PREFACE

Acid-related diseases are among the most commonly encountered disorders in clinical practice. The last decade has witnessed profound changes in the clinical approach to this family of conditions, which includes gastroesophageal reflux disease (GERD) in its protean manifestations, peptic ulcers of all etiologies, and dyspepsia of the uninvestigated and investigated (nonulcer dyspepsia) varieties. The changes have arisen largely from the discovery of *H. pylori*'s important role in various acid-related diseases and in response to the rising tide of patients with GERD. Major alterations in health care delivery, spawned by efforts to control health care costs, have also had an impact on the way clinicians deal with these diseases. One result has been the introduction of various practice guidelines that are intended to assist clinicians in managing their patients in a fashion that reflects recent advances in medical science as well as economics. In this field, however, the pace of advances quickly renders most guidelines obsolete. *Diseases of the Gastroesophageal Mucosa: The Acid-Related Disorders* is intended to help primary care physicians and clinical gastroenterologists stay abreast of the important developments in this field.

The emphasis is on diagnosis and treatment, but epidemiology and pathophysiology are not neglected in instances where their understanding sets the stage for management recommendations. The first section addresses the clinical evaluation of patients suspected of harboring peptic ulcers, and it provides specific information about drugs used in treating acid-related diseases. Subsequent chapters address ulcers of various causes, with particular emphasis on new aspects of *H. pylori* infection. A chapter is devoted to dyspepsia because this condition is ubiquitous in practice and new information is available to assist clinicians in efficiently managing patients with this condition. The section on GERD contains important developments in epidemiology, mechanisms of disease, and practical aspects of diagnosis and treatment. The extraesophageal manifestations of GERD, recognized increasingly in primary care, are addressed in a separate chapter in recognition of the new approaches to their management that have been described recently. Finally, upper gastrointestinal bleeding is addressed because an understanding of new management modalities can assist clinicians in triaging bleeding patients more effectively. No attempt has been made to include nonacid-related diseases of the upper gastrointestinal tract, such as esophageal opportunistic infections, malignancies, except those related to

GERD or *H. pylori* infection, and motor disturbances of the esophagus and stomach. The focus is on conditions in which gastric acid is fundamentally important in the pathophysiology and in which modulation of gastric acidity influences the clinical response.

The editor is grateful for the secretarial and administrative assistance of Dana A. Finello.

James W. Freston, MD, PhD

2

Helicobacter pylori -Related Diseases

*Demographics, Epidemiology,
and Pathophysiology of Gastritis,
Ulcers, and Cancer*

*James S. Hoffman, MD
and David R. Cave, MD, PhD*

INTRODUCTION

Helicobacter pylori (H. pylori) is a common bacterial infection of the gastric mucosa. The infection is generally asymptomatic, but it may cause a variety of gastrointestinal diseases, that are associated with significant morbidity and mortality. *H. pylori* infection always causes a histological gastritis, and can alter the normal physiology of the stomach in a number of different ways. In some cases, increased acid secretion can lead to the formation of duodenal ulcers. In other hosts, acid secretion may be reduced, leading to an association with gastric ulcers as well as gastric carcinoma and lymphoma.

DEMOGRAPHICS AND EPIDEMIOLOGY
Prevalence in Developing Countries

H. pylori is the most common bacterial infection in the world. It is estimated that one-half of the world's population is chronically infected *(1)*. *H. pylori* infection is usually acquired during childhood, and becomes a lifelong infection in most people unless treated. Epidemiological studies have shown that the risk of acquiring the infection is related to socioeconomic status *(2)*. Poor sanitary conditions, lack of running water, and overcrowding are risk factors for infection. In developing countries, the majority of children are infected before age 10 yr. The prevalence in the 45–55 yr-old age group may be as high as 90% *(3)*.

