

Pathogenesis of *Helicobacter pylori* Infection

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INTRODUCTION	450
HISTORY	450
MICROBIOLOGY	451
Genus Description and Phylogeny	451
Gastric <i>Helicobacter</i> species	451
(i) <i>Helicobacter felis</i>	451
(ii) <i>Helicobacter mustelae</i>	451
(iii) <i>Helicobacter acinonychis</i>	452
(iv) <i>Helicobacter heilmannii</i>	452
Enterohepatic <i>Helicobacter</i> species	452
Microbiology of <i>H. pylori</i>	453
Genome, plasmids, and strain diversity	453
Morphology	453
Growth requirements	453
Metabolism	454
(i) Respiration and oxidative stress defense	454
(ii) Nitrogen metabolism	454
(iii) Metal metabolism	455
Cell envelope, outer membrane, and LPS	456
Gene regulation	457
EPIDEMIOLOGY	457
Prevalence and Geographical Distribution	457
Transmission and Sources of Infection	458
CLINICAL ASPECTS OF <i>H. PYLORI</i>-ASSOCIATED DISEASES	458
Disease Types	458
Acute and chronic gastritis	458
(i) Acute gastritis	458
(ii) Chronic gastritis	458
Peptic ulcer disease	459
(i) Definitions	459
(ii) Association with <i>H. pylori</i>	459
(iii) Ulcer epidemiology	460
(iv) Ulcer complications	461
(v) <i>H. pylori</i> and NSAIDs	461
Non-ulcer dyspepsia	462
Atrophic gastritis, intestinal metaplasia, and gastric cancer	462
Gastric MALT lymphoma	463
GERD	463
Extragastrointestinal disorders	464
Histopathology	464
DIAGNOSIS AND TREATMENT	464
Diagnosis	464
Treatment	464
Vaccination	465
PATHOGENESIS OF INFECTION	466
<i>H. pylori</i>-Associated Pathogenesis	466
Animal Models	466
Mouse	466
Mongolian gerbil	466
Guinea pig	467
Gnotobiotic piglets	467

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Nonhuman primates.....	467
Role of <i>H. pylori</i> Virulence Factors	467
<i>cag</i> PAI	467
VacA vacuolating cytotoxin.....	468
Acid resistance	470
Adhesins and outer membrane proteins.....	470
(i) BabA (HopS).....	470
(ii) OipA (HopH).....	470
(iii) SabA (HopP).....	471
LPS	471
Immune Response	472
Role of antibodies in protective immunity	472
Immune modulation	472
Activation of the innate immune response.....	472
Resistance to phagocytosis and modulation of dendritic cell activity.....	472
Regulatory T cells	473
Contribution of Host Genetics	473
IL-1	474
Other cytokines	474
CONCLUSIONS	474
REFERENCES	474

INTRODUCTION

It has been known for more than a century that bacteria are present in the human stomach (56). These bacteria, however, were thought to be contaminants from digested food rather than true gastric colonizers. About 20 years ago, Barry Marshall and Robin Warren described the successful isolation and culture of a spiral bacterial species, later known as *Helicobacter pylori* (684), from the human stomach. Self-ingestion experiments by Marshall (398) and Morris (442) and later experiments with volunteers (443) demonstrated that these bacteria can colonize the human stomach, thereby inducing inflammation of the gastric mucosa. Marshall developed a transient gastritis after ingestion of *H. pylori*; the case described by Morris developed into a more persistent gastritis, which resolved after sequential therapy with first doxycycline and then bismuth subsalicylate. These initial data strongly stimulated further research, which showed that gastric colonization with *H. pylori* can lead to variety of upper gastrointestinal disorders, such as chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer. This knowledge had a major clinical impact with regard to the management of these diseases. In addition, the persistence of a pathogen in an environment long thought to be sterile also resulted in insights into the pathogenesis of chronic diseases. This discovery resulted in the awarding of the 2005 Nobel Prize in Physiology or Medicine to Robin Warren and Barry Marshall for their “discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease.”

The number of peer-reviewed publications on *Helicobacter* has rapidly increased, from less than 200 in 1990 to approximately 1,500 per year over the last few years (PubMed [www.pubmed.gov]). Despite this wide attention important issues, such as the transmission route of *H. pylori*, are still poorly understood. Although the prevalence of *H. pylori* in the Western world is decreasing, gastric colonization by *H. pylori* remains widespread in the developing world. Infection with *H. pylori* can be diagnosed by a variety of tests and can often be successfully treated with antibiotics. Unfortunately, the in-

crease in antibiotic resistance is starting to affect the efficacy of treatment, and, in spite of the impact of *H. pylori*, preventive vaccination strategies still do not exist. A better understanding of *H. pylori* persistence and pathogenesis is thus mandatory to aid the development of novel intervention and prevention strategies. This review focuses on the pathogenesis of *H. pylori* infection, with emphasis on its microbiological aspects.

HISTORY

By the late 19th and early 20th centuries, several investigators had reported the presence of spiral microorganisms in the stomachs of animals (56). Soon afterward, similar spiral bacteria were observed in humans (328, 379, 497), some of whom had peptic ulcer disease or gastric cancer. The etiological role of these bacteria in the development of peptic ulcer disease and gastric cancer was considered at the time, and patients were sometimes even treated with high doses of the antimicrobial compound bismuth (497). This possibility was later discarded as irrelevant, probably because of the high prevalence of these spiral bacteria in the stomachs of persons without any clinical signs. The bacteria observed in human stomachs were thus considered to be bacterial overgrowth or food contaminants until the early 1980s. At this time, Warren and Marshall performed their groundbreaking experiments, leading to the identification of a bacterium in 58 of 100 consecutive patients, with successful culture and later demonstration of eradication of the infection with bismuth and either amoxicillin or tinidazole (397–401, 684). The organism was initially named “*Campylobacter*-like organism,” “gastric *Campylobacter*-like organism,” “*Campylobacter pyloridis*,” and “*Campylobacter pylori*” but is now named *Helicobacter pylori* in recognition of the fact that this organism is distinct from members of the genus *Campylobacter* (234). It soon became clear that this bacterium causes chronic active gastritis, which in a subset of subjects may progress to other conditions, in particular, peptic ulcer disease, distal gastric adenocarcinomas, and gastric lymphomas (168).

TABLE 1. Characteristics of selected *Helicobacter* species

Species	Primary mammalian host	Pathology	Animal model
Gastric <i>Helicobacter</i> spp.			
<i>H. pylori</i>	Human, primate	Gastritis, peptic ulcer disease, gastric adenocarcinoma, MALT lymphoma	Mouse, Mongolian gerbil, guinea pig, gnotobiotic piglet
<i>H. felis</i>	Cat, dog, mouse	Gastritis in natural host; may cause peptic ulcers or gastric adenocarcinoma in mouse	Mouse
<i>H. mustelae</i>	Ferret	Gastritis, peptic ulcer disease, gastric adenocarcinoma, MALT lymphoma	None
<i>H. acinonychis</i>	Cheetah, tiger, other big cats	Gastritis, peptic ulcer disease	Mouse
<i>H. heilmannii</i>	Human, dog, cat, monkey, cheetah, rat	Gastritis, dyspeptic symptoms, MALT lymphoma	Mouse
Enterohepatic <i>Helicobacter</i> spp.			
<i>H. hepaticus</i>	Mouse, other rodents	Proliferative typhlocolitis, hepatitis, hepatocellular carcinoma	None

MICROBIOLOGY

Genus Description and Phylogeny

The genus *Helicobacter* belongs to the ϵ subdivision of the *Proteobacteria*, order *Campylobacterales*, family *Helicobacteraceae*. This family also includes the genera *Wolinella*, *Flexispira*, *Sulfurimonas*, *Thiomicrospira*, and *Thiovulum*. To date, the genus *Helicobacter* consists of over 20 recognized species, with many species awaiting formal recognition (194). Members of the genus *Helicobacter* are all microaerophilic organisms and in most cases are catalase and oxidase positive, and many but not all species are also urease positive.

Helicobacter species can be subdivided into two major lineages, the gastric *Helicobacter* species and the enterohepatic (nongastric) *Helicobacter* species. Both groups demonstrate a high level of organ specificity, such that gastric helicobacters in general are unable to colonize the intestine or liver, and vice versa. An extensive review of non-pylori *Helicobacter* species is available (587), and here we briefly discuss those *Helicobacter* species that are either associated with human disease or have relevance for animal models of human *Helicobacter* infections (Table 1).

Gastric *Helicobacter* species. Gastric *Helicobacter* species have adapted to the inhospitable conditions found at the gastric mucosal surface, and it is currently thought that the stomachs of all mammals can be colonized by members of the genus *Helicobacter*. All known gastric *Helicobacter* species are urease positive and highly motile through flagella (587, 710). Urease is thought to allow short-term survival in the highly acidic gastric lumen, whereas motility is thought to allow rapid movement toward the more neutral pH of the gastric mucosa; this may explain why both factors are prerequisites for colonization of the gastric mucosa (450, 550, 551). Upon entry, gastric *Helicobacter* species display urea- and bicarbonate-mediated chemotactic motility toward the mucus layer (710). The spiral morphology and flagellar motility then assist in penetration into the viscous mucus layer, where the more pH-neutral conditions allow growth of the gastric *Helicobacter* species.

(i) ***Helicobacter felis*.** The spiral-shaped *Helicobacter felis* was first isolated from the stomach of a cat (353) and was later also

found in dogs. Subsequently designated *H. felis* (493), it was probably also the *Helicobacter* species originally described by Bizzozero in 1893 (56). *H. felis* is one of the *Helicobacter* species with zoonotic potential (344, 351). It has a helical morphology with typical periplasmic fibers, which can be used for microscopic identification. *H. felis* requires high humidity and can only poorly, if at all, be cultured on standard growth media used for the culture of *H. pylori* (344). *H. felis* is highly motile; on agar plates it does not really form colonies but rather grows as a lawn (235).

The significance of *H. felis* in gastric disorders of cats and dogs is somewhat unclear, since there is no clear association between canine and feline gastritis and *H. felis* infection (78, 144, 566–568). It is therefore possible that *H. felis* comprises part of the normal gastric flora in cats and dogs. In contrast, *H. felis* has been used in murine models of *Helicobacter* infection (352), where it can induce gastritis, epithelial cell proliferation, and apoptosis (85, 98, 417). Murine infection with *H. felis* results in a mononuclear cell-predominant inflammatory response in the gastric corpus that may progress to atrophic gastritis (180, 432, 433).

There is at present little information available about the virulence genes, physiology, or metabolism of *H. felis*, since *H. felis* is only poorly amenable to the genetic techniques used for *H. pylori*. The bacterium contains a urease gene cluster resembling that of other gastric *Helicobacter* species (181, 182), as well as two flagellin genes (*flaA* and *flaB*) (297). The latter genes have been inactivated, and this resulted in truncated flagella and reduced motility. Mutation of *flaA* also resulted in the inability to colonize a murine model of infection (297).

(ii) ***Helicobacter mustelae*.** The ferret pathogen *H. mustelae* was isolated shortly after *H. pylori* and was originally classified as *Campylobacter pylori* subsp. *mustelae* (197, 202, 630). It was subsequently shown to have characteristics different from *H. pylori* (198) and was later classified as *H. mustelae* (234). *H. mustelae* is a relatively small rod, which has multiple polar and lateral sheathed flagella. Interestingly, *H. mustelae* is phylogenetically closer to the enterohepatic *Helicobacter* species (242), based on its 16S rRNA gene sequence, urease sequences, and fatty acid profile (242, 256), but to our knowledge *H. mustelae*

has not been implicated in enteric colonization in ferrets.

The ferret stomach resembles the human stomach at both the anatomical and physiological levels (193), and gastritis, gastric ulcer, gastric adenocarcinoma, and MALT lymphoma in ferrets have all been described (163, 199, 200). *H. mustelae* infection is very common in ferret populations (295), and this suggests that *H. mustelae* is a member of the resident flora of the ferret stomach. *H. mustelae* shares many virulence factors with *H. pylori*, including a urease enzyme (139), motility (604), and molecular mimicry of host blood group antigens (465). Ultrastructural studies have shown that *H. mustelae* adheres intimately to gastric epithelial cells in a manner that closely resembles the adherence of *H. pylori* (199, 475). *H. mustelae* also induces an autoantibody response similar to that observed in *H. pylori*-infected humans (464).

The similarities between these two natural infections suggest that *H. mustelae* infection of the ferret is a suitable model to characterize the role played by *Helicobacter* virulence factors in vivo (199). *H. mustelae* is also amenable to genetic manipulation; thus, *H. mustelae* is an interesting candidate for investigation of the role of *Helicobacter* virulence factors in the natural host. This will be aided by the ongoing determination of the complete genome sequence of *H. mustelae* (available at http://www.sanger.ac.uk/Projects/H_mustelae).

(iii) ***Helicobacter acinonychis***. *H. acinonychis*, a pathogen of cheetahs and other big cats (formerly named *Helicobacter acinonyx* [145]), is currently the closest known relative to *H. pylori* (242) and has been suggested to have diverged from its last common ancestor (*H. pylori*) only relatively recently (241). The presence of *H. acinonychis* is associated with chronic gastritis and ulceration, a frequent cause of death of cheetahs in captivity (444). Furthermore, eradication treatment of *H. acinonychis* led to the resolution of gastric lesions in tigers (77), similar to the effect of antibiotic treatment of *H. pylori* infection (228). *H. acinonychis* is susceptible to antibiotic therapy, as used for *H. pylori* infection, and utilizes similar mechanisms for antimicrobial resistance (509).

H. acinonychis is genetically amenable, by techniques similar to those developed for *H. pylori*, and *H. acinonychis* shares several virulence factors with *H. pylori* but contains only a degenerate copy of the *vacA* gene (111) and lacks the *cag* pathogenicity island (PAI) (241). Recently, mouse-colonizing strains of *H. acinonychis* have been described (111); this should allow further comparisons of the pathogenic properties of *H. acinonychis*, as well as comparison with the pathogenesis of *H. pylori* infection. Furthermore, the pending release of the complete genome sequence of *H. acinonychis* (241) will give further insight into the evolutionary relationship between *H. acinonychis* and *H. pylori*.

(iv) ***Helicobacter heilmannii***. The diverse species *H. heilmannii* was originally designated *Gastrospirillum hominis* and is a *Helicobacter* species with a wide host range (583, 586). It has been isolated from several domestic and wild animals, including dogs, cats, and nonhuman primates, and is also observed in a small percentage of humans with gastritis (194). In the latter, colonization may reflect a zoonosis, as there is an association between colonization with this bacterium and close contact with dogs and cats carrying the same bacterium (598). Its morphology resembles that of *H. felis*, but *H. heilmannii* lacks

the periplasmic fibers.

Human *H. heilmannii* infection may result in gastritis and dyspeptic symptoms (4), and in sporadic cases even in ulcer disease, but the inflammation is usually less marked than in *H. pylori*-positive subjects and may be spontaneously transient (598). In a mouse model of infection, different *H. heilmannii* isolates of both human and animal origin were able to induce gastric B-cell MALT lymphoma (476). Characterization of this *Helicobacter* species is difficult, since it has not been successfully cultured in vitro, and it may be necessary to make a further subdivision of the species *H. heilmannii*. Recent phylogenetic analyses have led to the proposal of the species designation "*Candidatus Helicobacter heilmannii*," but this is mostly based on 16S rRNA and urease sequence analyses and thus awaits further confirmation (478).

Enterohepatic *Helicobacter* species. Enterohepatic *Helicobacter* species colonize the lower gastrointestinal tract, including the ileum, colon, and biliary tree of humans and other mammals. They cause persistent infections, which are associated with chronic inflammation and epithelial cell hyperproliferation that can lead to neoplastic disease, and are associated with human hepatobiliary disease (31, 587, 664). The group of enterohepatic *Helicobacter* species consists of many different species, differing in morphology, ultrastructure, growth conditions, and the presence or absence of the urease virulence factor (587). Only one of these species has been more than superficially characterized, the murine pathogen *H. hepaticus*, and is discussed here.

The enterohepatic pathogen *H. hepaticus* infects rodents, in which it may cause chronic active hepatitis, hepatic tumors, and proliferative typhlocolitis (681, 683). It was initially isolated from a colony of male A/JCr mice with a high incidence of hepatitis and hepatic cancer (683). Subsequently it was shown that several inbred strains of mice were susceptible to hepatic lesions after infection with *H. hepaticus*. In addition, many commercially available mouse strains were shown to be naturally infected with *H. hepaticus* (562).

Although it was first identified in the liver, the primary site of *H. hepaticus* colonization is the intestinal tract; it has not been found in the stomach (587). In immunocompetent mice, infection with *H. hepaticus* results in mild intestinal inflammation, but in immunodeficient and SCID mice, infection with *H. hepaticus* leads to severe colitis, typhlitis, and proctitis, which resemble lesions found in animal models of inflammatory bowel disease (682). *H. hepaticus* is among several *Helicobacter* species identified in rodents with disease of the hepatobiliary or intestinal tracts, including *H. bilis*, *H. muridarum*, and *H. trogontum* (587). In a recent study, mice were fed a lithogenic diet and were coinfecting with *H. hepaticus* and *Helicobacter rodentium*. These mice developed cholesterol gallstones at 80% prevalence by 8 weeks, suggesting a link between infection with enterohepatic *Helicobacter* species and gallstone formation (404). In comparison, this association is not found when these mice are infected with *H. pylori* (405). *H. hepaticus* infection of mice can be treated with antibiotics (189, 534), and this results in resolution of lesions associated with the infection.

