REVIEW
OF
LITERATURE
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Robin Warren and Barry Marshall who first identified *Helicobacter pylori* (1983) described it as unidentified curved bacillus in close contact with gastric epithelium in biopsy sample showing active chronic gastritis. [9] In human stomach it has been found on luminal aspect of surface mucous secreting cell, underneath the surface of mucous within gastric pits *(Tricalt et C, Bruneva P, Camilleri H. 1986).*[10] This location protects it from gastric acid to which it is sensitive *(Rollason et al. 1984)*.[11] Mc. Nulty et al 1985) [12] found that *Helicobacter pylori* shows significant urease activity – a property that has been adopted for rapid diagnostic test for organism. This enzyme also helps in creating basic environment around bacteria thereby protecting it from acid media of stomach.

*Helicobacter pylori* is rarely seen in histologically normal antral mucosa, but if present almost always shows histological evidence of chronic type B. gastritis *(Marshall and Warren 1984, Mcnulty and Wattson 1984, Rollson et al. 1984).*[9,12,13]

THE ORGANISM – HELICOBACTER PYLORI:

When originally isolated, *Helicobacter pylori* was thought to be a member of genus campylobacter, but subsequently work has shown to
be the first member of new genus Helicobacter (Goodwin CS, Armstrong JA et al. 1986). [14]

*Helicobacter pylori* is worldwide in distribution, gram negative, micro aerophilic, spiral, nonsporing, motile bacilli, measuring, 0.5 μm x 3μm in size. When seen under electromicroscopy it has smooth wall and 4-6 sheathed flagellae projecting from either pole each with terminal bulb (Goodwin et al. 1985)[15]. It differs from campylobacter species which have unsheathed non bulbous flagellae and rugose cell wall. They have less urease content and they can reduce nitrate. *Helicobacter pylori* is an acid sensitive bacteria and lies in mucous layer which overlies epithelial cells in alkaline environment. One of the characteristic of *Helicobacter pylori* is possession of powerful urease, which may be responsible for its ability to survive in acidic environment of gastric lumen. The ammonia produced raises pH in its immediate vicinity and may protect it (Marshall BJ, Barrett L, Prakash et al. 1988).[16]

**EPIDEMIOLOGY OF HELICOBACTER PYLORI:**

Our understanding of the epidemiology of Helicobacter pylori infection in the general population is rapidly increasing. The infection seems to be acquired early in childhood and persists throughout life (Cullen DJE et al 1993)[17]. Most infected individuals do not develop
symptoms. Although type B chronic gastritis appears in the antral biopsies of all infected subjects (Drumm B et al 1987)[18].

The prevalence of the infection in adults is 30-35% in developed and 80-90% in developing countries (Taylor DN et al 1991)[19]. Helicobacter pylori infection in the general population correlates strongly with age (Teh BH et al 1994; Taylor DN et al 1991)[19,20], social class, educational level (The EUROGAST Study Group, 1993)[21] and overcrowding, bed sharing, and economic level during childhood (Patel P et al 1994)[22]. The rise of prevalence in older patients is due to a cohort effect, reflecting an increased risk of exposure during childhood rather than a continued risk of infection during adult life (Teh Bh et al 1994).[20]

TRANSMISSION:

High prevalence of Helicobacter pylori seen in some social groups such as homosexuals, and institutionalized mentally retarded patient, demonstrates man to man transmission. (Aceti et al. 1987).[23]

The Helicobacter pylori occurs in two morphologic forms (Bode G. et al. 1988)[24]. The typical replicative form is gram negative curved rod with 4-6 flagella, which converts to a coccoid form if allowed to grow for more than a few days on a culture plate. The coccoid form is of variable size, may or may not be flagellated.
The replicative form of *Helicobacter pylori* has been demonstrated to survive in water up to a week. While the coccoid form is a potential “Spore” candidate, there is no evidence to suggest that this is transmissible form of *Helicobacter pylori*.

