). Pernicious anemia and subsequent cancer. A population-based cohort study. *Cancer.* 71:745–50.
- Hsu, P.I., Lai, K.H., Hsu, P.N., Lo, G.H., Yu, H.C., Chen, W.C., Tsay, F.W., Lin, H.C., Tseng, H. H., Ger, L.P., and Chen, H.C. (2007). *Helicobacter pylori* infection and the risk of gastric malignancy. *Am J Gastroenterol.* 102:725–30.
- Huang, J.Q., Sridhar, S., Chen, Y., and Hunt, R.H. (1998). Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. *Gastroenterology.* 114:1169–79.
- Huang, J.Q., Zheng, G.F., Sumanac, K., Irvine, E.J., and Hunt, R.H. (2003). Meta-analysis of the relationship between *cagA* seropositivity and gastric cancer. *Gastroenterology.* 125:1636–44.
- Hulten, K., Han, S., Enroth, H., Klein, P., Opekun, A., Gilman, R., Evans, D., Engstrand, L., Graham, D., and El-Zaatari, F. (1996). *Helicobacter pylori* in the drinking water in Peru. *Gastroenterology.* 110:1031–1035.
- IARC (2004). Tobacco Smoke and Involuntary Smoking. IARC Monographs. 83.
- IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. (1994). *Helicobacter pylori* schistosomes, liver flukes and *Helicobacter pylori*: views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon: IARC; pp. 177.
- Ilver, D., Arnqvist, A., Ogren, J., Frick, I.M., Kersulyte, D., Incecik, E.T., Berg, D.E., Covacci, A., Engstrand, L., and Boren, T. (1998). *Helicobacter pylori* adhesin binding fucosylated histo-blood group antigens revealed by retagging. *Science.* 279(5349):373–7.
- Israel, D.A., Salama, N., Krishna, U., Rieger, U.M., Atherton, J.C., Falkow, S., and Peek, R.M., Jr. (2001). *Helicobacter pylori* genetic diversity within the gastric niche of a single human host. *Proc Natl Acad Sci USA.* 98:14625–30.
- Ito, L.S., Oba-Shinjo, S.M., Shinjo, S.K., Uno, M., Marie, S.K., and Hamajima, N. (2006). Community-based familial study of *Helicobacter pylori* infection among healthy Japanese Brazilians. *Gastric Cancer.* 9:208–16.
- Jeggli, S., Steiner, D., Joller, H., Tschopp, A., Steffen, R., and Hotz, P. (2004). Hepatitis E, *Helicobacter pylori*, and gastrointestinal symptoms in workers exposed to waste water. *Occup Environ Med.* 61:622–7.
- Jemal, A., Murray, T., Samuels, A., Ghafoor, A., Ward, E., and Thun, M.J. (2003). Cancer statistics, 2003. *CA Cancer J Clin.* 53:5–26.
- Ji, B.T., Chow, W.H., Yang, G., McLaughlin, J.K., Gao, R.N., Zheng, W., Shu, X.O., Jin, F., Fraumeni, J.F., Jr., and Gao, Y.T. (1997). Body mass index and the risk of cancers of the gastric cardia and distal stomach in Shanghai, China. *Cancer Epidemiol Biomarkers Prev.* 6:481–5.
- Kabir, S. (2007). The current status of *Helicobacter pylori* vaccines: a review. *Helicobacter.* 12:89–102.
- Kai, M., Luebeck, E.G., and Moolgavkar, S.H. (1997). Analysis of the incidence of solid cancer among atomic bomb survivors using a two-stage model of carcinogenesis. *Radiat Res.* 148:348–58.
- Kamangar, F., Dawsey, S.M., Blaser, M.J., Perez-Perez, G.I., Pietinen, P., Newschaffer, C.J., Abnet, C.C., Albanes, D., Virtamo, J., and Taylor, P.R. (2006). Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with *Helicobacter pylori* seropositivity. *J Natl Cancer Inst.* 98:1445–52.
- Karita, M., Teramukai, S., and Matsumoto, S. (2003). Risk of *Helicobacter pylori* transmission from drinking well water is higher than that from infected intrafamilial members in Japan. *Dig Dis Sci.* 48:1062–7.
- Kelly, S.M., Pitcher, M.C., Farmery, S.M., and Gibson, G.R. (1994). Isolation of *Helicobacter pylori* from feces of patients with dyspepsia in the United Kingdom. *Gastroenterology.* 107:1671.
- Kersulyte, D., Mukhopadhyay, A.K., Velapattino, B., Su, W., Pan, Z., Garcia, C., Hernandez, V., Valdez, Y., Mistry, R.S., Gilman, R.H., Yuan, Y., Gao, H., Alarcon, T., Lopez-Brea, M., Balakrishna Nair, G., Chowdhury, A., Datta, S., Shirai, M., Nakazawa, T., Ally, R., Segal, I., Wong, B.C., Lam, S.K., Olfat, F.O., Boren, T., Engstrand, L., Torres, O., Schneider, R.,

- Thomas, J.E., Czinn, S., and Berg, D.E. (2000). Differences in genotypes of *Helicobacter pylori* from different human populations. *J Bacteriol.* 182:3210–8.
- Kim, J.W., Kim, J.G., Chae, S.L., Cha, Y.J., and Park, S.M. (2004). High prevalence of multiple strain colonization of *Helicobacter pylori* in Korean patients: DNA diversity among clinical isolates from the gastric corpus, antrum and duodenum. *Korean J Intern Med.* 19:1–9.
- Kivi, M., Johansson, A.L., Reilly, M., and Tindberg, Y. (2005). *Helicobacter pylori* status in family members as risk factors for infection in children. *Epidemiol Infect.* 133:645–52.
