Gastric mucosal disease

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Chapter 1

Introduction

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General Introduction

For many decades the dictum “no acid, no ulcer” dominated thinking on the pathogenesis of peptic ulcer. With H₂-receptor antagonists, many clinicians believed it would lead to the removal of peptic ulceration as a clinically important disease. It was soon evident, however, that ulcers returned rapidly when the H₂-receptor antagonist was withdrawn and the concept of maintance therapy was born. In 1982, Marshall and Warren succeeded in culturing *Helicobacter pylori* isolated from the stomachs of the patients with peptic ulcer. The discovery of *Helicobacter pylori* not only turned the aetiopathogenesis of peptic ulceration on its head but soon emerged as a major factor in the causation of gastric cancer and mucosa associated lymphocytic tissue gastric lymphoma (MALT). The potential clinical impact of this organism continues to expand. Successful control of this chronic infection would reduce the occurrence of gastritis and peptic ulcer, and it might substantially lower the rates of one of the world’s deadliest neoplasms. The high prevalence of this organism worldwide presents clinicians and researchers with a formidable challenge with regards to its control at a population level.

Epidemiology

It is now clear that infection with *Helicobacter pylori* is extremely common worldwide, but the prevalence varies widely in different parts of the world with average rates of 40-50% in western countries rising to more than 90% in the developing world. Since *Helicobacter pylori* is chronic, lasting years to decades, it is not surprising that its prevalence increases progressively with age. The prevalence of infection increases with age from 10% at age 10 to 60% at age 60 in developed countries. *H. pylori* is an infection which is mainly acquired
in childhood. The overall prevalence of *H. pylori* in children is 10% in developed countries but can be as high as 30-40% in children from lower socioeconomic groups. In developing countries, children acquire *Hp* infection very early in life and more frequently than those in developed countries, the prevalence ranges from 80-100%. \(^{11-12}\) *H. pylori* infection acquired in childhood is now considered to be a significant risk factor for the development of gastric carcinoma.

The mode of transmission of *Hp* is vigorously debated, although current evidence suggests that it is predominantly by person-to-person contact. Transmission routes may vary being from oral-oral in the industrialized world and faecal-oral in the developing world, or improperly cleaned endoscopic equipment as cause of iatrogenic *Hp* infection\(^ {13}\). The possibilities of exposure to a common environmental reservoir or nonhuman reservoirs cannot be ruled out.

The argument still remained. Luman W et al\(^ {14}\) showed recently that the oral-oral route of transmission between spouses is unlikely to be an important mode for *H. pylori* infection and the lack of evidence for fecal-oral transmission of *H. pylori* infection in Taiwanese\(^ {15}\).

A lower socioeconomic status is associated with a higher prevalence of *Hp* infection and this association has been found worldwide, including countries in Asia\(^ {16-17}\), south America\(^ {18-19}\) and Africa\(^ {20}\). These studies have also demonstrated an inverse relationship between *Hp* prevalence and the educational level of the population studied. Environmental factors, such as general level of hygiene, water supply and sanitation, and crowding in the household, have been reported to be linked with *Hp* infection\(^ {21-22}\). All these factors are interrelated and are linked with the overall standard of socioeconomic development. Even when socioeconomic status is taken into account, marked difference in the seroprevalence of *Hp* have been observed between various ethnic and racial groups living in the same area. Although the exact
reason for the difference in \( H_p \) infection in different ethnic and racial group are not known, socioeconomic factors, environmental factors, socio-cultural practices, and genetic predisposition may all contribute toward acquisition of \( H_p \) infection. Data available from both developed and developing countries suggest those rates of \( H_p \) infection in men and woman are approximately the same

**Microbiology**

*Helicobacter pylori* is a Gram-negative, spiral-shaped bacterium with a number of features that enable it to be classified in the new genus, *Helicobacter*; the presence of sheathed flagella which give the organism its mobility, an external glycocalyx which is produced in vitro, the major isoprenoid quinone being menaquinone-6 and a G+C content of chromosomal DNA of 35-44 mol %. As culture age, the organism changes from the classic bacillary form to a coccoid form which is no longer culturable.