The meat handlers are more prone to *Helicobacter pylori* infection than other people (*D. Annastasio et al. 1988*).[25]

Infection has strong intrafamilial clustering, suggesting a person to person transmission in industrialized countries (*Malaty HM. et al. 1991*).[26] By contrast, the infection is probably waterborne in developing countries (*Klein PD et al. 1991*).[27]

**STRAIN HETEROGENEITY AND VIRULENCE:**

Most strains of *Helicobacter pylori* causes gastritis while infection with some strain may lead to more serious manifestation. To date four phenotypes that vary among *Helicobacter pylori* strains have been identified. Approximately 60% of *Helicobacter pylori* strain possess cag-A gene which encodes Cag-A protein. At present Cag-A genotype is thought to be associated with peptic ulcer disease while other strains are associated with simple gastritis (*Cover et al. 1990*) [28]. Recent work has identified a region of DNA in chromosome of *Helicobacter pylori* that is unique to some strains. This “pathogenicity island” which appears to include cag-A gene, have been preliminarily characterized
by nucleotide sequencing and are responsible for virulence of some strains.

**Colonization:**

The first step of infection requires that *Helicobacter pylori* must colonize the gastric mucosa. This process may take up to a week to complete. The organism must enter the stomach, survive brief exposure to acid, enter and successfully traverse the mucous layer, attach to epithelial cell receptor and adopt its physiology to the hostile environment. Urease is most prominent protein component of *Helicobacter pylori* and is critical for colonization of gastric mucosa. Urease produces alkaline media around bacillus, by producing ammonia from urea and protect it from hostile environment. Urease negative strain of *Helicobacter pylori* were unable to colonize the gastric mucosa, indirectly suggesting that urease is necessary for colonization (Eaton KA et al. 1992).[29]

The extraordinary motility of *Helicobacter pylori* through mucus is mediated by the polar flagella and it is thought that this process may help colonization (Eaton KA Morgan DR 1992).[29] Indeed flagella negative mutant of *Helicobacter pylori* are unable to colonize the gastric mucosa of antibiotic piglets. Although there is no direct evidence that adhesin are required by *Helicobacter pylori* to colonize but since *Helicobacter pylori* exhibits remarkable tissue and host specificity (i.e. it
binds to normal and metaplastic gastric epithelium), the existence of tissue specific adhesins seems to be extremely likely. There is also good evidence to suggest that *Helicobacter pylori* produces an acid inhibitory protein that blocks acid secretion from parietal cells. (Cave *et al.* 1989, Jablonowski H. *et al.* 1994)[30,31]

**TESTING FOR HELICOBACTER PYLORI IN CLINICAL PRACTICE:**

Two major categories of diagnostic tests for H. Pylori are available; - invasive and non-invasive methods.

**(A) INVASIVE DIAGNOSTIC TESTS:**

(1) Rapid Urease Test-

Rapid urease test has high specificity and moderate sensitivity (*Veldhugzen Van Senten SJO et al.* 1991)[32]. It is based on the principle that *Helicobacter pylori* has very high urease activity making it’s detection possible by observing a change in colour of indicator due to hydrolysis of urea to ammonia, in a media containing agar, urea, phenol red (indicator), at pH 6.8 and a bacteriostatic agent. The change of colour of medium from yellow to dark pink indicates a definite presence of *Helicobacter pylori* in biopsy specimen. The colour change is very rapid and takes place within 20 minutes to four hours or rarely it may take 8 -24 hours. Various kits are also available. Modified christensons urea media on agar slant in ‘Kahn’ test tube (*Nanivadekar*
liquid urea broth, phenol red or bromothymol as indicator (Hazell SL et al. 1986) [34] can also be used for detection of *Helicobacter pylori*. The rapid urease test is based on the presence of adequate number of bacteria with urease activity. Test sensitivity, therefore can be affected by use of agent that reduces gastric bacterial load or directly inhibits enzyme activity.