Prevalence in Developed Countries

In the United States and other developed countries, the overall prevalence of infection is approximately 40% *(4)*. The risk of infection during childhood is low in developed countries. However, the prevalence increases to 20–30% by the age of 40 yr, and sharply increases to 70% by age 70 yr. This phenomenon is explained by a cohort effect *(5)*. This effect is explained by the prevalence of *H. pylori* infection in children being much higher prior to World War II. The high prevalence of infection in the older population is a reflection of this effect. Improved water supplies, refrigeration and indoor plumbing may have much to do with the reduction in the prevalence of infection. Within any age group, infection rates are higher in African-American and Hispanic populations *(6)*. This may be a reflection of socioeconomic conditions and/or host factors.

Host Factors

Only a small proportion of patients infected with *H. pylori* develop peptic ulcer disease (PUD), and a smaller number still ever develop gastric cancer. Host factors, as well as environmental factors, contribute to which hosts develop significant diseases in addition to the ubiquitous chronic gastritis. For example, within a given geographic area, a population is exposed to the same general group of bacterial strains, but some individuals will develop gastric cancer, while others will only develop duodenal ulcers. Host genetics probably play a minor role in susceptibility to infection. For example, monozygotic twins raised apart have a greater concordance for infection than dizygotic twins raised apart *(7)*. The first good evidence of a specific predisposition to the evolution of gastric cancer has been demonstrated in the gene for interleukin 1 (IL-1). Certain polymorphisms in this gene are associated with reduced acid

secretion, which in turn is associated with a high prevalence of gastric cancer *(8)*. Other studies have suggested that certain human leukocyte antigen (genotypes are more common in *H. pylori* infected hosts *(9)*.

Route of Transmission

The mechanisms of *H. pylori* transmission are still not well defined. Clearly, the organism has to traverse the mouth and esophagus. The two most likely modes of infection are oral–oral and fecal–oral spread. Iatrogenic transmission has been rarely reported, and the role of insect vectors remains to be clarified.

ORAL–ORAL TRANSMISSION

Oral–oral transmission has not been confirmed. *H. pylori* has been identified in dental plaque, and has been rarely cultured from the mouth *(10)*. Yet, the incidence of *H. pylori* infection in hygienists and dentists is not increased, despite the occupational exposure to oral aerosols. On the other hand, gastroenterologists have a higher prevalence of infection than age-matched controls; 52%, compared with 21%. These differences were most marked in older gastroenterologists, who did not wear gloves in their early years of practice *(11)*. Investigators have also cultivated *H. pylori* from the vomitus and saliva from healthy infected volunteers *(12)*.

FECAL–ORAL TRANSMISSION

Fecal–oral spread is also a possibility. Contaminated water supplies in developing countries may serve as a source of the bacteria *(13)*. Polymerase chain reaction (PCR) techniques have shown evidence of *H. pylori* in municipal water supplies, and other studies suggest that the bacteria can remain viable in water for days. *H. pylori* has also been identified in the stools of children from Gambia, West Africa, where there is a 99% prevalence of infection *(14)*. Intrafamilial clustering of infection also supports person-to-person spread. Children infected with *H. pylori* are more likely to have parents and siblings infected with *H. pylori* than children who are not infected *(15)*. However, the isolates may not be the same within each family member, implying the involvement of other sources

IATROGENIC TRANSMISSION

Iatrogenic spread has also been documented. A contaminated pH probe infected 17/34 consecutive patients *(16)*. In another study, a volunteer was infected with a contaminated endoscope. The iatrogenic risk of transmission has been estimated at 4/1000 endoscopies in the developed world.

Nonhuman vectors may also play a role. Recent studies suggest that domestic cats may carry *H. pylori* but this is controversial *(17)*. Isolation of viable organisms from cat saliva suggests that transmission can occur. Recently, it has been shown that the housefly can carry and harbor *H. pylori (18)*. Flies from developing countries, as well as from the United States, had evidence of *H. pylori* infection, but may reflect environmental contamination, rather than a mode of transmission *(19)*.

Reinfection

In developed countries, reinfection after cure is unusual, and is estimated to be less than 1% per year *(20)*. Recurrence of infection most likely represents recrudescence. Reinfection rates in developing countries are higher and are approximately 8–15% *(21)*; however, it is not yet clear to whether this may be caused by in part inadequate monitoring of therapy. In developed countries, *H. pylori* infection in children is becoming uncommon, and is most likely a direct consequence of improved sanitary conditions.

