account for the decline in the rate of infection. *H. pylori* colonization is more common in individuals in lower socioeconomic strata compared with other groups. In the developing world, infection is far more common, with more than 80% of the population being infected by age 20 years. *H. pylori* infection is typically lifelong unless antimicrobial treatment is instituted.

H. pylori organisms reside in the mucus layer overlying gastric epithelium and are characterized as noninvasive organisms. Factors important in the organism's ability to colonize the stomach include its motility, the production of urease, and bacterial adherence. Ammonia generated from urea by *H. pylori* urease neutralizes acid, creating a more hospitable microclimate in which the bacteria can survive. *H. pylori* also have the ability to bind specifically to gastric-type epithelium, which prevents the organisms from being shed during cell turnover, mucus secretion, or gastric motility. Tissue injury is mediated by the production of lipopolysaccharide, leukocyte-activating factors, and vaculolating toxins, which have been associated with cytotoxic effects, inflammation, and cytokine activation. About 65% of *H. pylori* isolates produce a vacuolating toxin. Toxin-producing strains may be more pathogenic than those that do not produce toxins, and their presence correlates with a more intense polymorphonuclear cell infiltration. A cytotoxin-associated gene *(cagA)* is a marker for strains that make the vacuolating toxin, and patients infected with *cagA*-positive strains are more likely to develop ulcers (Fig. 36-3). Colonization causes acute and chronic inflammation consisting of neutrophils, plasma cells, T cells, and macrophages accompanied by varying degrees of epithelial cell injury, all of which resolve after effective treatment.

Although predicting the ultimate outcome of *H. pylori* infection is impossible, the clinical manifestations can be correlated with the distributions of gastric histopathologic states. Antral-predominant *H. pylori* gastritis is associated with duodenal ulcers; individuals infected with *H. pylori* have been shown to have a diminished number of somatostatin-secreting D cells, which decreases the magnitude of the response to luminal acidification. Thus, in patients with *H. pylori* infection limited to the antrum, the negative inhibition of gastrin release is disrupted, resulting in higher postprandial gastrin levels and hypersecretion

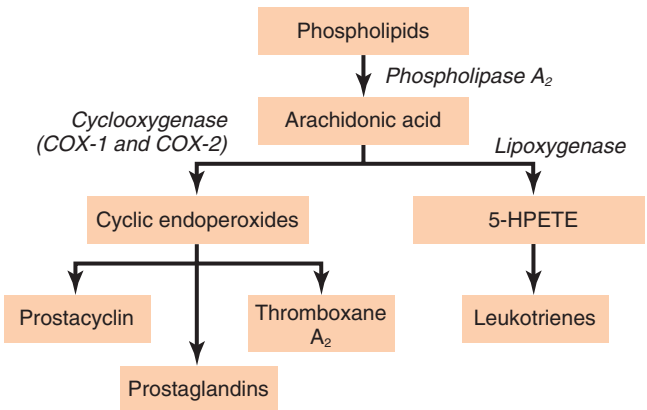

FIGURE 36-3 Mechanisms by which *Helicobacter pylori* may cause gastric ulcers **(A)** and duodenal ulcers **(B).** IL-8, interleukin-8. (From Peek RM, Blaser MJ: Pathophysiology of *Helicobacter pylori*–induced gastritis and peptic ulcer disease, Am J Med 102:200-207, 1997.)

of acid. Corporal and fundic colonizations, by contrast, are more likely to cause atrophic gastritis.

Other important factors that may influence the outcomes of the infection include the host response, environmental factors, and age at the time of infection. Virtually all patients with *H. pylori* infection have a chronic superficial gastritis; however, duodenal and gastric ulcers develop in only 20% of infected patients. Patients with *H. pylori* infection and severe atrophic gastritis, corpus-predominant gastritis, or both, along with intestinal metaplasia, are at increased risk for intestinal-type gastric cancer. Finally, the mucosal lymphocytic response to *H. pylori* infection may lead to a monoclonal B-cell proliferation in mucosa-associated lymphoid tissue (MALT). MALT lymphomas, also known as *maltomas*, are rare, with about 1 in 1 million infected patients developing the disease. Complete histologic regression has been demonstrated in 50% to 80% of maltomas following eradication of *H. pylori.* Flat, localized, nonbulky lesions of the distal stomach are associated with greater rates of cure after antibiotic therapy.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs are one of the most widely used classes of drugs. Although generally well tolerated, NSAIDs are associated with a small but significant percentage of adverse gastrointestinal (GI) events. Concepts regarding NSAID-induced gastroduodenal mucosal injury have evolved from a simple notion of topical injury to theories involving multiple mechanisms by which NSAIDs induce both local and systemic effects. According to the dual-injury model, NSAIDs have direct toxic effects on the gastroduodenal mucosa and indirect effects through active hepatic metabolites and decreased synthesis of mucosal prostaglandins. Hepatic metabolites are excreted into the bile and subsequently into the duodenum, where they may cause mucosal damage to the stomach by duodenogastric reflux and to the small intestine by antegrade passage through the GI tract. Prostaglandin inhibition, in turn, leads to reduction in epithelial mucus, decreased secretion of HCO_3, impaired mucosal blood flow, reduced epithelial proliferation, and decreased mucosal resistance to injury. The impairment in mucosal resistance facilitates mucosal injury by endogenous factors, including acid, pepsin, and bile salts.

Prostaglandins are derived from arachidonic acid, which originates from cell membrane phospholipids through the action of phospholipase A_2. The metabolism of arachidonic acid to prostaglandins and leukotrienes is catalyzed by the cyclooxygenase (COX) pathway and the 5-lipoxygenase (LOX) pathway, respectively (Fig. 36-4). Two related but unique isoforms of COX, designated COX-1 and COX-2, have been demonstrated in mammalian cells. Despite their structural similarities, each is encoded by distinct genes that differ with regard to their distribution and expression in tissues; the COX-1 gene is primarily expressed constitutively, whereas the COX-2 gene is inducible. COX-1 appears to function as a housekeeping enzyme in most tissues, including the gastric mucosa, whereas the expression of COX-2 can be induced by inflammatory stimuli and mitogens in many different types of tissue. It is postulated that the anti-inflammatory properties of NSAIDs are mediated through the inhibition of COX-2, whereas adverse effects, such as gastroduodenal ulceration, occur as a result of the effects on COX-1. The discovery of the two COX