Helicobacter pylori infection. Several studies on pathology and clinicopathology

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CHAPTER 1

General Introduction

HELIcobacter Pylori INFECTION

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INTRODUCTION

Since the discovery of Helicobacter pylori (H. pylori) in the gastric mucosa by Warren and Marshall in 1983, H. pylori has brought about a complete revision of our concepts of chronic gastritis and its consequences. The original description of Campylobacter pylori (now H. pylori) emphasized their close association with chronic active gastritis. Human volunteer and animal experiments and the resolution of inflammation following eradication of infection, clearly indicate a pathogenic role for H. pylori. Indeed it is now possible to explain all the principal histological features of chronic gastritis based on response to, or consequences of, H. pylori infection. We can now recognize H. pylori as the major cause of chronic gastritis worldwide. H. pylori infection can be associated with gastric adenocarcinoma and MALToma. The World Health Organization has classified H. pylori as a class I carcinogen.

EPIDEMIOLOGY

We now know that H. pylori infection is distributed throughout the world and that it is linked to important medical conditions. Its prevalence not only varies among the countries, notably in developing and developed countries, but also in different regions of the same country. The prevalence of H. pylori infection in developing countries is more frequent compared with developed countries. The prevalence rate of H. pylori infection increases with age and is related to low socioeconomic status in childhood. Many studies have shown that the geographical variation in
the prevalence was related to the difference in incidence of gastric cancer.\textsuperscript{27-29} The incidence of gastric carcinoma also varies greatly in different areas of the world.\textsuperscript{30-33}

**DETECTION OF HELICOBACTER PYLORI**

*H.pylori* is the organism that can be confidently recognized by histology. The micro-organism is able to colonize the human stomach, thereby surviving in a strongly acidic gastric luminal environment, with pH levels of 0.5-2.\textsuperscript{34} The organisms were first demonstrated using a silver impregnation method (the Warthin-Starry stain).\textsuperscript{35} Various alternative silver staining techniques are claimed to have great sensitivity. The most widely employed is the modified Giemsa stain\textsuperscript{36} but others such as Genta stain\textsuperscript{37} and carbol-fuchsins are equally capable of delineating the organisms. Studies which have compared the rate of detection of *H. pylori* in routine H&E sections with special methods have consistency shown false negatives. Scanty organisms will be missed if reliance is placed on H & E detection alone. The use of a special stain is strongly recommended, particularly when H&E fails to reveal organisms in a biopsy specimen with chronic active inflammation.\textsuperscript{38} Immunostains are also available for the demonstration of *H.pylori* \textsuperscript{39,40} and may be particularly useful in detecting coccoïd form. \textsuperscript{41} (Table 1)

The organisms are identifiable as *H.pylori* on the basis of their characteristic morphology. *H.pylori* are uniform, curved, wavy or 'seagull shaped', and microaerophilic Gram-negative rod, 3 μm long and 0.5-1.0 μm wide. They are closely applied to the surface epithelium under the mucous layer, and usually also
present in gastric mucus and in gastric foveolar. In most cases the organisms are numerous and are diffusely distributed on the surface of the gastric mucosa. Round coccoid forms are sometimes seen.

Table 1. Histochemical techniques for demonstrating *H. pylori*

<table>
<thead>
<tr>
<th>Non-specific staining methods</th>
<th>Specific staining techniques</th>
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<tr>
<td>Warthin-Starry</td>
<td>Immunostain</td>
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<td>modified Giemsa stain</td>
<td>In situ hybridization</td>
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<td>Genta stain</td>
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<td>Carbol-fuchsin</td>
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### TISSUE SPECIFICITY OF HELICOBACTER PYLORI INFECTION