H. hepaticus is morphologically similar to *Campylobacter* species, with bipolar sheathed flagella (201). It is urease, oxidase, and catalase positive and grows on most standard *H.*

pylori growth media, including β -cyclodextrin-supplemented media (45). Growth conditions are similar to those employed for *H. pylori*, and selective antibiotic supplements used for *H. pylori* can also be used for isolation and subsequent cultivation of *H. hepaticus* (45). Although it has been well established that infection with *H. hepaticus* causes diverse diseases in rodents, relatively little is known about its mechanisms of virulence. Several putative virulence factors of *H. hepaticus* have been identified, including the cytolethal distending toxin (CDT) and a potent urease enzyme (43), but mutational analysis demonstrating the role of these virulence factors in colonization or hepatic diseases is available only for CDT (712). Recently, the complete genome sequence of *H. hepaticus* was determined (605), and this revealed the presence of a potential PAI, coined HHGI1 (65, 605). Furthermore, *H. hepaticus* is also genetically amenable by both electroporation (415, 712) and natural transformation (45), albeit to a lower efficiency than *H. pylori* and other gastric *Helicobacter* species. Taken together, this makes *H. hepaticus* an attractive organism for elucidation of the molecular mechanisms involved in adaptation to the enteric and hepatic niches and of the mechanisms of enterohepatic pathogenesis.

Microbiology of *H. pylori*

Genome, plasmids, and strain diversity. The size of the two sequenced *H. pylori* genomes is approximately 1.7 Mbp, with a G+C content of 35 to 40%. The *H. pylori* strain 26695 genome includes 1,587 genes, whereas the genome of strain J99 includes only 1,491 genes (14, 62, 628). Both genomes contain two copies of the 16S, 23S, and 5S rRNA genes. Many strains carry one or more cryptic plasmids, which do not seem to carry antibiotic resistance genes or virulence genes (270). Some of these plasmids form the basis of *H. pylori*-*E. coli* shuttle vectors used in molecular cloning experiments (271). The existence of *H. pylori*-infecting bacteriophages has been reported, but detailed characterization is lacking (549).

In contrast to other bacterial pathogens that are highly clonal (such as *Shigella dysenteriae* and *Mycobacterium tuberculosis*), *H. pylori* is genetically heterogeneous, suggesting a lack of clonality. This results in every *H. pylori*-positive subject carrying a distinct strain (300), although differences within relatives may be small. The genetic heterogeneity is possibly an adaptation of *H. pylori* to the gastric conditions of its host, as well as to the distinct patterns of the host-mediated immune response to *H. pylori* infection (333). Genetic heterogeneity is thought to occur via several methods of DNA rearrangement and the introduction and deletion of foreign sequences (1, 176, 603). The latter usually have an aberrant G+C content and often carry genes involved in virulence. A striking example of this in *H. pylori* is the *cag* PAI, but other plasticity regions have also been suggested to play a role in the pathogenesis of *H. pylori* infection (115, 357, 462, 545).

Diversity is also seen at the nucleotide level via several mechanisms, including transcriptional and translational phase variation and mutation (1, 175, 602, 606). Phase variation often occurs via reversible slipped-strand mispairing in homopolymeric G or C tracts, which causes a shift in translation of the affected gene, thus resulting in phase variation via a single mutation. This leads to a reversible phenotypic diversity with

only minor genetic variation. Several virulence genes, such as the *sabA*, *sabB*, *hopZ*, and *oipA* outer membrane protein-encoding genes, display such phenotypic variation, as do lipopolysaccharide (LPS) biosynthetic enzymes (18, 28, 117, 387).

Morphology. *H. pylori* is a gram-negative bacterium, measuring 2 to 4 μm in length and 0.5 to 1 μm in width. Although usually spiral-shaped, the bacterium can appear as a rod, while coccoid shapes appear after prolonged in vitro culture or antibiotic treatment (342). These coccoids cannot be cultured in vitro and are thought to represent dead cells (342), although it has been suggested that coccoid forms may represent a viable, nonculturable state (162). The organism has 2 to 6 unipolar, sheathed flagella of approximately 3 μm in length, which often carry a distinctive bulb at the end (481). The flagella confer motility and allow rapid movement in viscous solutions such as the mucus layer overlying the gastric epithelial cells (481). In contrast to many other pathogens of the gastrointestinal tract, it lacks fimbrial adhesins.

Growth requirements. A key feature of *H. pylori* is its microaerophilicity, with optimal growth at O_2 levels of 2 to 5% and the additional need of 5 to 10% CO_2 and high humidity. There is no need for H_2 , although it is not detrimental to growth. Many laboratories utilize standard microaerobic conditions of 85% N_2 , 10% CO_2 , and 5% O_2 for *H. pylori* culture. Growth occurs at 34 to 40°C, with an optimum of 37°C. Although its natural habitat is the acidic gastric mucosa, *H. pylori* is considered to be a neutrophile. The bacterium will survive brief exposure to pHs of <4, but growth occurs only at the relatively narrow pH range of 5.5 to 8.0, with optimal growth at neutral pH (554, 595).

H. pylori is a fastidious microorganism and requires complex growth media. Often these media are supplemented with blood or serum. These supplements may act as additional sources of nutrients and possibly also protect against the toxic effects of long-chain fatty acids. The latter function may also be performed by more defined medium supplements, such as β -cyclodextrins or IsoVitaleX, or by using activated charcoal (616). Commonly used solid media for routine isolation and culture of *H. pylori* consist of Columbia or brucella agar supplemented with either (lysed) horse or sheep blood or, alternatively, newborn or fetal calf serum. For primary isolation but also routine culture, selective antibiotic mixtures are available, although these are not required per se. The often used Dent supplement consists of vancomycin, trimethoprim, cefsulodin, and amphotericin B (121), whereas the alternatively used Skirrow supplement consists of vancomycin, trimethoprim, polymyxin B, and amphotericin B (573). Both selective supplements are commercially available. Liquid media usually consist of either brucella, Mueller-Hinton, or brain heart infusion broth supplemented with 2 to 10% calf serum or 0.2 to 1.0% β -cyclodextrins, often together with either Dent or Skirrow supplement. Growth of *H. pylori* in chemically defined media has been reported (526), but these are not suitable for routine growth and isolation of *H. pylori*. Most of the commercially available synthetic media, such as tissue culture media, do not support the growth of *H. pylori* without the addition of serum, perhaps with the exception of Ham's F-12 nutrient mixture (622).

Isolation of *H. pylori* from gastric biopsy samples is difficult and not always successful. Cultures should be inspected from day 3 to day 14. *H. pylori* forms small (~1-mm), translucent,

smooth colonies (254). Upon successful subculturing, *H. pylori* isolates tend to adapt to the growth conditions used in the laboratory. Subsequently, good growth can generally be achieved following 1 to 3 days of incubation when reference strains and laboratory-adapted isolates of *H. pylori* are used. It should be noted that once a culture reaches the stationary phase, the growth rate rapidly declines, accompanied by the morphological change to a coccoid form (342). Prolonged culture does not lead to any significant increase in colony size but rather leads to a transition to the unculturable coccoid state. To facilitate optical detection of *H. pylori*, plates can be supplemented with triphenyltetrazolium chloride (TTC) to a final concentration of 0.004% (690). In the presence of TTC, *H. pylori* colonies appear dark red via the reduction of TTC to deep red formazan (60) and develop a golden shine. *H. pylori* can be stored for the long term at -80°C in brain heart infusion or brucella broth supplemented with either 15 to 20% glycerol or 10% dimethyl sulfoxide, but optimal viability requires the use of cultures less than 48 h old, with more than 90% spiral-shaped cells.

Metabolism. *H. pylori* exhibits a narrow host and target organ range, but infection is usually lifelong. This suggests strong adaptation to its natural habitat, the mucus layer overlying the gastric epithelial cells. As a consequence, *H. pylori* lacks several of the biosynthetic pathways commonly found in less specialized bacteria, such as many enteric bacteria (14, 49, 126, 392, 628). It has been inferred from genomic comparisons and metabolic studies that *H. pylori* has a stripped-down metabolic route with very few redundancies and lacks biosynthetic pathways for some amino acids. As a consequence, *H. pylori* can be grown only in chemically defined medium with the additional amino acids arginine, histidine, isoleucine, leucine, methionine, phenylalanine and valine, and some strains also require alanine and/or serine (456, 526). *H. pylori* is urease, catalase, and oxidase positive, characteristics which are often used in identification of *H. pylori*. *H. pylori* can catabolize glucose, and both genomic and biochemical information indicates that other sugars cannot be catabolized by *H. pylori* (49, 126, 392, 456).

Our understanding of the metabolism of *H. pylori* has been greatly facilitated by the availability of two complete genome sequences (14, 628). Many of the previously described biochemical deficiencies of *H. pylori* were confirmed by the apparent lack of genes encoding the corresponding enzymes for these metabolic routes (49, 126, 311, 312, 392). However, it must be stressed that many of these analyses are based on sequence homology and await further experimental validation. In this section we discuss only those systems involved in or connected to the virulence of *H. pylori*; for in-depth reviews of *H. pylori* metabolism, see references 126, 311, 312, and 392.

(i) Respiration and oxidative stress defense. *H. pylori* is a microaerophilic bacterium that does not tolerate high oxygen conditions, but it requires at least 2% O_2 (420). This is because *H. pylori* uses oxygen as a terminal electron acceptor. *H. pylori* cannot utilize alternative electron acceptors, such as nitrate or formate, although there is a single report on anaerobic growth of *H. pylori* using fumarate (578). In the human host, *H. pylori* is thought to be exposed to oxidative stress produced by the active immune response. To combat such forms of oxidative stress, *H. pylori* expresses several key components of bacterial oxidative stress resistance; these include the superoxide stress

defense mediated via the iron-cofactored superoxide dismutase (SodB) (38, 166, 561) and the peroxide stress defense mediated via catalase (KatA) and alkyl hydroperoxide reductase (AhpC) (257, 474). In addition, the two thioredoxins, its respective reductases, and the thiol-peroxidase Tcp mediate resistance to both nitrosative and oxidative stresses (36, 94, 473, 474, 675). The neutrophil activating protein (HP-NAP) (see also "Pathogenesis of Infection," below) is a member of the Dps family and is thought to protect DNA from the detrimental effects of reactive oxygen species (38, 473, 474). As indicated by its name, HP-NAP is also implicated in the activation of neutrophils, leading to the formation of reactive oxygen species (172), but this function is still under debate and may well be an artifact (38, 436). The formation of reactive oxygen species is connected with iron metabolism, as oxygen radicals can be produced via the Fenton and Haber-Weiss reactions ($\text{Fe}^{2+} + \text{O}_2 \rightarrow \text{Fe}^{3+} + \text{O}_2^-$ and $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}\cdot$). Thus, it is not surprising that proteins involved in iron metabolism, such as the global iron-responsive regulator Fur, the FeoB iron transporter, the iron-storage protein ferritin, and the iron-cofactored SodB, are involved in oxidative stress resistance (166, 474, 561, 659, 670). Interestingly, mutation of the carbon storage regulator protein CsrA also affects oxidative stress resistance, although the mechanism underlying this phenomenon has not yet been elucidated (38). Many of the components of oxidative stress defense are essential for host colonization, as the absence of one or more factors often results in lower levels or absence of colonization by *H. pylori* in animal models (8, 38, 73, 257, 258, 473, 474, 561, 673–675).

(ii) Nitrogen metabolism. Amino acids and urea are the two major sources of nitrogen in the gastric environment. Since ammonia is a key component in nitrogen metabolism as well as acid resistance (595), it is not surprising that *H. pylori* can utilize several alternative sources of ammonia (71, 406, 422, 574, 575, 656). The different pathways contributing to ammonia synthesis are regulated in response to different stimuli, which probably allows *H. pylori* to switch different pathways on or off depending on the environmental conditions (summarized in Fig. 1).

The main route of ammonia production is through the highly active urease enzyme, which functions in nitrogen metabolism but also in acid resistance and virulence. *H. pylori* produces large amounts of urease, and it has been estimated that up to 10% of the total protein content of *H. pylori* consists of urease (39). Urease is a nickel-containing enzyme that consists of 12 UreA and 12 UreB subunits (248). The UreA and UreB subunits have molecular masses of 27 kDa and 62 kDa (138), respectively, and the subunits are encoded by an operon containing the *ureA* and *ureB* genes (348). The urease gene cluster contains a second operon downstream of the *ureAB* genes which encodes the UreIEFGH proteins. The UreEFGH accessory proteins probably function in subunit assembly and incorporation of nickel in the active sites of urease (109, 430), whereas the UreI protein functions as an acid-activated urea channel (72, 576, 686, 687). Transcription of the *H. pylori* urease gene cluster occurs from two promoters, one upstream of the *ureA* gene (P_{ureA}) (2, 654) and one in the intergenic region between *ureB* and *ureI* (P_{ureI}) (2). Transcription from these two promoters, followed by pH-dependent differential

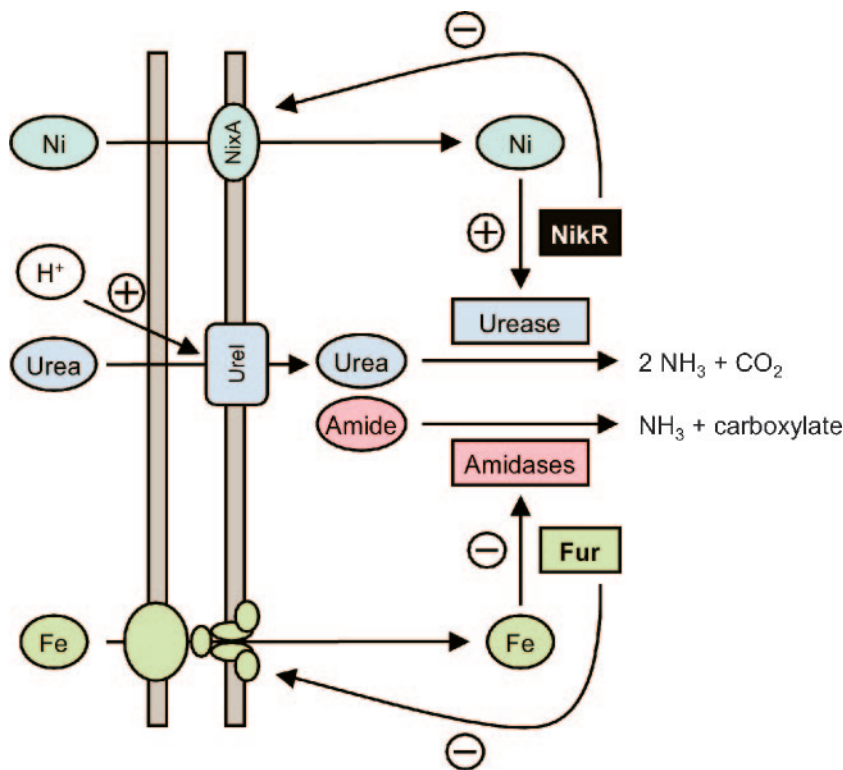


FIG. 1. Schematic representation of the relationships between acid resistance (urease activity and urea transport), nitrogen metabolism (ammonia production), metal metabolism (iron uptake and nickel uptake), and gene regulation (Fur and NikR) in *H. pylori*.

mRNA decay, leads to the formation of mRNAs containing *ureAB*, *ureABIE'*, *ureIE'*, and *ureF'GH* (2, 654). Urease activity is very high, but its effective activity is dependent on the availability of the urea substrate. Urea transport into the cell is controlled via the H⁺-gated urea channel UreI (72, 576, 686, 687), resulting in increased urea transport in acidic conditions. When excess ammonia is produced, this can be removed via the glutamate synthetase enzyme (213).

In addition to facilitating survival and growth in acidic conditions, the ammonia produced via enzymatic degradation of urea is used for amino acid biosynthesis. The importance of ammonia in *H. pylori* metabolism and virulence is underlined by the presence of several alternative routes for ammonia production, via enzymatic degradation of diverse amides as well as amino acids (Fig. 1) (71, 406, 422, 574, 575, 656). *H. pylori* expresses two paralogous amidases, the wide-range aliphatic amidase AmiE as well as the formamidase AmiF. Together with four amino acid deaminases, these probably serve as sources for ammonia in environments low in urea. It is remarkable that *H. pylori* also expresses several key components of the eukaryotic urea cycle (418) and thus may be able to produce urea from ammonia. One of the major components of the *H. pylori* urea cycle is the arginase (RocF) enzyme, which converts L-arginine to L-ornithine and urea. Mutation of the *rocF* gene did not affect urease activity but significantly reduced the acid resistance of *H. pylori* (406). Since the *rocF* mutation also decreased the activity of one of the amino acid deaminases via an unknown mechanism, it is unclear whether the reduced acid resistance is a direct effect of the lack of

arginase or an indirect effect (406). *H. pylori* arginase is also implicated in the control of nitric oxide production in eukaryotic cells (232), and arginine metabolism of the eukaryotic cell may also be controlled by *H. pylori* (231).

(iii) Metal metabolism. Metals play an important role in the metabolism of all organisms, which is reflected by the wide variety of chemical reactions in which they are involved. Metals are cofactors of enzymes, catalyzing basic functions such as electron transport, redox reactions, and energy metabolism, and are essential for maintaining the osmotic pressure of the cell. Since both metal limitation and metal overload delay growth and can cause cell death, metal homeostasis is of critical importance to all living organisms.

