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***Helicobacter pylori* infections – are these diseases relevant for surgical treatment?**

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Abstract *Helicobacter pylori* infection and its strong association with gastroduodenal diseases has revolutionized our views and treatment options in these diseases. Surgery has always been considered a mainstay in their treatment. The development of potent eradication regimes has changed indications for operative treatment. With endoscopic procedures being increasingly performed by the surgeon himself, it has become necessary that he educate him-

self in the diagnosis and treatment of *H. pylori* infection in order to be able to cope with these diseases in every day surgical practice. Treatment of *H. pylori* infection may not only be seen as an alternative to operative therapy, but also as an adjunct following surgical treatment of gastroduodenal disease.

Key words *Helicobacter pylori* · Gastroduodenal disease · Surgical treatment · Postoperative treatment

Since the discovery of *Helicobacter pylori* and its first recognition in 1983 as a possible pathogen causing chronic active gastritis, our views concerning gastroduodenal pathology and pathophysiology have been revolutionized [1]. This discovery may be considered to be the most important made in the study of gastroenterology during the 20th century. Due to the very high prevalence of gastroduodenal diseases with considerable morbidity and mortality over the past 100 years, surgeons have excelled in improving the surgical technique, making surgery a mainstay of treatment [2, 3]. As a consequence of this historical development, surgical training in general surgery has always laid great emphasis on the fundamental understanding of the pathophysiology and correct modern treatment modalities of gastroduodenal diseases. In Europe, and in particular in Germany, this aspect of surgical training has just recently gained even more significance, since endoscopy of the upper gastrointestinal tract has been firmly incorporated as a mandatory rotation within each surgical resident's training, and also for the subspecialty visceral surgery. Therefore, it is most important that the surgeon be well informed about the most recent developments in the area of *H. pylori*-associated gastro-

duodenal diseases and its effect on surgical as well as conservative treatment modalities.

The first questions concerning the relevance of *H. pylori* infections for surgical treatment were addressed by this journal 10 years ago [4]. At that time, not much was known about the infection and its associations. Physicians were split into groups of believers and non-believers. As we now realize, many conclusions that were made were wrong. Since then, our knowledge of this infection and its profound importance in disease development has risen exponentially and, unlike the situation 10 years ago, surgeons have come to realize its great relevance for surgical decision making and proper treatment choice [5]. Two aspects of the infection make it so important: the epidemiology of the infection and the variability of its role in the pathogenesis of different gastroduodenal diseases.

Epidemiology

One of the major reasons why *H. pylori* is so important and why the surgeon will be confronted with it in everyday clinical practice is its vast distribution throughout

different populations. *H. pylori* is a gram-negative spiral organism, which infects more than half the people in the world. The highest rates of infection are associated with low socioeconomic status, crowding, poor sanitation, and unclean water supplies [6].

In Western countries, *H. pylori* infects approximately 38–61% of the general population, which is lower than the prevalence rates seen in developing countries (80–100%). If all age groups are considered, 35% of the European population on average is infected. Age is the most important variable related to the prevalence of infection. Roughly more than half of the people over 60 years of age are affected, compared with 20% of those under 40 years [7]. Many studies have proven the cohort effect of the infection, which is typically acquired in childhood and is lifelong [8, 9, 10]. Children between the ages of 2 years and 8 years in developing nations acquire the infection at a rate of about 10% per year, whereas in Germany children become infected at a rate of less than 1% per year.

Altogether, the epidemiological data so far accumulated on the prevalence and incidence rates of *H. pylori* infection in different populations are numerous. Although there is a significant trend toward a decrease in prevalence rates in Western countries due to higher standards of living, epidemiologic studies underline the fact that *H. pylori*-associated diseases of the upper gastrointestinal tract will still be among the most common disorders seen in every gastrointestinal surgical practice during the upcoming first 50 years of this new millennium.

