Pathophysiology and Clinical Relevance

of *Helicobacter pylori*

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Considerable knowledge has recently accumulated on the mechanisms by which *Helicobacter pylori* (*H. pylori*) induces chronic gastritis. Although *H. pylori* is not an invasive bacterium, soluble surface constituents can provoke pepsinogen release from gastric chief cells or trigger local inflammation in the underlying tissue. Urease appears to be one of the prime chemoattractants for recruitment and activation of inflammatory cells. Release of cytokines, such as tumor necrosis factor alpha, interleukin 1 and 6, and oxygen radicals, leads to a further tissue inflammation accompanied by a potent systemic IgA and IgG type of immune response. Chronic inflammation and antigens on glandular epithelial cells lead to a progressive destruction with loss of the epithelial barrier function. Within the gastric mucosa, patches of intestinal metaplasia develop, which may be a risk factor for subsequent development of gastric carcinoma. Hyperacidity in duodenal ulcer patients induces gastric metaplasia in the duodenal bulb, which represents a target for *H. pylori* colonization and ulcer formation.

H. pylori can be detected in the majority of patients with peptic ulcers and, compared to age-matched healthy people, it is also found more often in patients with dyspepsia and gastric carcinoma. Although *H. pylori* can be detected in healthy people, the marked reduction of the ulcer recurrence rate by eradication of *H. pylori* (80 percent versus 20 percent relapse within one year) suggests that *H. pylori* is a major risk factor for duodenal ulcer formation. The potential role of *H. pylori* in non-ulcer dyspepsia and carcinogenesis is under investigation.

Current regimens aimed at eradicating *H. pylori* use a combination of several drugs that are potentially toxic. Since the risk of complications may exceed the potential benefit in most patients, eradication treatment should be limited to clinical trials and to patients with aggressive ulcer disease. New drug regimens, e.g., the combination of proton pump inhibitors with one antibiotic, may provide less toxic alternatives. Beyond ulcer treatment, effective and well-tolerated eradication regimens may have a place in prophylaxis of gastric carcinoma.

INTRODUCTION

Our knowledge about the pathogenesis of the major gastric disorders such as peptic ulcer disease and gastric malignancy is still very fragmentary. The extensive research which has evolved since the first reports of Warren [1] and Marshall [2], in the early 1980s, on gastric colonization by *Campylobacter pyloridis,* now referred to as *Helicobacter pylori* (*H. pylori*), has partly unraveled a few hitherto poorly understood phenomena accompanying gastric pathology, but has also raised many new questions. It is now well established that *H. pylori* colonizations represents one of the most widespread human infections. It occurs worldwide, with considerable variation,

depending on hygienic standards. The latter also influences the time of onset, which is considerably earlier in underdeveloped countries. In the industrialized world, approximately 50 percent of people above the age of 60 are infected [3]. It is now widely accepted that *H. pylori* infection is the most important cause of gastritis [1,4] and that it is strongly associated with peptic ulcer disease [5] and gastric cancer [6]. The majority of subjects infected do, however, never develop a peptic ulcer or gastric malignancy, indicating that *H. pylori* infection does not represent more than a co-factor in the pathogenesis of both diseases.

Little is known of the source and the spread of *H. pylori*. It appears to be a primate pathogen, since it has been detected mainly in humans and rhesus monkeys [7]. Based on endoscopic and serological data of family members, direct transmission by contact has been proposed [8,9]. Unique properties of *H. pylori* such as its ability to alter gastric mucus or to induce structural changes of epithelial cells, as well as several clinical observations demonstrating the induction of gastritis in human volunteers and a therapeutic effect of eradication of the bacteria, indicate that *H. pylori* plays a major role in the pathogenesis of gastroduodenal diseases [10]. This review is focused on the current knowledge of the pathophysiological mechanisms and the clinical relevance of *H. pylori*.