(2) Histology:

Two or more antral biopsies with hematoxylin and eosin staining should be sufficient to establish infection status in an untreated patient. *Helicobacter pylori* is distributed throughout the gastric mucosa, although its presence can be patchy. The presence of chronic active gastritis in an untreated patient should strongly suggest active infection. The absence of chronic mucosal inflammation reliably excludes *Helicobacter pylori* infection (Culter AF Havstad et al. 1995).[35]


(3) Culture:

The use of microbiological culture of gastric biopsies is limited due to the expense, limited availability and fastidious nature of the organism. (Barthel JS et al. 1990).[36] However the expected emergence of multiple antibacterial resistance among *Helicobacter pylori* may necessitate the increasing use of culture by clinical
gastroenterologist. There are many satisfactory culture media for *Helicobacter pylori*, most are blood enriched and contains appropriate antibiotic and/or antifungal agent (*Skirrow Formula*) to avoid overgrowth by oral bacteria (Good Win et al. 1985)[15]. *Helicobacter pylori* is fastidious bacteria and requires microaerophilic environment, with 10% CO₂ at 37°C. It grows in 3-7 days. Identification of *Helicobacter pylori* was based on colony morphology and visualization of gram-negative rod, which is urease positive. Culture sensitivity is 85-90% in most developed centre of world (Marshall BJ et al., Goodwin et al. 1985)[9,15] and 30-60% in India (Nanivadakar et al. 1989)[33].

(4) Other invasive tests:

Two other invasive test are available includes polymerase chain reaction (PCR) and phase contrast microscopy. PCR is research tool while phase contrast microscopy requires dark field examination of fresh gastric biopsies.

(B) NON- INVASIVE DIAGNOSTIC TESTS:
(1) Antibody Detection –

Chronic *Helicobacter pylori* infection elicits local and systemic immunologic responses leading to production of 1gG and 1gA antibodies. In general the measurement of serum 1gG level is preferred test basis, as level of this antibody is more accurate for infection status (*Perez-Perez 1989*)[37]. The diagnostic tests that detects *Helicobacter pylori* antibodies are inexpensive global test with typically high specificity and sensitivity (*Talley NJ et al. 1992*)[38]. Separated serum is subjected to quantitative ELISA test or qualitative in office immunoassays. Antibody detection has limited use in post treatment period. Immunoassays and whole blood are qualitative tests that will remain positive in post treatment period and therefore can not be used to determine bacterial eradication.

(2) Urea Breath Tests – (UBT) -

UBT will probably be optimum choice to confirm eradication in patient with complicated ulcer and in those patient with recurrent symptoms following treatment of *Helicobacter pylori* Although the test can be used to confirm eradication, test must be performed at least 4 week after completion of treatment. (*Logan RPH et al. 1995*)[39]. The UBT may have lower sensitivity in patient who have had previous gastric resections, as the contact time between bacteria and substrate will be reduced (*Well J. Bell GD et al. 1991*)[40]
CHOOSING A TEST:

Sensitivity, specificity and negative and positive predictive value of several diagnostic tests for *Helicobacter pylori* are given below:

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive (%)</th>
<th>Negative (%)</th>
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<tbody>
<tr>
<td><strong>INVASIVE</strong> -</td>
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<tr>
<td>- Chronic inflammation in Biopsy</td>
<td>100</td>
<td>66</td>
<td>84</td>
<td>100</td>
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<tr>
<td>- Acute Inflammation in Biopsy</td>
<td>87</td>
<td>93</td>
<td>96</td>
<td>79</td>
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<tr>
<td>- Rapid urease test</td>
<td>90</td>
<td>100</td>
<td>100</td>
<td>84</td>
</tr>
<tr>
<td><strong>NON-INVASIVE</strong> -</td>
<td></td>
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<tr>
<td>- UBT</td>
<td>90</td>
<td>96</td>
<td>98</td>
<td>84</td>
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<tr>
<td>- S. IgG</td>
<td>91</td>
<td>91</td>
<td>95</td>
<td>85</td>
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<tr>
<td>- S. IgA</td>
<td>71</td>
<td>85</td>
<td>90</td>
<td>62</td>
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Accuracy of modality, cost of the test, whether upper GI endoscopy is planned and clinical circumstances all are considered while choosing a test.
Any of the biopsy based methods that are rapid urease test culture and histology are not sufficient alone for the diagnosis of *Helicobacter pylori*. However, they should be recommended when endoscopy is performed, since isolation by culture and histology will provide additional information about antibiotic susceptibility, the type and severity of inflammatory changes in the mucosa and also of premalignant changes if any.