PATHOPHYSIOLOGY

H. pylori infection can disrupt the normal physiology of the stomach by having direct effects on the gastric epithelium, as well as exciting a host immune response that leads to an intense inflammatory reaction that results in further physiological change.

Bacteriology

H. pylori is a Gram-negative microaerophilic, spiral-shaped bacterium. This bacterium has several unique features that allow it to colonize the stomach. *H. pylori* lives within or beneath the gastric mucus layer. It is not an invasive organism. It has 3–7 unipolar flagella that enable the organism to move through the mucus layer of the stomach. *H. pylori* will only colonize gastric mucosa or cells with a gastric phenotype, e.g., Barrett's esophagus, or duodenal metaplasia. A small percentage of bacteria adhere directly to the surface epithelium via attachment pedestals, comparable to enteropathic *Escherichia coli*.

Virulence Factors

H. pylori has several virulence factors that allow it to colonize the gastric mucosa, evade host defenses, and damage gastric mucosa (Table 1). These factors include adhesins, as well as enzymes that are released and damage the mucosa.

Table 1
Virulence Factors of *H. pylori*

Adhesins
Urease
Phospholipase
Catalase
Heat shock proteins
Cytotoxin (VacA)
Lipopolysaccharide

ADHESINS

H. pylori can only colonize gastric epithelium. *H. pylori* has specific adhesins that bind to host receptors expressed on the epithelial surface *(22)*. Some studies suggest that Lewis blood group Ags mediate attachment *(23)*. Hence, certain individuals may be more susceptible to infection based on Lewis phenotype.

ENZYMES

H. pylori releases a number of enzymes that can cause cellular damage, including phospholipases, which can disrupt the gastric mucus and lead to cellular injury. *H. pylori* is one of the most potent producers of urease. This enzyme has been shown to be essential for infectivity, and hydrolyzes urea to form ammonia and bicarbonate. Ammonia or ammonium, depending on the local pH, may protect the organism from the acidic milieu of the stomach, as well as directly damage the gastric epithelium. In addition, urease is antigenic, and may stimulate the host immune system *(24)*. *H. pylori* also produces catalase and superoxide dismutase. These antioxidant enzymes may help to protect the bacterium from toxic metabolites released by inflammatory cells.

HEAT SHOCK PROTEINS

H. pylori produces high levels of heat shock proteins that may allow it to tolerate the hostile conditions of the gastric environment when the organism first colonizes the stomach. These proteins maintain the integrity of the organism during periods of stress.

TOXINS

Certain strains of *H. pylori* may be more likely to produce injury than others. All *H. pylori* strains contain a gene encoding for an 87-KDa vacuolating cytotoxin (VacA) *(25)*. This toxin has been shown to cause cell injury in vitro in an animal model, but its role in the pathogenesis

of infection in man has yet to be fully defined. In the Western world, about 60% of strains contain the cytotoxin-associated gene A (cagA). This gene codes for a 128-kDa protein (CagA), and this is necessary for the co-expression of VacA protein. Strains that produce both VacA and CagA cause more tissue injury. This may be mediated by the induction of larger amounts of IL-8 release. In turn this is associated with more inflammation and higher bacterial density of infection. Patients with duodenal ulcers are more likely to be infected by CagA strains, in the Western Hemisphere *(26)*.

ANTIGEN RESPONSE

H. pylori stimulates a predominantly helper T-cell 1 immune response as a major part of the induced chronic gastric inflammation. The bacterium produces several Ag substances, including urease, a heat shock protein, and lipopolysaccharide, which leads to an increased production of cytokines by the infected host, including tumor necrosis factor-α, Il-1B, and IL-8. IL-8 is a potent chemotactic factor that recruits neutrophils into the mucosa *(27)*. Neutrophils can subsequently release toxic metabolites that damage the gastric epithelium.

Infected hosts produce an antibody response to *H. pylori* infection. Initially, there is an immunoglobulin-M response followed by immunoglobulin-G and immunoglobulin-A antibodies. Their persistence for months or years after successful treatment makes them useless as a means of monitoring therapy. Unfortunately, these antibodies are not protective, and only serve as a marker of infection.