*H. pylori* is observed to be oxidase-positive, catalase-positive, and strongly urease-positive. They are approximately 3 \( \mu \text{m} \) in length and 0.5 \( \mu \text{m} \) in width. The bacilli grow on chocolate agar at 37 °C under microaerobic condition. After 2-4 days incubation, they can be isolated. Although spiral, microaerophilic, asaccharolytic, non-spore-forming, gram-negative rods befit the genus *Campylobacter*, a number of significant morphologic, structural, biochemical, and genomic features indicated that these organisms should be placed in a new genus now named *Helicobacter*. *H. pylori* is the type species. \( H. pylori \) strains share similar protein profiles in whole cell, outer membrane, and acid-extracted preparations, and several of those proteins are conserved as group antigens. Restriction endonuclease digestion of \( H. pylori \) chromosomal DNA has indicated considerable diversity and has been used to type
strains. Plasmids appear to be present in a minority of strain. A serotyping scheme for \textit{H. pylori} has not been developed. Lipopolysaccharides are varied and may form the basis for a typing system.

The complete genome sequence of \textit{H. pylori} has been reported. The organism has a circular genome with more than 1.6 million base pairs and 1590 predicted coding sequences. Genomic analysis will undoubtedly provoke new ideas on pathogenesis and add additional understanding to the mechanisms of acid tolerance and antigen’s variation.

**Pathogenesis**

Gastric inflammation is an inevitable consequence of \textit{Hp} infection. The organism interacts with the gastric epithelial cell intimately attaching to the apical membrane, producing an attaching-effacing effect. Adherence itself, therefore produces a direct injurious effect on the epithelium which is amplified by production and release of a vacuolating cytotoxin, VacA. \textit{Hp} releases a variety of other enzymes, notably phospholipases, which produce toxic products. Although \textit{Hp} urease is thought primarily to enhance the organism’s acid tolerance by ammonia production, this way, at the same time, be toxic to the epithelium. Direct damage to the epithelium results in the release of chemokines such as IL-8 and GRO-\textsubscript{1}, which have chemotactic activity for neutrophils, and RANTES and EMIP-1 which have effects on monocytes and lymphocytes. Non-specific immunity predominately due to neutrophil infiltration is an important component of gastric inflammation and secondary epithelial cell damage, particularly through the generation of reactive oxygen metabolites. Mononuclear cells are a secondary source of proinflammatory mediators and act as antigen presenting cells which initiate specific immune responses, particularly T-cell activation.
The severity of the gastric mucosal inflammation is *Hp* strain dependent, being more evident in organisms that are Cag A gene positive. Organisms carrying the CagA gene induce a more profound proinflammatory cytokine response and a more severe gastritis.

One of the most engaging aspects is the possibility that autoimmunity may play a role in epithelial cell destruction and mucosal damage. Infected patients’ sera contain autoantibodies which recognize gastric mucosa and also antibodies against the human blood group antigen Lewis x which is surprisingly expressed by *Hp* lipopolysaccharide. The presence of the cross-reacting antigens in *Hp* and the possibility that the host antibody response may, therefore, be directed towards host structures supports the suggestion that autoimmunity may be an additional mechanism by which the organism damages host gastric epithelium and induces gastritis. Itoh T et al \(^{33}\) found recently that IFN-γ by gastric T cells may participate in pathogenesis of the *H. pylori* infected stomach by directing an isotype-switch of anti-*H. pylori* antibodies to complement-binding subclass and by augmenting cytotoxic activity of a certain autoantibody. This may explain a host-dependent diversity in gastric pathology of the patients with *H. pylori* infection.

**Associated Gastroduodenal disorder**

Recent years have seen great advances in many fields of medicine, but in few have they been more remarkable than in upper gastrointestinal disease. The discovery of *H. pylori* and the acceptance of its role in gastric pathophysiology represents a fundamental change in our understanding of gastroduodenal disease.