An important aspect of the pathogenicity of *H. pylori* is its ability to bind to the membrane of gastric epithelial cells. Such attachment ensures more effective colonization and may enhance nutrition of the bacterium, as well as facilitating the delivery of cytotoxic agents and antigens to the mucosa. Bacterial attachment is dependent upon the production of binding molecules-adhesions, which link the organism to proteins or glycoconjugates on the surface of eukaryotic cells. The more specific the adhesion, the more limited is the range of cells to which the organism can attach. *H. pylori* attachment appears to be totally specific for gastric surface and foveolar mucous cells. The precise nature of the receptor or the *H. pylori* adhesion are not known, although the receptor is a fucose containing
glycoconjugate. Recent study indicates that the receptor includes the Lewis B blood group antigen within its structure. Only epithelial cells expressing this specific receptor can be successfully colonized by \textit{H.pylori} which explains the tropism between the organism and cells of gastric surface or foveolar phenotype. Thus \textit{H.pylori} can only colonize the stomach and sites where there is heterotopic or metaplastic gastric epithelium.

The most common extra-gastric site of colonization is on patches of metaplastic gastric cells in the duodenum. Another 'ectopic' site for gastric-type epithelium is in Barrett's esophagus. \textit{H.pylori} have been found in rarer sites, such as over the heterotopic gastric epithelium in Meckel's diverticula and rectum. The later finding lends support to the faecal-oral route of transmission. Subsequently \textit{H.pylori} has been successfully cultured from faeces.

**CHRONIC HELICOBACTER PYLORI GASTRITIS**

Classification

For several decades chronic 'non-specific' gastritis has been an enigma. The lack of a recognized aetiology and its dubious clinical relevance have led to considerable confusion over interpretation and nomenclature. Faber originally distinguished between superficial and atrophic forms and later introduced the concept of a gradation of involvement through to gastric atrophy in 1927. The term 'gastric atrophy' was used to describe end-stage disease where glandular atrophy was complete and inflammatory cells were scanty or absent, these being the
characteristic histological findings in patients with pernicious anaemia. In practice
the diagnosis of gastric atrophy is difficult to apply and serves to confuse rather than
clarity the issue. Even the distinction between superficial and atrophic gastritis has
remained an area of dispute.

Chronic superficial gastritis, now named as non-atrophic gastritis has generally
been defined as an increase in chronic inflammatory cells in the lamina propria of
the mucosa between the gastric foveolae, whereas chronic atrophic gastritis is
diagnosed when there is full thickness infiltration by chronic inflammatory cells and
glandular atrophy. However, many gastric biopsies reveal inflammatory cell
infiltration of the full mucosal thickness without demonstrable atrophy; there is no
widely accepted term for this category. Thus 'preatrophic' gastritis has been
proposed but in practice most pathologists allocate such cases into the superficial
or atrophic gastritis categories according to different criteria.53

Classifications based on topography and clinical association at first brought some
clarification but their subsequent multiplication has only added to the confusion.
Two major categories of chronic gastritis with atrophy were recognized by Strickland
and Mackay in 197354: type A, an autoimmune type mainly affecting body mucosa;
and type B, showing predominantly antral involvement. The aetiology of this
category was unknown although there was no shortage of suggestion such as: bile
reflux, therapeutic drugs, hot drinks and salted or spicy foods were all proposed with
varying degrees of conviction. A further category, type AB, was suggested by Glass
and Pitchumoni in 197555, where there was patchy involvement by gastritis and
atrophy in both antrum and corpus. AB gastritis is characterized by multifocal atrophy and intestinal metaplasia, and carries and increased risk of gastric ulceration and carcinoma. Later, Correa introduced an epidemiological basis for his classification in which 'hypersecretory' gastritis was associated with duodenal ulceration, and 'environmental' gastritis (like the AB type) was linked to gastric ulceration and an increased cancer risk in 1980. He later modified these categories along topographical lines and recognized diffuse corporal gastritis (autoimmune), diffuse antral gastritis and multifocal atrophic gastritis (as in type AB) in 1988.