GASTRITIS

H. pylori infection always causes gastritis, which is a superficial process and predominantly affects the antrum. In some patients, there is predominant corpus gastritis. Eventually, varying degrees of gastric metaplasia and atrophy may develop.

Acute Gastritis

Acute gastritis is characterized by neutrophilic infiltration; chronic gastritis is associated with mononuclear cells, such as lymphocytes and plasma cells. For the pathologist, the presence of neutrophils implies that *H. pylori* infection is present. Typically, the normal gastric mucosa is devoid of lymphoid follicles, however, lymphoid follicles can develop with *H. pylori* gastritis. The majority of acute infections are asymptomatic, and thus not recognized. However, when acute infections are investigated, intense inflammation is seen, characterized by mucosal edema,

hyperemia, and a pronounced neutrophilic infiltration is seen. After about 1 wk of infection with *H. pylori* some individuals become achlorhydric. The profound reduction in acid secretion can last indefinitely in some. A 92-kDa acid-inhibitory protein has been isolated and cloned *(28)*. This acid-inhibitory factor has been shown to inhibit acid secretion in various animal gastric glands in vitro *(29)*.

Chronic Gastritis

Acute gastritis will evolve into a chronic gastritis, unless the *H. pylori* infection is successfully treated. In most hosts *H. pylori* is found in the antrum and body of the stomach. Patients who are colonized more in the body of the stomach may develop decreased acid secretion secondary to mucosal atrophy and intestinal metaplasia. This phenomenon may be the result of *H. pylori* mediated damage to oxyntic mucosa. *H. pylori* strains that express CagA tend to produce more inflammation and greater epithelial injury. After eradication of *H. pylori*, neutrophils disappear rapidly, and lymphocytes and plasma cells disappear more slowly, usually disappearing by 1 yr. It is unclear if intestinal metaplasia and atrophy resolve, nor is it clear whether its progression is prevented.

PEPTIC ULCER DISEASE

The lifetime risk of developing a duodenal ulcer in the United States is 10% *(30)*. Yet, the prevalence of *H. pylori* infection is about 40%. How is it that only a minority of *H. pylori* infected patients develops ulcers? The answer to this question is still not entirely apparent. However, a greater understanding of *H. pylori's* virulence factors and host responses will one day provide answers to this question.

Association Between **H. pylori** *and Duodenal Ulcer*

There are several lines of evidence that link *H. pylori* to duodenal ulcer formation. First, most patients who have a duodenal ulcer and who are not taking nonsteriodal anti-inflammatory drugs (NSAIDS) are infected with *H. pylori*. Second, *H. pylori* can be detected before the occurrence of duodenal ulcer formation and is a risk factor for peptic ulcer disease *(31)*. Finally, eradication of *H. pylori* results in ulcer healing and reduces ulcer recurrence rates *(32)*.

Pathogenesis of Ulcer Formation

H.pylori infection can disrupt the normal physiology of the stomach. Infected patients with duodenal ulcers often have elevated gastrin levels and increased acid secretion.

ALTERATIONS IN ACID SECRETION

Acute infection induces a period of hypochlorhydria. However, chronic infection of the gastric antrum may lead to increased basal and stimulated gastric acid output. These levels return to normal when *H. pylori* is eradicated. It is still unclear why the same infection produces different patterns of acid secretion in different individuals. The distribution of the gastritis may also play a role. Patients with duodenal ulcers tend to have the gastritis restricted to the antrum; patients with gastric cancer tend to have a pan-gastritis. There is also an inverse correlation between the severity of *H. pylori* gastritis in the body and the level of acid secretion. Duodenal ulcer patients have the mildest degree of gastritis and the highest acid output; patients with atrophic gastritis have the lowest acid output. Finally, patients with duodenal ulcers infected with *H. pylori* have 3× as many enterochromaffin-like cells in their gastric mucosa, compared to controls. Thus, excessive acid secretion may be related to increased histamine release.