*Chronic Gastritis*
Gastric inflammation is an invariable finding in patients infected with *H. pylori*. Histologically, *H. pylori* associated chronic gastritis is characterized by surface epithelial degeneration, infiltration of the mucosa by chronic inflammatory cells (lymphocytes, plasma cells, and occasional eosinophils), and a characteristic but variable "active" component consisting of neutrophils. Qualitative or quantitative differences in *H. pylori*-induced gastritis may play a pivotal role in determining the varied clinical outcomes of infection. Two main patterns of *H. pylori* gastritis may occur. In the non-atrophic, chronic, active gastritis, the inflammation is primarily located in the antrum, the corpus being only mildly affected. This type of gastritis may persist indefinitely without causing disease or clinical manifestations. In a minority of patients, this antral-predominant gastritis predisposes to development of duodenal ulcer. This type of gastritis is clearly not associated with an increased risk of gastric cancer. The second type of gastritis is known as multifocal atrophic gastritis (MAG) or, as recently proposed, progressive intestinalizing pangastritis (PIP). MAG is characterized by atrophy and foci of intestinal metaplasia which arise in the incisura angularis and progressively expand both proximally and distally and may become confluent. MAG is associated with gastric ulcer and is widely believed to represent a strong risk factor for the development of the intestinal type of gastric carcinoma. The evidence for this association is derived mostly from studies performed in countries where this type of gastritis is highly prevalent (Colombia, Japan and Finland). Since in many parts of the world *H. pylori* is highly prevalent and atrophic gastritis uncommon, it is widely believed that environmental factors act in concert with the infection to cause this type of gastritis. In a similar fashion, *H. pylori* gastritis is believed to lead to development of intestinal metaplasia.

**Peptic Ulcers**

It is now clear that *Helicobacter pylori* is a major aetiological factor in peptic ulcer disease. About 95% of patients with duodenal ulcers and perhaps 80% of patients with gastric ulcers
are infected with this bacterium and its eradication greatly diminishes recurrence of these ulcers $^{36-39}$. Overall, about a third of *H. pylori*-associated peptic ulcers, which have already bled, rebleed during follow up for 1-2 years. Rebleeding is diminished to about 10% by long-term acid suppression but virtually abolished by eradication of *H. pylori*. Both the acute and chronic inflammatory components of the gastritis so commonly associated with peptic ulcer disease subside after eradication of *H. pylori* infection. Therefore, successful treatment of *H. pylori* infection not only heals the ulcer but heals the entire stomach. Many patients are still not receiving the benefit of this treatment, however. Most patients who have peptic ulcers without *H. pylori* infection are taking non-steroidal anti-inflammatory drugs (NSAIDs), although this may not be recognized or admitted. Such patients have to be managed by withdrawal of these agents or by giving protective agents. If *H. pylori* is present in a patient who develops an ulcer whilst taking NSAIDs, it remains unclear whether it is beneficial to eradicate the infection, but this seems advisable in case the ulcer is due to the infection in that particular patient.

**Non-ulcer dyspepsia**

The current international definition of dyspepsia is “persistent or recurrent pain or discomfort centred in the upper abdomen”, and excludes those with heartburn alone$^{40}$. The prevalence of dyspepsia in the general population is close to 25% if predominant reflux symptoms are excluded; approximately 50% of patients with dyspepsia do not have a peptic ulcer, oesophagitis, cancer or another definite structural explanation for their symptoms and these patients are considered to have functional or non-ulcer dyspepsia (NUD)$^{40-42}$. *H. pylori* infection is present in 30-60% of patients with NUD in Western countries$^{42}$, but studies attempting to establish a causal role for *H. pylori* infection in NUD continue to yield conflicting results. Although a meta-analysis identified an overall benefit of *H. pylori* therapy, only selected trials could be included. Some studies have suggested that significant symptom
improvement requires up to 12 months follow-up to be documentable. Paediatric clinical trial data are available but of limited relevance. While it is possible that *H. pylori* may be responsible for symptom in a small proportion of patients with non-ulcer dyspepsia and in some of these cases anti-*H. pylori* therapy may be beneficial, this remains to be established.