- Kivi, M., Tindberg, Y., Sorberg, M., Casswall, T.H., Befrits, R., Hellstrom, P.M., Bengtsson, C., Engstrand, L., and Granstrom, M. (2003). Concordance of *Helicobacter pylori* strains within families. *J Clin Microbiol.* 41:5604–8.
- Klein, P.D., Gilman, R.H., Leon-Barua, R., Diaz, F., Smith, E.O., and Graham, D.Y. (1994). The epidemiology of *Helicobacter pylori* in Peruvian children between 6 and 30 months of age. *Am J Gastroenterol.* 89:2196.
- Klein, P.D., Graham, D.Y., Gaillour, A., Opekun, A.R., and Smith, E.O. (1991). Water source as risk factor for *Helicobacter pylori* infection in Peruvian children. Gastrointestinal Physiology Working Group. *Lancet.* 337:1503–6.
- Kneller, R.W., You, W.C., Chang, Y.S., Liu, W.D., Zhang, L., Zhao, L., Xu, G.W., Fraumeni, J.F., Jr., and Blot, W.J. (1992). Cigarette smoking and other risk factors for progression of precancerous stomach lesions. *J Natl Cancer Inst.* 84:1261.
- Kokkola, A., Sjoblom, S.M., Haapiainen, R., Sipponen, P., Puolakkainen, P., and Jarvinen, H. (1998). The risk of gastric carcinoma and carcinoid tumours in patients with pernicious anaemia. A prospective follow-up study. *Scand J Gastroenterol.* 33:88–92.
- Kolonel, L.N., Nomura, A.M., Hirohata, T., Hankin, J.H., and Hinds, M.W. (1981). Association of diet and place of birth with stomach cancer incidence in Hawaii Japanese and Caucasians. *Am J Clin Nutr.* 34:2478–85.
- Kosunen, T.U., Hook-Nikanne, J., Salomaa, A., Sarna, S., Aromaa, A., and Haahtela, T. (2002). Increase of allergen-specific immunoglobulin E antibodies from 1973 to 1994 in a Finnish population and a possible relationship to *Helicobacter pylori* infections. *Clin Exp Allergy.* 32:373–8.
- Krajden, S., Fuksa, M., Anderson, J., Kempston, J., Boccia, A., Petrea, C., Babida, C., Karmali, M., and Penner, J.L. (1989). Examination of human stomach biopsies, saliva, and dental plaque for *Campylobacter pylori*. *J Clin Microbiol.* 27:1397.
- Kreinitz, W. (1906). Ueber das Auftreten von Spirochaeten verschiedener Form im Mageninhalt bei Carcinoma ventriculi. *Dtsch Med Wochenschr.* 32:872.
- Kuipers, E.J., Lundell, L., Klinkenberg-Knol, E.C., Havu, N., Festen, H.P., Liedman, B., Lamers, C.B., Jansen, J.B., Dalenback, J., and Snel, P. (1996). Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med.* 334:1018.
- Kuo, C.H., Poon, S.K., Su, Y.C., Su, R., Chang, C.S., and Wang, W.C. (1999). Heterogeneous *Helicobacter pylori* isolates from *H. pylori*-infected couples in Taiwan. *J Infect Dis.* 180:2064–8.
- Lagergren, J., Bergstrom, R., Lindgren, A., and Nyren, O. (1999). Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med.* 340:825–31.
- Langenberg, W., Rauws, E.A., Oudbier, J.H., and Tytgat, G.N. (1990). Patient-to-patient transmission of *Campylobacter pylori* infection by fiberoptic gastroduodenoscopy and biopsy. *J Infect Dis.* 161:507.
- Lauren, P. (1965). The two histological main types of gastric cancer: diffuse and so-called intestinal type carcinoma. *Acta Pathol Microbiol Scand.* 64:31.
- Lee, W.P., Tai, D.I., Lan, K.H., Li, A.F., Hsu, H.C., Lin, E.J., Lin, Y.P., Sheu, M.L., Li, C.P., Chang, F.Y., Chao, Y., Yen, S.H., and Lee, S.D. (2005). The –251T allele of the interleukin-8 promoter is associated with increased risk of gastric carcinoma featuring diffuse-type histopathology in Chinese population. *Clin Cancer Res.* 11:6431–41.
- Leung, W.K., Sung, J.Y., Siu, K.L.K., Kwok, K.L., Cheng, A.F.B., and Sung, R. (1998). Isolation of *H. pylori* from vomitus in children. *Gastroenterology.* 114.

- Ley, C., Mohar, A., Guarner, J., Herrera-Goepfert, R., Figueroa, L.S., Halperin, D., Johnstone, I., and Parsonnet, J. (2004). *Helicobacter pylori* eradication and gastric preneoplastic conditions: a randomized, double-blind, placebo-controlled trial. *Cancer Epidemiol Biomarkers Prev.* 13:4–10.
- Li, Z., Chen, D., Zhang, C., Li, Y., Cao, B., Ning, T., Zhao, Y., You, W., and Ke, Y. (2005). HLA polymorphisms are associated with *Helicobacter pylori* infected gastric cancer in a high risk population, China. *Immunogenetics.* 56:781–7.
- Lin, H.Y., Chuang, C.K., Lee, H.C., Chiu, N.C., Lin, S.P., and Yeung, C.Y. (2005). A seroepidemiologic study of *Helicobacter pylori* and hepatitis A virus infection in primary school students in Taipei. *J Microbiol Immunol Infect.* 38:176–82.