ELEVATED GASTRIN LEVELS

Patients with *H. pylori* infection have elevated levels of basal and stimulated gastrin secretion *(33)*. Gastrin is a potent hormone that stimulates enterochromaffin-like cells to release histamine, which in turn is a potent stimulator of parietal cells. Gastrin also has a trophic effect on parietal cells. Gastrin levels return to normal after *H. pylori* eradication.

DECREASED SOMATOSTATIN LEVELS

Patients with *H. pylori* infection have a decreased concentration of somatostatin *(34)*. Somatostatin is released by D cells in the antrum and duodenum, and inhibits acid secretion. It is felt that nonspecific injury to the D cells in the antrum leads to decreased somatostatin production, and allows for an increase in gastrin production. One study has shown that after eradication of *H. pylori* somatostatin levels, as well as the number of D cells increased *(34)*.

GASTRIC METAPLASIA

H. pylori infection is probably responsible for the development of gastric metaplasia in the duodenum. Gastric metaplasia refers to the presence of gastric epithelium in the duodenal bulb, and occurs in response to a low pH in the duodenal lumen. This allows for *H. pylori* colonization of the duodenal mucosa and the subsequent development of duodenitis. The presence of duodenal metaplasia colonized by *H. pylori* is a strong risk factor for the development of duodenal ulcer disease.

IMPAIRMENT OF HOST DEFENSES

H. pylori can also impair some mucosal defense factors. Protective factors, such as epidermal growth factor and proximal duodenal bicarbonate secretion, are increased after *H. pylori* eradication *(35)*.

GENETIC FACTORS

Genetic factors also determine susceptibility to ulcer formation. Some studies suggest that *H. pylori* infected patients who develop a duodenal ulcer have a higher parietal cell mass, or are more sensitive to gastrin. Whether duodenal ulcer patients have a higher parietal cell mass to begin with, or acquire it during infection remains to be seen. The presence of increased pepsinogen levels in ulcers kindreds was once thought to provide a genetic basis for duodenal ulcer disease. Subsequently, it has been shown that *H. pylori* is responsible for increased pepsinigen levels, which disappear on eradication of infection.

ENVIRONMENTAL FACTORS

Environmental factors also play a role in ulcer formation in *H. pylori* infected patients. Smoking and NSAID increase the risk of ulcer formation in *H. pylori* infected patients. Smoking decreases proximal duodenal bicarbonate secretion, making the mucosa more susceptible to acid injury.

Gastric Ulcer

H. pylori is strongly associated with gastric ulcers. Compared to duodenal ulcer patients, gastric ulcer patients have a more severe antritis, with antral gland disruption and intestinal metaplasia. In addition, patients with gastric ulcers associated with *H. pylori* infection have a moderate gastritis of the body, and the acid-secreting oxyntic mucosa is more inflamed. Over time, fundic gland atrophy occurs, with hyposecretion of acid and pepsin. NSAIDs are responsible for the majority of gastric ulcers not caused by *H. pylori*. The presence of *H. pylori* should be confirmed in gastric ulcer patients prior to initiating antibiotic therapy, because up to 30% of patients with gastric ulcers are not infected.

GASTRIC CANCER

Today, gastric cancer remains the second leading cause of cancer deaths worldwide. At the turn of the century, gastric cancer was the leading cause of cancer deaths in the United States. The prevalence of gastric cancer in the United States has fallen fivefold over the past 60 yr, the prevalence of *H. pylori* has not fallen more than 50%. Although there

is a strong association between gastric cancer and *H. pylori* infection, other environmental and host factors also play a role. *H. pylori* infection leads to changes in many factors that play a role in the pathogenesis of gastric cancer. These factors include vitamin C content of gastric juice, reactive oxygen metabolites, and epithelial cell proliferation. In 1994, the International Agency for Research on Cancer, a working part of the World Health Organization, classified *H. pylori* as a type I carcinogen *(36)*.