PATHOPHYSIOLOGICAL MECHANISMS

H. pylori *Discovery: More Questions than Answers*

H. pylori is a gram-negative, curved, S-shaped, or spiral bacillus with one to five sheathed unipolar flagellae. Its length is approximately 2.5–3.5 μm, its diameter 0.5–1.0 μm. Discovery of *H. pylori* has given a clear answer as to why patients suffering from peptic ulcer disease in general have an increased ammonia concentration in the gastric juice. While this condition was initially attributed to urease production by gastric epithelial cells [11], the fact is now well established that it is caused by the almost ubiquitous colonization of the stomachs of these patients by *H. pylori*, a bacterium with high urease activity which splits urea to ammonia [12]. The high urease activity facilitates detection of this organism. There are now a variety of direct and indirect diagnostic tests available for the detection of this bacterium, but *H. pylori* culture still represents the gold standard. Detection based on staining of histological sections or determination of urease activity in mucosal biopsies yields highly specific results, but the sensitivity varies between 69 and 100 percent [13,14]. The high urease activity of *H. pylori* allowed the development of breath tests based on hydrolysis of urea labeled with carbon isotopes ^{13}C and ^{14}C [15]. During hydrolysis, CO_2 is produced and can be recovered from the expired air as measurable $^{13}CO_2$ or $^{14}CO_2$. Breath tests have a sensitivity of about 90 percent and a specificity that varies between 90–94 percent [16,17]. A series of serological tests has also been developed, and several ELISAs based on sonicated and acid-extracted antigens from *H. pylori* are commercially available. Their sensitivity and specificity vary considerably, but, with newer techniques utilizing purified antigens, both parameters are close to 100 percent [18]. These sereological tests are particularly useful for screening. They do, however, not reflect the actual inflammatory activity in the gastric mucosa and tend to fall only after three or more months following successful eradication of *H. pylori* [19,20].

It is now proven beyond doubt that *H. pylori* is the principal cause of the so-called

type B gastritis [4] and that it is an important co-factor in associated diseases, including gastric malignancy. The discovery of *H. pylori* has changed the previous concept that duodeno-gastric reflux is the main cause of the gastritis found in ulcer patients. Indeed, duodeno-gastric reflux can today at best be considered as a co-factor of *H. pylori*-induced damage of the gastric mucosa, especially in reflux gastritis following gastric surgery. *H. pylori* is mainly found in gastric mucus and at intercellular junctions. It only rarely invades epithelial cells [21], and it was initially considered by many as an innocent bystander in previously damaged mucosa. From many incidental observations, including those made on two human subjects who intentionally ingested *H. pylori* [22,23], it is, however, now well established that following *H. pylori* infection the gastric mucosa is infiltrated with inflammatory cells, including neutrophils, eosinophils, basophils, macrophages, monocytes, plasma cells, and mast cells. The inflammatory response is accompanied by a substantial systemic IgA and IgG antibody response, which is the proof that *H. pylori* is not simply a commensal organism [4]. Despite this immunologically hostile microenvironment, *H. pylori* appears to persist lifelong [24]. The presence of specific antibodies does not even protect against recurrence of infection after a temporary clearance [24]. This fact suggests that the organism is either inaccessible to the host immune response or that the responses are rendered ineffective. It is now well established that type B gastritis is largely reversible, following eradication of *H. pylori* at any stage of the infection [9,25]. It has also been shown that *H. pylori* can causally elevate plasma gastrin [26]. The original concept that the ammonia produced by *H. pylori* urease neutralizes gastric acid and therefore interferes with the acid-gastrin feedback is probably an oversimplification [27,28]. Of special interest are recent observations suggesting that patients with *H. pylori*-associated gastritis have a selective suppression of the D cells with subsequent loss of the normal inhibition of D cells on G cells [29–31]. *H. pylori* is also responsible for elevation of serum pepsinogen I levels in duodenal ulcer disease [32] because, similar to gastrin levels, those of pepsinogen can be reversed to control levels following *H. pylori* eradication. In contrast, neither maximum acid output nor the sensitivity of the parietal cell to gastrin appears to be influenced by *H. pylori* [33].