- Lin, S.K., Lambert, J.R., Schembri, M.A., Nicholson, L., and Korman, M.G. (1994). *Helicobacter pylori* prevalence in endoscopy and medical staff. *J Gastroenterol Hepatol.* 9:319.
- Lindblad, M., Rodriguez, L.A., and Lagergren, J. (2005). Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Control.* 16:285–94.
- Linz, B., Balloux, F., Moodley, Y., Manica, A., Liu, H., Roumagnac, P., Falush, D., Stamer, C., Prugnolle, F., van der Merwe, S.W., Yamaoka, Y., Graham, D.Y., Perez-Trallero, E., Wadstrom, T., Suerbaum, S., and Achtman, M. (2007). An African origin for the intimate association between humans and *Helicobacter pylori*. *Nature.* 445:915–8.
- Louw, J.A., Kidd, M.S., Kummer, A.F., Taylor, K., Kotze, U., and Hanslo, D. (2001). The relationship between *Helicobacter pylori* infection, the virulence genotypes of the infecting strain and gastric cancer in the African setting. *Helicobacter.* 6:268–73.
- Lu, Y., Redlinger, T.E., Avitia, R., Galindo, A., and Goodman, K. (2002). Isolation and genotyping of *Helicobacter pylori* from untreated municipal wastewater. *Appl Environ Microbiol.* 68:1436–9.
- Lugli, A., Zlobec, I., Singer, G., Kopp, A., Terracciano, L.M., and Genta, R.M. (2007). Napoleon Bonaparte's gastric cancer: a clinicopathologic approach to staging, pathogenesis, and etiology. *Nat Clin Pract Gastroenterol Hepatol.* 4:52–7.
- Luman, W., Zhao, Y., Ng, H.S., and Ling, K.L. (2002). *Helicobacter pylori* infection is unlikely to be transmitted between partners: evidence from genotypic study in partners of infected patients. *Eur J Gastroenterol Hepatol.* 14:521–8.
- Luzza, F., Mancuso, M., Imeneo, M., Contaldo, A., Giancotti, L., Pensabene, L., Doldo, P., Liberto, M.C., Strisciuglio, P., Foca, A., Guandalini, S., and Pallone, F. (2000). Evidence favouring the gastro-oral route in the transmission of *Helicobacter pylori* infection in children. *Eur J Gastroenterol Hepatol.* 12:623–7.
- Machado, J.C., Figueiredo, C., Canedo, P., Pharoah, P., Carvalho, R., Nabais, S., Castro Alves, C., Campos, M.L., Van Doorn, L.J., Caldas, C., Seruca, R., Carneiro, F., and Sobrinho-Simoes, M. (2003). A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. *Gastroenterology.* 125:364–71.
- Magalhaes Queiroz, D.M., and Luzza, F. (2006). Epidemiology of *Helicobacter pylori* infection. *Helicobacter.* 11(Suppl 1):1–5.
- Malaty, H.M., El-Kasabany, A., Graham, D.Y., Miller, C.C., Reddy, S.G., Srinivasan, S.R., Yamaoka, Y., and Berenson, G.S. (2002). Age at acquisition of *Helicobacter pylori* infection: a follow-up study from infancy to adulthood. *Lancet.* 359:931–5.
- Malaty, H.M., Evans, D.J., Jr., Abramovitch, K., Evans, D.G., and Graham, D.Y. (1992). *Helicobacter pylori* infection in dental workers: a seroepidemiology study. *Am J Gastroenterol.* 87:1728.
- Malaty, H.M., Kumagai, T., Tanaka, E., Ota, H., Kiyosawa, K., Graham, D.Y., and Katsuyama, T. (2000). Evidence from a nine-year birth cohort study in Japan of transmission pathways of *Helicobacter pylori* infection. *J Clin Microbiol.* 38:1971–3.
- Malfertheiner, P., Megraud, F., O'Morain, C., Bazzoli, F., El-Omar, E., Graham, D., Hunt, R., Rokkas, T., Vakil, N., and Kuipers, E.J. (2007). Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut.* 56:772–81.
- Mapstone, N.P., Lynch, D.A., Lewis, F.A., Axon, A.T., Tompkins, D.S., Dixon, M.F., and Quirke, P. (1993). Identification of *Helicobacter pylori* DNA in the mouths and stomachs of patients with gastritis using PCR. *J Clin Pathol.* 46:540.

- Marshall, B.J., Armstrong, J.A., McGeche, D.B., and Glancy, R.J. (1985a). Attempt to fulfill Koch's postulates for pyloric *Campylobacter*. *Med J Aust.* 142:436.
- Marshall, B.J., McGeche, D.B., Rogers, P.A., and Glancy, R.J. (1985b). Pyloric *Campylobacter* infection and gastroduodenal disease. *Med J Aust.* 142:439.
- Marshall, B.J., and Warren, J.R. (1984). Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet.* 1:1311.
- Masci, E., Viale, E., Freschi, M., Porcellati, M., and Tittobello, A. (1996). Precancerous gastric lesions and *Helicobacter pylori*. *Hepatogastroenterology.* 43:854.
- Mason, J., Axon, A.T., Forman, D., Duffett, S., Drummond, M., Crocombe, W., Feltbower, R., Mason, S., Brown, J., and Moayyedi, P. (2002). The cost-effectiveness of population *Helicobacter pylori* screening and treatment: a Markov model using economic data from a randomized controlled trial. *Aliment Pharmacol Ther.* 16:559–68.
- Matteo, M.J., Granados, G., Perez, C.V., Olmos, M., Sanchez, C., and Catalano, M. (2007). *Helicobacter pylori* cag pathogenicity island genotype diversity within the gastric niche of a single host. *J Med Microbiol.* 56:664–9.