(a) *Nickel.* *H. pylori* requires efficient acquisition of nickel, as this is the metal cofactor of the essential colonization factors urease and hydrogenase. Nickel availability in human serum is very low (2 to 11 nM), and the nickel concentration in ingested food varies significantly depending on the diet and on food sources (91, 608). One certain and several potential nickel transporters have been identified in *H. pylori*. The NixA protein (HP1077) is a 37-kDa protein located in the cytoplasmic membrane and has been demonstrated to have a high affinity for nickel (Fig. 1) (206, 428). Mutation of the *nixA* gene results in strongly reduced nickel transport and lowered urease activity (40). Absence of *nixA* also affected colonization efficiency in a mouse model of *H. pylori* infection, presumably due to the reduced urease activity (459). A second putative nickel transport system may be encoded by the *abcCD* locus (266), since *abcC nixA* double mutants showed only residual urease activ-

ity. However, a role of the *abcCD* system in nickel transport has not yet been demonstrated. A third system thought to be involved in nickel transport is the Dpp dipeptide permease, but mutation of this gene did not affect overall urease activity (112). It is still unclear how nickel enters *H. pylori*; however, since mutation of *nixA* complemented the nickel sensitivity of an *H. pylori nikR* mutant (95, 167, 655), this strongly supports an important role of NixA in nickel transport of *H. pylori*.

Several urease- and hydrogenase-associated systems have adapted to the central role of nickel, as is demonstrated by the effect of hydrogenase accessory proteins on urease activity (46, 413, 414) and the presence of a nickel-binding motif on the HspA chaperone (299). Next to the nickel transporters and urease/hydrogenase accessory proteins, *H. pylori* also expresses one or two small, very histidine-rich proteins (Hpn), which show strong binding to nickel (225, 429). Mutation of the *hpn* gene rendered *H. pylori* sensitive to nickel (429), which is suggestive of a role of Hpn in nickel storage or nickel sequestration, but this remains to be proven experimentally.

(b) *Iron*. In tissues of human or animal hosts, the concentration of free iron is too low to support bacterial growth, as most iron is complexed into hemoglobin or chelated by transferrin in serum or by lactoferrin at mucosal surfaces (652). Iron sources available in the gastric mucosa are lactoferrin, heme compounds released from damaged tissues, and iron derived from pepsin-degraded food. It is thought that metals such as iron display increased solubility under the acidic conditions of the gastric mucosa and that eukaryotic iron-complexing proteins display lowered binding affinity under these conditions. The *H. pylori* genome encodes 11 proteins predicted to be involved in iron transport and 2 proteins thought to function as iron storage proteins (14, 49, 628, 652). In the acidic, microaerobic gastric environment, ferrous iron (Fe^{2+}) is thought to constitute the main form of free iron, and this is transported by *H. pylori* via the FeoB protein (HP0687) (659). FeoB-mediated iron acquisition is of major importance to *H. pylori*, as isogenic *feoB* mutants were unable to colonize the gastric mucosa of mice (659). *H. pylori* also possesses ferric reductase activity, which converts ferric iron (Fe^{3+}) to Fe^{2+} , which is then subsequently transported by the FeoB system (695). However, the importance of ferric reductase activity in gastric colonization remains to be assessed. Finally, *H. pylori* also possesses several ferric iron transport systems (652, 657). Due to the insolubility of ferric iron, ferric iron transport requires an outer membrane receptor to transport the iron over the outer membrane, as well as an ABC transporter to transport the iron from the periplasm to the cytoplasm. *H. pylori* has three copies of the putative ferric citrate outer membrane receptor FecA and three copies of the FrpB outer membrane receptor, for which the substrate is unknown (14, 49, 628, 652). There are two copies of the periplasmic binding protein CeuE and finally a single inner membrane permease (FecD) and an ATP-binding protein (FecE). Currently, only mutants in the *fecDE* system and in one of the *fecA* genes have been described (659). Rather surprisingly, this did not affect iron transport. Thus, the contribution of ferric iron uptake in *H. pylori* remains to be clarified. Two iron storage proteins in *H. pylori* have been characterized, the Pfr ferritin and HP-NAP bacterioferritin. The 19-kDa Pfr ferritin serves as an intracellular iron deposit and protects *H. pylori* against iron toxicity and free iron-mediated oxidative stress (47, 48, 125, 205, 670). Iron stored in Pfr can be released and reused to support growth under iron-limited conditions (670). HP-NAP was originally isolated as an immunodominant protein that activates neutrophilic granulocytes in vitro (172). It was subsequently shown to also mediate adhesion of *H. pylori* to mucin (452). The HP-NAP protein is homologous both to bacterioferritins and to the DNA-binding proteins of the Dps family (137, 631). However, a role of HP-NAP in *H. pylori* iron storage, although suggested, is yet to be demonstrated (631).

(c) *Copper*. Copper is a cofactor for several proteins involved in electron transport, oxidases, and hydroxylases, but may also contribute to the formation of reactive oxygen species (525). *H. pylori* expresses several proteins which either are involved in copper transport or may act as copper chaperones. It is currently unclear whether there is a specific import system for copper or whether it is transported by other metal transporters such as FeoB or NixA. However, *H. pylori* expresses several proteins involved in copper export, including the CopA (HP1073) and CopA2 (HP1503) P-type ATPases (41, 44, 216, 416) and the CrdA (HP1365) copper resistance determinant (671). Furthermore, *H. pylori* also expresses a small protein, CopP, that may function as a copper chaperone (41, 44, 216, 416).

(d) *Cobalt*. The trace metal cobalt is a cofactor of the arginase enzyme, which plays an important role in nitrogen metabolism of *H. pylori* (406, 419) but also in modulating the immune response to *H. pylori* (231, 232). It has been noted that *H. pylori* is exquisitely sensitive to cobalt in vitro (95), and it has been suggested that cobalt may be used in nonantibiotic therapy of *H. pylori* infections (68, 74).

Cell envelope, outer membrane, and LPS. The overall composition of the cell envelope of *H. pylori* is similar to that of other gram-negative bacteria. It consists of an inner (cytoplasmic) membrane, periplasm with peptidoglycan, and an outer membrane. The outer membrane consists of phospholipids and LPS. The *H. pylori* outer membrane phospholipid moiety contains cholesterol glucosides (69, 256, 618, 619), which is very rare in bacteria. LPS usually consists of lipid A, core oligosaccharide, and an O side chain. The lipid A moiety of *H. pylori* LPS has low biological activity compared to lipid A from other bacteria (446). Clinical isolates of *H. pylori* produce high-molecular-weight (smooth) LPS with an O antigen, but during in vitro culturing the bacteria may convert to rough LPS variants, which lack the O side chain (440, 672). The O side chain of *H. pylori* can be fucosylated and mimics Lewis blood group antigens (Lewis x [Le^x] and Le^y), aiding molecular mimicry of host antigens and associated immune evasion (20). The O antigen can also mimic other blood group antigens (437). *H. pylori* LPS displays phase variation through length variation of poly(C) tracts in the genes encoding α -1,3-fucosyltransferases (18) and a poly(C) tract and poly(TAA) repeats in the gene encoding the α -1,2-fucosyltransferase (676). This LPS phase variation contributes to population heterogeneity and may allow adaptation of *H. pylori* to changing conditions in the gastric mucosa (440, 619, 620).

The *H. pylori* genome encodes a large array of outer membrane proteins, which have been grouped into five paralogous families (13, 128). The largest gene family consists of 21 Hop and 12 Hor outer membrane proteins, and this family includes

the known (putative) adhesins of *H. pylori* (171). Other families include porins (127), iron transporters (see above), flagellum-associated proteins, and proteins of unknown function. The outer membrane of *H. pylori* often also contains urease and heat shock proteins, which are otherwise found only in the cytoplasm. Although specific export of these proteins cannot be completely excluded (649), this may be due to "altruistic lysis," a process wherein part of the population of bacterial cells lyses and releases its cytoplasmic proteins, which are subsequently used by surviving bacteria to coat their outer membrane with proteins from lysed cells (395, 507). The function of this process is not yet understood, but it can be envisaged that it aids in protection against environmental stresses and functions in diversion of the immune response of the host.

Gene regulation. Rapid responses to stressful changes in environmental conditions are often mediated via changes in transcription of sets of genes that encode some factor involved in dealing with these stresses. Examples of this are the expression of oxidative stress defense genes in response to oxidative stress. In many bacteria, such stress-responsive systems are often encoded by genes organized in an operon, and the transcription is regulated by one or two regulatory proteins.

The only known niche of *H. pylori* is the human gastric mucosa, and this niche was considered to offer relatively stable conditions and limited competition with other bacteria. This hypothesis was consistent with the relatively low number of predicted regulatory proteins in the *H. pylori* genome (122). *H. pylori* lacks several two-component regulatory systems, which are thought to function as sensors of changes in the environment. The *H. pylori* genome contains only 4 complete two-component regulatory systems, which strongly contrasts to the 36 complete two-component regulatory systems found in *Escherichia coli* K-12 (479, 701). The repertoire of regulatory proteins mediating regulation in response to cytoplasmic changes is similar to that of related bacteria, such as *Campylobacter*, but also lower than that of *E. coli*. Overall, *H. pylori* contains only three sigma factors (σ^{80} , σ^{28} , and σ^{54}), two metalloregulatory proteins, two heat shock regulators, four complete two-component regulatory systems, two orphan response regulators, and a few other regulatory proteins (122, 546, 658).

It is becoming apparent, however, that the gastric mucosa may not be the relatively stable environment previously envisaged. Examples of complex, overlapping regulatory responses are becoming apparent with comparison of transcriptional profiling studies using different environmental stimuli (73, 165, 422, 423, 653, 658, 688). The regulatory responses to iron restriction, nickel, and acid show considerable overlap with each other and with growth phase-regulated genes (Fig. 1) (95, 165–167, 422, 423, 653, 654, 657, 658, 688). In addition, regulatory proteins seem to have acquired extra functions to compensate for the lack of specific regulatory proteins, as seen in the Fur-responsive regulation of the paralogous amidases of *H. pylori* (73, 95, 653, 656).

Transcriptional profiling studies using array hybridization indicate that approximately half of the *H. pylori* genome is expressed under in vitro conditions (95, 165, 422, 423, 626, 688). Of these genes, ~5 to 10% display regulated expression in response to diverse environmental stresses, suggesting that *H. pylori* may not so much respond to specific stresses as combat environmental stresses, such as decreases in pH, using

general stress-responsive mechanisms. This view is supported by the fact that the response of *H. pylori* to different environmental stimuli appears to be multifactorial and to be mediated via several regulatory systems, which may be connected via regulatory cross talk and cascades (658). This is exemplified by the nickel-responsive regulator NikR, which controls transcription of the iron-responsive regulator Fur and thus mediates regulation of both nickel- and iron-responsive genes (55, 73, 95, 653, 658). In addition, the HP0166-HP0165 (ArsRS) two-component regulatory system is implicated in acid-responsive regulation of urease expression (505, 506), and mutation of genes involved in posttranscriptional modification of RNA may also affect the overall expression level of genes (2, 38). Thus, it may well be that there is a hierarchical structure of regulatory networks in *H. pylori*, which allows moderate but optimal responses to environmental stresses in the gastric environment. Alternatively, the overlap between the different regulons may allow modulation of the level of gene expression rather than switching expression of genes on or off.

EPIDEMIOLOGY

Prevalence and Geographical Distribution

The prevalence of *H. pylori* shows large geographical variations. In various developing countries, more than 80% of the population is *H. pylori* positive, even at young ages (500). The prevalence of *H. pylori* in industrialized countries generally remains under 40% and is considerably lower in children and adolescents than in adults and elderly people (510). Within geographical areas, the prevalence of *H. pylori* inversely correlates with socioeconomic status, in particular in relation to living conditions during childhood (389). In Western countries, the prevalence of this bacterium is often considerably higher among first- and second-generation immigrants from the developing world (499, 635). While the prevalence of *H. pylori* infection in developing countries remains relatively constant, it is rapidly declining in the industrialized world (220). The latter is thought to be caused by the reduced chances of childhood infection due to improved hygiene and sanitation and the active elimination of carriership via antimicrobial treatment. In developing countries, *H. pylori* infection rates rise rapidly in the first 5 years of life and remain constantly high thereafter, indicating that *H. pylori* is acquired early in childhood (184). However, in industrialized countries the prevalence of *H. pylori* infection is low early in childhood and slowly rises with increasing age. This increase results only to a small extent from *H. pylori* acquisition at later age. The incidence of new *H. pylori* infections among adults in the Western world is less than 0.5% per year; the higher prevalence of infection among the elderly thus reflects a birth cohort effect with higher infection rates in the past (336, 488). The active elimination of *H. pylori* from the population and improved hygiene and housing conditions have resulted in a lower infection rate in children, which is reflected in the age distribution of this lifelong-colonizing bacterium (322, 524, 531). Overall, new infection more commonly occurs in childhood and lasts for life unless specifically treated.

Transmission and Sources of Infection

The exact mechanisms whereby *H. pylori* is acquired are largely unknown. *H. pylori* has a narrow host range and is found almost exclusively in humans and some nonhuman primates. *H. pylori* has on rare occasions been isolated from pet animals; thus, the presence of pets may be a risk factor for *H. pylori* infection (66, 67, 130, 269). As conclusive evidence for zoonotic transmission of *H. pylori* is not yet available (195), new infections are thought to occur as a consequence of direct human-to-human transmission, via either an oral-oral or fecal-oral route or both. *H. pylori* has been detected in saliva, vomitus, gastric refluxate, and feces (10, 177, 178, 298, 361, 492, 569), but there is no conclusive evidence for predominant transmission via any of these products. This may be due to the fact that most research on transmission has focused on adults. It appeared that there was no clear increased risk for being a carrier of *H. pylori* among dentists, gastroenterologists, nurses, partners of an *H. pylori*-positive spouse, or visitors to a clinic for sexually transmitted diseases (411). As a result of these and other investigations, it is generally believed that acquisition mostly occurs in early childhood, most likely from close family members (316, 320, 523, 532, 617, 644). Premastication of food by the parent is an uncertain risk factor for transmission of *H. pylori* (341). Childhood crowding in and outside the family are all positively associated with *H. pylori* prevalence (233, 666), whereas among adults crowding appears less important, with the exception of certain circumstances, such as among army recruits (207, 346, 532). Several studies have reported the presence of *H. pylori* DNA in environmental water sources (161, 262, 514), but this probably reflects contamination with either naked DNA or dead *H. pylori* organisms. To our knowledge there is only a single report of *H. pylori* being successfully cultured from water, but this involved wastewater and as such may well represent fecal contamination of the water source (378). Spread via fecal contaminants is supported by the occurrence of *H. pylori* infections among institutionalized young people during outbreaks of gastroenteritis (350). Other possible sources include contaminated food, as *H. pylori* may survive briefly on refrigerated food (508). Coupled with the extreme sensitivity of *H. pylori* to atmospheric oxygen pressure, lack of nutrients, and temperatures outside the 34 to 40°C range (342), direct person-to-person transmission remains the most likely transmission route.

CLINICAL ASPECTS OF *H. PYLORI*-ASSOCIATED DISEASES

Colonization with *H. pylori* is not a disease in itself but a condition that affects the relative risk of developing various clinical disorders of the upper gastrointestinal tract and possibly the hepatobiliary tract. Testing for *H. pylori* therefore has no relevance by itself but should be performed to find the cause of an underlying condition, such as peptic ulcer disease, or for the purpose of disease prevention, such as in subjects with familial gastric cancer. In these cases, a positive test result justifies treatment and a negative test result may indicate the need to search for other etiologic factors or preventive measures. For these reasons, a correct understanding of the clinical

course of *H. pylori*-associated disorders and the effect of *H. pylori* eradication is needed.

Disease Types

Although gastric colonization with *H. pylori* induces histologic gastritis in all infected individuals, only a minority develop any apparent clinical signs of this colonization. It is estimated that *H. pylori*-positive patients have a 10 to 20% lifetime risk of developing ulcer disease and a 1 to 2% risk of developing distal gastric cancer (168, 331, 338). The risk of development of these disorders in the presence of *H. pylori* infection depends on a variety of bacterial, host, and environmental factors that mostly relate to the pattern and severity of gastritis (Fig. 2).

Acute and chronic gastritis. Colonization with *H. pylori* virtually always leads to infiltration of the gastric mucosa in both antrum and corpus with neutrophilic and mononuclear cells (Fig. 3A). This chronic active gastritis is the primary condition related to *H. pylori* colonization, and other *H. pylori*-associated disorders in particular result from this chronic inflammatory process.

(i) Acute gastritis. Data on the acute phase of infection are scarce and largely come from reports of subjects who deliberately or inadvertently ingested *H. pylori* or underwent procedures with contaminated material (236, 398, 442, 582). Recently, a human challenge model for *H. pylori* infection was introduced; it allowed controlled studies of the acute phase of infection with deliberate infection of healthy volunteers with a well-characterized laboratory strain of *H. pylori* (238). Together, these reports showed that the acute phase of colonization with *H. pylori* may be associated with transient nonspecific dyspeptic symptoms, such as fullness, nausea, and vomiting, and with considerable inflammation of both the proximal and distal stomach mucosa, or pangastritis. This phase is often associated with hypochlorhydria, which can last for months. It is unclear whether this initial colonization can be followed by spontaneous clearance and resolution of gastritis and, if so, how often this occurs. Follow-up studies of young children with serology or breath tests suggested that infection may spontaneously disappear in some patients in this age group (239, 390, 501); this has not been observed in adults other than under specific circumstances, such as development of atrophic gastritis. However, studies of homozygotic twins showed a concordance in their *H. pylori* status irrespective of whether they had grown up together or apart (388). Such a concordance was not observed among heterozygotic twins. This suggests that some individuals are prone to *H. pylori* colonization while others may be able to prevent colonization or clear an established infection. This hypothesis is also supported by the observation that in many developing countries the level of exposure to *H. pylori* is very high (i.e., $\geq 90\%$) at young ages and yet some individuals never develop persistent *H. pylori* infection.