**Gastric Cancer**

Gastric cancer is the second most common fatal malignancy in the world[^43] and is the cause of more than 750,000 deaths annually[^44]. In 1990, it was the fourteenth most frequent cause of death globally[^44] and, despite a general worldwide decline in age-specific incidence rates[^45], projections indicate that the annual number of new cases will increase significantly in the developing world during the next few decades as a result of population growth and the changing age structure of populations[^46]. Without specialized screening facilities, gastric cancer is nearly always diagnosed at a relatively advanced stage and survival is uniformly poor, in most countries no more than 15%, 5 years after diagnosis[^47]. The evidence supportive of an aetiological association between *H. pylori* infection and gastric cancer was sufficient for a Working Group of the international Agency for Research on Cancer to classify such infection as a definite cause of cancer[^48]. As the infection is rarely self-limiting, it initiates a sequence of inflammatory mediated changes within the gastric epithelium, causing first acute and then chronic gastritis and, over a period of decades, increasingly degenerative changes and evolution towards the well-established precancerous conditions of atrophic gastritis, metaplasia and dysplasia[^49]. One longitudinal study[^50], comparing *H. pylori* positive to negative individuals over an 11 years periods, established that there was a significantly increased risk of developing precancerous gastric conditions associated with infection and reported an odds ratio of 9.0 (95% confidence intervals, 1.9-41.3). In addition, much of the descriptive epidemiology of gastric cancer parallels that for *H. pylori* infection[^51], most notably the strong association of both cancer and infection with poor socio-economic conditions.

[^43]: 17
Formal correlation studies carried out within China and internationally, have both shown a significant geographic relationship between gastric cancer mortality rates and the prevalence of \textit{H. pylori} infection.

\textbf{Gastric lymphoma}

Gastric lymphoma of mucosa associated lymphoid tissue (MALT) has characteristic clinicopathological features that are different from nodal-type B cell lymphomas. Before a lymphoma can arise within the stomach, MALT has to be acquired as part of a response to an immunological stimulus. In most instances, gastric MALT is acquired in response to infection by \textit{Helicobacter pylori}. The close association between gastric MALT lymphoma and \textit{H. pylori} is beyond doubt and is seen in 72-98\% of low grade cases. \textit{H. pylori} is less commonly found in high grade gastric lymphomas being seen in up to 71\% of cases with a concomitant low grade component, but only in 38-51\% of high grade tumors with no specific MALT features. \textit{H. pylori} infection is only seen in approximately 51\% of individuals with secondary involvement of the stomach by lymphoma of nodal-type. In a retrospective serologically based study, Parsonnet et al demonstrated that infection by \textit{H. pylori} predated the development of the lymphoma by many years and was associated with an odds ratio for the development of lymphoma of 6.3. The features of MALT lymphoma, such as plasma cell differentiation and follicular colonization, suggest that these lymphomas, although demonstrated on the basis of clonality studies to be neoplastic, retain some immunological drive. In vitro studies have shown that co-culturing cells derived from low grade MALT lymphomas with \textit{H. pylori} results in tumor cell proliferation in a T cell dependent manner.

Clinical studies have taken this discovery further and shown that patients with early low grade gastric MALT lymphoma treated with anti-\textit{Helicobacter} therapy can show regression of their tumors. It is now generally accepted that eradication of \textit{H. pylori} is a central component of the management of MALT lymphoma.
**Hypergastrinemia and hypo/chlorhydia**

An important adaptation of *H. pylori* to the gastric environment may be its ability to alter gastric acid secretion. Acute infection is associated with transient hypochlorhydia, whereas chronic infection is associated with hypergastrinemia and decreased somatostatin levels. Thus, the survival of *Hp* in the gastric environment may be attributed to both the development of specialized intrinsic defenses and the organism’s ability to induce physiological alteration in the host environment.