- Mayne, S.T., and Navarro, S.A. (2002). Diet, obesity and reflux in the etiology of adenocarcinomas of the esophagus and gastric cardia in humans. *J Nutr.* 132:3467S–70S.
- McMichael, A.J., McCall, M.G., Hartshorne, J.M., and Woodings, T.L. (1980). Patterns of gastrointestinal cancer in European migrants to Australia: the role of dietary change. *Int J Cancer.* 25:431.
- Mendall, M.A., Goggin, P.M., Molineaux, N., Levy, J., Toosy, T., Strachan, D., and Northfield, T.C. (1992). Childhood living conditions and *Helicobacter pylori* seropositivity in adult life. *Lancet.* 339:896.
- Mera, R., Fontham, E.T., Bravo, L.E., Bravo, J.C., Piazuelo, M.B., Camargo, M.C., and Correa, P. (2005). Long term follow up of patients treated for *Helicobacter pylori* infection. *Gut.* 54:1536–40.
- Mitchell, H.M., Ally, R., Wade, A., Wiseman, M., and Segal, I. (2002). Major differences in the IgG subclass response to *Helicobacter pylori* in the first and third worlds. *Scand J Gastroenterol.* 37:517.
- Mitchell, H.M., Lee, A., Berkowicz, J., and Borody, T. (1988). The use of serology to diagnose active *Campylobacter pylori* infection. *Med J Aust.* 149:604–9.
- Miwa, H., Go, M.F., and Sato, N. (2002). *H. pylori* and gastric cancer: the Asian enigma. *Am J Gastroenterol.* 97:1106.
- Miyaji, H., Azuma, T., Ito, S., Abe, Y., Gejyo, F., Hashimoto, N., Sugimoto, H., Suto, H., Ito, Y., Yamazaki, Y., Kohli, Y., and Kuriyama, M. (2000). *Helicobacter pylori* infection occurs via close contact with infected individuals in early childhood. *J Gastroenterol Hepatol.* 15:257–62.
- Miyamoto, A., Kuriyama, S., Nishino, Y., Tsubono, Y., Nakaya, N., Ohmori, K., Kurashima, K., Shibuya, D., and Tsuji, I. (2007). Lower risk of death from gastric cancer among participants of gastric cancer screening in Japan: a population-based cohort study. *Prev Med.* 44:12–9.
- Morris, A., Nicholson, G., Lloyd, G., Haines, D., Rogers, A., and Taylor, D. (1986). Seroepidemiology of *Campylobacter pyloridis*. *NZ Med J.* 99:657.
- Mourad-Baars, P.E., Verspaget, H.W., Mertens, B.J., and Mearin, M.L. (2007). Low prevalence of *Helicobacter pylori* infection in young children in the Netherlands. *Eur J Gastroenterol Hepatol.* 19:213–6.
- Nakagawa, S., Asaka, M., Kato, M., Nakamura, T., Kato, C., Fujioka, T., Tatsuta, M., Keida, K., Terao, S., Takahashi, S., Uemura, N., Kato, T., Aoyama, N., Saito, D., Suzuki, M., Imamura, A., Sato, K., Miwa, H., Nomura, H., Kaise, M., Oohara, S., Kawai, T., Urabe, K., Sakaki, N., Ito, S., Noda, Y., Yanaka, A., Kusugami, K., Goto, H., Furuta, T., Fujino, M., Kinjyou, F., and Oookusa, T. (2006). *Helicobacter pylori* eradication and metachronous gastric cancer after endoscopic mucosal resection of early gastric cancer. *Aliment Pharmacol Ther.* 24(Suppl 4):214–8.
- National Cancer Institute, Bethesda. (2007). <http://www.cancer.gov/cancertopics/pdq/screening/gastric/healthprofessional/allpages>. Accessed March 5, 2007.
- Neugut, A.I., Hayek, M., and Howe, G. (1996). Epidemiology of gastric cancer. *Semin Oncol.* 23:281–91.

- Nguyen, V.B., Nguyen, G.K., Phung, D.C., Okrainec, K., Raymond, J., Dupond, C., Kremp, O., Kalach, N., and Vidal-Trecan, G. (2006). Intra-familial transmission of *Helicobacter pylori* infection in children of households with multiple generations in Vietnam. *Eur J Epidemiol.* 21:459–63.
- Nurgalieva, Z.Z., Malaty, H.M., Graham, D.Y., Almuchambetova, R., Machmudova, A., Kapsultanova, D., Osato, M.S., Hollinger, F.B., and Zhangabylov, A. (2002). *Helicobacter pylori* infection in Kazakhstan: effect of water source and household hygiene. *Am J Trop Med Hyg.* 67:201–6.
- Nurgalieva, Z.Z., Opekun, A.R., and Graham, D.Y. (2006). Problem of distinguishing false-positive tests from acute or transient *Helicobacter pylori* infections. *Helicobacter.* 11:69–74.
- Odze, R.D. (2005). Pathology of the gastroesophageal junction. *Semin Diagn Pathol.* 22:256–65.
- Ohata, H., Kitauchi, S., Yoshimura, N., Mugitani, K., Iwane, M., Nakamura, H., Yoshikawa, A., Yanaoka, K., Arai, K., Tamai, H., Shimizu, Y., Takeshita, T., Mohara, O., and Ichinose, M. (2004). Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer. *Int J Cancer.* 109:138–43.
- Oliveira, C., Bordin, M.C., Grehan, N., Huntsman, D., Suriano, G., Machado, J.C., Kiviluoto, T., Aaltonen, L., Jackson, C.E., Seruca, R., and Caldas, C. (2002). Screening E-cadherin in gastric cancer families reveals germline mutations only in hereditary diffuse gastric cancer kindred. *Hum Mutat.* 19:510–7.