Following the discovery of *H. pylori* it is now widely accepted that 'diffuse antral gastritis', a pattern which has long been recognized as an accompaniment of duodenal and pre-pyloric ulcers, is a result of infection. However, the varying patterns of mucosal involvement by chronic inflammation and geographic differences in the prevalence of atrophy and metaplasia, continue to persuade many investigators, particularly in Japan and the United States, that there are other nosological entities separate from 'H.pylori-associated' gastritis within non-autoimmune chronic gastritis. While certain 'special' forms of gastritis such as lymphocytic and chemical (reflux-type) gastritis have been distinguished, there are strong grounds for concluding that *H. pylori* is the major cause of non-autoimmune chronic gastritis. This does not exclude other factors in the histogenesis of atrophy and intestinal metaplasia. On the contrary, *H pylori*-associated gastritis may well provide the background substrate on which other aetiological agents operate, giving rise to variations on the theme rather than separate pathological entities.
In order to take account of recent developments and in an attempt to remove diagnostic confusion, the Sydney System for the grading and classification of chronic gastritis was introduced by Misiewicz in 1990, and it was later updated in 1994. As well as underlining the importance of topographical differences in the distribution of gastritis, the System has a morphological section which is a novel attempt to produce a 'flexible matrix of rules' by which five histological variable (see blow) are graded independently on a simple four point scale (absent or normal, mild, moderate and severe abnormality). The System provides the framework for a standardized description of chronic gastritis which is not confined to aetiological categories, and should prove useful in clinico-pathological research as well as providing a sound basis for routine diagnosis. The grading approach is useful in assessing *H. pylori*-related and autoimmune-type chronic gastritis, and those cases of chronic gastritis in which *H. pylori* is not histologically detectable. Special form of gastritis are considered separately and not subjected to grading.
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<td>Morphological description</td>
<td>Topographical</td>
<td>Topographical</td>
<td>Aetio-pathogenetic entities</td>
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<td>Topographical with aetiology where known</td>
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<tr>
<td>Chronic superficial</td>
<td>Type A = Chronic atrophic gastritis of corpus with parietal cell antibodies (autoimmune type)</td>
<td>Type A = Corpus gastritis</td>
<td>Autoimmune gastritis</td>
<td>chronic diffuse antral gastritis</td>
<td>Chronic gastritis of antrum or antral predominant (usually H. pylori +) ± atrophy/IM</td>
<td>Typical pattern of H. pylori-associated gastritis, and characteristic of patients with duodenal ulcer disease</td>
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<tr>
<td>Chronic atrophic</td>
<td>Type B = Antral gastritis ± corpus involvement, no parietal cell antibodies</td>
<td>Hypersecretory gastritis</td>
<td>Chronic diffuse antral gastritis</td>
<td>Chronic gastritis of antrum or antral predominant (usually H. pylori +) ± atrophy/IM</td>
<td>Typical pattern of H. pylori-associated gastritis, and characteristic of patients with duodenal ulcer disease</td>
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<tr>
<td>Type AB = Antrum + Corpus gastritis</td>
<td>Environmental gastritis</td>
<td>Chronic diffuse antral gastritis</td>
<td>Chronic gastritis</td>
<td>Chronic gastritis</td>
<td>Chronic gastritis of antrum or antral predominant (usually H. pylori +) ± atrophy/IM</td>
<td>Typical pattern of H. pylori-associated gastritis, and characteristic of patients with duodenal ulcer disease</td>
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<tr>
<td>Chronic superficial gastritis</td>
<td>Without atrophy/IM (usually H. pylori +)</td>
<td>Chronic gastritis</td>
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IM = intestinal metaplasia
HISTOLOGICAL FEATURES

The histological picture of chronic gastritis is well known, but only since the advent of *H. pylori* have the various histological components had a rational explanation. The features comprise graded variables (such as *H. pylori* density, neutrophil polymorph, chronic inflammatory cell infiltration, glandular atrophy and IM) and nongraded variables (such as epithelial degeneration, lymphoid follicles, foveolar hyperplasia, and pseudopyloric metaplasia).

**H. pylori density**

Whether *H. pylori* is present is the most important information for clinical management purposes. Variations in *H. pylori* density may have a bearing on disease associations and have epidemiological importance. The density of *H. pylori* should be evaluated on gastric epithelium alone or averaged over the length of the entire mucosa since the presence of metaplasia is not prone to colonize by *H. pylori*.