(ii) Chronic gastritis. When colonization does become persistent, a close correlation exists between the level of acid secretion and the distribution of gastritis (Fig. 4). This correlation results from the counteractive effects of acid on bacterial growth versus those of bacterial growth and associated mucosal inflammation on acid secretion and regulation. This interaction is crucial in the determination of outcomes of *H. pylori*

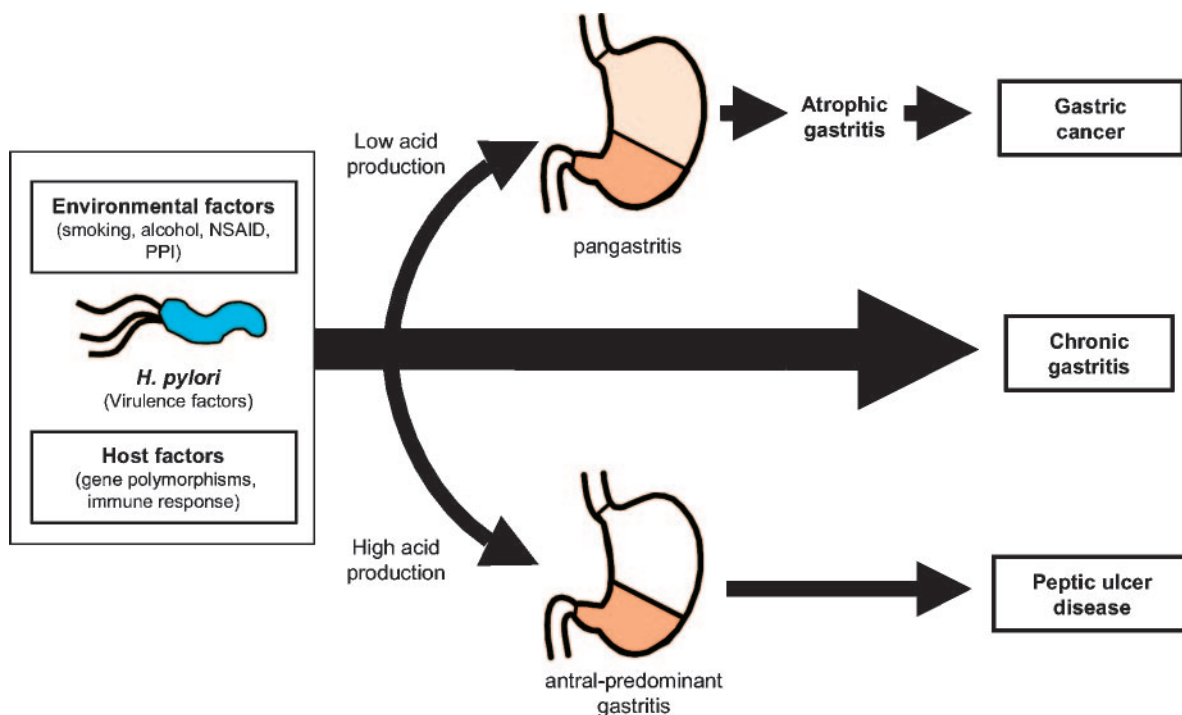


FIG. 2. Schematic representation of the factors contributing to gastric pathology and disease outcome in *H. pylori* infection.

infection. In subjects with intact acid secretion, *H. pylori* in particular colonizes the gastric antrum, where few acid-secreting parietal cells are present. This colonization pattern is associated with an antrum-predominant gastritis. Histological evaluation of gastric corpus specimens in these cases reveals limited chronic inactive inflammation and low numbers of superficially colonizing *H. pylori* bacteria. Subjects in whom acid secretion is impaired, due to whatever mechanism, have a more even distribution of bacteria in antrum and corpus, and bacteria in the corpus are in closer contact with the mucosa, leading to a corpus-predominant pangastritis (339). The reduction in acid secretion can be due to a loss of parietal cells as a result of atrophic gastritis, but it can also occur when acid-secreting capacity is intact but parietal cell function is inhibited by vagotomy or acid-suppressive drugs, in particular, proton pump inhibitors (PPIs) (339). The resulting active inflammation of the corpus mucosa further augments hypochlorhydria, paralleling the acute phase of infection, as local inflammatory factors such as cytokines, including interleukin-1 β (IL-1 β), have a strong suppressive effect on parietal cell function. This is illustrated by various observations. Firstly, *H. pylori* corpus gastritis is often associated with hypochlorhydria, and eradication therapy leads to increased acid secretion in these subjects (158, 533). Secondly, *H. pylori* corpus gastritis augments the acid-suppressive effects of PPIs (663). As a result, *H. pylori*-positive patients with gastroesophageal reflux disease (GERD) may respond somewhat faster to PPI treatment both with respect to symptom resolution and with healing of esophagitis (275), but this effect is minimal and largely irrelevant in daily clinical practice. This means that there is no general need to take *H. pylori* status into account when decisions on the dose of PPI treatment for GERD must be made. A third obser-

vation in support of the acid-suppressive effects of active corpus gastritis comes from more recent, important research showing that subjects with proinflammatory genotypes have a higher risk of corpus-predominant pangastritis, predisposing them to atrophic gastritis, intestinal metaplasia, and gastric cancer (157).

Although colonization with *H. pylori* is almost invariably associated with the presence of gastritis, and gastritis is mostly due to *H. pylori* colonization, other causes of gastritis include infections such as cytomegalovirus, chronic idiopathic inflammatory and autoimmune disorders such as Crohn's disease and pernicious anemia, and chemical damage due to alcohol abuse or nonsteroidal anti-inflammatory drug (NSAID) use.

Peptic ulcer disease. (i) Definitions. Gastric or duodenal ulcers (commonly referred to as peptic ulcers) are defined as mucosal defects with a diameter of at least 0.5 cm penetrating through the muscularis mucosa (Fig. 3B). Gastric ulcers mostly occur along the lesser curvature of the stomach, in particular, at the transition from corpus to antrum mucosa (661). Duodenal ulcers usually occur in the duodenal bulb, which is the area most exposed to gastric acid. In Western countries, duodenal ulcers are approximately fourfold more common than gastric ulcers; elsewhere, gastric ulcers are more common. Duodenal ulcers in particular occur between 20 and 50 years of age, while gastric ulcers predominantly arise in subjects over 40 years old.

(ii) Association with *H. pylori*. Both gastric and duodenal ulcer diseases are strongly related to *H. pylori*. In initial reports from all over the world in the first decade after the discovery of *H. pylori*, approximately 95% of duodenal ulcers and 85% of gastric ulcers occurred in the presence of *H. pylori* infection (338). Several cohort studies estimated that the lifetime risk

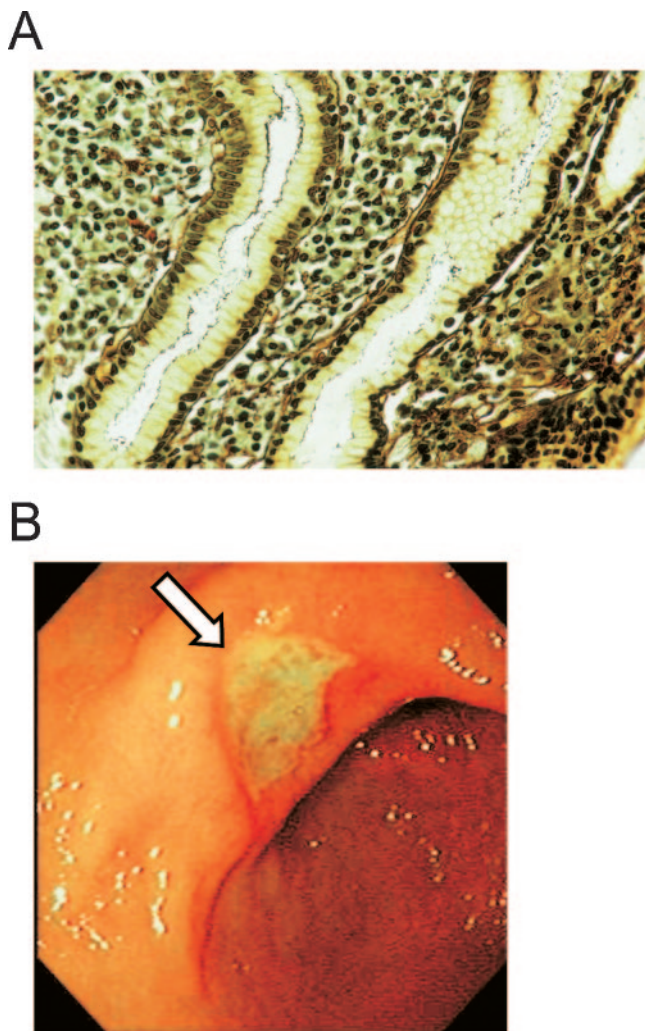


FIG. 3. (A) Gastric glands abundantly colonized with *Helicobacter pylori*, shown as dark, curved bacilli closely aligning with the mucosal surface. (B) Endoscopic view of a gastric ulcer, with a clean base at the angulus.

for ulcer disease in *H. pylori*-positive subjects is 3 to 10 times higher than in *H. pylori*-negative subjects (460) and that 10 to 15% of *H. pylori*-positive subjects developed ulcer disease during long-term follow-up (571; D. J. E. Cullen, J. Collins, K. J. Christiansen, J. Epis, J. R. Warren, and K. J. Cullen, abstract from the Digestive Diseases Week 1993, Gastroenterology **104**:A60, 1993). These data came from studies in developed areas of the world. It is unknown whether *H. pylori*-positive subjects in developing countries have similar disease risks. Introduction of *H. pylori* eradication regimens completed the evidence for a causal relation between *H. pylori* and ulcer disease by showing that eradication of this bacterium strongly reduced the risk of recurrent ulcer disease (522). This has had a major impact on the treatment and course of peptic ulcer disease in daily clinical practice. In earlier days, this disease was a chronic, recurrent disorder with high morbidity, frequently requiring acid-suppressive maintenance therapy or surgery. Approximately 50% of patients with *H. pylori*-associated peptic ulcer disease suffered ulcer recurrence within 1

year (268, 522). Eradication of *H. pylori* dramatically changes the natural course of ulcer disease and almost completely prevents ulcer recurrence (268, 522, 634, 645). Ulcer recurrences after *H. pylori* eradication therapy can be due to persistent or renewed *H. pylori* infection, use of NSAIDs, or idiopathic ulcer disease.

Ulcer development in the presence of *H. pylori* is influenced by a variety of host and bacterial factors. Ulcers mostly occur at sites where mucosal inflammation is most severe (661) (Fig. 4). In subjects with decreased acid output, this usually is the gastric transitional zone between corpus and antrum, giving rise to gastric ulcer disease. If acid production is normal to high, the most severe inflammation usually is found in the distal stomach and proximal duodenum, giving rise to juxta-pyloric and duodenal ulcer disease.

(iii) **Ulcer epidemiology.** The incidence of peptic ulcer disease has shown large variation over the past 150 years. In the late 19th century, the risk of developing peptic ulcers rose strongly in subsequent birth cohorts and then declined in subsequent generations. The birth cohorts with the highest risk of developing gastric ulcer were born 10 to 20 years before those with the highest risk of duodenal ulcer. Similar phenomena were found in Europe, the United States, Australia, and Japan (590, 591). It is assumed that the prevalence of *H. pylori* was high in these different geographic regions in the late 19th and early 20th centuries. The existence of a birth cohort phenomenon for peptic ulcer disease against a presumed background of high *H. pylori* prevalence implies that exogenous risk factors are responsible for the occurrence of peptic ulcer and that subjects are exposed to these risk factors during a limited period in childhood or early adulthood. Hypotheses regarding these factors focus on diet, living conditions, and occupation, related to industrialization in the 19th and 20th centuries. The incidence of peptic ulcers has steadily further decreased in Western countries in the last two decades; the current estimated annual incidence is on the order of two to three peptic ulcers per 1,000 individuals. The decreasing prevalence of peptic ulcers is thought to result both from strong reduction of the formerly large pool of patients with recurrent ulcer disease by *H. pylori* eradication at first presentation and from the decreasing prevalence of *H. pylori* infection in the population (336, 488, 531). The latter is related to several factors, such as improved hygiene and living conditions, decreased family sizes, and the use of antimicrobial therapy. As a result, the prevalence of *H. pylori* in patients with peptic ulcer disease is decreasing. In other words, as the incidence of *H. pylori*-associated ulcer disease decreases in relation to the decreasing prevalence of *H. pylori* infection, the role of this bacterium in ulcer disease becomes less prominent. This necessitates a proper diagnosis of *H. pylori* infection in ulcer patients, which contrasts with the formerly widespread policy of refraining from testing for *H. pylori* in ulcer patients. In areas where incidence is still high, ulcer patients may still receive *H. pylori* treatment without prior testing, as the chance of a false-negative diagnostic test is probably higher than the chance of an ulcer not being due to *H. pylori* infection. For most Western countries, however, recognition of the cause of ulcer disease in an individual patient is relevant for treatment choice and to determine the risk of disease recurrence during follow-up.

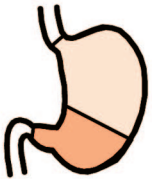

Pattern of gastritis	Gastric histology	Duodenal histology	Acid secretion	Clinical condition
 <p>Pan-gastritis</p>	<ul style="list-style-type: none"> • Chronic inflammation • Atrophy • Intestinal metaplasia 	<ul style="list-style-type: none"> • Normal 	<ul style="list-style-type: none"> • Reduced 	<ul style="list-style-type: none"> • Gastric ulcer • Gastric cancer
 <p>Antral-predominant</p>	<ul style="list-style-type: none"> • Chronic inflammation • Polymorph activity 	<ul style="list-style-type: none"> • Gastric metaplasia • Active chronic inflammation 	<ul style="list-style-type: none"> • Increased 	<ul style="list-style-type: none"> • Duodenal ulcer

FIG. 4. Acid secretion and the associated pattern of gastritis play an important role in disease outcome in *H. pylori* infection. The figure displays the correlations between the pattern of *H. pylori* colonization, inflammation, acid secretion, gastric and duodenal histology, and clinical outcome.

(iv) Ulcer complications. Complications of ulcer disease include bleeding, perforation, and stricture formation. Bleeding is the most common complication of ulcer disease and is estimated to occur in 15 to 20% of ulcers. Approximately 40% of patients presenting with upper gastrointestinal bleeding have a bleeding ulcer. Ulcer disease is thus the most important cause of upper gastrointestinal bleeding; the remainder of bleeding is caused by a wide variety of disorders, such as esophageal varices and esophagitis. The primary treatment for bleeding ulcer disease is endoscopic therapy, aimed at establishing the cause of bleeding; treatment of persistent bleeding; and estimating and reducing the risk of recurrent bleeding. Endoscopic therapy can be performed by several methods, including injection of adrenalin, coagulation with a heater probe, or clipping of the bleeding vessel. Subsequently, profound acid suppression by PPIs is indicated. After the acute phase, it is mandatory to establish the cause of the bleeding ulcer. Eradication of *H. pylori* strongly reduces the otherwise high risk of renewed bleeding ulcers in those patients in whom the ulcer bleeding was due to *H. pylori* infection (226, 370, 563). Ulcer perforation requires surgical therapy, after which acid suppression and eradication therapy in *H. pylori*-positive patients is required. Recurrent ulcer disease, in particular from the pyloric and bulbar region, can lead to scarring with stricture formation and gastric outlet obstruction. In such patients, underlying malignancy as a cause of the stricture must first be ruled out. Non-malignant *H. pylori*-associated strictures often respond well to eradication therapy alone, leading to the disappearance of inflammation with swelling and edema. Otherwise, additional endoscopic balloon dilation is required and, in refractory patients, surgery with either local reconstruction or distal gastric resection.

As mentioned previously, the incidence of uncomplicated peptic ulcer disease has strongly decreased over the past 25 years in relation to *H. pylori* prevalence and treatment. The

incidence of ulcer bleeding and perforations, however, has remained much more stable, presumably because a decrease in *H. pylori*-associated bleeding ulcers has been matched by an increase in NSAID-associated bleeding due to more widespread use, including over-the-counter use, and insufficient gastroprotection (282, 651).

(v) *H. pylori* and NSAIDs. *H. pylori* and NSAIDs are the major causes of gastroduodenal ulcer disease. Their potential interaction in the induction of ulcer disease remains a controversial area. A thorough analysis of interaction data revealed that the ulcer-inducing effects of both risk factors are cumulative (280). Eradication of *H. pylori* in chronic NSAID users decreases the incidence of ulcer disease. In a study from Hong Kong, patients starting with NSAID maintenance therapy were randomized to eradication therapy or placebo. After 6 months of follow-up, the incidence of ulcers was 12.1% (95% confidence interval [CI], 3.1 to 21.1) in the eradication group and 34.4% (95% CI, 21.1 to 47.7) in the placebo group ($P = 0.0085$). The corresponding 6-month probabilities of complicated ulcers were 4.2% (95% CI, 1.3 to 9.7) and 27.1% (95% CI, 14.7 to 39.5) ($P = 0.0026$), respectively (83). These data showed that, in an Asian population, screening and treatment for *H. pylori* infection significantly reduced the risk of ulcers for patients starting long-term NSAID treatment but also that eradication alone is insufficient to prevent ulcers and ulcer complications and thus is also insufficient as a gastroprotective measure in high-risk cases. Along this line, the same investigators showed in another study that *H. pylori* eradication was inferior to omeprazole maintenance treatment for prevention of recurrent NSAID-associated ulcer bleeding (82). Other investigators showed that *H. pylori* eradication is inferior to omeprazole treatment for healing of NSAID-associated ulcers (261). Based on these results, international guidelines on the management of *H. pylori* infection do not yet advocate a test-and-treat strategy in patients requiring long-term NSAID or aspirin

therapy, other than in patients with a previous history of ulcer disease prior to the start of NSAIDs.