- O'Rourke, K., Goodman, K.J., Grazioplene, M., Redlinger, T., and Day, R.S. (2003). Determinants of geographic variation in *Helicobacter pylori* infection among children on the US-Mexico border. *Am J Epidemiol.* 158:816–24.
- Osato, M.S., Ayub, K., Le, H.H., Reddy, R., and Graham, D.Y. (1998). Houseflies are an unlikely reservoir or vector for *Helicobacter pylori*. *J Clin Microbiol.* 36:2786–8.
- Osawa, H., Inoue, F., and Yoshida, Y. (1996). Inverse relation of serum *Helicobacter pylori* antibody titres and extent of intestinal metaplasia. *J Clin Pathol.* 49:112–5.
- Palmer, E.D. (1954). Investigation of the gastric spirochaetes of the human. *Gastroenterology.* 27:218.
- Pardo-Mindan, F.J., Joly, M., Robledo, C., Sola, J., and Valerdez, S. (1989). Duodenal ulcer “epidemic” in a pathology department. *Lancet.* 1:153.
- Parente, J.M., da Silva, B.B., Palha-Dias, M.P., Zaterka, S., Nishimura, N.F., and Zeitune, J.M. (2006). *Helicobacter pylori* infection in children of low and high socioeconomic status in northeastern Brazil. *Am J Trop Med Hyg.* 75:509–12.
- Parkin, D.M. (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer.* 118:3030–44.
- Parkin, D.M., Pisani, P., and Ferlay, J. (1999a). Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer.* 80:827–41.
- Parkin, D.M., Pisani, P., and Ferlay, J. (1999b). Global cancer statistics. *CA Cancer J Clin.* 49:33–64.
- Parsonnet, J. (1995). The incidence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 9(Suppl 2):45–51.
- Parsonnet, J., Blaser, M.J., Perez-Perez, G.I., Hargrett-Bean, N., and Tauxe, R.V. (1992). Symptoms and risk factors of *Helicobacter pylori* infection in a cohort of epidemiologists. *Gastroenterology.* 102:41.
- Parsonnet, J., and Forman, D. (2004). *Helicobacter pylori* infection and gastric cancer—for want of more outcomes. *JAMA.* 291:244–5.
- Parsonnet, J., Harris, R., Hack, H.M., and Owens, D.K. (1996). Modelling cost effectiveness of *Helicobacter pylori* screening to prevent gastric cancer: a mandate for clinical trials. *Lancet.* 348:150–4.
- Parsonnet, J., Replogle, M., Yang, S., and Hiatt, R. (1997). Seroprevalence of CagA-positive strains among *Helicobacter pylori*-infected, healthy young adults. *J Infect Dis.* 175:1240.
- Parsonnet, J., Shmueli, H., and Haggerty, T. (1999). Fecal and oral shedding of *Helicobacter pylori* from healthy infected adults. *JAMA.* 282:2240–5.
- Perez-Perez, G.I., Olivares, A.Z., Foo, F.Y., Foo, S., Neusy, A.J., Ng, C., Holzman, R.S., Marmor, M., and Blaser, M.J. (2005). Seroprevalence of *Helicobacter pylori* in New York City populations originating in East Asia. *J Urban Health.* 82:510–6.

- Perez-Perez, G.I., Witkin, S.S., Decker, M.D., and Blaser, M.J. (1991). Seroprevalence of *Helicobacter pylori* infection in couples. *J Clin Microbiol.* 29:642–4.
- Perri, F., Piepoli, A., Quitadamo, M., Quarticelli, M., Merla, A., and Bisceglia, M. (2002). HLA-DQA1 and -DQB1 genes and *Helicobacter pylori* infection in Italian patients with gastric adenocarcinoma. *Tissue Antigens.* 59:55–7.
- Perry, S., De Jong, B.C., Hill, P., Adegbola, R., and Parsonnet, J. (2007). *Helicobacter pylori* and the outcome of *M. tuberculosis* infection. *Infectious Disease Society of America, annual meeting.* San Diego, CA: IDSA; pp. LB-22.
- Perry, S., de la Luz Sanchez, M., Hurst, P.K., and Parsonnet, J. (2005). Household transmission of gastroenteritis. *Emerg Infect Dis.* 11:1093–6.
- Perry, S., de la Luz Sanchez, M., Yang, S., Haggerty, T.D., Hurst, P., Perez-Perez, G., and Parsonnet, J. (2006). Gastroenteritis and transmission of *Helicobacter pylori* infection in households. *Emerg Infect Dis.* 12:1701–8.
- Perry, S., and Parsonnet, J. (2005). Commentary: *H. pylori* infection in early life and the problem of imperfect tests. *Int J Epidemiol.* 34:1356–8.
- Perry, S., Sanchez, L., Yang, S., Haggerty, T.D., Hurst, P., and Parsonnet, J. (2004). *Helicobacter pylori* and risk of gastroenteritis. *J Infect Dis.* 190:303–10.
- Pessi, T., Virta, M., Adjers, K., Karjalainen, J., Rautelin, H., Kosunen, T.U., and Hurme, M. (2005). Genetic and environmental factors in the immunopathogenesis of atopy: interaction of *Helicobacter pylori* infection and IL4 genetics. *Int Arch Allergy Immunol.* 137:282–8.
- Pharoah, P.D., Guilford, P., and Caldas, C. (2001). Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology.* 121:1348–53.