Role of *H. pylori* infection in the pathogenesis of gastroduodenal disease – relevance for surgical treatment

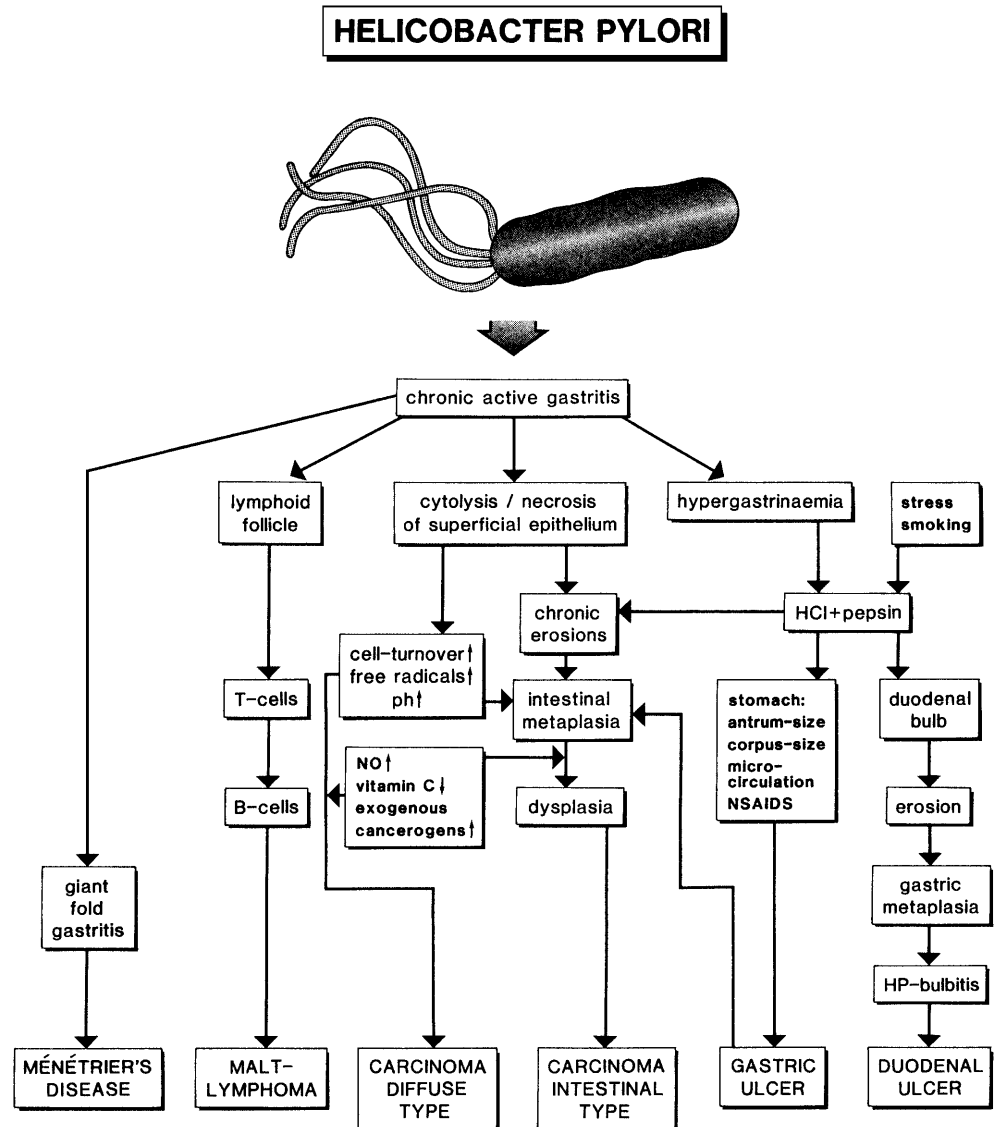
For a long, long time, a common consensus existed without conclusive data that the harsh acidic environment within the stomach would permit no long-term colonization by a bacterial pathogen. However, unlike other pathogens colonizing the gastrointestinal tract, *H. pylori* is unique because it has effective mechanisms permitting it to survive in the hostile environment of the stomach. Therefore, it is not unusual that once a bacterium has been able to colonize the stomach it may go on to cause mucosal damage. It is, in fact, the host's response to the bacterium itself that causes the pathologic changes within the mucosa. These changes are seen by the pathologist and have been named chronic active gastritis or *H. pylori*-associated (-induced) gastritis. The intensity of inflammation by the bacterium is graded according to the updated Sydney system [11] using a visual analog scale into three grades: mild, moderate, and marked. Usually, inflammation caused by the bacterium is, in the beginning, restricted to non-acid-secreting portions of the stomach, in particular the antrum. As time passes on,

gastritis tends to extend from the antrum into the corpus, resulting in a reduction in acid secretion and eventual loss of parietal cells and development of atrophy [12, 13]. One of the most relevant characteristics of this infection is that infected individuals cannot eliminate the bacterium, thus leading to a lifelong persistence of chronic inflammatory changes within the gastric mucosa, followed by atrophy. This remains so, although the host mounts a marked systemic and local immune response against *H. pylori* [14]. It is this inflammatory reaction that interferes with well-known physiologic functions in the stomach such as gastrin homeostasis and acid secretion [15].