The definition of a ‘gold standard’ seems to be difficult. Previously, either culture of *Helicobacter pylori* or demonstration of HLO in histologic sections was regarded as the ‘gold standard’. Later it has been proposed that a third test (UBT, CLO test, or serology) should be included, and the *Helicobacter pylori* status is considered positive when one or more of three tests is positive.

In conclusion, it is recommended that a reliable evaluation by diagnostic tests include at least one test from each group of methods based on different principle and that the ‘gold standard’ should be regarded as two positive of these five tests.
DYSPHAGIA

Dysphagia is a common complaint, with a prevalence of 14% to 26% if predominant reflux symptoms are excluded[41]. The prevalence of dysphagia is higher among women and, somewhat surprisingly, is stable or even declines with age[42,43].

Dysphagia has been defined as 'recurrent upper or retrosternal pain, vomiting or other symptoms felt to be referable to upper GI tract'.[1] Talley et al proposed that it should be defined as pain or discomfort centered in the upper abdomen present for at least a month[44].

The prevalence of dysphagia in the community over a 6 month period is about 40%, with 70% of the population having experienced this symptom at sometime in the past[45]. The majority of dysphagia sufferers have mild symptoms not interfering with their lives or relieved by over-the-counter medications.

In a study of dysphagia in the community by Lydeard S. Jones R.1998, 48% were sufferers, and of these 70% reported mild symptoms and 9% reported severe symptoms, but was determined by fear of serious pathology and low socio-economic group[46].
According to Jones RH 1993, dyspepsia comprises about 5% of general practice consultations, with only 10% of these being referred for further specialist evaluation in hospital [47].

Knill-Jones RP 1991, in his study found that consultation for dyspepsia account for up to 40% of referrals to gastro-enterology outpatients [48].

Nicholas J, Talley et al (1993) [49] based on their responses to the questionnaire, classified the patients with dyspepsia into the following symptoms subgroups [49]

1. **Ulcer like dyspepsia**

   This was defined as dyspepsia and three or more of the following symptoms: abdominal pain or discomfort before meals or when hungry often or usually; night pain (waking the subject from sleep); pain or discomfort relieved by food often or usually; pain or discomfort relieved by antacids often or usually; periodic pain or discomfort; and well-localized abdominal pain or discomfort.

2. **Dysmotility like dyspepsia**

   This was defined as three or more of the following symptoms: nausea once a month or more; retching or vomiting once a month or more; upper abdominal bloating usually. In the absence of visible distension; early satiety often or usually, upper abdominal pain or
discomfort aggravated by food or milk often or usually, and postprandial upper abdominal pain or discomfort often or usually.

3. **Reflux like dyspepsia.**
   This included dyspepsia and heart-burn or acid regurgitation once a week or more.

4. **Nonspecific dyspepsia.**
   This included dyspepsia with symptoms not fitting into categories 1, 2, or 3.

*Armstrong D. 1996 and Talley NJ. 1996[50:51], on the basis of endoscopy report classified the patients into following diagnostic groups:*

1. **Functional or Non-ulcer dyspepsia.**
   This was defined as documented upper abdominal pain or discomfort, with essentially normal endoscopical findings (no esophagitis, erosions, chronic peptic ulceration, or gastric cancer).

2. **Chronic peptic ulceration.**
   This was defined as a >3mm ulcer with depth in the stomach and/or duodenum at endoscopy. Gastric ulcers were included in this group only if malignancy was ruled out.
3. Acute peptic ulceration.

   This was defined as a <3mm erosion without depth in the absence of chronic peptic ulceration.

4. Reflux esophagitis.

   Defined as endoscopic evidence of gastroesophageal reflux (GER), using the Savary-Miller grading system [52] as follows -

   **Grade 1** - Linear, nonconfluent erythema or erosions

   **Grade 2** - Longitudinal, confluent, noncircumferential erosions

   **Grade 3** - Longitudinal, confluent, circumferential erosions that may bleed easily.

   **Grade 4** - Esophageal ulceration and/or presence of a peptic stricture.

5. Gastric carcinoma.

   Confirmed by biopsy
HELCOBACTER PYLORI AND DYSPEPSIA

*Helicobacter pylori* is a major etiological factor in peptic ulcer disease. About 95% of patients with duodenal ulcers and perhaps 80% of gastric ulcers are infected with this bacterium and its eradication greatly diminishes recurrence of these ulcers.