*Hp* infection has been found to decrease local expression of the inhibitory peptide somatostatin, and to increase release of the acid-stimulating hormone gastrin when compared with non-infected patients. And *Hp* eradication is associated with a significant decrease in basal and stimulated gastrin levels.

There is evidence of a two way interaction between gastric acid secretion and *Hp* associated gastritis. Gastric acid secretion influences the density of *Hp* colonization, its distribution within the stomach and the severity of the mucosal inflammation. In addition, *Hp* gastritis alters gastric acid secretion. In subjects with a predominant antral gastritis, it increases acid secretion predisposing to duodenal ulcer, whereas in others with predominant body gastritis, acid secretion is impaired and the subjects have an increased risk of gastric ulcer and intestinal type gastric cancer. The two way interaction between acid secretion and *Hp* gastritis is observed when *Hp* positive subjects are treated with proton pump inhibitor agents. The inhibition of acid secretion induces a body gastritis and this inflammation of the body mucosa inhibits acid secretion thus augmenting the anti-secretory effect of the drug. The reason why the infection exerts these divergent effects on gastric morphology and function remains unclear and is a challenge for ongoing research.
Histological Features

**Gastric atrophy and atrophic gastritis**

Gastric atrophy is defined as the loss of appropriate glands in a given gastric compartment. This is a purely histopathological definition and indicates that in the portion of gastric mucosa under examination the glands expected to be present (e.g. oxyntic glands in the mucosa of the corpus) are no longer there, and have been replaced by something else that does not belong to that area. This ”something else” may be extracellular matrix, fibrosis, or other glands that normally are not there (e.g. intestinal-type glands or pseudopyloric glands). While atrophic gastritis is defined as a type of gastritis characterized by the presence of significant areas of atrophy. The two most common causes of atrophic gastritis are chronic infection with *Hp* and the autoimmune gastritis that may become associated with pernicious anaemia. It is more severe in the antrum (antral-predominant) found in most subjects infected with *Hp*.

Atrophic gastritis is usually characterized by extensive areas of intestinal metaplasia and has been known for several decades to represent a significant risk factor for gastric adenocarcinoma\(^{68-69}\). A diagnosis so loaded with significant prognostic implications ought not to be made lightly but, surprisingly, the histopathological criteria for atrophic gastritis have been and remain vague.

**Intestinal Metaplasia**

When the gastric glands native to a region of the stomach have been destroyed, they may be replaced by other types of glands. Most commonly, an intestinal-type epithelium refurbishes the injured mucosa with intestinal type crypts. The epithelium may consist of globet cells, Paneth cells and absorptive cells. The metaplastic mucosa, which may consist of a few cells or extend to cover much of the gastric mucosa, is generally inhospitable for *Hp* colonization\(^{70}\). If the native glands have been replaced by metaplastic epithelium, then the conditions of the
definition of atrophy are fully satisfied. Three types of intestinal metaplasia are usually considered: (1) type I or complete or small intestine type, composed of columnar crypt/absorptive enterocytes with sparse globet cells, with or without Paneth cells and intestinal type endocrine cells; (2) type II or incomplete sulphomucin-negative type, consisting of globet cells scattered among gastric foveolar and neck cells; (3) type III or incomplete sulphomucin-positive type, showing globet cells scattered among sulphomucin-producing columnar cells.

The inability of $H_{p}$ to attach to intestinal type epithelium, raises the possibility that intestinal metaplasia is a defence response against infection. Likewise intestinal epithelium is more resistant than gastric epithelium to the damaging effects of bile reflux. Thus, in the process of IM, gastric epithelium is substituted by an epithelium better suited to counteract two adverse factors: $H_{p}$ infection and bile reflux. Interestingly, when well-developed IM is present in $H_{p}$ related gastritis, there is an appreciable decline in inflammatory cells in the underlying lamina propria. This observation suggests that the inflammatory infiltrate is closely related to sites of bacterial attachment and not simply a diffuse response to $H_{p}$ in the stomach. It also explains why the severely atrophic and metaplastic gastric mucosa of an 'end-stage' chronic gastritis, frequently contains very few inflammatory cells and may by described as 'quiescent'.