Non-ulcer dyspepsia. Non-ulcer or functional dyspepsia is defined as the presence of symptoms of upper gastrointestinal distress without any identifiable structural abnormality during diagnostic work-up, in particular including upper gastrointestinal endoscopy. Uninvestigated dyspepsia is defined as the presence of dyspeptic symptoms for which no further diagnostic evaluation has been performed. Dyspeptic symptoms may have a reflux-like character, with heartburn and regurgitation as predominant signs; may appear dysmotility-like, with early satiety and nausea; or may be ulcer-like, with pain and vomiting. Together, these symptoms are very common; they are frequently experienced by 20 to 40% of the adult population of the Western world. Thirty to 60% of patients with functional dyspepsia carry *H. pylori*, but this prevalence is not much different from that in the unaffected population (615). Various studies have focused on the effect of *H. pylori* eradication in patients with both non-ulcer and uninvestigated dyspepsia. A meta-analysis of 13 randomized studies of non-ulcer dyspepsia showed that when dyspepsia outcomes were dichotomized into minimal/resolved versus same/worse symptoms, *H. pylori* eradication was associated with an 8% relative risk reduction compared to placebo (95% CI, 3% to 12%) (427). The calculated number needed to treat to cure one case of dyspepsia was 18 (95% CI, 12 to 48). Apart from the focus on cure of symptoms, cost efficiency is also an issue in treatment for larger groups of patients. With the reported number needed to treat, it remains as yet unclear whether *H. pylori* eradication is a cost-effective strategy. In a Canadian primary care study, *H. pylori* eradication, however, was reported to be more cost-effective after 1 year of follow-up than empirical diagnosis and treatment (88, 89).

Another Cochrane meta-analysis compared treatment strategies for uninvestigated dyspepsia (118). Individual strategies consisted of initial pharmacological therapy (with endoscopy for treatment failures), early endoscopy, testing for *H. pylori* and endoscopy only of those positive, or *H. pylori* eradication therapy with or without prior testing. The analysis showed that PPIs are effective in the treatment of dyspepsia. Early investigation by endoscopy or *H. pylori* testing benefited some patients with dyspepsia but was not cost-effective as part of an overall management strategy (118). A meta-analysis of five studies comparing prompt endoscopy followed by targeted treatment with an *H. pylori* test-and-treat strategy without further investigation reported that endoscopy was associated with a small symptom benefit at 1 year (relative risk, 0.95; 95% CI, 0.92 to 0.99), but this strategy was not cost-effective (190). In summary, *H. pylori* plays a role in the etiology of dyspeptic symptoms; thus, *H. pylori* test-and-treat strategies are effective for a subgroup of patients with dyspepsia. For patients with uninvestigated dyspepsia, an *H. pylori* test-and-treat strategy is an appropriate option, although empirical acid-suppressive therapy can be more efficient in populations with a low *H. pylori* prevalence. Also, in patients with investigated non-ulcer dyspepsia, *H. pylori* eradication is a relevant option. In both situations, patients must be aware that symptom resolution may take months after completion of therapy.

Atrophic gastritis, intestinal metaplasia, and gastric cancer.

Chronic *H. pylori*-induced inflammation can eventually lead to loss of the normal gastric mucosal architecture, with destruction of gastric glands and replacement by fibrosis and intestinal-type epithelium. This process of atrophic gastritis and intestinal metaplasia occurs in approximately half of the *H. pylori*-colonized population, first in those subjects and at those sites where inflammation is most severe (340). The risk for atrophic gastritis depends on the distribution and pattern of chronic active inflammation. As such, subjects with decreased acid output show a more rapid progression towards atrophy (334) (Fig. 4). Areas of gland loss and intestinal metaplasia extend with time multifocally, and although they do not give rise to any specific symptoms, they increase the risk for gastric cancer by 5- to 90-fold depending on the extent and severity of atrophy (570).

Evidence that *H. pylori* increases the risk of gastric cancer development via the sequence of atrophy and metaplasia originates from various studies, in which it was shown that *H. pylori*-positive subjects develop these conditions more often than do uninfected controls (332). This is supported by data that showed geographical associations between the prevalence of *H. pylori* and the incidence of gastric cancer (191, 623). On the basis of these findings, it was estimated that *H. pylori* colonization increases the risk of gastric cancer approximately 10-fold and *H. pylori* was designated a class I carcinogen by the WHO (289). Later case-control studies that looked more extensively into signs of previous *H. pylori* infection in gastric cancer patients and controls reported even higher odds ratios, up to 68, for development of distal gastric cancer in the presence of *H. pylori* infection (155). This is supported by data from animal models, most notably the Mongolian gerbil model, in which *H. pylori* infection induces atrophic gastritis and gastric cancer (277, 527, 685). The risk of development of atrophy and cancer in the presence of *H. pylori* is again related to host and bacterial factors, which influence the severity of the chronic inflammatory response. As such, the risk is increased in subjects colonized with *cagA*-positive strains (337, 489), but also in those with a genetic predisposition to higher IL-1 production in response to colonization (157). The lifetime gastric cancer risk among *H. pylori*-positive subjects is estimated to be approximately 1 to 2% in Western countries (331). In the developed world, 60% to 80% of gastric cancers are therefore related to the long-term presence of *H. pylori*. Interestingly, the incidence of gastric cancer has significantly decreased over the past decades in Western countries. This decrease parallels the aforementioned decrease in the prevalence of *H. pylori*. This is, however, a slow process over decades and generations and thus is not relevant for an individual subject who is *H. pylori* positive. Furthermore, in spite of the decline in gastric cancer incidence in Western countries, gastric cancer is the fourth most common cancer in the world, as the incidence of this disease remains very high in large areas of the world, particularly in regions of East Asia and South America (487). As a result of the persistent high gastric cancer incidence in these countries, with their expanding populations, it is expected that the current number of 850,000 gastric cancer cases diagnosed each year will further increase in the coming 20 years. For these reasons, much research now focuses on the cancer-preventive effect of *H. pylori* eradication, when aimed both at the general population and at patients with precancer-

ous conditions, particularly atrophic gastritis and intestinal metaplasia. To start with the latter, several placebo-controlled randomized studies have now reported that *H. pylori* eradication can halt the progression of these lesions and even to some extent induce a regression of atrophy (335, 360, 364, 421, 548). The effect of these interventions on gastric cancer prevention is, however, less evident. In several studies, *H. pylori* eradication had in the first years of follow-up no significant effect on gastric cancer incidence (360, 421, 693). In all of these studies, there was no significant difference between the eradication and placebo groups with respect to the incidence of gastric cancer in the first 4 to 12 years after treatment. The striking observation in all of these studies, however, was that those gastric cancers that occurred after eradication treatment were in particular confined to those subjects who already had atrophic gastritis and intestinal metaplasia at baseline. This suggests that the major cancer-preventive effect of *H. pylori* eradication is to be expected in subjects without those precancerous conditions; those with those conditions may at least in part already have passed the point of no return. If confirmed by other studies, this means that the observed regression of the severity of atrophy is of no direct relevance with respect to cancer risk. One study differed from the others in that it did observe a significant preventive effect of *H. pylori* eradication on gastric cancer development (614). The investigators monitored 1,120 patients in a nonrandomized study for a mean of 3.4 years (range, 1 to 8 years) after *H. pylori* eradication treatment. Gastric cancer developed in 8 of 944 patients cured of infection and in 4 of 176 who had persistent infection ($P = 0.04$ [log rank test]). The remarkable observation was that gastric cancers occurred only in patients with previous gastric ulcers and not in patients with former duodenal ulcers ($P = 0.005$ [Fisher's exact test]) (614). This is in line with the aforementioned hypothesis (Fig. 4) that gastric ulcer patients, in contrast to duodenal ulcer patients, are characterized by reduced gastric acid secretion, corpus-predominant pangastritis, and accelerated progression toward atrophic gastritis and intestinal metaplasia. Accordingly, previous studies have also shown that gastric ulcer patients are at higher risk for gastric cancer than are duodenal ulcer patients (255). The above-mentioned preventive studies, taken together, described cancer development in 29 (1.5%) of 1,896 subjects receiving placebo and in 25 (0.9%) of 2,754 subjects receiving eradication treatment, which would correspond to an odds ratio of 0.54 for cancer development after *H. pylori* eradication compared to placebo, suggesting that *H. pylori* eradication may decrease the risk for development of distal gastric cancer. Further studies are being performed in this field, the results of which will allow a more precise determination of the cancer-preventive effect of *H. pylori* eradication, whether or not atrophy and metaplasia are conditions beyond the point of no return, and the side effects and costs of such preventive measures. Gastric cancer prevention thus remains a major area of research on *H. pylori*.

Gastric MALT lymphoma. The gastric mucosa does not normally contain lymphoid tissue, but MALT nearly always appears in response to colonization with *H. pylori*. In rare cases, a monoclonal population of B cells may arise from this tissue and slowly proliferate to form a MALT lymphoma. The histological criteria for the diagnosis of MALT lymphoma and the differentiation from polyclonal reactive infiltrates remain con-

troversial. In particular, diagnosis is based on histological appearance during routine microscopy and on demonstration of clonality by immunohistochemistry or molecular techniques, such as PCR. Nearly all MALT lymphoma patients are *H. pylori* positive (154), and *H. pylori*-positive subjects have a significantly increased risk for the development of gastric MALT lymphoma (490). Because of the diagnostic controversies and the relative rarity of this disorder, the exact incidence in *H. pylori*-positive subjects is unknown, but MALT lymphomas occur in fewer than 1% of *H. pylori*-positive subjects (491). Randomized trials for the effect of *H. pylori* eradication in MALT lymphoma patients are therefore not feasible, but various case series reported that eradication can lead to complete remission in patients with stage IE MALT lymphoma confined to the stomach (120, 186, 451, 698). Overall, approximately 60 to 80% of these patients reach complete remission following *H. pylori* eradication, some 10% continue to have signs of minimal residual disease, and the remainder show no response or disease progression. The variation in response between different series may in part have been due to different criteria for the diagnosis of MALT lymphoma, potentially including some patients with benign lymphoid aggregates. Ten to 35% of those who initially reach complete remission after *H. pylori* eradication show recurrent disease during further follow-up. For that reason, long-term follow-up of MALT lymphoma patients is mandatory (518). A major predictor for response appears to be the presence of a t(11;18)(q21;q21) translocation. This translocation is associated with *API2-MALT1* fusion, the former being involved in regulation of apoptosis, the latter resembling a caspase-like protein, but with as-yet-unknown biological function. Together, the fusion leads to suppression of apoptosis. Several studies have reported that MALT lymphomas with this translocation do not at all or only rarely respond to *H. pylori* eradication (287, 371).

GERD. GERD has long been considered to occur independently of *H. pylori* colonization, i.e., to occur with the same frequency and severity in *H. pylori*-positive and *H. pylori*-negative subjects. This opinion was based on cross-sectional observations which suggested that the prevalence of *H. pylori* among GERD patients was similar to that among controls (689). However, further studies suggested that *H. pylori* might protect against the development of GERD and as such also be of benefit to their hosts. This slowly emerging concept came from repeated observations of a low prevalence of *H. pylori* among GERD patients, particularly of more virulent strains (174); opposing time and geographical trends for *H. pylori* prevalence compared with the incidence of GERD and its complications; a potentially increased incidence of GERD after *H. pylori* eradication (347); and the recognition that *H. pylori*-induced corpus gastritis reduced acid secretion. The hypothesis was that *H. pylori*-induced inflammation of the gastric corpus had an acid-suppressive effect, thus preventing patients from contracting GERD. For individual subjects, these insights so far have limited relevance other than that they underline the concept that eradication therapy should be prescribed only when there is a clear indication for *H. pylori* diagnosis and treatment. There is, with further data having become available, no evidence that *H. pylori* eradication has a considerable impact on either the new development of GERD (641), the worsening of preexisting GERD when treatment has been

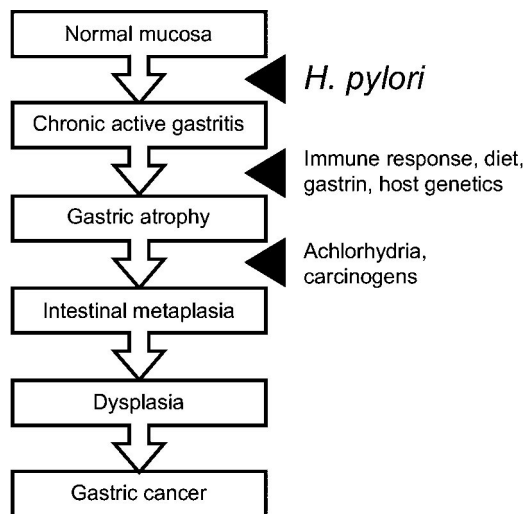


FIG. 5. Model representing the role of *H. pylori* and other factors in gastric carcinogenesis, based on the cascade proposed by Correa et al. (96).

withdrawn during disease remission (552), or preexistent GERD in remission during PPI maintenance therapy (335, 548). Together, these data show that although epidemiologic data suggest that there may be an inverse relation between *H. pylori* and GERD, the risk for new development or worsening of preexistent GERD is not an issue in the decision of whether or not to treat *H. pylori*.

Extragastric disorders. *H. pylori* has been linked to a variety of extragastric disorders. These include coronary heart disease, dermatological disorders such as rosacea and idiopathic urticaria, autoimmune thyroid disease and thrombocytopenic purpura, iron deficiency anemia, Raynaud's phenomenon, scleroderma, migraine, and Guillain-Barré syndrome. The underlying hypothetical mechanisms include chronic low-grade activation of the coagulation cascade, accelerating atherosclerosis, and antigenic mimicry between *H. pylori* and host epitopes leading to autoimmune disorders (214). This has led to large numbers of case studies of patients with these disorders. Several groups in particular have studied patients with idiopathic thrombocytopenic purpura and showed that when these patients are colonized with *H. pylori*, eradication therapy has a significant effect over placebo for improvement of thrombocyte counts (215, 291, 612). *H. pylori* testing and treatment should be considered for these patients. In patients with the other conditions mentioned above, there is as yet no role for *H. pylori* eradication, and further adequate, randomized trials are needed (37, 343, 358).

Histopathology

Infection with *H. pylori* results in a typical sequence of events, ultimately resulting in the development of gastric diseases. The sequence depicted in Fig. 5 was first suggested by Correa et al. (96) and has since been supported by many other studies. Colonization of the gastric mucosa by *H. pylori* first results in the induction of an inflammatory response, predominantly of the Th1 type. The initial acute gastritis is followed by

active chronic gastritis, which lasts for life if the infection is not treated (340). Nevertheless, *H. pylori*-positive subjects are mostly unaware of this inflammation due to the lack of clinical symptoms.

This inflammatory response is characterized by an influx of neutrophils, mononuclear cells, and T-helper 1 (Th1) cells, typically aimed at clearing intracellular infections (see "Immune Response," below). However, *H. pylori* is not an intracellular pathogen, and thus the Th1 response results in epithelial cell damage rather than in the removal of *H. pylori*. The ongoing presence of *H. pylori* thus causes a lifelong proinflammatory response coupled to cellular damage and initiates the histological cascade depicted in Fig. 5. The continuous production of reactive oxygen species that results from the ongoing inflammation can give rise to DNA damage, thus inducing the multiple mutations thought to be required for initiation of the cancer cascade (Fig. 5).

DIAGNOSIS AND TREATMENT

Diagnosis

Various tests have been developed for the detection of *H. pylori*, each with their specific advantages and disadvantages (Table 2). The available tests are generally divided into invasive tests, based on gastric specimens for histology, culture, or other methods, and noninvasive tests, based on peripheral samples, such as blood, breath samples, stools, urine, or saliva for detection of antibodies, bacterial antigens, or urease activity. The choice of a specific test for an individual patient depends on local experience and the clinical setting (for reviews, see references 372, 640, and 713). In research protocols, a combination of two methods is often applied. In daily clinical practice, use of a single test is generally adequate, and most tests are sufficiently accurate to be used for this purpose. For routine diagnostic purposes, histology, urea breath testing, and culture are currently most often used, whereas the use of serology is most appropriate for large epidemiological studies (Table 2). In hospital-based care, many patients undergo endoscopy, which is then combined with an invasive test for *H. pylori*. Otherwise, breath tests and serology are commonly used. For children, fecal antigen tests offer the opportunity to assess *H. pylori* status without the need for endoscopy or vena puncture (Table 2).

Treatment

Although *H. pylori* is sensitive to a wide range of antibiotics in vitro, they all fail as monotherapy in vivo. In infected patients, the most effective single drug is clarithromycin, which leads to an approximate eradication rate of 40% when given twice daily for 10 to 14 days (237, 409, 504). The lack of efficacy of monotherapy is related to the niche of *H. pylori*, residing at lower pH in a viscous mucus layer. Dual therapies, combining twice-daily-dosed PPI with, in particular, amoxicillin, are still in use in some countries, but dual therapies have mostly been replaced by triple therapies. These combine two antibiotics with either a bismuth compound or a PPI. A further alternative is provided by quadruple therapies, which combine the bismuth compound and PPI with two antibiotics. The exact mode

TABLE 2. Diagnosis of *H. pylori* infection

Diagnostic method	Sensitivity and specificity ^a	Typical application	Remarks
Invasive methods			
Histology	>95%	“Gold standard” in routine hospital diagnostics	Requires expert pathologist; also provides histological data on inflammation and atrophy
Culture biopsy	>95%	Alternative gold standard	Allows for testing of antimicrobial sensitivity; requires specific microbiological expertise
Rapid urease (CLO) test	>90%	Cost-effective and rapid test	Requires an additional test for confirmation of <i>H. pylori</i> infection
Noninvasive methods			
Urea breath test	>95%	Alternative gold standard	Very useful, reliable test to evaluate success of eradication treatment of <i>H. pylori</i> ; limited availability due to requirement of expensive equipment
Fecal antigen test	>90%	Not widely used yet	Simple test but may not be reliable for evaluation of success of eradication treatment of <i>H. pylori</i>
Serology	80–90%	Mainly used for epidemiological studies	Insufficient reliability for routine screening; cannot prove ongoing infection due to immunological memory

^a Global range, depending on regional variations and subjects.

of action of bismuth compounds is unknown, but *H. pylori* is susceptible to these compounds both in vivo and in vitro (23, 349, 667). Tetracycline, amoxicillin, imidazoles (predominantly metronidazole and tinidazole), and a few selected macrolides (in particular clarithromycin, sometimes azithromycin) are probably the drugs most widely used for *H. pylori* eradication therapy (412). Recently, the use of rifabutin (502, 503) and furazolidone (152, 173, 245, 699) has been promoted. However, as their effectiveness is limited and many patients do not tolerate furazolidone, the primary use of these two antibiotics is a second-line rescue therapy of patients harboring metronidazole-resistant isolates (227, 410, 486). Occasionally the use of ciprofloxacin and related fluoroquinolones (131, 192) and other antibiotics, such as rifampin and streptomycin (544), has been reported, but these drugs seem to have no serious advantages over the aforementioned ones. The use of these drugs has resulted in effective therapies against *H. pylori*, with consistent eradication rates over 80%. Various treatment durations, doses, and drug combinations have been studied, but none have consistently reached eradication levels in excess of 90 to 95%. Failures are in particular related to insufficient therapy adherence, often because of side effects, and to the presence of antimicrobial resistance. Such resistance is common in patients who have had previous antibiotic treatment, including failed eradication therapies (408).