Mechanisms by Which H. pylori *Damages Gastric Mucosa*

Of particular interest are the mechanisms by which *H. pylori* damages gastric mucosa. Locomotion is presumably required to allow *H. pylori* to move from the gastric lumen into the viscous environment of gastric mucus [34]. Curved bacteria have been detected within the phagocytic vacuoles of neutrophils located between gastric epithelial cells, but invasion of *H. pylori* below the basal membrane has not been observed [35]. These findings suggest that *H. pylori* recruits inflammatory cells by releasing cell components or by shedding membrane components which, after absorption into the mucosa, attract and activate leukocytes, monocytes, and macrophages (Fig. 1). Among the surface proteins, purified *H. pylori* urease has been identified as an activator of leukocytes [35]. Like other gram-negative bacteria, *H. pylori* contains lipopolysaccharides (LPS) and N-formylated oligopeptides (FMLP), which are both potent chemotactic agents [36]. They stimulate monocytes and macrophages which then release cytokines, such as tumor necrosis factor (TNF alpha) and interleukins (IL-1 and -6), and oxygen radicals, such as superoxide anions (O_2^-) [36–38]. All these cell products and probably additional unknown factors lead
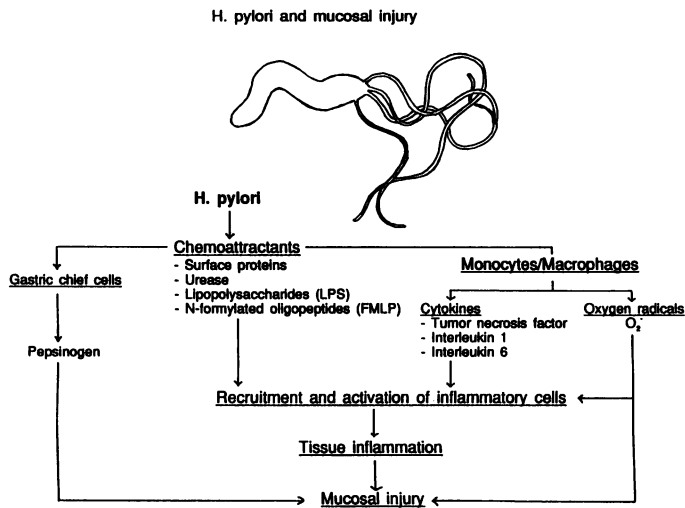
H. pylori and mucosal injury

FIG. 1. Hypothetical sequence of cellular and biochemical changes leading from H. pylori infection to mucosal injury.

to recruitment and activation of inflammatory cells, tissue inflammation, and tissue injury. These in vitro findings help to explain the histopathological observation of H. pylori-associated gastritis.

Bacterial LPS appear to be strategic in pepsinogen stimulation. As recently shown by Young and co-workers, H. pylori LPS induced a fiftyfold increase of pepsinogen secretion, whereas E. coli LPS produced a much lower response [39]. An increase of pepsin secretion was also observed when isolated glands from rabbit gastric mucosa were exposed to a sonicated H. pylori preparation [40]. These in vitro findings support the hypothesis that elevated serum pepsinogen I levels in patients with duodenal ulcer disease are due to H. pylori infection. The stimulation of pepsin secretion appears to be an additional mechanism by which H. pylori produces mucosal injury (Fig. 1).

A pathogenetic role has been proposed for several other virulence factors including catalase, phospholipase, adhesins, and cytotoxin [41]. When exposed to cultured epithelial cells, culture filtrates from H. pylori strains found in patients with duodenal ulcer produced intracytoplasmatic vacuoles, whereas culture filtrates from H. pylori strains found in non-ulcer patients produced less cytotoxic effects [42]. Final proof whether such factors modulate the virulence of H. pylori strains might come from manipulation of the H. pylori genome [43]. Identification of virulence factors is limited by the lack of satisfactory animal models of H. pylori infection.