**Gastric carcinoma**

Gastric carcinoma can be classified into early and advanced gastric carcinoma. Early stage of gastric carcinoma involves either the mucosa or submucosa, not extending into the muscularis propria, whether with lymph node metastasis or not. The majority of the gastric carcinoma are detected at an advanced stage, i.e., they have extended into or beyond the muscularis propria of the stomach. Hence the overall 5-year survival is very poor. Although no classification of gastric carcinoma is entirely satisfactory, that of Lauren has proven to be the most useful, particularly for comparative epidemiologic and pathologic studies. In this classification,
gastric carcinoma are divided into two types: intestinal and diffuse. As a group, the intestinal type are the well-differentiated cancers, are highly associated with histologic evidence of chronic mucosal injury and are expansile in its growth pattern. In contrast, diffuse type of gastric carcinoma are the poorly-differentiated and signet ring cell lesions, are much less often associated with chronic mucosal injury and precancerous changes, and are noncohesive and infiltrating in its growth pattern.

**Gastric Endocrine cells**

Gastrin (G) cells and Somatostatin (D) cells are two important endocrine cells in the antrum, which are related to acid secretion. It was reported\(^7\)\(^2\) that in antrum about 50% of the whole endocrine cell population are G cells and 15% are D cells while in the corpus mucosa, however, a major portion of the endocrine cells are ECL cells.

**Diagnosis and treatment**

The recognition that \(Hp\) plays a pivotal role in the pathogenesis of several gastroduodenal pathologies makes its diagnosis necessary in many different circumstances. Numerous reliable invasive and non-invasive diagnostic tests have been developed. Each has advantages and disadvantages which will make it more or less appropriate depending on the clinical situation. The invasive biopsy-based tests which include rapid urease test, histology and culture are important in the assessment of \(Hp\) status pretreatment, as endoscopy allows assessment of treatment indications such as ulcer diseases. The non-invasive tests obviate the need for endoscopy and comprise sensitive and specific serological tests for screening and the urea breath test, using either \(^{13}\)C or \(^{14}\)C. In view of the patchy distribution of \(H. pylori\), all biopsy-based tests may theoretically fail to diagnose the infection. The inherent risk of sampling error can, however, be virtually eliminated by obtaining several biopsy samples from the gastric corpus as well as from the antrum. In contrast to biopsy-based methods, non-invasive tests are
useful for epidemiologic tools and for confirming the success of eradication therapy. They can assess the global presence of *Hp* in the stomach even when the organisms are irregularly distributed on the gastric mucosa. Non endoscopic tests, particularly serology, are cheaper and more convenient, and should be preferred in situation where the conditional information yielded by an endoscopy is not needed.

During the past years, a myriad of treatment regimens have been offered to clinicians for the eradication of *Hp*. Following many trials it is now clear that multi-drug regimens are essentials, the treatment of choice now being triple therapy with a proton pump inhibitor and two antibiotics. An alternative regimen using ranitidine bismuth citrate combined with one or two antibiotics has also been proposed, although clinical experience with this regimen is substantially less than with proton pump inhibitor-based triple therapy.

**Future development**

After development of suitable immunological diagnostic tests for *H. Pylori* (ELISA and Immunoblotting) development of the tests which can identify pathogenic or virulent strains of *Hp* responsible for most cases of peptic ulcer disease are eagerly awaited. An ELISA using a recombinant fragment of Cag A (Oravac, Inc. Cambridge, Ma, USA) is now under clinical study.

*H. pylori* infection remains the most common infection worldwide. Global eradication if this is thought to be ultimately beneficial, could only be achieved by widespread vaccination.