**Chronic inflammation**

The normal gastric mucosa contains very few lymphocytes in the lamina propria. An influx of lymphocytes and plasma cells is the key diagnostic feature of chronic gastritis. The corpus mucosa contains scattered small lymphoid aggregates which about onto the muscularis mucosa, but like the antrum, there are few if any lymphocytes and plasma cells in the superficial lamina propria. Thus the presence of plasma cells (however few) in the superficial lamina propria of the gastric mucosa
is indicative of gastritis.²⁹

The degree of chronic inflammatory cell infiltration is correlated to the extent and density of *H. pylori* colonization, and is greater in the antrum than in the corpus, and this agrees with the generally increased degree of inflammatory cell infiltration seen in the antrum.⁶⁶

Formerly the chronic inflammatory component of gastritis was attributed to some 'non-specific' response to ill-defined mucosal injury. With the discovery of *H. pylori*, the presence of numerous lymphoid cells in the gastric mucosa can now be understood as the mucosal immune response to bacterial infection. *H. pylori* produces several important antigens including urease, lipopolysaccharide (LPS)-endotoxin, a 62K heat shock protein, the 87K cytotoxin and a 128K cytotoxin-associated protein.⁶⁷ Initially these antigens are taken up by monocytes and dendritic cells in the lamina propria as a consequence of which they produce tumour necrosis factor (TNF-α) and interleukins 1 and 6.⁶⁸ Tumour necrosis factor promotes the adhesion of leukocytes to endothelial cells and recruits leukocytes to the site of infection. Direct acting antigens and processed antigens, together with interleukins 1 and 6, stimulate T-helper-cells (CD4 positive), and these produce a variety of cytokines including interleukins 4, 5 and 6 and interferon.⁶⁹ Such interleukins, and particularly IL-6, stimulate the differentiation of B-cells into specific antibody producing plasma cells. Interferon γ stimulates the expression of HLA-DR on gastric epithelial cells and this may represent an alternative mechanism of antigen presentation.⁷⁰ Production of IgM, secretory IgA, and IgG follows the B-cell
response. While secretory IgA may play a 'blocking' role in reducing bacterial adhesion, opsonization and complement activation IgG forms the main arm of the mucosal immune response. IgG antibodies promote complement-dependent phagocytosis and killing of *H. pylori* by polymorphs, but the antibodies quickly lose their adhesive properties in an acidic environment, and catalase production by the organism offers some protection against polymorph attack. Other inflammatory mediators produced by activated monocytes and polymorphs include prostaglandins (PGE2), leukotrienes, proteases and reactive oxygen metabolites (ROMs). Polymorph and monocytes release of proteases and ROMs are likely to be important in causing tissue damage, particularly where there is a relative deficiency of antioxidants such as vitamins C and E. The tendency for polymorphs to congregate around the proliferative compartment of the pit isthmus may cause lethal damage to stem cells and result in glandular atrophy.

**Neutrophil infiltration**

Polymorph infiltration is an important aspect of *H. pylori* gastritis and gives rise to the epithet 'active' chronic gastritis. Infiltration is seen in both the lamina propria and in the epithelium. Epithelial infiltration is closely related topographically to colonization by *H. pylori* but not to their numbers, and is invariably associated with some degree of epithelial degeneration (Photo 1, cover 2).

Polymorph infiltration results from a continuation of those chemotactic mechanisms applying in the acute phase together with other factors which become operative. Cytokine production by monocytes and lymphocytes leads to the
expression of leukocyte adhesion molecules (ICAM, VCAM) on vascular endothelium and promotes polymorph emigration. Cytokines also up-regulate the production of interleukin 8 (IL-8) by epithelial cells in response to bacterial cagA protein. Finally, the complement pathway could be activated by IgG anti-*H. pylori* antibodies produced as part of the mucosal immune response to infection.\(^\text{74}\)

Despite the influx of polymorphs and the production of specific anti-bodies, *H. pylori* infection persists throughout life in the majority of individuals. Cross-sectional data on the prevalence of polymorph activity in European subjects with chronic gastritis suggests that the active phase lasts into old age. Only above the age of 70 years does activity diminish with such individuals frequently showing marked glandular atrophy.\(^\text{75}\) This occurs at a younger age in countries where infection in early childhood is the norm. In such populations the earlier onset of atrophy and metaplasia will be accompanied by diminishing activity (and loss of organisms) in middle age.