- Pritchard, D.M., and Przemeck, S.M. (2004). Review article: How useful are the rodent animal models of gastric adenocarcinoma? *Aliment Pharmacol Ther.* 19:841–59.
- Quintero, E., Pizarro, M.A., Rodrigo, L., Pique, J.M., Lanas, A., Ponce, J., Mino, G., Gisbert, J., Jurado, A., Herrero, M.J., Jimenez, A., Torrado, J., Ponte, A., Diaz-de-Rojas, F., and Salido, E. (2005). Association of *Helicobacter pylori*-related distal gastric cancer with the HLA class II gene DQB10602 and *cagA* strains in a southern European population. *Helicobacter.* 10:12–21.
- Raghunath, A., Hungin, A.P., Wooff, D., and Childs, S. (2003). Prevalence of *Helicobacter pylori* in patients with gastro-oesophageal reflux disease: systematic review. *BMJ.* 326:737.
- Ramsey, E.J., Carey, K.V., Peterson, W.L., Jackson, J.J., Murphy, F.K., Read, N.W., Taylor, K.B., Trier, J.S., and Fordtran, J.S. (1979). Epidemic gastritis with hypochlorhydria. *Gastroenterology.* 76:1449.
- Raymond, J., Thiberg, J.M., Chevalier, C., Kalach, N., Bergeret, M., Labigne, A., and Dauga, C. (2004). Genetic and transmission analysis of *Helicobacter pylori* strains within a family. *Emerg Infect Dis.* 10:1816–21.
- Richter, J.E. (2007). Gastroesophageal reflux disease. *Best Pract Res Clin Gastroenterol.* 21:609–31.
- Ries, L.A.G., Melbert, D., Krapcho, M., Mariotto, A., Miller, B.A., Feuer, E.J., Clegg, L., Horner, M.J., Howlader, N., Eisner, M.P., Reichman, M., and Edwards, B.K. (based on November 2006 SEER data submission, posted to the SEER Web site, 2007). *SEER Cancer Statistics Review, 1975–2004:* National Cancer Institute, Bethesda, MD.
- Roderick, P., Davies, R., Raftery, J., Crabbe, D., Pearce, R., Patel, P., and Bhandari, P. (2003). Cost-effectiveness of population screening for *Helicobacter pylori* in preventing gastric cancer and peptic ulcer disease, using simulation. *J Med Screen.* 10:148–56.
- Roosendaal, R., Kuipers, E.J., Buitenwerf, J., van Uffelen, C., Meuwissen, S.G., van Kamp, G.J., and Vandenbroucke-Grauls, C.M. (1997). *Helicobacter pylori* and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. *Am J Gastroenterol.* 92:1480.
- Rosenstock, S., Jorgensen, T., Andersen, L., and Bonnevie, O. (2000). Seroconversion and seroreversion in IgG antibodies to *Helicobacter pylori*: a serology based prospective cohort study. *J Epidemiol Community Health.* 54:444.

- Rothenbacher, D., Bode, G., and Brenner, H. (2002). Dynamics of *Helicobacter pylori* infection in early childhood in a high-risk group living in Germany: loss of infection higher than acquisition. *Aliment Pharmacol Ther* 16:1663–8.
- Rowland, M., Daly, L., Vaughan, M., Higgins, A., Bourke, B., and Drumm, B. (2006). Age-specific incidence of *Helicobacter pylori*. *Gastroenterology*. 130:65–72; quiz 211.
- Rupnow, M.F., Owens, D.K., Shachter, R., and Parsonnet, J. (1999). *Helicobacter pylori* vaccine development and use: a cost-effectiveness analysis using the Institute of Medicine methodology. *Helicobacter*. 4:272–80.
- Rupnow, M.F., Shachter, R.D., Owens, D.K., and Parsonnet, J. (2001). Quantifying the population impact of a prophylactic *Helicobacter pylori* vaccine. *Vaccine*. 20:879–85.
- Shikata, K., Kiyohara, Y., Kubo, M., Yonemoto, K., Ninomiya, T., Shiota, T., Tanizaki, Y., Doi, Y., Tanaka, K., Oishi, Y., Matsumoto, T., and Iida, M. (2006). A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer*. 119:196–201.
- Shinmura, K., Kohno, T., Takahashi, M., Sasaki, A., Ochiai, A., Guilford, P., Hunter, A., Reeve, A.E., Sugimura, H., Yamaguchi, N., and Yokota, J. (1999). Familial gastric cancer: clinico-pathological characteristics, RER phenotype and germline p53 and E-cadherin mutations. *Carcinogenesis*. 20:1127–31.
- Singh, K., and Ghoshal, U.C. (2006). Causal role of *Helicobacter pylori* infection in gastric cancer: an Asian enigma. *World J Gastroenterol*. 12:1346–51.
- Singh, V., Trikha, B., Vaiphei, K., Nain, C.K., Thennarasu, K., and Singh, K. (1999). *Helicobacter pylori*: evidence for spouse-to-spouse transmission. *J Gastroenterol Hepatol*. 14:519–22.
- Smith, R.A., Cokkinides, V., and Eyre, H.J. (2003). American Cancer Society guidelines for the early detection of cancer, 2003. *CA Cancer J Clin*. 53:27–43.
- Solnick, J.V., Fong, J., Hansen, L.M., Chang, K., Canfield, D.R., and Parsonnet, J. (2006). Acquisition of *Helicobacter pylori* infection in rhesus macaques is most consistent with oral-oral transmission. *J Clin Microbiol*. 44:3799–803.
- Sorberg, M., Nilsson, M., Hanberger, H., and Nilsson, L.E. (1996). Morphologic conversion of *Helicobacter pylori* from bacillary to coccoid form. *Eur J Clin Microbiol Infect Dis*. 15:216–9.