Association of **H. pylori** *and Gastric Cancer*

A number of epidemiological studies have demonstrated a strong correlation between *H. pylori* infection and gastric cancer of the intestinal type. There have been three nested-case control studies that used stored serum samples of patients with known adenocarcinoma of the stomach, and that of matched controls which assessed the relationship between *H. pylori* infection and the subsequent risk of gastric cancer *(37–39)*. The matched odds ratios ranged from 2.8 to 6.0, for patients infected with *H. pylori*. The EUROGAST study, from 13 different countries, found a sixfold increased risk of gastric cancer in *H. pylori* infected patients, compared to noninfected controls *(40)*.

Pathogenesis of **H. pylori** *and Gastric Cancer*

The exact mechanism by which *H. pylori* contributes to the development of gastric cancer has not been elucidated. Correa et al. *(41)* have developed a hypothesis for the development of intestinal-type gastric adenocarcinoma. Longitudinal studies suggest that gastric cancer progresses in a stepwise fashion from chronic active gastritis to multifocal atrophic gastritis to intestinal metaplasia to dysplasia to adenocarcinoma. *H. pylori* is known to cause chronic active gastritis and atrophic gastritis. Once adenocarcinoma develops, tests for *H. pylori* may be negative, because the organism's usual niche has been replaced by intestinal metaplasia. Other possible mechanisms include the release of reactive oxygen metabolites that damage DNA. These compounds are released by neutrophils that are activated by *H. pylori*. *H. pylori* also produces acchlorhydria. Subsequently, nitrate-producing bacteria can then colonize the stomach and produce nitrite. Ascorbic acid helps protect against the development of gastric cancer because it can scavenge nitrates and free radicals. Gastric juice of healthy individuals contains high concentrations of ascorbic acid, but *H. pylori* infected individuals have reduced levels of ascorbic acid *(42)*. This can lead to oxidative and *N*-nitroso-mediated DNA damage.

Strains that produce CagA produce more epithelial damage, and are more likely to be associated with gastric cancer. Hyperproliferation has

been seen in CagA-infected patients, and there may be resistance to apoptosis.

Fortunately, only a small portion of *H. pylori* infected patients will develop gastric cancer. Some studies even suggest that patients with *H. pylori* related duodenal ulcers are protected from gastric cancer, which may be explained by the fact that atrophic gastritis is an early step in the pathogenesis of gastric cancer and does not occur in duodenal ulcer disease, but does occur with gastric ulcers. It is still unclear whether eradicating *H. pylori* reduces the risk of gastric cancer.

Gastric Lymphoma

Studies have shown that primary gastric lymphoma is also associated with *H. pylori*. The normal stomach is devoid of lymphoid tissue. *H. pylori* infection leads to gastritis and the formation of lymphoid aggregates and lymphoid follicle formation. It is believed that the chronic inflammatory response induced by *H. pylori* can lead to the development of a monoclonal neoplasm. The lesions are often flat and multicentric, and diagnosis requires a high index of suspicion on the part of the endoscopist.

MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA

Mucosa-associated lymphoid tissue (MALT) is a consequence of *H. pylori* infection. It is believed that MALT is an immunological defense system to control local infection caused by *H. pylori*. Several epidemiological studies have demonstrated an association between *H. pylori* infection and MALT lymphomas *(43)*. Gastric MALT lymphomas are low-grade, T-cell-dependent, B-cell lymphomas, whose antigen stimulus is thought to be *H. pylori*. MALT lymphomas are more likely to occur with *H. pylori* strains expressing the CagA protein *(44)*. Several small studies have shown endoscopic and histologic remission of low-grade MALT lymphomas following eradication of *H. pylori* infection *(45)*. It is still unknown if these remissions are long-term and represent a cure. Close follow-up is needed, and treatment failure may result from to the presence of a high-grade lymphoma.

REFERENCES

1. Cave DR. (1996) Transmission and epidemiology of *Helicobacter pylori. Am J Med* 100(Suppl 5A):12S–17S.
2. Veldhuyzen VanZanten SJO. (1995) Do socioeconomic status, marital status, and occupation influence the prevalence of *Helicobacter pylori* infection? *Aliment Pharmacol Ther* 9(Suppl 2):41–45.
3. Hazel SL. (1993) *H. pylori* in developing countries. In: *Helicobacter pylori Basic Mechanisms to Clinical Cure,* Hunt RH, Tytgat GNJ, eds., Boston: Kluwer Academic, pp. 85–94.