A peptic ulcer is a breach in the gastric or duodenal epithelium associated with acute and chronic inflammation. In most countries, duodenal ulcers are about 3 times more common than gastric ulcers.

*Ihamaki T, Varis K et al (1979)*[53], in their study conducted in Finland, found that at any time 1.4% of a population had duodenal ulcer, whereas 0.3% of the population had chronic gastric ulcer.

*Langman MJS (1979)* found lifetime prevalence of duodenal ulcers to be 10% in males and 4% in females and of gastric ulcers to be 4% in males and 3% in females[54]. The incidence of duodenal ulcers gradually rises with age but peaks at about 50 years of age. The prevalence of gastric ulcers was found similar in males and females. They were rare under the age of 40 years and tend to occur in the lower socio-economic groups[54].

*Marshall B, Warren J (1984)* showed that the mucosa of the stomach, which was previously thought to be sterile, is frequently infected with *Helicobacter pylori* and, moreover, that > 90% of duodenal ulcer patients are infected compared with about 40% of controls.

In the studies done by Rauws EA, Tytgat GN, 1990 in Amsterdam the recurrence rate was zero so that disease was regarded as cure[56].

Hopkins et al,[57]reviewed 14 duodenal ulcer eradication studies and noted overall recurrence rate of 6% following successful eradication of Helicobacter pylori compared with 67% when infection remained.

According to McColl KE et al, 1993, rate of recurrence after successful eradication may also depend on how carefully the less common causes of duodenal ulceration; NSAIDs, Crohn's disease, gastrinoma, are excluded[58].

Huang JQ et al, 1996, observed that apart from diminishing recurrence, eradication of Helicobacter pylori leads to faster healing of duodenal ulcers than suppression of acid secretion alone[59].

According to Lanas A et al, 1995, a substantial minority of gastric ulcer patients are genuinely not infected and have ulcers due to ingestion of NSAIDs, which may be denied by as many as 44% of patients[60].
However, it is now clear that eradication of *Helicobacter pylori* from infected gastric ulcer patients who are not taking NSAIDs greatly diminishes the recurrence of these ulcers. *Graham et al* reported 2 year relapse rates of 13% after ranitidine plus triple therapy, compared with 74% in patients given ranitidine alone[61].

*Karita et al* reported 1 year gastric ulcer relapse rates of 0% after successful eradication compared with 75% in those with persisting infection[62].

*Bayerdorffer* reported recurrence rates of 2% and 49%, respectively, in gastric ulcer patients who had or had not *Helicobacter pylori* eradicated during endoscopic follow up for 18 months[63].

In a Meta-analysis of 5 trials, *Hopkins et al* noted a gastric ulcer recurrence rate of 4% after successful eradication, compared with 59% when the infection persisted [57].

*Labenz et al* found that gastric ulcers heal more rapidly if the regimen eradicates the infection. The rate of ulcer healing at 6 weeks was 85% if the bacterium was eventually eradicated compared with 60% if it was not [64].

*Hawkey CJ [1990]* in his study relating NSAIDS and peptic ulcers found that of patients taking NSAIDs, 8-16% have gastrointestinal symptoms at any time, and the potential of NSAID-ulcers to bleed or
perforate is considerable, particularly in the elderly who cope with these complications badly[65].

_Griffith MR et al (1991)_ documented that NSAIDs causes gastric ulcers more often than DUs. Early damage consists of multiple erosions. gastric ulcer Chronic ulcers which are larger and deeper, appear later[66].

_Lipscombe et al(1996)_ examined the effect of _Helicobacter pylori_ status on acute NSAID - induced gastric damage. They gave naproxen 500 mg b.d. to 24 healthy volunteers for 4 weeks and found that the _Helicobacter pylori_ status had no effect on mucosal blood flow or gastric mucosal damage[67].

_Bianchi- Porro et al (1996)[68]_ studied arthritis patients taking long- term NSAIDs and had chronic ulcers with _Helicobacter pylori_ infection. They were randomised to receive either omeprazole for 4 weeks with amoxycillin or omeprazole alone, whilst uninfected patients with arthritis also received omeprazole. Ulcer healing did not differ between the 3 groups. However, there was a trend to more frequent recurrence in those with persisting infection (46%) compared with those uninfected (27%).