H. pylori: *Degree and Extension of Gastritis*

H. pylori-induced chronic inflammation of the gastric mucosa has important cellular consequences. In acute type B gastritis, polymorph leukocytes tend to congregate specifically around the gland neck. The damage to the stem cells located at this site may provoke an increased cell turnover, as observed in chronic gastritis. Although mucosal injury appears to induce secretion of mitogenic factors, such as epidermal growth factor (EGF), preliminary in vitro experiments indicate that H. pylori inhibits EGF-stimulated epithelial cell proliferation [44–50]. The interaction

between *H. pylori* and mucosal growth factors is largely unknown and needs further investigation [51].

Various degrees of antral and body gastritis may develop over time, and it is well established that, in patients with type B gastritis, mucosal atrophy increases with age. It appears that secondary immunological damage contributes to tissue destruction. Antibodies produced against *H. pylori* are common but are not effective in the defense against the bacillus. Moreover, it appears that the antibodies against *H. pylori* cross-react with the antigens on glandular epithelial cells, leading to destruction of the epithelial structure and loss of the epithelial barrier function [52]. Glandular atrophy mainly affects gastric mucosa of the body and, over the years, the corpus-antrum border moves proximally [53]. Extension of gastritis leads to a decreased acid secretory capacity of the stomach, which may explain the "burnout phenomenon" of peptic ulcer disease [54,5]. It appears, however, that the continuous advancement of gastritis from the antrum to the body and fundus is more a feature of gastric than of duodenal ulcer disease [55].

Patches of intestinal metaplasia (IM) are common in chronic atrophic gastritis. Since IM is found in many patients with gastric cancer, especially the intestinal type of adenocarcinoma, it has been concluded that IM represents a pre-malignant condition [56]. The notion that *H. pylori* may, at least in part, be responsible for IM comes from observations made on dyspeptic patients in whom IM was more frequent in *H. pylori*-infected subjects. *H. pylori* does not, however, adhere to metaplastic areas, and it is thus possible that intestinal metaplasia represents a defense response; i.e., replacement of gastric epithelium by an epithelium which is less susceptible to chronic injury. A less pronounced inflammation was indeed found in the lamina propria below patches of intestinal metaplasia [57–59]. It is likely that the metaplastic epithelium does not present antigenic material to the same degree as the inflamed *H. pylori*-positive gastric epithelium, and this possibility may be a reason why "end-stage" gastritis often becomes *H. pylori*-negative. The question remains open whether different strains of *H. pylori* vary in their damaging effect on gastric mucosa, e.g., why two-thirds of *H. pylori* strains isolated from patients with peptic ulcers produce a cytotoxin, while this condition was found in only 30 percent of patients without ulcers [41].

Gastric metaplasia (GM), i.e., gastric-type epithelium within the duodenal bulb mucosa, is common in patients with duodenal ulcer disease. It is mainly found in the first part of the duodenum but may extend to the second part in patients with extensive involvement [59]. Gastric metaplasia is closely related to a low pH in the fasting gastric juice [59]. Since duodenal ulcer disease is generally accompanied by gastric hyperacidity, it is likely that gastric metaplasia develops as a result of increased acid delivery from the stomach. Organisms passing into the duodenum from the infected gastric mucosa may infect the metaplastic areas and provoke an inflammatory cell response. The resultant cytotoxic injury reduces mucosal resistance below a critical level so that acid-pepsin exposure leads to erosive and ulcerative damage. *H. pylori* has a predilection for gastric-type epithelium. Whether found in the stomach, the duodenum, or in Barrett's esophagus [60], only gastric epithelial cells appear to possess receptor sites capable of binding the bacterial attachment molecules or ligands. Thus, there is a direct sequence of events from *H. pylori*-induced cellular injury through diminished mucosal defense and enhanced

mucosal susceptibility to injurious agents (e.g., acid, pepsin, drugs like non-steroidal inflammatory agents) to mucosal erosion or ulcers.