4.   Pounder RE, Ng D. (1995) The prevalence of *Helicobacter pylori* infection in different countries. *Aliment Pharmacol Ther* 9(Suppl 2):33–39.

5.   Marshall BJ. (1993) Epidemiology of *Helicobacter pylori* in western countries. In *Helicobacter pylori Basic Mechanisms to Clinical Cure,* Hunt RH, Tytgat GNJ, eds., Boston: Kluwer Academic, pp. 75–84.

6.   Smoak BL, Kelley PW, Taylor DN. (1994) Seroprevalence of *Helicobacter pylori* infections in a cohort of young army recruits. *Am J Epidemiol* 139:513.

7.   Malaty HM, Engstrand L, Pederson NL, Graham DY. (1994) *H. pylori* infection: genetic and environmental influences. A study of twins. *Ann Intern Med* 120:982–986.

8.   El-Omar EM, Carrington M, Chow WH, et al. (2000) Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 404:398–399.

9.   Azuma T, Konishi T, Tanaka Y, et al. (1994) Contribution of HLA-DQA gene to host's response against *Helicobacter pylori*. *Lancet* 343:542–543.

10. Hardo PG, Tugnait A, Hassan F. (1995) *Helicobacter pylori* and dental care. *Gut* 37:44–46.

11. Mitchell HM, Lee A, Carrick J. (1989) Increased incidence of *Campylobacter pylori* infection in gastroenterologists: further evidence to support person to person transmission. *Scand J Gastroenterol* 24:396–400.

12. Parsonnet J, Shmuely H, Haggerty T. (1999) Fecal and oral shedding of *Helicobcter pylori* from healthy infected adults. *JAMA* 282:2240–2245.

13. Hulten K, Han SW, Enroth H, et al. (1996) *Helicobacter pylori* in the drinking water in Peru. *Gastroenterology* 110:1031–1035. .

14. Thomas JE, Gibson GR, Darboe MK, et al. (1992) Isolation of *Helicobacter pylori* from human faeces. *Lancet* 340:1194–1195.

15. Drumm B, Perez-Perez GI, Blaser MJ, Sherman PM. (1990) Intrafamilial clustering of *Helicobacter pylori*. *N Engl J Med* 322:356–363.

16. Ramsey EJ, Clarey KV, Peterson WL, et al. (1979) Epidemic gastritis with hypochlorhydria. *Gastroenterology* 76:1449–1457.

17. Handt LK, Fox JG, Stalis IH, et al. (1995) Characterization of feline *Helicobacter pylori* strains and associated gastritis in a colony of domestic cats. *J Clin Microbiol* 33:2280–2289.

18. Grubel P, Hoffman JS, Chong FK, et al. (1997) Vector potential of houseflies (Musca domestica) for *Helicobacter pylori*. *J Clin Microbiol* 35:1300–1303.

19. Grubel P, Huang L, Masubuchi N. (1998) Detection of *Helicobacter pylori* in houseflies on three continents. *Lancet* 352:788–789.

20. Parsonnet J. (1995) The incidence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 9(Suppl 2):45–51.

21. Rollan A, Giancaaspero R, Fuster F, et al. (2000) The long-term reinfection rate and the course of duodenal ulcer disease after eradication of *Helicobacter pylori* in a developing country. *Am J Gastroenterol* 95:50–56.

22. Mobley H. (1996) Defining *Helicobacter pylori* as a pathogen: strain heterogeneity and virulence. *Am J Med* 100(Suppl 5A):2S–7S.

23. Boren T, Falk P, Roth KA, et al. (1993) Attachment of *Helicobacter pylori* to human gastric epithelium mediated by blood group antigens. *Science* 262:1892–1895.

24. Mobley H. (1996) The role of *Helicobacter pylori* urease in the pathogenesis of gastric and peptic ulceration. *Aliment Pharmacol Ther* 10(Suppl 1):57–62.