The key to understanding the role of *H. pylori* infection in gastroduodenal diseases that are relevant to the surgeon is the fact that *H. pylori*-induced chronic active gastritis is the main pathogenic denominator from which starting point other clinical disease entities may originate depending on additional genetic or environmental factors of the individual. So far, the following *H. pylori* gastritis-associated diseases have been identified: gastric and duodenal ulcer, gastric adenocarcinoma, primary gastric B-cell lymphoma and Ménétrier's disease (Fig. 1). The inference that gastritis is a necessary predisposition for the development of other diseases such as peptic ulcer is not new. This association extends back at least 70 years. It was Faber in 1927 [16] and Konjetzny in 1928 [17] who correctly pointed out that duodenal ulcer was strongly associated with antral predominant gastritis.

H. pylori-induced gastritis is the most common, comprising 80–90% of all gastritis types [18]. C-gastritis, which means chemical gastritis, caused for the most part by the intake of non-steroidal anti-inflammatory drugs (NSAIDs) and by bile reflux most often seen after Billroth-II gastrectomy, is the second most common form of gastritis [19]. Both of these types, *H. pylori*- and C-gastritis, may often occur in combination due to the high prevalence of both in the population. The last main group of gastritis is autoimmune gastritis or A-gastritis, making up 3–6% of all types seen. Typical for A-gastritis is atrophy in the stomach fundus and corpus region, with the formation of parietal cell antibodies in 90% and/or autoantibodies against intrinsic factor in 50% of the patients affected. Recent studies suggest that autoantibodies produced against *H. pylori* may play a pathogenic role in the development of autoimmune gastritis [20]. It is important to recognize that infection with *H. pylori* will always cause gastritis. According to a 32-year follow-up study, complete healing of the infected mucosa is very rare, with rates being 0.4% per patient year [13]. This means the infection is lifelong, causing chronic gastritis. Most of the patients will remain asymptomatic. Approximately 25% of these will develop chronic atrophic gastritis with the development of hypochlorhydria or chlorhydria. Atrophic gastritis is the central precursor lesion in the progression from superficial gastritis to gas-

Fig. 1 Role of *Helicobacter pylori* in the pathogenesis of gastroduodenal diseases



tric cancer (Fig. 1). Of persons infected, 14%–17% will develop peptic ulcer disease. Interestingly, duodenal ulcer patients do not progress to develop atrophy in the antrum or corpus of the stomach, and gastritis remains localized to the antrum [21].

A very special form of gastritis is giant fold gastritis, which may lead to Ménétrier's disease (=hypertrophic gastropathy). Protein loss from the stomach is found in more than three quarters of these patients, and edema may be the first clinical sign. A further life-threatening complication of this disease due to protein loss is hypogammaglobulinemia, which increases the risk of fatal infections and the risk of subsequent cancer. In most cases, *H. pylori* eradication will lead to normalization of histologic changes and stop protein loss [22]. If changes do not regress completely after eradication therapy, gastric cancer or gastric lymphoma must be considered.

Peptic ulcer disease

It is now a well-accepted fact that peptic ulceration is an infectious disease [23]. This is supported by the following three pillars of evidence. First, more than 95% of patients with duodenal ulcers and more than 80% of patients with gastric ulcers are infected with *H. pylori*. These do not include ulcers caused by gastrinoma or by the usage of NSAIDs. Second, duodenal ulcers develop far more frequently in persons infected with *H. pylori* than in non-infected persons. Finally, the recurrence of both duodenal and gastric ulcers is markedly decreased after eradication of *H. pylori* infection [24, 25].