CLINICAL RELEVANCE OF *H. PYLORI*

Peptic Ulcer Disease

The possibility that *H. pylori* is the sole cause of duodenal ulcer is far from being established. Infection with *H. pylori* in the presence of normal gastric acid secretion is, however, considered to be the most important factor in the etiology of duodenal ulcer disease. Close to 100 percent of all patients suffering from duodenal ulcer, and some 80 percent of those with gastric ulcer, harbor this infectious agent in their stomachs. Nevertheless, despite *H. pylori* infection, most ulcers heal if treated with potent inhibitors of gastric acid secretion such as H_2-receptor antagonists or proton pump inhibitors, and chronic use of the same drugs is effective for prevention of ulcer relapse. The main clinical implication of *H. pylori* infection comes from the observation that eradication of *H. pylori* currently represents the only treatment modality to keep duodenal ulcers healed. This fact would make prophylactic use of acid-inhibiting drugs or surgery unnecessary in most cases. Eradication of *H. pylori*, defined as absence of *H. pylori* infection one month after the end of treatment, leads to a long-term remission, whereas the relapse rate of duodenal ulcers is 70–80 percent if *H. pylori* is not eradicated [61]. From studies performed before *H. pylori* was identified, it is well known that the recurrence rate was smaller in patients treated with colloidal bismuth as compared to those treated with H_2-receptor antagonists [61–63]. When bismuth was subsequently found to suppress *H. pylori*, it was hypothesized that the therapeutic gain resulting from bismuth was related to the eradication of *H. pylori*.

Bismuth alone, however, suppresses *H. pylori* only temporarily [64], and more aggressive therapeutic regimens, generally a three-drug combination of bismuth with metronidazole and an additional antibiotic such as tetracycline, amoxicillin, or erythromycin, given for two to four weeks, yields the best eradication rates of 80–90 percent (Table 1). Complete eradication of *H. pylori* will keep approximately four-fifths of all ulcers healed for several years, whereas only one-fourth to one-fifth of the patients without antimicrobial therapy or failed eradication attempt remain relapse-free [65–72].

Arguments against a general propagation of the rather cumbersome and expensive multi-drug therapy are difficulties with patient compliance, emergence of resistant strains, and potentially dangerous side effects such as diarrhea or *Clostridium difficile*-associated colitis. Therefore, we currently limit treatment of *H. pylori* to patients with complicated or recurrent peptic ulcer disease.

In an attempt to make treatment of *H. pylori* more acceptable to the patient, Logan et al. developed a one-week treatment regimen consisting of tripotassium dicitrato bismuthate, amoxicillin, and metronidazole [73] (Table 1). This regimen yielded an eradication rate of 72 percent (median follow-up, 9.3 months), and the best eradication rate was found in patients with metronidazole-sensitive *H. pylori* strains (93 percent). Recently it has become apparent that the proton pump inhibitor omeprazole possesses antimicrobial activity *in vitro*. Given in mono-therapy, omeprazole could suppress but not eradicate *H. pylori* infection (Table 2) [74–77,79]. Combined with amoxicillin, eradication rates rose to 82 percent [78,79], which makes this

TABLE 1
Standard Triple Therapy and Eradication of *Helicobacter pylori*

Author [Ref.]	No. of Patients	Drug Combination (dose/duration)	Eradication (%)
Marshall et al. [67]	22	Cimetidine/placebo	0
1988	29	Cimetidine/tinidazole	4
	22	CBS/placebo	27
	27	CBS, 1 tablet qds/8 weeks	
		Tinidazole, 500 mg bid/day 1–10	74
		If sensitive to tinidazole	85
Borody et al. [69]	100	Tripotassium dicitrato	
1988		bismuthate, qds/4 weeks	
		Tetracycline, 500 mg qds/4 weeks	
		Metronidazole, 200 mg qds/2 weeks	94
Rauws and Tytgat [71]	26	CBS, 1 tablet qds/4 weeks	10
1990	24	CBS, 1 tablet qds/4 weeks	
		Amoxicillin, 350 mg tds/4 weeks	
		Metronidazole, 500 mg tds/day 18–28	88
Logan et al. [73]	106	Tripotassium dicitrato	72
1991		bismuthate, 120 mg qds/1 week	
		Amoxicillin, 500 mg qds/1 week	
		Metronidazole, 400 mg × 5/day 5–7	
		Metronidazole-sensitive	93

CBS, colloidal bismuth subcitrate

treatment regimen an acceptable alternative. These results are based on small patient groups and need further confirmation.