Vaccination

In the past decade, much effort has been devoted to the development of alternative treatments for *H. pylori*, in particular, vaccination. Colonization of the stomach with *H. pylori* results in the induction of a strong but unprotective inflammatory response, mainly polarized toward Th1 cells (432). It is currently believed that effective vaccination depends on the induction of a humoral and Th2 cell immune response. Mucosal immunization with a variety of antigens in combination with mucosal adjuvants such as cholera toxin (AB5 toxin, CT), the heat-labile toxin of *Escherichia coli*, or Freund adjuvants,

which induce a Th2 response, prevents or cures an infection by *Helicobacter* spp., while Th1 response-inducing adjuvants enhance inflammation rather than eliminating it. The first indications that these mucosal immunizations against *Helicobacter* induce a Th2 response were seen in studies showing specific salivary secretory immunoglobulin A (IgA) and serum IgG1 antibodies after oral immunization of mice (183, 355). Subsequent studies (543) indicated that mucosal immunization with urease resulted in a Th2 CD4⁺ T-cell response that effectively eliminated an ongoing *Helicobacter felis* infection in BALB/c mice. Apparently, if a vaccine against *H. pylori* drives the immune response toward a Th2 response it can both prevent and eradicate *H. pylori* infections. Other indications for therapeutic use of *H. pylori* vaccines come from experiments with chronically infected animals, in which either a significant proportion could be cured of gastric *Helicobacter* infections or the effectiveness of antibiotic regimens was shown to be greatly enhanced (97, 106, 124, 224, 278). Thus, even in the absence of complete eradication, therapeutic vaccination may already be beneficial, as it reduces the numbers of bacteria exposed to antibiotics and thus decreases the possibility of inducing antibiotic-resistant *H. pylori* organisms. Although one should be aware of the limitations of animal models with regard to therapeutics, preliminary human vaccine trials have already been performed and further results are awaited (294, 310, 327, 425, 668).

Vaccines and antibiotics, however, are not the only means for prevention and cure of *H. pylori*-associated disease. Poor socioeconomic status, living conditions, and hygiene have been repeatedly demonstrated to be major risk factors for *H. pylori* infection and *H. pylori*-associated disease (269, 694). As a result, it is plausible to assume that improvements of these aspects could have a large preventive impact (660). There are indications that it may not be necessary to completely remove the bacterium in order to prevent disease. *H. pylori*-positive individuals who have concurrent helminth infection have standard *H. pylori* colonization and gastritis patterns, but they display significantly less *Helicobacter*-associated disease (132,

160). This suggests that the enteric helminth infection can modulate the host's immune system to attenuate *H. pylori*-induced gastric ulceration, atrophy, and cancer (196, 382). This is an intriguing concept that might result in administration of low doses of immunomodulating agents to *H. pylori*-positive patients.

Another approach would be to use probiotics. Probiotics prevent infection with pathogenic bacteria both through activation of the host's immune system and through direct competition of the probiotic bacteria with the pathogen. There is good evidence that *H. pylori* is killed by lactobacilli both in vitro and to a limited extent in vivo (24, 25, 76, 93, 373, 426, 540). It is unlikely that such an approach will lead to complete eradication of *H. pylori* bacteria in the stomach, but, as indicated above, complete eradication is not needed to prevent disease: either reduction of the amount of bacteria or altering of the immune response might result in a significant decrease in inflammation, thus reducing the induction of peptic ulcers and cancer.

In summary, antimicrobial triple and quadruple therapies remain the mainstay for therapy of *H. pylori* infections, with good efficacy but with failure in a minority of patients. Rescue therapies with alternative antimicrobial combinations are available. New treatment modalities, however, are awaited, in particular when eradication treatment is implemented for cancer prevention in certain regions of the world in the future.

PATHOGENESIS OF INFECTION

H. pylori-Associated Pathogenesis

The primary disorder, which occurs after colonization with *H. pylori*, is chronic active gastritis. This condition can be observed in all *H. pylori*-positive subjects. The intragastric distribution and severity of this chronic inflammatory process depend on a variety of factors, such as characteristics of the colonizing strain, host genetics and immune response, diet, and the level of acid production. *H. pylori*-induced ulcer disease, gastric cancer, and lymphoma are all complications of this chronic inflammation; ulcer disease and gastric cancer in particular occur in those individuals and at those sites with the most severe inflammation. Understanding of these factors is thus crucial for the recognition of the role of *H. pylori* in the etiology of upper gastrointestinal pathology.

Animal Models

Soon after Marshall and Warren had fulfilled Koch's postulates for *H. pylori* and acute gastritis via the infamous self-infection experiment (398, 401, 684), it was apparent that an animal model was required to allow elucidation of the mechanisms governing disease development and the pathogenic properties of *H. pylori*, as well as for testing the effects of treatment and vaccination on the pathogenesis of *H. pylori* infection. However, the choice of the most appropriate animal model has proven to be quite difficult, as all of the models used so far have deficiencies that may prevent translation to the human situation. As each model has its pros and cons, the choice of the most appropriate model is dependent on the hypothesis

that is being tested. Here we briefly discuss the most commonly used animal models for *H. pylori*.

Mouse. The mouse is the most widely used animal host for investigations of the pathogenicity of *H. pylori* and other bacteria. The murine immune response has been well documented, and many different knockout mice that lack specific components of the immune system are available. In addition, mice are readily available and their housing is relatively cheap. However, the mouse model has distinct limitations (reviewed in references 318, 477, and 512). *H. pylori* infection of many commonly used mouse strains results mostly in lymphocytic gastritis without progression to *H. pylori*-associated pathology, such as peptic ulcers or gastric cancer (318, 477, 512). Also, the architecture of the murine stomach is distinct from that of the human stomach and may lack components involved in the development of gastric pathology. Finally, the murine stomach is not sterile, in contrast to the healthy human stomach, and so other bacteria may influence the outcome of *H. pylori* infection (318, 477, 512). Therefore, the use of the mouse model is mostly restricted to testing the colonization properties of distinct *H. pylori* mutants.

Early studies of murine infection with *H. pylori* had to use either euthymic or nude mice, since wild-type mice could not be infected by *H. pylori* isolates (302). To be able to use wild-type mouse strains, an alternative mouse model that used *H. felis* infection of the mouse was put forward (352). The latter model has been extensively used since then, especially for testing of the efficacy of vaccination against *H. pylori* (477). Long-term colonization of the murine stomach by *H. felis* results in atrophic gastritis, as well as gastric and B-cell lymphomas, but development of adenocarcinoma has not yet been reported. However, *H. felis* is poorly characterized at the species level and difficult to manipulate genetically, and it has notable differences from *H. pylori*.

During the 1990s, several authors reported on the adaptation of the mouse model for *H. pylori* infection. To our knowledge, the first description of a successful infection of mice with *H. pylori* dates to 1994 (79); it was quickly followed by other reports (223, 393). Lee and coauthors (354) described the use of a mouse-adapted *H. pylori* strain (SS1) that is able to colonize the murine stomach. However, while SS1 does contain the virulence-associated *cag* PAI, this is probably nonfunctional (107). There are indications that there is a strong selection against the *cag* PAI during murine colonization (592), and this makes the mouse model a poor choice for studying the in vivo role of the Cag system in the pathogenesis of *H. pylori* infection. Recently, another mouse-colonizing strain has been described (SS2000) (625), but there is insufficient experience with this strain to judge whether it can replace the SS1 mouse model.

Colonization of the murine stomach by *H. pylori* and *H. felis* results in the development of lymphocytic gastritis, but it does not progress to peptic ulcer or gastric adenocarcinoma. There are, however, transgenic mice which are prone to the development of gastric cancer when given either a high-salt diet or chemical carcinogens, and infection with *H. pylori* decreases the time required for this (203, 679). For a more detailed overview of this subject, refer to recent reviews (477, 512).

Mongolian gerbil. As early as 1991, it was reported that *H. pylori* could colonize the gastric mucosa of Mongolian gerbils

(*Meriones unguiculatus*) (709); this animal model has advantages similar to the mouse model in ease of husbandry and animal size. Disadvantages of the gerbil model are the facts that gerbils are outbred and that defined knowledge of the immune system and tools for genetic mutations are lacking. Probably due to the availability of the aforementioned mouse model, the gerbil model was largely ignored until it became apparent that, in contrast to mice, long-term colonization of gerbils by *H. pylori* resulted in gastric pathology similar to that found in human subjects. This includes the development of peptic ulcers, intestinal metaplasia (274, 276, 402), and gastric adenocarcinoma (204, 277, 564, 607, 680, 685). Subsequently, the Mongolian gerbil model was validated by testing the colonization abilities of defined *H. pylori* mutants (692), and it has been used extensively since then for testing of bacterial colonization, identification of virulence factors, and determinations of the efficacy of treatment and vaccination (292, 306, 449, 461, 471, 512, 527). However, there is variability between laboratories regarding the development of gastric cancer in the Mongolian gerbil model (512), and the lack of a method for producing transgenic gerbils limits its value for determination of the role of the host in the development of *H. pylori*-induced gastric pathology.

Guinea pig. The guinea pig model of *H. pylori* infection was first described in the late 1990s (565, 600). The guinea pig model has advantages similar to the mouse model in ease of husbandry and animal size. In addition, the guinea pig stomach has several features in common with the human stomach, such as sterility, the production of IL-8, the lack of a nonglandular region, and the presence of a cylindrical epithelium (140, 309, 528). Furthermore, like humans, the guinea pig has a nutritional requirement for vitamin C. This may be relevant, as lowered vitamin C levels in humans are related to *H. pylori* infection (582). A limitation of the guinea pig model is that long-term colonization leads only to gastritis, without progression to peptic ulcer, lymphoma, or adenocarcinoma. Furthermore, rodent-adapted *H. pylori* strains are still required. Therefore, the use of the guinea pig model has been limited to testing the effects of *H. pylori* immunization and vaccination (140, 309, 528), vitamin supplementation (572), and the mutation of adhesins of *H. pylori* (114).

Gnotobiotic piglets. One of the important disadvantages of the models mentioned above is that the anatomy and architecture of the rodent stomach are notably different from those of humans. One of the first animal models for *H. pylori* was based on the gnotobiotic piglet (325). The pig is a monogastric mammal with dietary habits similar to those of humans, and it has a stomach with similar anatomical and physiological characteristics (325). Colonization of gnotobiotic piglets with *H. pylori* results in gastritis (146), but occurrence of gastric ulcers and MALT lymphoma has been reported (240, 324, 326). Many early studies of the role of virulence factors of *H. pylori* infection were performed with this model, such as those proving the importance of *H. pylori* urease activity and motility for gastric colonization (141, 150), as well as for other virulence factors (6, 142, 143, 147). It has also been used for testing antimicrobial therapies and vaccination (151, 323) but is currently no longer widely used.

Nonhuman primates. A natural choice for an animal model of *H. pylori* infection would be nonhuman primates, as these

are genetically the most related to humans. However, the use of this model has been limited due to the high cost of housing and limited availability of animals. A rhesus monkey model was described in the early 1990s (134, 135, 169, 584). Colonization of rhesus monkeys with *H. pylori* results in gastritis and a predominantly Th1 immune response (259, 403), and atrophic gastritis associated with p53 mutations has also been reported (447, 466), but the development of peptic ulcers or gastric cancer has not yet been reported. The model has been used for testing the efficacy of therapeutic intervention by antimicrobials (133), antiadhesion compounds (448), and vaccines (136), and it has permitted study of the role of mucins and Lewis antigens in adhesion of *H. pylori* (366, 387).

Role of *H. pylori* Virulence Factors

cag PAI. Although infection with *H. pylori* almost always results in chronic active gastritis, most infected patients develop no other complications and are free of any obvious clinical symptoms of this infection (57). This led to the notion that some strains may be more virulent than others. Early investigations of the differential pathogenic properties of *H. pylori* strains indicated that this increased pathogenicity correlated with the ability of these more virulent strains to induce morphological changes, vacuolization, and successive degeneration of in vitro-cultured cells (363). This activity was then linked to the presence of a protein with a molecular mass of approximately 140 kDa that was named CagA (for "cytotoxin-associated gene A"). The CagA protein is a highly immunogenic protein encoded by the *cagA* gene (99). This gene is present in approximately 50 to 70% of *H. pylori* strains (90, 103, 637) and is a marker for the presence of a genomic PAI of about 40 kb that, depending on the strain analyzed, encodes between 27 and 31 proteins (5, 80, 99). Strains carrying the *cag* PAI are referred to as CagA⁺ strains, as they are commonly identified in patients by their potential to induce significant antibody titers against the CagA marker protein. Patients infected with CagA⁺ strains usually have a higher inflammatory response and are significantly more at risk for developing a symptomatic outcome (peptic ulcer or gastric cancer) in Western populations (58, 337, 646), though not in Asian populations (42, 229, 253, 496). Although CagA⁺ strains are associated with more severe gastritis, and thus with a higher risk for ulcer disease, atrophic gastritis, and gastric cancer, strains lacking the *cag* PAI are also found in patients with peptic ulcers or gastric cancer, albeit at lower frequencies. To complicate matters even further, most CagA⁺ strains contain a complete and contiguous *cag* PAI (5), but a significant proportion of strains (~10%) carry an incomplete, and thus not fully functional, *cag* PAI (385, 646). The effect of this on disease outcome is still unclear.

Eighteen of the *cag* PAI-encoded proteins serve as building blocks of a type IV secretion apparatus, which forms a syringe-like structure capable of penetrating the gastric epithelial cells and facilitating the translocation of CagA, peptidoglycan, and possibly other bacterial factors into host cells (26, 92, 99, 187, 468, 469, 555) (Fig. 6). Once delivered inside the cell, the CagA protein is phosphorylated at tyrosine residues in EPIYA motifs (26, 273, 469, 555, 594) by Src family kinases (557, 593). Phosphorylated CagA then interacts with a range of host signaling

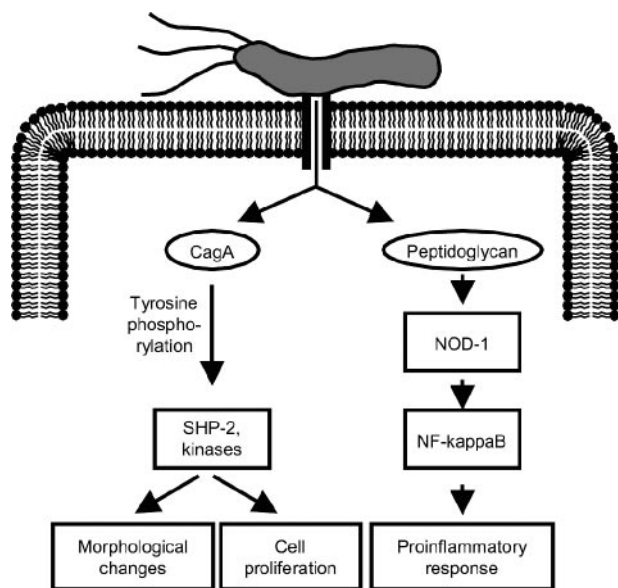


FIG. 6. Schematic representation of the different roles of the Cag type IV secretion system in immune modulation, cell proliferation, and morphological changes.

molecules, such as the tyrosine phosphatase SHP-2 (272, 707), which results in morphological changes in the epithelial cells (431, 455, 556) (Fig. 6). The details of these specific interactions have been the subject of many research papers; these details and their implications are discussed in several recent reviews (64, 260, 454), but they go beyond the scope of this review. The *cag* PAI also affects the immune response due to its ability to induce apoptosis of T cells (494, 678). The interaction between the type IV structure and the host cell also results in the induction of proinflammatory cytokines in epithelial cells (469, 555). Initially it was thought that the CagA protein itself induces these proinflammatory cytokines, but it is currently believed that CagA plays only a minor role, if any, in their activation (9, 187). They are most likely induced by peptidoglycan leaking into the eukaryotic cell as a result of the intimate interaction with the type IV structure (665) (Fig. 6), although it cannot be ruled out completely that the activation of the IL-8 signaling cascade results from the translocation of a thus-far-unknown bacterial factor (187).