**Atrophy**

Atrophy can be defined as the loss of specialised glandular tissue, partly characterised by replacement by IM. Atrophy leads to thinning of the gastric mucosa and is a common denominator of all pathological processes causing severe of progressive mucosal damage. Thus, loss of glands may result from erosion or ulceration of the mucosa with destruction of the glandular layer, or a prolonged inflammatory process where individual glands undergo 'piecemeal' destruction. When this loss occurs, it may be followed by fibrous replacement or by a collapse of
the existing supporting matrix.

Gastric glandular atrophy is relatively easy to detect when it is severe, however, recognition of minor degrees of atrophy in the antrum is difficult (Photo 2, cover 2)\(^{58,76-78}\). A useful way to judge antral atrophy is the demonstration that the three to four gland cross sections that normally span the lower antral mucosa are reduced to two or fewer cross section\(^{58}\).

The prevalence and severity of atrophy among patients with chronic gastritis increases steadily with age. This is not an effect of ageing per se; there is no evidence that atrophy occurs as a physiological ageing phenomenon and elderly subjects without gastritis have normal acid output.\(^{79}\) It is believed that there is a transition from non-atrophic gastritis according to the duration severity of inflammation. This is most commonly attributable to \(H.\ pylon\) but other forms of long-standing gastritis, such as autoimmune or reactive gastritis, could have the same effect.

The prevalence of \(H.\ pylon\) positivity in the stomach declines with increasing glandular atrophy. There are three main reasons for the loss of organisms. First, as \(H.\ pylon\) colonizes only gastric epithelium, the organisms are absent from areas of IM that are usually present in atrophic stomachs. Secondly, the hypochlorhydric stomach is inimical to \(H.\ pylon\) and it appears that the organism requires a partially acidic environment in which to thrive. In vitro studies suggest that at high pH level, ammonia produced by urease activity remains unneutralized, accumulates and becomes toxic to the bacterium.\(^{80}\) Thirdly, acidic glycoproteins secreted by
metaplastic epithelium may provide a more hostile environment for *H. pylori* than the neutral glycoproteins of the normal mucous layer. Therefore the failure to demonstrate *H. pylori* in the atrophic stomach does not deny a role for infection in the underlying gastritis.

Atrophy in *H. pylori* related gastritis could result from direct bacterial effects, or might be a consequence of the inflammatory response. Thus, cellular destruction by cytotoxins, ammonia products, or proteases and ROMs released by polymorphs and other inflammatory cells may be involved. A further possibility is that the immune reaction mounted against *H. pylori* cross-reacts with antigens on glandular epithelial cells and destroys them.\(^8\) It is also likely that other factors such as bile reflux act in synergy with *H. pylori* gastritis and accelerate the development of atrophy. Conversely, certain dietary factors may exert a protective influence against the development of atrophy; in particular the anti-oxidant vitamins-vitamin C, vitamin E, and \(\beta\) carotene are likely to play some part.

**Intestinal Metaplasia (IM)**

IM(Photo 3, cover 3) is a common finding in chronic gastritis and appears to increase in prevalence according to its duration. Given that *H. pylori* infection is the major cause of gastritis there are wide variations in the incidence of metaplasia between countries and ethnic groups according to the peak age of acquisition of infection.\(^6\,15\,82\,83\)

IM is found more frequently in *H. pylori* positive than negative cases, despite the tendency for stomachs with extensive metaplasia to lose *H. pylori*.\(^84\) Similarly it has
been shown that *H. pylori* is an additional independent risk factor for IM separate from bile reflux.\(^6\) It seems likely therefore that, as with atrophy, there is some synergy between *H. pylori* and bile in the production of IM. Epithelium already sustaining damage from *H. pylori* is more likely to be eroded by bile reflux and be substituted by intestinal type cells during the regenerative process. Such 'regenerative' metaplasia is likely to be transient, but with repetitive injury IM becomes more extensive and permanent.