The dogma of Schwarz [26], who at the start of the century in 1910 postulated that “no ulcer without acid”, must now be extended to “no ulcer without *Helicobacter pylori*”. What does this mean for ulcer treatment? The

Table 1 New treatment concepts in gastroduodenal disease – *Helicobacter pylori* (*H.p*) eradication as an alternative or adjunct to surgical therapy

	<i>H.p.</i> eradication	Surgical treatment
Uncomplicated peptic ulcer	Always in <i>H.p.</i> -positive ulcers	After failure of multiple eradication attempts Low patient compliance Recurrent <i>H.p.</i> -negative ulcers
Complicated peptic ulcer	Always in <i>H.p.</i> -positive ulcers as an adjunct to immediate surgical or endoscopic intervention	Endoscopic, open or laparoscopic surgical intervention
Gastric B-cell (MALT) lymphoma	Always in low-grade MALT lymphoma in clinical stage E-I 1 (only within clinical trials)	In low-grade MALT lymphoma stages E-I 2, E-II 1, E-II 2 In low-grade MALT lymphoma stages E-I 1 if no remission is achieved by eradication In high-grade lymphoma stages E-I 1 to E-II 2 Palliative resection in stages E-III + E-IV in select cases
Gastric carcinoma	In patients with high gastric cancer risk only within clinical prevention trials Following partial gastrectomy for distal cancer or local mucosal resection in early cancer	Surgical resection always indicated

first line of treatment for uncomplicated ulcer disease in *H. pylori*-positive patients must always be eradication therapy (Table 1). Simple, well-studied and very effective regimes are available, and we recommend further reading, since a detailed description at this point would go beyond the scope of this review [27, 28, 29].

Although elective surgery for recurrent uncomplicated ulcer disease is becoming increasingly rare, the following may still be considered valid indications for operative treatment (Table 1): the failure of multiple attempts to achieve eradication, low patient compliance with medical treatments, and recurrent *H. pylori*-negative ulcers. In these selected cases, surgery, especially laparoscopic procedures performed with minimal access, may be a valuable alternative [30, 31, 32].

Nevertheless, in this new millenium, surgery for peptic ulcer disease will for the most part deal with its complications. Although eradication therapy has now been around for 10 years, its expected impact on the incidence of ulcer complications seen has so far been missed. Probably this has two reasons:

1. As pointed out earlier, the epidemiology of the infection. For example, the lifetime risk of an individual from an industrialized nation to suffer a peptic ulcer during his lifetime is approximately 10%. Annually, 2% of the German population present with symptoms due to peptic ulcer disease [33]. Of these, 1–2% of the patients will experience a major and life-threatening complication, such as hemorrhage, perforation, or

gastric outlet obstruction. Mortality from upper gastrointestinal hemorrhage, even when modern endoscopic hemostasis is used with or without surgical intervention, is still 7% and in ulcer perforation near 5% [34, 35].

2. The broad use of NSAIDs within the population has led to a rise of *H. pylori*-negative ulcer complications and has a synergistic effect on ulcer development if *H. pylori* infection is present [36, 37, 38].

Bleeding is the most common complication of peptic ulceration, and endoscopic hemorrhage control is always considered as a first line treatment modality to reach hemostasis [39]. Surgical departments throughout Germany and Europe, including our own, perform endoscopic hemostasis on their own that permits the best possible surveillance of the patient and allows for immediate surgical intervention if re-bleeding occurs [35, 40]. Today, eradication treatment following endoscopic or operative hemostasis is indicated since several recent studies have proven that recurrent ulceration bleeding can be prevented by *H. pylori* eradication [38, 41]. Long-term follow-up studies showed that patients who remained *H. pylori* negative throughout the follow-up did not experience re-bleeding. Parallel studies, looking at the second most common ulcer complication – perforation – have reported ulcers to be *H. pylori* associated in 70% of the cases, and when NSAID users were excluded this number rose to 80% [42, 43]. So far, no studies have addressed the effect of eradication of *H. pylori* on the natural history of peptic ulcer perforation.

What does this mean for the surgeon, who is most often the first contact for patients presenting with an ulcer complication? First, he must always assume that peptic ulcer is associated with active *H. pylori* infection until proven otherwise. Therefore, he must always try to evaluate the patient's *H. pylori* status, preferably prior to or, at the latest, after endoscopic or operative intervention [44]. If the patient is *H. pylori* negative, the Zollinger-Ellison-syndrome should be ruled out or the possibility of a NSAID use induced ulcer should be considered. In such cases, an elective ulcer-definitive operation in the uninfected patient who has received reasonable prior medical therapy may be indicated. In *H. pylori*-infected patients, treatment with combined medical therapy is mandatory following surgical intervention for ulcer complications [45, 46]. One such approach has been recently reported combining laparoscopic closure of ulcer perforations using an omental plug followed by immediate *H. pylori* eradication [47].