Tyrosine phosphorylation occurs within the CagA EPIYA motif and is required for the binding of CagA to SHP-2 (27, 594, 636). There is considerable variation in the number of the EPIYA tyrosine phosphorylation motifs among the CagA proteins of different *H. pylori* isolates (33, 482, 593). The amount of tyrosine phosphorylation of CagA is directly associated with the number of repeats (22, 272). Strains possessing CagA with greater numbers of these repeats induce more pronounced morphological changes in cultured epithelial cells (22, 272) and have been associated with an increased risk of gastric carcinogenesis (33, 707). CagA also interacts with the C-terminal Src kinase via SH2 domains, leading to inactivation of the c-Src protein tyrosine kinases. As this kinase mediates the tyrosine phosphorylation of CagA, this inactivation leads to a reduction of CagA phosphorylation, thus providing a feedback loop regulating CagA activity (558, 636). Such host-pathogen cross talk

results in controlled virulence and may thus contribute to the lifelong colonization of the host.

VacA vacuolating cytotoxin. Approximately 50% of all *H. pylori* strains secrete VacA, a highly immunogenic 95-kDa protein that induces massive vacuolization in epithelial cells in vitro (102). The VacA protein plays an important role in the pathogenesis of both peptic ulceration and gastric cancer (29, 393, 471, 669). Although VacA is not essential for in vitro growth of *H. pylori*, it was reported to significantly contribute to murine gastric colonization by *H. pylori* (542).

The activities of VacA include membrane channel formation, disruption of endosomal and lysosomal activity, effects on integrin receptor-induced cell signaling, interference with cytoskeleton-dependent cell functions, induction of apoptosis, and immune modulation (Fig. 7) (101, 267). Although vacuolization is readily observed in vitro, it does not seem to occur in vivo (100, 101). The VacA protein is produced as a 140-kDa protoxin that is cleaved into the 95-kDa mature form when secreted. Although all strains carry a functional *vacA* gene, there is considerable variation in vacuolating activities among strains (100, 102, 113, 362). This is due to the sequence heterogeneity within the *vacA* gene (29, 647) at the signal region (s) and the middle region (m). The s region of the gene, which encodes the signal peptide, occurs as either an s1 or s2 type, whereas the m region, which contains the p58 cell binding domain, exists as an m1 or m2 type (647). Vacuolating activity is high in s1/m1 genotypes, intermediate in s1/m2 genotypes, and absent in s2/m2 genotypes (29). In line with this, *vacA* s1/m1 genotypes are more frequently associated with peptic ulceration and gastric carcinoma (29). Even within one specific patient-strain combination, the VacA expression levels differ over time due to the rapid evolution of the bacterium, which seems to be constantly adapting its genetic makeup to facilitate persistent infection (32, 175, 333). This microevolution also results in altered toxicity, and the constantly changing toxicity may (in part) explain the constant growing and shrinking of ulcers (32).

VacA forms pores in epithelial cell membranes, thus inducing the release of urea and anions from the host cells. It also increases transcellular permeability, leading to the release of nutrients and cations (436). Interestingly, a significant part of the secreted toxin is not released into the environment but remains associated with the outer membrane of *H. pylori* (188, 286). Upon bacterial contact with host cells, these toxin clusters are transferred to the host cell surface and exert their toxic action (286). This contact-dependent direct delivery mechanism suggests the involvement of specific receptors that mediate the bacterium-cell contact (188). However, such a receptor has not yet been identified. The specifics of the interaction of VacA with host cell receptors have been the subject of many research papers; their details and implications are discussed in several recent reviews (101, 217) but go beyond the scope of this review.

Secreted VacA can be further processed into a 33-kDa N-terminal fragment and a 55-kDa C-terminal fragment through proteolytic cleavage. The N-terminal protein performs an essential function in the formation of anion channels, while the C-terminal protein mediates cell binding (293, 314, 483, 633). In spite of the proteolytic cleavage, these fragments remain noncovalently associated with each other (621). Purified VacA spontaneously forms oligomeric aggregates (>900 kDa) and

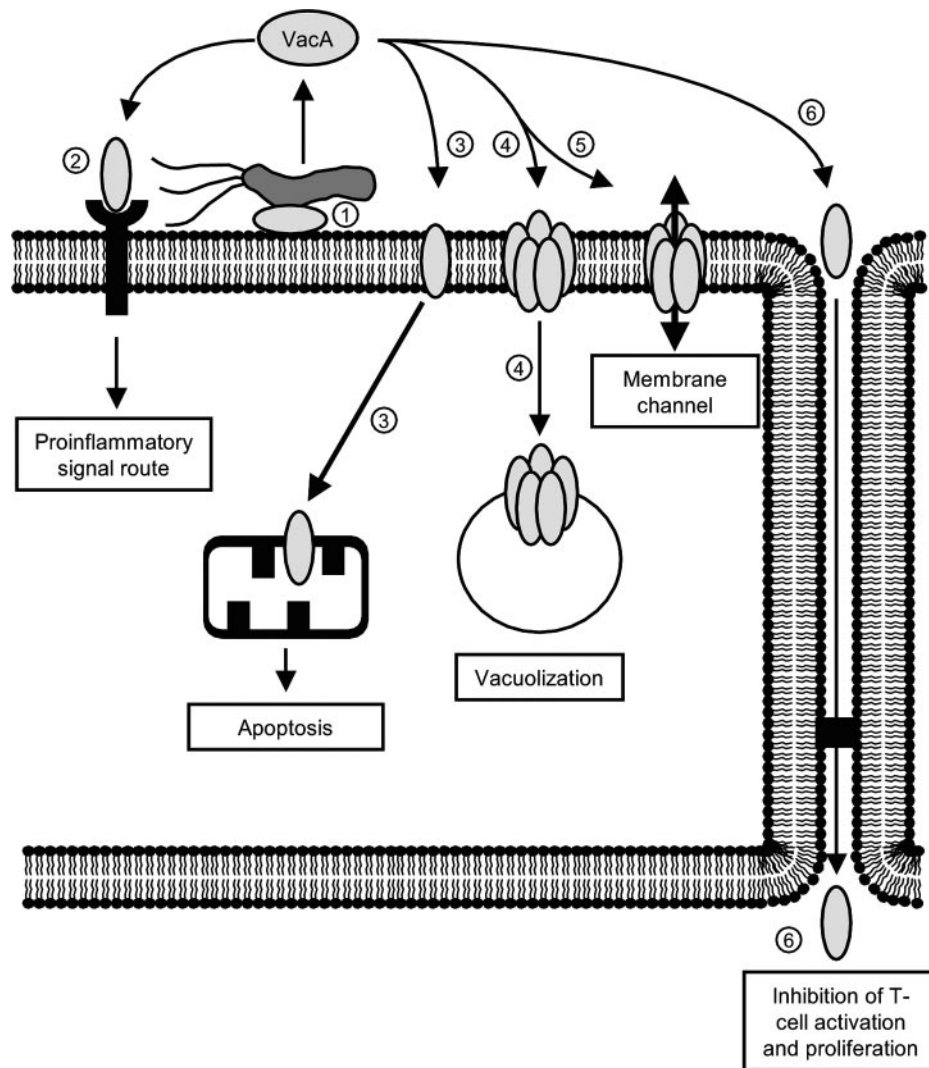


FIG. 7. The VacA protein influences cellular processes via different routes, thus assisting in chronic colonization of the gastric mucosa by *H. pylori*. (1) Surface-bound VacA may be directly delivered to the cell membrane. Secreted VacA may either (2) bind to a cell membrane receptor and initiate a proinflammatory response, (3) be taken up directly by the cell and be trafficked to the mitochondria and induce apoptosis, (4) be taken up by pinocytosis and induce vacuolization, (5) form a membrane channel, resulting in leakage of nutrients to the extracellular space, or (6) pass through the tight junctions and inhibit T-cell activation and proliferation. (Modified with permission from *Nature Reviews Microbiology* [101], copyright Macmillan Magazines Ltd.)

upon exposure to acidic pH disassembles into the active monomers that form pores in the cell membrane (104, 380, 436). This autoaggregation and subsequent acid activation have been claimed to be crucial for the toxic activity (434, 629) but are likely to be an *in vitro* artifact (286, 363, 498).

Although many of the VacA-mediated effects either directly or indirectly result from membrane binding and pore formation, VacA also enters the cytosol, subsequently accumulates in the mitochondrial inner membrane, and activates endogenous mitochondrial channels, thereby inducing apoptosis (105, 212, 329, 691). The proapoptotic effect of VacA is cell type dependent and may be limited to gastric epithelial cells such as parietal cells (61, 218, 457, 609). This may result in reduced acid secretion (317, 457), thereby predisposing for development of gastric cancer (Fig. 1 and 3).

Although many of the effects of VacA are described only for

gastric epithelial cells, secreted VacA does seem to penetrate into deeper tissues, where it can interact with other relevant cell types such as granulocytes, monocytes, B cells, and T cells. The interaction of VacA with these immune cells results in inhibition of antigen presentation and T-cell proliferation (Fig. 7) (435). Part of this activity is based on the active inhibition of lymphocyte activation (52). Unlike CagA, VacA does not seem to induce the apoptosis of T cells (218, 678). The proliferation of T cells, however, is severely reduced by VacA (61, 218, 609), adding an extra dimension to its functions in the pathogenesis of *H. pylori* infection.

There is a strong correlation between toxin activity and the pathogenicity of *H. pylori*, with the s1/m1 type of VacA being the most virulent in Western populations (29, 30, 244, 308, 647, 677). In contrast, such an association was not observed when Asian subjects were studied. Interestingly, the s1/m1 type of

vacA is clearly linked with the *cagA*⁺ genotype; thus, neither virulence marker can be considered an independent factor for disease outcome. This was confirmed by a recent study in which the *vacA* type alone was found to be a poor predictive marker for disease severity (704).

Acid resistance. One of the striking features of *H. pylori* is that it is able to colonize the acidic gastric environment, although the bacterium is not an acidophile. The pH of the gastric mucosa is thought to vary between 4 and 6.5, but occasional acid shocks may occur (547). *H. pylori* thus requires mechanisms to protect itself from acute acid shocks and mechanisms to grow at pH values around 5.5 (54, 595). Upon entry, *H. pylori* was originally thought to move rapidly toward the gastric mucus layer by chemotactic motility using the urea and bicarbonate gradients present in the gastric environment. Rapid movement toward the more neutral pH is required for *H. pylori*, since it loses its motility in the acidic gastric lumen (550). Interestingly, it was recently elegantly shown in a gerbil-based animal model that *H. pylori* does not use either the urea or bicarbonate gradient, since disturbance of either gradient did not affect the spatial orientation of *H. pylori* in the gastric mucus. However, when the pH gradient was disturbed, this resulted in a perturbation of the spatial orientation of *H. pylori* (551).

The main component of *H. pylori* acid resistance is the urease enzyme, which converts urea into ammonia and carbamate, which spontaneously decomposes into another ammonia molecule and carbon dioxide (70). Urease activity is present in all *H. pylori* isolates, although the levels of urease activity differ significantly between strains and are dependent on the growth conditions (95, 654). The ammonia produced by this reaction increases the pH. Initially it was thought that *H. pylori* neutralizes the microenvironment, since the urease enzyme is also associated with the outer membrane of *H. pylori* (595). However, it is unlikely that the outer membrane urease contributes significantly to acid resistance, as the urease enzyme is rapidly inactivated at this low pH (248, 535). Both the ammonia and bicarbonate produced by urease have been implicated in the pathogenesis of *H. pylori* infection. Ammonia is thought to have a cytotoxic effect on gastric epithelial cells (580), whereas bicarbonate is thought to suppress the bactericidal effect of peroxyxynitrite, a nitric oxide metabolite (345). Furthermore, the urease subunits UreA and UreB are immunodominant proteins and have been used for therapeutic vaccination by different routes (461, 662).

Cytoplasmic urease activity is under strict pH-mediated control, with the intracellular urea concentration being controlled by the H⁺-gated urea channel UreI (72, 553, 686). *H. pylori* produces large amounts of urease, and the expression of the urease subunits and accessory proteins is controlled at several levels, including the transcriptional, posttranscriptional, and posttranslational levels (2, 38, 73, 506, 554, 653–655, 658). Overall, the exact mechanism of the urease-mediated acid resistance of *H. pylori* is still under debate, as is summarized in several recent publications (72, 394, 536, 595, 596).

In contrast to the mechanisms involved in the resistance to acid shocks, relatively little is known about the mechanisms allowing growth under mildly acidic conditions (pH ~5.5). The chronicity of colonization, however, suggests that *H. pylori* is able to grow at mildly acidic pH. Growth at acidic pH induces

changes in LPS composition (407, 440, 620), increases the expression of chaperone-like proteins (281), and affects the expression of several genes at the transcriptional and protein expression levels (39, 54, 73, 422, 506, 577, 653). However, the exact roles in acid resistance of many of these factors are largely unknown.

Adhesins and outer membrane proteins. Many bacterial factors mediate the adhesion of *H. pylori* to the gastric epithelium (14, 153, 170, 296, 369, 452, 470, 628, 642). Given the narrow host range, the multitude of adhesins probably reflects their importance for the bacterium, but it makes it extremely difficult to test for the contribution of each individual adhesin. Thus, we concentrate here only on the three Hop proteins for which sufficient data are available to discuss their putative role in the pathogenesis of *H. pylori* infection. A noncomprehensive summary of these and several other less-characterized adhesins and outer membrane proteins, as well as their primary functions in virulence, is given in Table 3.

(i) **BabA (HopS).** The 78-kDa BabA protein probably represents the best-characterized *H. pylori* adhesion protein; it is encoded by the *babA* gene. BabA mediates binding to fucosylated Lewis b (Le^b) blood group antigens on the human host cells (63, 285). There are two distinct *babA* alleles, *babA1* and *babA2*, but due to a 10-bp insertion in the 3' end of the gene, only *babA2* can encode a full-sized (active) bacterial adhesion protein. Interestingly, the activity of the *babA* genes is modulated through recombination into the closely related *babB* locus (35) or by recombination with silent *babA* alleles (585). Animal studies suggest that BabA-mediated adhesion is relevant for the colonization and pathogenesis of *H. pylori* (246, 516). The majority of *H. pylori* bacteria reside in the gastric mucus overlying the epithelium. The colocalization of *H. pylori* with the MUC5AC gastric mucin suggests that adhesion is predominantly toward MUC5AC-specific ligands (643a). Recognition of the Le^b antigen by BabA seems to be a key factor in this site-specific colonization (367, 643), but additional epitopes and/or adhesins must be involved, as BabA binding to Le^b-negative MUC5AC of nonsecretors also occurred (643).

BabA is thought to have a role in the virulence of *H. pylori*, as the *babA2* allele is strongly associated with peptic ulcer disease and gastric adenocarcinoma (221), but this correlation is controversial (702). Although the distribution of the *babA* alleles may be associated with more severe disease (511, 516), the presence of the *babA2* allele is clearly linked to the *vacA* s1 and *cagA* alleles and thus again may not represent an independent disease marker (702).

(ii) **OipA (HopH).** The 34-kDa OipA protein is another member of the Hop protein family that may well serve as an adhesin but was originally identified as a proinflammatory response-inducing protein (705). The gene encoding the OipA protein is present in all *H. pylori* strains, but expression is modulated by phase variation via a variable number of CT dinucleotide repeats in the 5' region of *oipA* (705). Expression of OipA is strongly associated with increased *in vitro* and *in vivo* IL-8 expression, but since the OipA and CagA statuses are linked, this observation requires further study to assess the relative contribution of OipA in gastric inflammation (17, 702). As this gene has only recently been discovered, there is currently not much data on its relevance as a disease-specific marker.

TABLE 3. Adhesins and virulence-associated proteins of *H. pylori*

Protein/gene cluster	Predicted role	Association with <i>H. pylori</i> -related disease	Reference(s)
BabA	Binds to fucosylated Le ^b blood group antigen on cells	<i>babA2</i> allele has been implicated in peptic ulcer disease and gastric cancer	63, 221, 246, 285, 511, 516, 702, 703
SabA	Binds to sialyl-Le ^x and sialyl-Le ^a antigens and is involved in activation of neutrophils	None	117, 387, 639
SabB	Binding specificity is unknown	Absence of SabB expression via phase variation is associated with duodenal ulcers	117
OipA	OipA has been reported to assist in IL-8 induction, but this association is not universal	Expression of OipA is linked to <i>cag</i> status and development of duodenal ulcers and gastric cancer	16, 17, 246, 330, 705, 706
AlpA and AlpB	Inactivation of the <i>alpA</i> and <i>alpB</i> genes results in decreased adherence to gastric epithelial cells and absence of colonization in a guinea pig model	Unknown	114, 467, 470
HP-NAP	HP-NAP is reported to activate neutrophils and is a possible adhesin to mucin; possible function in protection of <i>H. pylori</i> DNA or iron storage	Unknown	172, 438, 439, 452, 631
Plasticity region (<i>jhp0947–jhp0950</i>)	Unknown	Presence of the plasticity region is associated with development of gastric cancer, MALT lymphoma, and duodenal ulcers	84, 115, 462, 463, 545
IceA	The <i>iceA1</i> allele encodes a CATG-recognizing restriction endonuclease	IceA1 has been associated with peptic ulcer disease, but this association is not universal	129, 185, 313, 495, 648, 700, 704
DupA	The <i>dupA</i> gene encodes a VirB4 ATPase homolog	Associated with duodenal ulcers but also with reduced risk for gastric atrophy and cancer	376

(iii) **SabA (HopP).** SabA mediates binding to sialic acid-containing glycoconjugates (387, 529). *H. pylori*-induced gastric inflammation and gastric carcinoma are associated with the replacement of nonsialylated Lewis antigens by sialylated Le^x and sialylated Le^a (387, 480, 541). Thus, the role of SabA is probably during the chronic inflammatory and atrophic disease stages (387). Human granulocytes also carry sialylated carbohydrates on their surface, and as a consequence these cells are specifically recognized by SabA. In vitro binding of *H. pylori* to granulocytes results in the nonopsonic activation of these cells (639), potentially allowing the bacterium to control these cells. SabA also seems to be involved in the binding of the extracellular matrix protein laminin (672a). This may promote an intimate association with the host cell that does not simply assist in evasion of the immune surveillance but might actually allow the bacterium to control the immune response through direct transfer of CagA, VacA, and other virulence factors.