- Stalnikowicz, R., and Benbassat, J. (1990). Risk of gastric cancer after gastric surgery for benign disorders. *Arch Intern Med*. 150:2022–6.
- Stein, M., Bagnoli, F., Halenbeck, R., Rappuoli, R., Fantl, W.J., and Covacci, A. (2002). c-Src/Lyn kinases activate *Helicobacter pylori* CagA through tyrosine phosphorylation of the EPIYA motifs. *Mol Microbiol*. 43:971–80.
- Stone, J., Bevan, S., Cunningham, D., Hill, A., Rahman, N., Peto, J., Marossy, A., and Houlston, R.S. (1999). Low frequency of germline E-cadherin mutations in familial and nonfamilial gastric cancer. *Br J Cancer*. 79:1935–7.
- Stone, M.A., Taub, N., Barnett, D.B., and Mayberry, J.F. (2000). Increased risk of infection with *Helicobacter pylori* in spouses of infected subjects: observations in a general population sample from the UK. *Hepatogastroenterology*. 47:433–6.
- Suerbaum, S., and Michetti, P. (2002). *Helicobacter pylori* infection. *N Engl J Med*. 347:1175–86.
- Sung, J.J., Lin, S.R., Ching, J.Y., Zhou, L.Y., To, K.F., Wang, R.T., Leung, W.K., Ng, E.K., Lau, J.Y., Lee, Y.T., Yeung, C.K., Chao, W., and Chung, S.C. (2000). Atrophy and intestinal metaplasia one year after cure of *H. pylori* infection: a prospective, randomized study. *Gastroenterology*. 119:7.
- Suzuki, J., Muraoka, H., Kobayasi, I., Fujita, T., and Mine, T. (1999). Rare incidence of inter-spousal transmission of *Helicobacter pylori* in asymptomatic individuals in Japan. *J Clin Microbiol*. 37:4174–6.
- Takada, K. (2000). Epstein-Barr virus and gastric carcinoma. *Mol Pathol*. 53:255–61.
- Targownik, L.E., and Nabalamba, A. (2006). Trends in management and outcomes of acute non-variceal upper gastrointestinal bleeding: 1993–2003. *Clin Gastroenterol Hepatol*. 4:1459–66.
- Tatematsu, M., Nozaki, K., and Tsukamoto, T. (2003). *Helicobacter pylori* infection and gastric carcinogenesis in animal models. *Gastric Cancer*. 6:1–7.

- Taylor, D.N., Parsonnet, J. (1995). The epidemiology and natural history of *Helicobacter pylori* infection. In: Blaser, M.J., Smith, P.D., Ravdin, J.I., Grenber, H.B., Guerrant, R.L. (eds). *Infections of the Gastrointestinal Tract*. New York: Raven Press, pp. 551–64.
- Terry, M.B., Gaudet, M.M., and Gammon, M.D. (2002). The epidemiology of gastric cancer. *Semin Radiat Oncol.* 12:111–27.
- Tersmette, A.C., Offerhaus, G.J., Tersmette, K.W., Giardiello, F.M., Moore, G.W., Tytgat, G.N., and Vandenbroucke, J.P. (1990). Meta-analysis of the risk of gastric stump cancer: detection of high risk patient subsets for stomach cancer after remote partial gastrectomy for benign conditions. *Cancer Res.* 50:6486–9.
- Thomas, J.E., Dale, A., Harding, M., Coward, W.A., Cole, T.J., and Weaver, L.T. (1999). *Helicobacter pylori* colonization in early life. *Pediatr Res.* 45:218–23.
- Tindberg, Y., Bengtsson, C., Granath, F., Blennow, M., Nyren, O., and Granstrom, M. (2001). *Helicobacter pylori* infection in Swedish school children: lack of evidence of child-to-child transmission outside the family. *Gastroenterology.* 121:310–6.
- Tokudome, S., Soeripto, Triningsih, F.X., Ananta, I., Suzuki, S., Kuriki, K., Akasaka, S., Kosaka, H., Ishikawa, H., Azuma, T., and Moore, M.A. (2005). Rare *Helicobacter pylori* infection as a factor for the very low stomach cancer incidence in Yogyakarta, Indonesia. *Cancer Lett.* 219:57–61.
- Torres, J., Leal-Herrera, Y., Perez-Perez, G., Gomez, A., Camorlinga-Ponce, M., Cedillo-Rivera, R., Tapia-Conyer, R., and Munoz, O. (1998). A community-based seroepidemiologic study of *Helicobacter pylori* infection in Mexico. *J Infect Dis.* 178:1089–94.
- Tsai, C.J., Perry, S., Sanchez, L., and Parsonnet, J. (2005). *Helicobacter pylori* infection in different generations of Hispanics in the San Francisco Bay Area. *Am J Epidemiol.* 162:351–7.
- Tytgat, G.N.J. (1995). Endoscopic transmission of *Helicobacter pylori* infection. *Aliment Pharmacol Ther.* 9(Suppl 2):105.
- Ueda, M., Kikuchi, S., Kasugai, T., Shunichi, T., and Miyake, C. (2003). *Helicobacter pylori* risk associated with childhood home environment. *Cancer Sci.* 94:914–8.
- Uemura, N., Mukai, T., Okamoto, S., Yamaguchi, S., Mashiba, H., Taniyam, K., Sasaki, N., Haruma, K., Sumii, K., and Kajiyama, G. (1997). Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. *Cancer Epidemiol Biomarkers Prev.* 6:639.