In short, therefore, currently available data, including randomized trials, give inconclusive results, but leave open the possibility that
Helicobacter pylori exacerbates the tendency of NSAIDs to cause chronic ulcers.

Several studies have compared the prevalence of Helicobacter pylori in symptomatic and asymptomatic individuals. While some investigators have reported a higher prevalence of Helicobacter pylori in dyspepsia than in controls, others have found no difference in the prevalence between the two groups, or even a higher prevalence in the controls.

Bemersen et al (1992)[69] endoscopy 309 subjects with dyspepsia and 310 controls in an elegant Norwegian population-based study. They found that, overall, 48% of dyspeptic subjects had Helicobacter pylori compared with 36% of the controls, which was a significant difference; the prevalence was 53% and 35%, respectively in dyspeptic subjects and controls with normal endoscopic findings.

Schlemper et al (1995)[70] reported that anti- H. pylori IgG antibodies were present in 25% of individuals with non-ulcer dyspepsia and 29% of those without non-ulcer dyspepsia.

Early therapeutic clinical trials in Helicobacter pylori – positive patients with non-ulcer dyspepsia provided very conflicting results. Talley NJ (1994) analysed 16 published trials; eight reported that anti-H. pylori therapy was efficacious and eight failed to detect a statistically significant benefit[71].
Laheij et al (1996), in a meta-analysis, reported that symptoms improved in 73% of the patients who became Helicobacter pylori negative and in 45% of those with persistent infection. If eradication of Helicobacter pylori failed, symptoms only improved for a short period of time but, when Helicobacter pylori was eradicated, symptom improvement appeared to be more pronounced[72].

Elta et al[73] treated both Helicobacter pylori infected and uninfected patients with a double therapy but observed similar symptom improvement in both groups, with a mean follow-up of 34 months.

Murakami et al[74] have observed that gastric emptying significantly improved in 7 of 11 patients whose infection was eradicated and whose symptoms disappeared, but this needs to be confirmed.

Gastric cancer is the second most common fatal malignancy in the world and is the cause of more than 750,000 deaths annually [75]. The evidence supportive of an etiological association between Helicobacter 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[76].

Kuipers EJ et al (1995)[77] in a longitudinal study, comparing Helicobacter pylori positive to negative individuals over a 11 year period, 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).

Goodman KJ (1995) [78] added that much of the descriptive epidemiology of gastric cancer parallels that for Helicobacter pylori infection, most notably the strong association of both cancer and infection with poor socio-economic conditions.

Pisani P et al (1997)[79] estimated the risk and indicated that 53% and 60% of gastric cancers in the developing and developed world respectively, can be attributed to Helicobacter pylori.

There is much that remains to be established about the relationship between Helicobacter pylori infection and gastric cancer. Some epidemiological features of gastric cancer can not be explained by the infection, for example the male to female ratio of gastric cancer is usually in the order of 2.1 in nearly all populations [80], whereas Helicobacter pylori prevalence rates usually do not show any consistent sex difference [81].

Primary gastric lymphoma comprises about 3-6% of all gastric malignancies. Almost all are B cell non-Hodgkin’s lymphomas most commonly of high grade. Gastric T cell lymphomas and Hodgkin’s disease are extremely rare. In 1983, Isaacson and Wright[82] recognised that the low grade B cell lymphomas that arose specifically
within dedicated extra nodal lymphoid tissue known as mucosa associated lymphoid (MALT).

The most frequent event associated with the finding of organised lymphoid tissue in the gastric mucosa is infection with Helicobacter pylori [83]. In the most comprehensive study by Genta et al[84], lymphoid follicles were found in all patients with Helicobacter pylori infection but were absent in normal controls.

Wotherspoon et al(1991)[85] demonstrated that the lymphoid tissue seen in Helicobacter pylori infected stomachs had all the morphological features of MALT.

Wotherspoon and co-workers(1993)[86] observed the effect of eradication of the organism on a small series of early lymphomas. They found tumour regression in 5/6 cases treated by Helicobacter pylori eradication alone.