Gastric B-cell lymphoma

Over 92% of the patients with a gastric mucosa-associated lymphoid tissue (MALT) lymphoma have active *H. pylori* infection [48]. These observations inspired Wotherspoon et al. [49] to eradicate *H. pylori* in patients suffering from low-grade B-cell gastric MALT lymphoma, which led to complete remission of this malignant disease in most patients. Recently, a follow-up study of 2 years showed that a complete remission of low-grade gastric MALT lymphoma after the cure of *H. pylori* infection appears to be stable, although most patients do display evidence of monoclonal B cells during follow-up [50].

How does such recent data affect surgical therapy in gastric B-cell lymphomas, which comprise 5% of all gastric malignancies? In general, an official recommendation has been issued by the German Society for Gastrointestinal and Metabolic Diseases (DGVS) [51], in which a course of combined medical treatment should be given to patients presenting with low-grade malignant gastric B-cell lymphoma (classification according to Isaacson and Norton) [52], with the goal of eradicating *H. pylori* infection in the early clinical stage E-I 1 (modified classification of Musshoff according to Fischbach and Böhm) [53]. However, it is very important that these patients who undergo eradication should enter an ongoing clinical trial to ensure proper surveillance.

In all other stages of low-grade MALT lymphoma, especially in clinical stages E-I2 to E-II2, subtotal or total gastrectomy should be considered with or without adjuvant radio- or chemotherapy. All highly malignant lymphomas from stages E-I1 to E-II2 should undergo subtotal or total gastrectomy, depending on the extent of the disease with selective N2-lymph-node dissection, if node involvement is present. The more extensive disease

stages E-III or E-IV of low-grade or high-grade lymphomas that cannot undergo radical resection must be referred for chemo- and/or radiotherapy. In these cases, resection may be indicated for the palliation of symptoms. It is most important that the *H. pylori* status of the patient be determined prior to any form of operative treatment. In our own study assessing the long-term follow-up of patients who had undergone subtotal gastrectomy for gastric B-cell lymphoma in stages E-I1 to E-II2, we found persistent *H. pylori* infection within the gastric remnant in 24 of 29 cases, associated in one case with lymphoma recurrence [54]. We therefore recommend eradication therapy following subtotal gastrectomy for gastric lymphoma at all stages to prevent recurrence.

Gastric cancer

The very first report that microbial spiral-like organisms could be linked to gastric cancer was published in 1906 by the German pathologist Krienitz [55]. Since its rediscovery in 1983, numerous studies have shown that there is a sixfold increased risk in patients with *H. pylori* infection to develop gastric cancer as opposed to non-infected individuals. Foreman et al. [56] was able to show that this association was also present within Europe, and our own study confirmed this relationship for the Southern German population [57]. The fact that *H. pylori* infection may play a role in the multi-factorial pathogenesis of gastric cancer is a subject of intense research at the moment and will be discussed in depth in a subsequent review.

So far, *H. pylori* infection has not yet had a significant impact on the established recommendations on surgical treatment of gastric cancer. However, it is important for the surgeon to know that research during the upcoming first decade of the new millennium will generate clinically relevant data in this area. We now know that the association of *H. pylori* infection is primarily limited to the distal parts of the stomach being body and antrum of the stomach [57, 58]. Carcinoma of the cardia does not show a significant association. The incidence of adenocarcinoma of the distal stomach in developed countries has been steadily declining since the mid-1950s [58].

As Kikuchi et al. [59] showed, acquirement of the infection at a young age increases the risk of developing cancer even further, reaching a risk greater than 13 times the uninfected population. This data suggests that the earlier the infection in childhood starts, the longer *H. pylori* may exert a carcinogenic effect within the stomach [60]. It means that, in clinical practice, emphasis will be laid on the early detection of infected individuals at risk for developing carcinoma. Our group showed that the expression of *H. pylori*-associated gastritis in patients with gastric cancer is higher in the corpus than in the an-

trum, and that corpus gastritis is more frequently associated with intestinal metaplasia and atrophy [61]. This finding prompted us to develop a gastric carcinoma risk index in patients infected with *H. pylori* [62, 63]. In view of the possibility of defining infected populations at risk for developing gastric cancer, prevention studies have been initiated in various countries, including Germany [64].