The inability of *H. pylori* to attach to intestinal-type epithelial cells, raises the possibility that IM 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. pylori* infection and bile reflux. The concept of IM as an adaptive response is against the long held belief that IM is a mutational event in the multi-stage process leading to gastric cancer.\(^5\) While metaplasia could result from a reversible mutation, there is no evidence that mutation is a necessary event. Modern theories of metaplasia implicate divergent differentiation from stem cells that react to an adverse environment by 'switching on' genes whose products induce differentiation along an alternative, but 'normal', pathway.\(^7\) Such divergent differentiation gives rise to end-cells that have a survival advantage over the original epithelium. Thus gastric mucosal stem cells can diverge to intestinal epithelium when subjected to repeated injury in the same way as esophageal epithelium diverges from squamous to columnar epithelium in
the face of acid injury.

Interestingly, when well-developed IM is present in *H. pylori* 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. pylori* 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'.

**Epithelial degeneration**

Surface epithelial degeneration is a continuing, but much more variable, feature of the chronic phase. While in general the degree of degeneration parallels the density of *H.pylori* colonization, this is by no means always the case at an individual level. Some biopsies that show marked degeneration have only scanty bacteria, whereas dense colonization is occasionally seen over normal, or near normal, epithelium. This could reflect differences in virulence among strains of *H.pylori*, but degeneration is also dependent upon the proportion of organisms attached to epithelial cell. The degenerative changes rapidly revert to normal following successful eradication of infection, lending support to a direct role of bacterial products in their causation.

**Lymphoid follicles**

The finding of lymphoid follicles in *H.pylori*-associated gastritis is of particular
interest. The normal gastric mucosa contains few if any T and B lymphocytes. The presence of aggregates of lymphocytes with germinal centres indicating B-lymphocyte proliferation is a conspicuous feature of *H. pylori* related gastritis, and represents an example of acquired mucosa-associated lymphoid tissue (MALT) (Photo 4, cover 3). If *H.pylori* infection is the major determinant of the development of gastric lymphoid tissue, it is highly likely that it is a crucial factor in the aetiology of gastric B-cell lymphomas (MALTomas). Using a standard biopsy protocol Edt and Stolte found lymphoid follicles or aggregates in 54% of cases of *H. pylori*. However, if sufficient biopsies and sections are examined, it is claimed that follicles will be found in all *H. pylori* positive cases. Lymphoid follicles are sufficiently prominent in childhood infection to produce a distinctive nodularity in the gastric antrum. On rare occasions the lymphoid infiltration can take on features which raise the suspicion of gastric lymphoma. Such cases reveal a greatly expanded population with large follicles and lymphocyte encroachment on epithelial structures analogous to the lympho-epithelial lesions of frank lymphoma. However, before making a diagnosis of lymphoma it would be wise to undertake a trial of anti-helicobacter therapy as we have seen striking resolution of lymphoid infiltration following elimination of infection. Indeed, some cases which satisfy the currently accepted criteria of malignant lymphoma have been successfully treated by *H.pylori* eradication treatment.
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OUTLINE OF THESE THESIS

Since the initial isolation of *Helicobacter pylori* (*H. pylori*) from the human stomach by Warren and Marshall in Australia in 1983, a great deal of research has been done and astonishing amount of papers has appeared in the world literatures over the last ten years. The studies on this topic have gained significant impetus. These research papers cover a broad spectrum of issues varying from epidemiology, pathogenesis, associated-diseases, diagnosis and treatment of *H. pylori*. We now know that *H. pylori* infection is distributed throughout the world and is linked to important medical conditions including chronic gastritis, peptic ulcer disease, adenocarcinoma of the stomach, and gastric lymphoproliferative disorders, including lymphoma.