LPS. The majority of *H. pylori* strains express LPS that contains fucosylated oligosaccharide antigens that are structurally and immunologically closely related to human blood group antigens. These bacterial antigens (Lewis antigens) display marked antigenic variation and are thought to contribute to immune evasion. Initially thought to mediate cell adhesion, current data indicate that Lewis antigens seem to have only a limited role in adhesion (386) and colonization (613). The finding that Lewis antigen expression enhances bacterial internalization by epithelial cells (374) suggests that Lewis antigen

expression potentially affects the innate immune response. *H. pylori* LPS stimulates NF- κ B and IL-8 production in both epithelial cells and immune cells in a CagA-independent manner (53, 359, 384), but the NF- κ B activation observed in epithelial cells upon stimulation with *H. pylori* is not mediated by LPS (445). Compared to other gram-negative bacteria, the LPS of *H. pylori* is a poor activator of the innate immune response (59, 446). As a consequence, *H. pylori* LPS is unlikely to represent a major factor in the immune activation by *H. pylori*. It is unclear whether the ability to mimic a wide range of host blood group antigens through phase variation of the Lewis antigenic determinants carried by the LPS either promotes gastric autoimmunity (15) or even further attenuates the immune-stimulatory effects of LPS. Bacterial expression of Lewis antigens similar to self-epitopes is thought of as a form of molecular mimicry, possibly contributing to bacterial persistence through immune evasion (19, 437). This mimicry has been suggested to lead to the induction of promoting autoantibodies, e.g., against the Lewis antigen-containing gastric proton pump of the parietal cells. Gastric H⁺/K⁺-ATPase activities, however, are not associated with *H. pylori* status in patients, nor do they seem to increase upon *H. pylori* eradication (627). Although both antibodies against parietal cells (51, 638) and Th1 cells that recognize the cross-reactive epitopes shared by the H⁺/K⁺-ATPase and *H. pylori* (15) have been observed in a minority of infected patients, these apparently do not result in significant

gastric autoimmunity, as disease does not seem to be more pronounced in these patients.

Immune Response

Role of antibodies in protective immunity. Based on analogy with other mucosal infections, it was initially assumed that a protective immune response against *H. pylori* would predominantly be mediated by antibodies. Reports on a good correlation between the presence of *H. pylori* antibodies in the milk of Gambian mothers and the absence of *H. pylori* infection in their breast-fed children (624) supported this assumption. Early animal experiments also seemed to confirm this line of reasoning (110, 321). Subsequent experiments have indicated that the relevance of the humoral system for protective immunity is only marginal. Antibodies can effectively prevent infection and reduce colonization in animal models (396, 461).

H. pylori infection results in an induction of a Th1-polarized response that does not result, however, in clearance of the infection (368, 432, 581). This is striking, as it is the cellular rather than the humoral immunity that has been reported to play the principal role in sterilizing immunity (149, 164, 485, 610), although it is now generally accepted that the development of *H. pylori*-induced gastritis and/or pathology depends predominantly on Th1 cells and Th1 cytokines (196, 265, 432, 581, 588, 597). Although a Th2-polarized response protects against this specific pathology, this does not necessarily imply that Th2 cells are responsible for protection after immunization. In fact, Th1-polarized, rather than Th2-polarized, T cells recruit mononuclear cells to the site of infection, resulting in elimination of the bacteria (3, 119, 249, 581, 589).

Immune modulation. *H. pylori* infection always results in a strong immune response of the host against the infecting strain, but this response seldom (if ever) results in clearance of the infection. It can even be argued that much of the pathology associated with *H. pylori* infection results from the activities of the host's immune system rather than from direct bacterial activity. *H. pylori* is thought to downregulate inflammation and control the host's immune response through a wide range of virulence factors that are involved in both provoking and maintaining a proinflammatory immune response. Transfer of unfractionated splenocytes from *H. pylori*-infected mice induces gastritis, delayed-type hypersensitivity, and even metaplasia in mice (148), providing support for *H. pylori*-induced pathology being predominantly a T-cell-mediated disease. This adaptive immune response is initiated and maintained by monocytes and Th1 lymphocytes rather than by epithelial cells. This is because the differentiation of naive T cells into activated Th1 cells requires the presence of IL-12, which is predominantly produced by mononuclear cells. The presence of *H. pylori* in the gastric mucosa is associated with strong IL-12 production (303) and the presence of large numbers of Th1 cells (424). Although *cag* PAI-induced peptidoglycan transfer does result in IL-12 induction, the key virulence factors, such as CagA and VacA, do not represent major factors in this induction (665). This implies that the mechanisms involved in the production of cytokines by monocytes clearly differ from that of gastric epithelial cells, and these new insights offer new angles for creating protective immunity.

Activation of the innate immune response. Toll-like receptors (TLRs) on epithelial cells recognize and react to semiconserved bacterial products such as flagella (TLR5), peptidoglycan (TLR2), CpG motifs (TLR9), and LPS (TLR4) (279). The obvious cue for intracellular pathogens is the presence of such antigens within the cell, but apparently extracellular bacterial pathogens such as *H. pylori* are also recognized and can be discriminated from commensal organisms (179, 279). While for most gram-negative pathogens, TLR4-mediated recognition of bacterial LPS is a key activator of the innate immune response in epithelial cells, *H. pylori* LPS is a relatively weak inducer. *H. pylori* LPS does activate NF- κ B, but this is via TLR2 rather than via TLR4 (34, 384, 579). Although TLR4 is involved in the induction of an immune response against *H. pylori* (307), TLR2 and TLR5, rather than TLR4, seem to be the predominant receptors for *H. pylori* antigen-induced NF- κ B activation and chemokine expression in the cells of the gastric mucosa (123, 391, 579, 632). However, compared to other gram-negative bacterial antigens, TLRs seem to play only a minor role in the induction of the innate immune response against *H. pylori* (222, 356, 384, 441). TLR-independent mechanisms seem to predominate in the activation of the innate response against *H. pylori*, as, e.g., the recognition of the bacterial heat shock protein Hsp60 is not mediated via these TLRs (230).

The intracellular peptidoglycan, transferred into the cytoplasm by *cag* PAI-mediated contact between the epithelial cell and the bacterium, may be a key activator of the innate response against *H. pylori* (665). This intracellular peptidoglycan is recognized by Nod1 (665), a member of the recently discovered Nod family. Two members of this protein family, Nod1 (also known as CARD4) and Nod2 (CARD15), are involved in the recognition of bacterial peptidoglycans and seem to act as intracellular (Nod1) and extracellular (Nod2) receptors for gram-negative bacteria in epithelial cells (81, 288). A mouse model of *H. pylori* infection provides data that indicate that the in vitro-observed Nod1-mediated activation of the innate immune system is also important in vivo (665). Thus, at least for *cag* PAI-positive *H. pylori* strains, the Nod1-mediated signaling seems to be a key factor in the recognition and subsequent activation of the proinflammatory response in gastric epithelial cells (665). However, only some of the *H. pylori* cells in the mucus layer actually attach to the gastric epithelial cells (63, 703); thus, differences in adhesion mediated by *H. pylori* properties and differences in host cell receptors may well influence the degree of inflammation mediated by *H. pylori* infection. This may have an important effect on the subsequent development of gastritis and disease.

Resistance to phagocytosis and modulation of dendritic cell activity. Although the gastric mucosal recognition of *H. pylori* is positively affected by the presence of the *cag* PAI, it does not involve CagA. NF- κ B activation, and consequently IL-12 induction by macrophages/monocytes, even seems to be completely independent of *cag* PAI (116); in contrast to epithelial cells, however, it does involve CD14 and TLR4 (34, 384, 601). *H. pylori* infection results in upregulation of MIP-3 α gene expression in gastric epithelial cells, thus inducing an influx of monocytic cells into the lamina propria of the gastric mucosa (458). These cells may be functionally impaired, as *H. pylori* is capable of inhibiting phagocytosis by macrophages through an as-yet-unknown pathway (11, 12, 520, 521). This not only re-

TABLE 4. Genetic polymorphisms and *H. pylori* infection

Polymorphism site	Effect	Association with <i>H. pylori</i> infection	Reference(s)
Immune mediators			
IL-1 gene cluster	IL-1B*-511T, IL-1B*-31C, and IL-1RN*2/*2 result in higher IL-1B expression	Higher expression of IL-1B results in a proinflammatory response coupled to hypochlorhydria, pangastritis, and increased risk of atrophic gastritis and gastric cancer	156, 157, 159, 208, 283, 383, 517, 715
IL-8 (-251A/T)	Presence of the -251A allele results in increased expression of IL-8	In a Japanese population, increased risk of gastric cancer and gastric ulcer; in a Hungarian population, increased risk of duodenal ulcers	247, 250, 377
IL-10 (ATA/GCC haplotypes)	GCC haplotype results in increased expression of IL-10	GCC haplotype is associated with colonization by more-virulent <i>H. pylori</i> strains (<i>cagA</i> ⁺ , <i>vacA</i> s1 ⁺ , and <i>babA2</i> ⁺); ATA haplotype is associated with increased risk of gastric cancer	159, 250, 264, 377, 515, 697, 714
TNF-A	TNF-A*-308A allele is associated with increased TNF- α expression and increased gastrin expression	TNF-A*-308A is associated with higher levels of <i>H. pylori</i> infection and increased risk of gastric cancer	159, 252, 365, 375, 383, 696, 708, 714
MPO	MPO*-463A allele is associated with low-level expression of myeloperoxidase	MPO*-463A genotype is associated with lower <i>H. pylori</i> infection rates	251
Other			
CD14	CD14*-159T polymorphism results in elevated expression of CD14	CD14*-159T genotype is associated with higher <i>H. pylori</i> infection rates	301, 319
TLR4	TLR4*Asp299Gly results in diminished immune response	TLR4*Asp299Gly allele may be involved in development of gastric MALT lymphoma	263
FUT2 and FUT3	Polymorphisms in the fucosyltransferase genes affect synthesis of Lewis antigens	FUT2 secretor (Se) and FUT3 le/le genotypes increase risk of <i>H. pylori</i> infection	284, 559
CYP2C19	Polymorphisms in cytochrome P450 influence metabolism of compounds such as antibiotics and PPIs	CYP2C19 polymorphism negatively affects eradication rates of <i>H. pylori</i> antibiotic treatment	209–211, 315, 537, 538
GST t1/m1	GST t1 null and m1 null alleles are associated with decreased antioxidative capacity	GST t1 null genotype is associated with increased risk of gastric cancer and gastric lymphoma	86, 304, 305, 484, 530, 560, 711

sults in reduced anti-*H. pylori* activity of the macrophages but more importantly results in decreased and altered processing of *H. pylori* antigens by activated macrophages (dendritic cells). Since the activation of B and T cells is dependent on the presentation of *H. pylori* antigens by dendritic cells, this is of crucial importance for the outcome of the immune response. Although the exact mode whereby *H. pylori* mediates this effect is unknown, the dendritic cell-specific surface receptor C-type lectin ICAM-3-grabbing nonintegrin (DC-SIGN; CD209) may be involved. DC-SIGN is known to act as a receptor for some pathogens, such as human immunodeficiency virus type 1 (219, 650), and can also act as a ligand for *H. pylori*, as binding of *H. pylori* to monocytic cells can be blocked with anti-DC-SIGN monoclonal antibodies (21). DC-SIGN recognition seems to require the presence of the Lewis blood group determinants on the LPS, as only *H. pylori* variants that carry the Lewis blood group determinants (Le⁺) bind to DC-SIGN (50). This leads to a Le⁺-specific blocking of Th1 cell activation and IL-6 production (21). Lewis antigen is prone to phase variation; hence, there will always be a significant proportion of Le⁻ variants within an isolate, and as this fraction increases, the inhibition of the Th1 cell response is reduced. Interestingly, *H. pylori* preferentially induces IL-12—not IL-6 or IL-10, as most

other extracellular bacteria tend to do—in human dendritic cells (243).

Regulatory T cells. IL-10-producing T cells seem to be crucial in the control of *H. pylori*-induced inflammation and enable the bacterium to persist in the gastric mucosa. For example, *H. pylori* is unable to persist in IL-10 knockout mice (87, 290). CD25⁺ regulatory T cells probably play a key role in this, as mice lacking CD25⁺ cells developed more severe gastritis while having reduced bacterial loads in the gastric mucosa (519). Similarly, removal of CD25⁺ cells from *H. pylori*-positive volunteers resulted in increased in vitro proliferation and gamma interferon production, indicating that *H. pylori* infection results in downregulation of the immune response through interaction with regulatory T cells (599).

Contribution of Host Genetics

It has become apparent that not only the characteristics of the pathogen but also host genetics play an important role in determining susceptibility to and severity of infections. Genetic polymorphisms can directly affect the expression levels of gene products by generation or deletion of transcription factor sites or by affecting RNA splicing and subsequent translation. Al-

ternatively, they can either influence the metabolism of certain compounds or indirectly affect the expression of immune mediators downstream of the gene with the specific polymorphism.

In recent years, a large body of evidence demonstrating the importance of host genetic polymorphisms in *H. pylori*-related diseases has been generated; this evidence is summarized in Table 4. Early studies focused on the role of certain mutations in the gene encoding cytochrome P450, which affects the metabolism of PPIs and antibiotics and thus influences the efficacy of eradication treatment of *H. pylori* (reviewed in reference 211), and on mutations in genes encoding antioxidative proteins such as glutathione *S*-transferase (GST) (86, 304, 305, 484, 530, 560, 711). However, these mutations do not directly affect *H. pylori* colonization.

Many of the pathogenic effects of *H. pylori* infection are related to chronic active inflammation, which is controlled and maintained by the complex interplay of proinflammatory and anti-inflammatory mediators (381). Many genetic polymorphisms that affect the expression levels of these inflammatory mediators have been described, and their role in *H. pylori*-related gastric disorders has been shown in recent years in many independent studies (Table 4). Overall, it can be concluded that proinflammatory genetic polymorphisms tend to increase the risk of development of gastric cancer, as has been elegantly shown for IL-1.

IL-1. The level of gastric acid secretion (Table 4; Fig. 4) and the presence of a proinflammatory response contribute significantly to the development of either duodenal ulcer disease or atrophic gastritis (Fig. 4). The IL-1 cytokine is encoded by a gene cluster that contains the polymorphic IL-1B (encoding the IL-1 β cytokine) and IL-RN (encoding the IL-1 receptor antagonist) genes. IL-1 β is a potent proinflammatory cytokine and the most potent known inhibitor of acid secretion (75, 157). The IL-1 gene cluster contains several polymorphisms, such as IL-1B*31C, IL-1B*511T, and IL-1RN*2/*2, which lead to high-level expression of IL-1 β . This subsequently leads to reduced acid output, which is associated with corpus-predominant colonization by *H. pylori*, resulting in pangastritis, formation of atrophic gastritis, and increased risk of gastric cancer (156, 157, 159, 208, 283, 383, 517, 715).

Other cytokines. Similar effects have been observed for polymorphisms in other inflammation-associated genes (Table 4), e.g., the genes encoding tumor necrosis factor alpha (TNF- α) and IL-10. TNF- α is a proinflammatory cytokine, and several polymorphisms in the TNF-A gene are known. The TNF-A*308A genotype is associated with increased TNF- α production, which, together with IL-1, influences gastrin production and thus acid production by gastric parietal cells (611). The TNF-A*308A genotype is therefore associated with *H. pylori* infection and increased risk of gastric cancer (159, 472, 515, 708, 714). Similarly, expression of the anti-inflammatory cytokine IL-10 is affected by the haplotypes described for the IL-10 gene. The GCC haplotype is associated with a higher expression level of IL-10 and hence favors an anti-inflammatory response, whereas the ATA haplotype results in lowered IL-10 levels and a shift toward a proinflammatory response (159, 250, 264, 377, 515, 697, 714). The GCC haplotype is associated with colonization with more-virulent *H. pylori* strains (515), whereas the ATA haplotype is associated with increased risk of gastric

cancer (159, 250, 264, 377, 697, 714). Interestingly, several independent studies have shown that while single polymorphisms may increase the risk of development of gastric cancer only two- to threefold, the presence of multiple proinflammatory genotypes increases this risk substantially (159, 377, 381, 383, 515, 714).

Overall, it is difficult to attribute the increased risk of development of gastric cancer to a specific polymorphism, as infection with *H. pylori* is an essential component in the equation (513, 517, 715). Rather, it is the interaction between the different pro- and anti-inflammatory polymorphisms, the immune status of the host, and the characteristics of the colonizing *H. pylori* strain that jointly determine disease outcome.

CONCLUSIONS

The role of *H. pylori* in gastroduodenal disease has become firmly established. Two decades of intense research into *H. pylori* virulence factors such as the VacA and CagA proteins have revealed many aspects of the relationships between this bacterium, the gastric mucosal surface, and the induction of disease. Disease outcome is the result of the intricate, ongoing interplay between environmental, bacterial, and host factors. Strain-to-strain genetic variability in bacterial virulence factors such as *vacA* and *cagA* not only affects the ability of the organism to colonize and cause disease but also affects inflammation and gastric acid output. In the continuous interactions with the host, the bacteria are able to adapt by mutations and DNA rearrangements, rendering novel genotypes. On the host side, variations in the host immune response to the chronic presence of *H. pylori* directly impact *H. pylori*-associated gastric disease and affect gastric acid output and thereby the density and location of *H. pylori* cells. Many of these *H. pylori*-host interactions have similarities with the interactions between the gut flora and the gastrointestinal tract and may serve as paradigms for the interactions between bacteria and their hosts.

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