Non-Ulcer Dyspepsia

It has long been debated whether chronic gastritis is responsible for dyspeptic symptoms [80]. Studies performed before the recognition of *H. pylori* have generally yielded a negative result [81]. No satisfactory answer to the question whether *H. pylori* infection is more common in patients with chronic dyspepsia than in asymptomatic subjects is currently available. This difficulty is related to various factors, such as differences in classification of the degree of gastritis, the increase of the prevalence of *H. pylori* infection with age, and the wide variations of clinical symptomatology. Several studies show a slight preponderance of infected individuals in the chronic dyspepsia group compared with controls, but the difference is small [82].

Some investigators found that some symptoms like "burping" [83], postprandial bloating [84,85], or epigastric burning and fullness [86] were found more often in *H. pylori*-positive dyspeptic patients. In contrast, no significant differences in symptoms could be found between *H. pylori*-positive and *H. pylori*-negative patients in several other studies [87–89]. It is thus likely that *H. pylori* infection does not cause a constant and specific dyspeptic symptomatology. Indeed, very large population

TABLE 2
Omeprazole and Eradication of *Helicobacter pylori*

Author [Ref.]	No. of Patients	Drug Combination (dose/duration)	Eradication (%)
Unge et al. [74] 1989	8	Omeprazole, 40 mg om/2 weeks	0
	7	Amoxicillin, 750 mg bd/2 weeks	14
	8	Omeprazole, 40 mg om/2 weeks Amoxicillin, 750 mg bd/2 weeks	63
De Koster et al. [75] 1991	9	CBS, 120 mg qds/1 week Omeprazole, 40 mg om/1 week	0
	18	CBS, 120 mg qds/1 week Omeprazole, 40 mg om/1 week Erythromycin, 500 mg qds/1 week	50
	12	CBS, 120 mg qds/1 week Omeprazole, 40 mg om/1 week Amoxicillin, 500 mg qds/1 week Minocyclin, 100 mg bd/1 week	50
Lamouliatte et al. [76] 1991	20	Omeprazole, 20 mg daily/4 weeks Amoxicillin, 2 g daily/2 weeks Tinidazole, 1 g daily for 10 days	90
	20	Ranitidine, 300 mg daily/6 weeks Amoxicillin, 2 g daily/2 weeks Tinidazole, 1 g daily/2 weeks	80
Bell et al. [77] 1991	16	Omeprazole, 20 mg at night/4 weeks Amoxicillin, syrup, 250 mg tds/2 weeks	31
	14	Omeprazole, 20 mg at night/4 weeks CBS, 240 mg bd/4 weeks	14
Bayesdörffes et al. [79] 1992	27	Omeprazole, 40 mg bd for 10 days Amoxicillin, 1 g bd for 10 days followed by omeprazole, 20 mg daily/6 weeks	82
	26	Omeprazole, 40 mg bd for 10 days followed by omeprazole, 20 mg daily/6 weeks	0

CBS, colloidal bismuth subcitrate

samples would be necessary to confirm or refute the possibility of a specific *H. pylori*-associated syndrome. Many clinicians consider routine biopsy sampling aimed at identifying *H. pylori* infection in patients with common upper gastrointestinal symptoms as premature, since the risk of complications from the current multi-drug regimen may well exceed the potential benefits.

Gastric Malignancy

Recently, evidence has accumulated that *H. pylori* increases the risk of gastric carcinoma [90–92,6]; it appears that population groups infected at an early age are
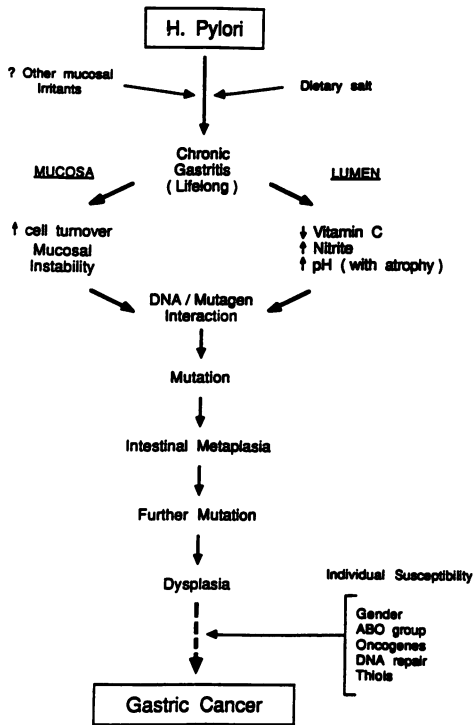
FIG. 2. Hypothetical sequence of cellular and biochemical changes leading from *H. pylori* infection to gastric cancer (from [96], with permission).