25. Phadnis SH, Liver D, Janzon L, et al. (1994) Pathological significance and molecular characterization of the vacuolating toxin gene of *Helicobacter pylori*. *Infect Immun* 62:1557–1565.

26. Blaser MJ. (1996) Role of vacA and cagA locus of *Helicobacter pylori* in human disease. *Aliment Pharmacol Ther* 10(Suppl 1):73–77.

27. Crowe SE, Alverez L, Sherman PM, et al. (1995) Expression of interleukin-8 and CD54 by human gastric epithelium after *Helicobacter pylori* infection *in vitro*. *Gastroenterology* 108:65–74.

28. Cave DR, King WW, Hoffman JS. (1995) Production of two chemically distinct acid-inhibitory factors by *Helicobacter pylori*. *Eur J Gastroenterol Hepatol* 5:S23–S27.

29. Hoffman JS, King WW, Fox J, et al. (1995) Rabbit and ferret parietal cell inhibition by Helicobacter species. *Dig Dis Sci* 40:147–152.

30. Isenberg J, McQuaid KR, Laine L, Walsh JH. (1995) Acid-peptic disorders. In *Textbook of Gastroenterology,* Yamada T, ed., Philadelphia: JB Lippincott, pp. 1347–1430.

31. Leoci C, Ierardi E, Chiloiro M, et al. (1995) Incidence and risk factors of duodenal ulcer. *J Clin Gastroenterol* 20:104–109.

32. Hopkins RJ, Girardi LS, Turney EA. (1996) Relationship between *H. pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. *Gastroenterology* 110:1244–1252.

33. Beardshall K Moss S, Gill J, et al. (1992) Suppression of *Helicobacter pylori* reduces gastrin releasing peptide stimulated gastrin release in duodenal ulcer patients . *Gut* 33:601–603.

34. Moss SF, Legon S, Bishop AE, et al. (1992) Effect of *Helicobacter pylori* on gastric somatostatin in duodenal ulcer disease. *Lancet* 340:930–932.

35. Konturek PC, Ernst H, Konturek SJ, et al. (1997) Mucosal expression and luminal release of epidermal and transforming growth factors in patients with duodenal ulcer before and after eradication of *Helicobacter pylori*. *Gut* 40:463–469.

36. World Health Organization, International Agency for Research on Cancer. (1994) IARC monographs on the evaluation of carcinogenic risks to humans. Schistosomes, liver flukes and *Helicobacter pylori*. Vol. 61. Lyon, France: IARC.

37. Forman D, Newell DG, Fullerton F, et al. (1991) Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *Br Med J* 302:1302–1305.

38. Parsonnet J, Friedman GD, Vandersteen DP, et al. (1991) *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 325:1127–1131.

39. Nomura A, Stemmermann GN, Chyou PH, et al. (1991) *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. *N Engl J Med* 325:1132–1136.

40. The EuroGast Study Group. (1993) An international association between *Helicobacter pylori* infection and gastric cancer. *Lancet* 341:1359–1362.

41. Correa P, Haenszel W, Cuello C, et al. (1995) A model for gastric cancer epidemiology. *Lancet* 2:58–59.

42. Banerjee S, Hawksby C, Miller S, et al. (1996) Effect of *Helicobacter pylori* and its eradication on gastric juice ascorbic acid. *Gut* 38:177–181.

43. Wotherspoon AC, Ortiz–Hidalgo C, Falzon MR, Isaacson PG. (1991) *Helicobacter pylori* associated gastritis and primary B–cell gastric lymphoma. *Lancet* 338:1175–1176.

44. Eck M, et al. (1997) MALT-type lymphoma of the stomach is associated with *Helicobacter pylori* strains expressing the CagA protein. *Gastroenterology* 112:1482–1486.

45. Bayerdorffer E, Neubauer A, Rudolph B, et al. (1995) Regression of primary gastric lymphoma of the mucosa associated lymphoid tissue type after cure of *Helicobacter pylori* infection. MALT Lymphoma Study Group. *Lancet* 345:1591–1594.