Preliminary studies in mice suggest that vaccine development is achievable and that an appropriate vaccine may not only induce protective immune responses and prevent infection in the uninfected, but might also be used as an adjunct to eradication therapy. Further work is
clearly required to develop a vaccine that can be used in human infection. If successful, vaccination may indeed be able to end the coexistence of humans and \textit{H. pylori}.

\textbf{Scope of this thesis}

The discovery of \textit{H. pylori} and the gradual realisation of its importance in upper gastroduodenal diseases represents one of the most important developments in medicine of the past recent. The aim of the work described in this thesis was to obtain a better understanding of this organism – \textit{H. pylori}, with our main focus on the epidemiologic and histopathological aspects of its related gastroduodenal diseases. \textit{H. pylori} has a global distribution and infects human gastric mucosa exclusively. Its prevalence varies widely in different parts of the world. There are significant geographical differences regarding its prevalence, the clinical manifestations and its histological features. In Chapter 2 we compare the gastric mucosa in various age cohort in \textit{Hp} infected patients from several geographical areas in the world. We compare the degree and severity of atrophy and intestinal metaplasia according to age by using a standardized grading system according to a modified Sydney classification. In addition, we also investigate the association between the prevalence of atrophy and intestinal metaplasia, and the gastric cancer incidence in each area. \textit{Hp} infection causes chronic gastritis, and the current view is that the persistent \textit{Hp} infection can lead to the loss of glands, resulting in multifocal atrophic gastritis. It has been estimated that the risk of gastric carcinoma in patients with gastric atrophy is much higher than that in subjects without atrophy. Although the significance of atrophy for the subsequent development of gastric carcinoma is widely accepted, the assessment of atrophy remains a special problem. It is important to improve the diagnostic methodology for adequate scoring of atrophic gastritis. Therefore, in Chapter 3, we use the Japanese endoscopic scoring system for
atrophy—endoscopic atrophic border, to investigate the strength of the agreement between the endoscopic border and the histologic score for atrophy, in order to improve the diagnosis of atrophic gastritis.

As we know from the correlation studies in China and internationally, there is a significant geographical relationship between gastric cancer mortality rates and the prevalence of *Hp* infection. Gastric cancer is the most common fatal malignancy in China and the majority of the death are attributed to the local invasion and/or distant metastasis. The management of the patients is far from satisfaction. So in **Chapter 4** we use a cysteine proteinase - Cathepsin B, which functions in the proteolysis step in tumor invasion and metastasis, to compare its expression in gastric carcinoma with non-neoplastic tissue, and to investigate the association among the expression, the depth of invasion, the growth pattern of tumor and the lymph nodes metastasis, in order to provide a new marker for invasion and metastasis.

The gastric mucosa is endowed with a rich array of endocrine cell types. The major endocrine cells known to play an important role in acid secretion are the gastrin (G) cell of the antrum, the somatostatin (D) cells of the antrum and fundus, and ECL cell of the oxyntic mucosa. They either up-regulate or down-regulate acid secretion by the parietal cells. In **Chapter 5** we give a short review to discuss the regulation and effect of these endocrine cells on gastric acid secretion and their pathologic situation.

It was reported that the majority of *Hp* infected individuals do not develop clinically apparent disease but there is now indisputable evidence that some of infections (6-20%) result in peptic ulceration and a smaller proportion (less than 1%) are associated with gastric cancer. It seems likely that infection in a given individual will result either in the peptic ulcer pathway with associated increased acid output, or the chronic atrophic gastritis-carcinoma pathway which is associated with hypo- or achlorhydia. Therefore in **Chapter 6** we investigate the Gastrin G cell and Somatostatin D cell—two important regulators of gastric acid secretion, in *Hp*.
infecte dd  an  d  non-infecte d  subjects,  t o  determin e  thei r  ke y  rol e  in 
Hp associate d  gastroduodenal  diseases.  

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