Despite this unrivaled scientific research, many questions remain unsolved. The main of the thesis is to contribute to knowledge of: 1. interobserver variation between East and West in the assessment of *H. pylori* associated gastritis according to the Sydney system for classification of chronic gastritis; 2. geographical differences in precancerous conditions-atrophy and intestinal metaplasia (IM) from two distinct populations (China and the Netherlands) in *H. pylori*-associated gastritis; 3. the relationship between *H.pylori*-associated gastric diseases and lymphoid tissue hyperplasia in Chinese; 4. relevance of VacA and gastric mucosal morphological changes in Chinese patients with gastroduodenal
diseases after *H. pylori* eradication; 5. effect of *H. pylori* infection on cyclooxygenase-2 express in gastric antral mucosa.

In **Chapter 2** the interobserver variation, especially between East and West, in grading various pathological features of *H. pylori*-associated gastritis is investigated. Since the updated Sydney System for classification of chronic gastritis was introduced in 1994, several studies on interobserver variation on the assessment of *H. pylori* associated gastritis have been reported. Despite reproducibility of grading *H. pylori* associated gastritis is high using the updated Sydney system, there was still remained imperfect agreement on grading atrophy, especially with a low level of atrophy, which suggest there need to be improvement in the criteria for grading atrophy.

In **Chapter 3** the discrepancies in the prevalence and the severity of atrophy and IM in antral mucosa of *H. pylori* associated gastritis, and difference in age of onset among Chinese and Dutch patients are investigated. The pathological changes of *H. pylori* associated gastritis; especially regarding the precancerous conditions (atrophy and IM), have been studied extensively in recent years. However, very few data are available concerning gastric mucosa from different countries using the same grading criteria and with the samples being assessed by the same pathologist. In our study, the degrees of atrophy and IM from two distinct populations (China with a higher incidence of gastric cancer and the Netherlands with a relatively lower incidence of gastric cancer) were graded by the same pathologist according to the
updated Sydney scoring system. Atrophy and IM were more prevalent and began earlier in life in Chinese patients, which suggests that infection with *H. pylori* occurs earlier in life and has a higher prevalence in China.

In **chapter 4** the relationship between lymphoid tissue hyperplasia and *H. pylori*-associated gastroduodenal diseases in the antral mucosa and its evolution after eradication of *H. pylori* are investigated. This study shows a very high frequency of lymphoid follicles and aggregates in Chinese patients with several *H. pylori*-associated gastroduodenal diseases, especially in patients with gastric ulcer. The lymphoid tissue hyperplasia in Chinese population is stronger than in western population. It correlated strongly with the activity and severity of gastric inflammation. Successful eradication of *H. pylori* resulted in a decrease in the prevalence and density of lymphoid follicles and aggregates in the gastric antral mucosa. Lymphoid reaction in gastric antral mucosa is strongly associated with *H. pylori* infection.

In **chapter 5** we examined the vacuolating cytotoxin activity (VacA) has any influence on the gastric mucosal changes (the degree of acute or chronic inflammation, epithelial damage, atrophy, IM and the number of lymphoid follicles) prior to and after *H. pylori* eradication in Chinese patients with gastroduodenal diseases. VacA and cagA have been found to be associated with peptic ulcer disease in the Western World. Our study shows that the role of vaculating cytotoxin
appears to be less important in Chinese populations when contrasted with the western experience. VacA positive strains do not cause more significant alterations or diseases than VacA negative *H. pylori* strains among Chinese patients. Successful eradication of *H. pylori* infection does not improve atrophic lesion of gastric mucosa, but there is some improvement of IM. However, the number of patients is rather small and the follow-up period is relatively short in this study, which needs further study.

In chapter 6 the effect of *H. pylori* infection on COX-2 express in gastric antral mucosa is investigated by immunohistochemistry. This study shows cytoplasmic staining of COX-2 protein can be detected in the surface epithelial cells and inherent glands in the antrum both before and after eradication of *H. pylori*. COX-2 expression is significantly higher in *H. pylori* infected antral mucosa, successful eradication of *H. pylori* leads to down-regulation of COX-2 expression. Our results show that *H. pylori* infection leads to gastric mucosal overexpression of COX-2 protein, suggesting that the enzyme is involved in *H. pylori*-related gastric pathology in humans.