DIABETES MELLITUS, DYSPEPSIA AND HELICOBACTER PYLORI

Diabetic patients often suffer from symptoms arising from the gastrointestinal apparatus [91-93]. The first report on gastric abnormalities occurring in diabetic subjects was published in 1945 [94].

Nevertheless, much later its principal clinical expression, the so-called ‘gastroparesis diabeticorum’, was described and its association with the autonomic neuropathy recognised [95]. Subjects suffering from gastro-enteric abnormalities may be completely asymptomatic or affected only by a general dyspepsia [96,97].

In addition to autonomic neuropathy, other factors may also be considered causative of esophageal or gastric dysfunctions - abnormalities of the esophageal and/or gastric motility.

1. Direct effect of hypoglycemia and hyperinsulinemia [98] on gastro-enteric motility [99].

2. Altered production of gastrointestinal hormones, related or not to autonomic neuropathy [91,96,100].

3. Susceptibility to infectious diseases frequently observed in patients with an unsatisfactory metabolic control [97,101].

Qvist. N. et al (1994) found prevalence of Helicobacter pylori infection to reach up to 76% when concomitant abnormalities of gastrointestinal motility were present [105].


Kojeccky et al.(1993) described no significant difference between 91 NIDDM unselected patients (affected by dyspepsia, gastritis, gastric and/or duodenal ulcer) and comparable non-diabetic subjects[107].

Malecki M, Bien Al, et al (1996), based on histological demonstration of the presense of Helicobacter pylori stated the prevalence of infection to be lower in patients with diabetes than in controls [109].

The study of Oldenburg et al (1996), based on serologic antibody determinations, indicated a higher prevalence in patients with diabetes than in controls in nearly all of their age-based subgroups [112].

A U Morollo M et al (2001), in their study showed a higher prevalence of Helicobacter pylori infection in diabetes mellitus patients with dyspepsia. Helicobacter pylori infection was significantly associated with presence of endoscopic lesions and chronic gastritis in diabetic patients, but not in controls.[113]

A U Quatrini M et al (2001) also found higher prevalence of Helicobacter pylori infection, esophagitis and peptic ulcer in their patients with diabetes (with or without dyspepsia) suggesting that diabetics should be considered at risk for Helicobacter pylori infection and are suitable candidates for treatment.[114]

Persico M et al (1996) in their study also documented higher prevalence of Helicobacter pylori infection in patients affected by type 2 diabetes and non-ulcer dyspepsia with a significant higher prevalence in subjects with autonomic neuropathy.[115]

Zelenkova J et al (2002) in their study showed a lower seroprevalence of Helicobacter pylori in diabetic patients of type I and II in comparison with the healthy population[116]
Sato T et al (2002) also showed higher prevalence of peptic ulcer disease in asymptomatic diabetic patients and suggested that the eradication of Helicobacter pylori becomes the first therapy in peptic ulcer patients with non-insulin dependent diabetes mellitus. [117]

Ko GT, Chan FK et al (2001) found the rate of Helicobacter pylori infection in Hong Kong Chinese subjects with type 2 diabetes to be around 50%, which was similar to control subjects. No association was found between Helicobacter pylori infection, glycaemic status, and duration of diabetes and upper gastrointestinal symptoms in these diabetic subjects.[118]

Ojetti V, Pitocco D et al (2001) observed a significantly higher incidence of Helicobacter pylori re-infection in IDDM patients when compared to non IDDM controls [119].

Guvenen N, Akcan Y (1999) in their study concluded that the prevalence of Helicobacter pylori gastritis is higher in asymptomatic diabetic patients compared with healthy people. But they found no association between the alterations in GET and the presence of Helicobacter pylori gastritis as indicated.[120]

Gasbarrini A, Ojetti V et al (1999) observed that IDDM patients showed a significantly lower Helicobacter pylori eradication rate when compared to that observed in dyspeptic subjects. The impairment of the
gastrointestinal mucosa microvasculature with a reduction of antibiotic absorption may be the mechanisms underlying the observation[121].

Gentile S, Turco S et al (1998) for the first time, provided direct evidence for a higher frequency of *Helicobacter pylori* infection in dyspeptic patients affected with DM2 than in non-diabetic subjects and associated it with autonomic neuropathy.[122].