particularly at risk [93–95]. In American men of Japanese ancestry in Hawaii, affected with gastric carcinoma, the odds ratio of having serum antibodies against *H. pylori* was 6.0 as compared to matched controls without gastric tumor [92]. Nevertheless, most human subjects infected with *H. pylori* will not develop gastric cancer, and there are even data indicating that the presence of a peptic ulcer protects patients infected with *H. pylori* from developing gastric carcinoma [91]. It is therefore evident that *H. pylori* is neither sufficient nor necessary for gastric carcinogenesis, and environmental factors and carcinogens are likely to be important co-factors [96] (Fig. 2). There is circumstantial evidence that long-standing *H. pylori* infection predisposes to formation of intestinal metaplasia. In a recent study including 533 subjects, intestinal metaplasia was found in 135 patients (25 percent) and *H. pylori* in 289 patients (54 percent) [55]. Intestinal metaplasia was encountered more often in *H. pylori*-positive patients as compared with *H. pylori*-negative subjects (34 percent versus 15 percent, $p < 0.001$). The prevalence of intestinal metaplasia and *H. pylori* was age-related, being more common in patients over 50 years as compared with patients under 50 years. The mean age of patients with intestinal metaplasia who were also *H. pylori*-positive was 64 years, whereas the mean age of patients with intestinal metaplasia who were *H. pylori*-negative was 72 years ($p < 0.005$).

Screening for growth factor expression in gastric tissue may have a potential to detect patients at risk. Immunohistochemical studies revealed an increase in expression of growth factors close to the proliferative zone in inflamed antral mucosa, especially in *H. pylori*-positive patients [97]. Epidermal growth factor (EGF) may have an oncogenic potential in the stomach [98,99]. EGF receptors have been verified in a poorly differentiated gastric cancer cell line [100] and in surgically

resected gastric carcinomas [101]. In this context, it would be of interest to compare growth factor expression in different stages of intestinal metaplasia and to evaluate whether this comparison could serve as a screening method in high-risk patients.

A still open question is why only a small fraction of subjects infected with *H. pylori* develop gastric cancer. It has been suggested that differences in the virulence of *H. pylori* strains might determine their carcinogenic potential [102]. A similar open question is why, in some individuals, the lymphoid infiltrates which accumulate in the gastric mucosa in response to *H. pylori* infection undergo malignant transformation and develop to malignant lymphoma [103].

OUTLOOK

Progress on *H. pylori* is hampered by several shortcomings. Of particular importance are the lack of a cheap small animal model, the lack of methods for identifying *H. pylori* strains with different virulence, and the unavailability of a simple non-toxic therapeutic regimen for eradication of *H. pylori*.

Current assay methods for *H. pylori* need to be improved. Progress is in sight with regard to new assays based on in situ hybridization [104] or on the polymerase chain reaction [105–107]. Once these molecular biology techniques are established as the gold standard, both the sensitivity and specificity of current assay methods may have to be revised. These new developments might also help to evaluate the existence of particularly virulent strains.

From a clinical standpoint, the prospect of simpler and less toxic therapeutic measures aimed at eradication of *H. pylori* is of special importance. The promising results obtained with a treatment regimen combining proton pump inhibitors with a non-toxic antibiotic urgently need further confirmation and extension. A serological test able to detect seroconversion to normal shortly after eradication of *H. pylori* would greatly help to evaluate new treatment regimens.

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