- Uemura, N., Okamoto, S., Yamamoto, S., Matsumura, N., Yamaguchi, S., Yamakido, M., Taniyama, K., Sasaki, N., and Schlemper, R.J. (2001). *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med.* 345:784.
- Van Doorn, L.J., Figueiredo, C., Megraud, F., Pena, S., Midolo, P., Queiroz, D.M., Carneiro, F., Vanderborght, B., Pegado, M.D., Sanna, R., De Boer, W., Schneeberger, P.M., Correa, P., Ng, E.K., Atherton, J., Blaser, M.J., and Quint, W.G. (1999). Geographic distribution of *vacA* allelic types of *Helicobacter pylori*. *Gastroenterology.* 116:823–30.
- Wang, J.T., Sheu, J.C., Lin, J.T., Wang, T.H., and Wu, M.S. (1993). Direct DNA amplification and restriction pattern analysis of *Helicobacter pylori* in patients with duodenal ulcer and their families. *J Infect Dis.* 168:1544.
- Watanabe, Y., Aoyama, N., Sakai, T., Shirasaka, D., Maekawa, S., Kuroda, K., Wambura, C., Tamura, T., Nose, Y., and Kasuga, M. (2006). HLA-DQB1 locus and gastric cancer in *Helicobacter pylori* infection. *J Gastroenterol Hepatol.* 21:420–4.
- Webb, P.M., Knight, T., Greaves, S., Wilson, A., Newell, D.G., Elder, J., and Forman, D. (1994). Relation between infection with *Helicobacter pylori* and living conditions in childhood: evidence for person to person transmission in early life. *BMJ.* 308:750.
- Weisse, A.B. (1996). Barry Marshall and the resurrection of Johannes Fibiger. *Hosp Pract.* 31:105.
- Weyermann, M., Adler, G., Brenner, H., and Rothenbacher, D. (2006). The mother as source of *Helicobacter pylori* infection. *Epidemiology.* 17:332–4.
- Whary, M.T., Sundina, N., Bravo, L.E., Correa, P., Quinones, F., Caro, F., and Fox, J. (2005). Intestinal helminthiasis in Colombian children promotes a Th2 response to *Helicobacter pylori*: possible implications for gastric carcinogenesis. *Cancer Epidemiol Biomarkers Prev.* 14:1464–9.

- Windsor, H.M., Abioye-Kuteyi, E.A., Leber, J.M., Morrow, S.D., Bulsara, M.K., and Marshall, B.J. (2005). Prevalence of *Helicobacter pylori* in Indigenous Western Australians: comparison between urban and remote rural populations. *Med J Aust.* 182:210–3.
- Wizla-Derambure, N., Michaud, L., Ategbo, S., Vincent, P., Ganga-Zandzou, S., Turck, D., and Gottrand, F. (2001). Familial and community environmental risk factors for *Helicobacter pylori* infection in children and adolescents. *J Pediatr Gastroenterol Nutr.* 33:58–63.
- Wong, B.C., Lam, S.K., Wong, W.M., Chen, J.S., Zheng, T.T., Feng, R.E., Lai, K.C., Hu, W.H., Yuen, S.T., Leung, S.Y., Fong, D.Y., Ho, J., Ching, C.K., and Chen, J.S. (2004). *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA.* 291:187–94.
- World Cancer Research Fund, and American Institute for Cancer Research. (1997). Stomach, food, nutrition and the prevention of cancer: a global perspective. Washington, D.C.: American Institute for Cancer Research; pp. 148–75.
- Wu, M.S., Shun, C.T., Wu, C.C., Hsu, T.Y., Lin, M.T., Chang, M.C., Wang, H.P., and Lin, J.T. (2000). Epstein-Barr virus-associated gastric carcinomas: relation to *H. pylori* infection and genetic alterations. *Gastroenterology.* 118:1031–8.
- Yabuta, T., Shinmura, K., Tani, M., Yamaguchi, S., Yoshimura, K., Katai, H., Nakajima, T., Mochiki, E., Tsujinaka, T., Takami, M., Hirose, K., Yamaguchi, A., Takenoshita, S., and Yokota, J. (2002). E-cadherin gene variants in gastric cancer families whose probands are diagnosed with diffuse gastric cancer. *Int J Cancer.* 101:434–41.
- Yamaoka, Y., Osato, M.S., Sepulveda, A.R., Gutierrez, O., Figura, N., Kim, J.G., Kodama, T., Kashima, K., and Graham, D.Y. (2000). Molecular epidemiology of *Helicobacter pylori*: separation of *H. pylori* from East Asian and non-Asian countries. *Epidemiol Infect.* 124:91–6.
- Yamazaki, S., Yamakawa, A., Ito, Y., Ohtani, M., Higashi, H., Hatakeyama, M., and Azuma, T. (2003). The CagA protein of *Helicobacter pylori* is translocated into epithelial cells and binds to SHP-2 in human gastric mucosa. *J Infect Dis.* 187:334–7.
- Yang, P.C., and Davis, S. (1988). Epidemiological characteristics of adenocarcinoma of the gastric cardia and distal stomach in the United States, 1973–1982. *Int J Epidemiol.* 17:293.
- Yoon, K.A., Ku, J.L., Yang, H.K., Kim, W.H., Park, S.Y., and Park, J.G. (1999). Germline mutations of E-cadherin gene in Korean familial gastric cancer patients. *J Hum Genet.* 44:177–80.

The Biology of Gastric Cancers

Wang, T.; Fox, J.; Giraud, A. (Eds.)

2009, XX, 332 p. 45 illus., 8 illus. in color., Hardcover

ISBN: 978-0-387-69181-7