Relevance of *H. pylori* infections following surgical treatment

One question that is particularly relevant to the surgeon is the fate of *H. pylori* infection in the gastric remnant following partial gastrectomy (Billroth-I-, Billroth-II-procedure) or vagotomy [65, 66, 67, 68, 69]. Many studies have been reported that show a high prevalence of *H. pylori* in patients who have undergone vagotomy for duodenal and gastric ulcer disease, which reaches 98% in studies with long-term follow-up. Peetsalu et al. [70] showed that the overall ulcer recurrence rates in vagotomized patients 14 years after surgery was 18%. All recurrent ulcers were *H. pylori* associated and were only seen in those patients with a positive endoscopic Congo-red test. Such a reaction is called rapid acid secretion and is associated with a partially intact vagus nerve innervation in the gastric corpus. In patients with correctly performed complete vagotomy and *H. pylori* infection, no recurrent ulcer was encountered. These very interesting findings suggest that proximal selective vagotomy, if done properly, still shows good long-term results with almost no ulcer recurrence, even in the presence of *H. pylori* infection. However, as the study of Peetsalu showed, the incidence of incomplete vagotomy was very high, reaching 70% of all patients subjected to the procedure. Therefore, one must also conclude that postoperative *H. pylori* eradication is indicated in each of these patients to ensure complete ulcer recurrence control in any case.

The situation in the gastric remnant following partial gastrectomy for carcinoma or ulcer complications is somewhat different. Resection with B-I reconstruction shows an incidence of *H. pylori* infection of approximately 70%, followed by a significantly lower rate of infection in B-II anastomosis of 45% [71]. The lower rate of *H. pylori* infection found in B-II stomachs may reflect the role of bile reflux, which is more common in B-II than B-I and has been shown to interfere with the colonization by *H. pylori*. However, there is evidence that the synergistic effect of bile reflux and *H. pylori* infection in B-II anastomosis increases epithelial proliferation in the gastric remnant [68]. As recently reported by Leivonen et al. [72], this may contribute to the increased risk of cancer after partial gastrectomy. Although at the moment no common consensus exists concerning the question whether to eradicate the bacterium following partial re-

section, in our opinion, this is indicated in all *H. pylori*-positive patients who have undergone gastric resection or vagotomy. We comply with the conclusions of Danesh et al. [45], who systematically reviewed 36 studies concerning this question.

Evidence that *H. pylori* infection may influence the development of mucosal dysplasia following curative endoscopic resection of early gastric cancer has been indicated by Uernura et al. [73]. They showed that in patients who were followed 2 years after local excision, no recurrence was encountered in patients who had undergone adjunct eradication treatment post-resection as opposed to patients in whom no eradication therapy was performed. The group in which *H. pylori* infection persisted had a recurrence rate of up to 9%. Histological examination of tissues during follow-up showed that *H. pylori* eradication led to a decrease in intestinal metaplasia and to a decrease in the incidence of mucosal dysplasia. Such data may have a great impact on the surgery of early gastric cancer if, in the future, new techniques of local excision either by endoscopic means, laparoscopically, or by a transgastric endoscopic approach, as suggested by Ohgami [74, 75], undergo further refinements.

Future trends

In recent years, data has been accumulating suggesting that a particular group of *Helicobacter* species different from *H. pylori* may be involved in the pathogenesis of liver diseases, such as liver cirrhosis with its typical complication of hepatic encephalopathy [76], in hepatic carcinoma [77], in biliary tract disease as in chronic cholecystitis [78], and in cancer of the gall bladder. The species that are associated are *H. bilis*, *H. pylorum*, and *H. hepaticus*, which have been shown to be tolerant to bile, colonize bile canaliculi and the gall bladder, and cause hepatitis and cholecystitis. Again, as was the case 15 years ago with the discovery of the close association of *H. pylori* infection with peptic ulcer disease, much skepticism has been raised concerning these observations. The primary question that must be raised is "do these *Helicobacter* species play a causative role or are they just bystanders colonizing diseased tissues of the hepatobiliary tract system?". An intense research effort will be mounted to answer these questions in the near future. At the moment, these new revelations will not affect surgical treatment. However, the surgeon should carefully follow these developments and from the beginning initiate basic and clinical research programs in this area.

In conclusion, *H. pylori* infections and their close association with gastroduodenal diseases, which throughout modern medicine have been classical areas of major importance in surgery of the alimentary tract, have had a great impact on surgical decision making. The alimenta-

ry tract surgeon with his broad training in endoscopy and minimal invasive techniques must consider *H. pylori* in the diagnosis and treatment of upper gastrointestinal diseases. Not only have the indications for surgical procedures changed, but surgeons must increasingly consider

eradication therapy as an alternative or as an adjunct to surgery.

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