# GERMS AND THE HUMAN STOMACH - THE *HELICOBACTER PYLORI* STORY

**KL GOH**
*Department of Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia*

## Discovery of *Helicobacter pylori*

The discovery of *Helicobacter pylori*, and its association with chronic gastritis in 1983 by Warren and Marshall, ranks as one of the most important discoveries in medicine, in recent times (1,2). At the time of its discovery, no one could imagine that bacteria could exist in the human stomach with its harsh acidic milieu of a pH of 1.2. It is known, after all, that one of the basic functions of gastric acid, is precisely, to kill off any bacteria that may enter the stomach and to protect the human host from being colonized and infected by germs. We now know, that not only does *H.pylori* exist in the human stomach but it in fact, thrives in the gastric microenvironment, where it has carved out its own special ecological niche. Once infected, unless treated, infection persists life-long in the human host.

The story of *Helicobacter pylori* is one of repeated observations by several workers over a long period of time... and one of repeated "misses" as well, until its "discovery" by Warren and Marshall in 1983. In two "back to back" letters to the editor of Lancet (1, 2), Warren and Marshall described the presence of what they called "unidentified curved bacilli" and its "close association with active chronic gastritis". Their first definitive paper was published a year later (3), also in the Lancet. In an accompanying editorial, this paper was described as "an unusual paper from Western Australia concerning the unanswered questions surrounding peptic ulcer and gastritis." (4)

Germs in the human stomach have been observed for close to 100 years prior to Warren and Marshall's report (5). But they have been repeatedly observed, reported and then forgotten. With the advent of fibreoptic endoscopy, Steer and Colin-Jones in 1975, observed gram-negative bacilli in 80% of their patients with gastric ulcers (6). They thought that these bacteria were *Pseudomonas* and possibly contaminants and these bacteria were once again ignored and forgotten. Fung et al (7) in 1979, a gastroenterologist working in the Royal Perth Hospital, Australia, again observed bacteria in their study entitled "Endoscopic, histological and ultrastructural correlations in chronic gastritis". They reported their findings in the American Journal of Gastroenterology but to their subsequent chagrin, only made a passing reference to the observation with no comment on their possible clinical significance. They noted that many of these bacteria, although abutting directly on to the plasmalemma of the epithelial cell, were never seen within the cell and were therefore assumed to be of little significance.

Robin Warren, a pathologist working, ironically, in the same hospital as Fung in Perth, independently observed the presence of these bacteria in 1979 (Fig.1 & 2). In his memoirs (8), Dr Warren recalled " In June 1979, the early days of *Helicobacter pylori* began for me. A biopsy showed severe active chronic gastritis and I saw an unusual blue line on the surface. With higher magnification I thought I could see numerous small bacilli, closely adherent to the epithelium. My colleagues did not agree until a Warthin Starry stain was very successful and showed vast numbers of bacteria."

Barry Marshall's involvement in the *Helicobacter pylori* story was entirely serendipitous. In Robin Warren's words: "I was almost ready to publish my findings in 1981 when I met Barry Marshall, who asked to see my work. He was the gastroenterology registrar and was expected to publish a paper. Dr Marshall did not like one suggested project, so someone told him to see "that pathologist who was trying to make gastritis into a bacterial infection"(8). The rest is history. Barry Marshall completed his Gastroenterology training in Perth, Australia and subsequently took up a job as Assistant Professor at the University of Virginia, Charlottesville, and USA where he continued with numerous important studies on Helicobacter *pylori*. Barry Marshall has now returned to Perth and is Clinical Professor of Medicine at the University of Western Australia. Robin Warren has retired and is Emeritus Professor of Pathology at the same University.

## Nomenclature

The new bacterium closely resembled a campylobacter and Marshall and Warren initially called it a pyloric campylobacter (3). The name *Campylobacter pyloridis* was proposed by Marshall *et al* in 1984 (9). Although its flagellar characteristics were not that of campylobacter, the name was ratified in 1985 (10). Hartmann and von Graevenitz (11), however pointed out that the name pyloridis was grammatically incor-

Correpsondence:
Professor Dato' KL Goh
Department of Medicine, Faculty of Medicine
University of Malaya, 50603 Kuala Lumpur, Malaysia
gohkl@ummc.edu.my

*(This article is the write-up of Professor Dato' KL Goh's "Syarahan Perdana", Professorial lecture delivered on 5th November 1999.)*

rect and that it should be change to pylori. Marshall and Goodwin duly revised the name to *C. pylori* (12) in 1987. Ultrastructurally it had greater affinities to the genus Spirillum than to Campylobacter and Jones *et al* (13) observed that there were insufficient data to place these bacteria in their exact taxonomic position. Finally in 1989, Goodwin *et al* (14) proposed the establishment of a new genus called Helicobacter and that *C. pylori* be transferred to the genus as *H. pylori*

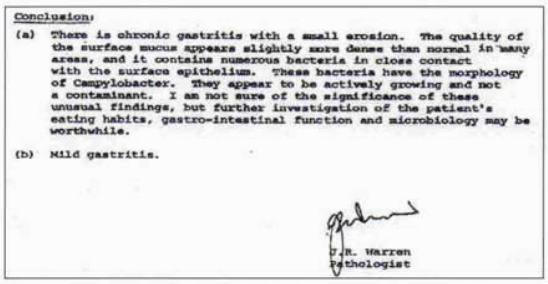
## *H. pylori* the pathogen

*H. pylori* is the most common bacterial infection in the world today. It is the major cause of peptic ulcers and an uncommon lymphoma called "maltoma" (lymphoma of gastric mucosal associated lymphoid tissue). It plays a critical role in carcinogenesis of the stomach and is implicated in the pathogenesis of at least, a subset of patients with non-ulcer dyspepsia.

*H.pylori* is a true human pathogen. That *Helicobacter pylori* is the cause of histological gastritis is now proven beyond doubt. *H. pylori* is always present when active superficial gastritis is present. When *H. pylori* is eradicated, gastritis resolves. Koch's postulates have been proven, with Dr Barry Marshall infecting himself with *H. pylori*, developing gastritis and symptoms of acute dyspepsia. He had treatment with successful eradication of the bacteria and resolution of gastritis (15). Dr Arthur Morris from New Zealand, repeated the same experiment with similar disease outcome except it took him several years before he was finally cured! (16). *H. pylori* is also not found in other types of gastritis such as autoimmune, lymphocytic and bile reflux gastritis indicating that it is not merely a commensal colonizing a damaged mucosa. The association of chronic gastritis with peptic ulcer had been known for a long time, before the discovery of *H. pylori*. But the association between the two was not clear until the discovery of the association between *H.pylori* and gastritis.

## Research into *H. pylori* infection

While the Royal Perth Hospital will always remains the home of *H.pylori*, many groups around the world were more involved in scientific research in gastric diseases at that time and were quick to jump into *H. pylori* research. Professor Colm O'Morain and his colleagues in Dublin, Ireland were the first to report on the decreased incidence of recurrent ulcers with *H.pylori* eradication in 1987 (17). This was an important observation and again it was the journal, Lancet which published the paper. In Amsterdam, Guido Tytgat, an eminent gastroenterologist, has been in the forefront of gastrointestinal research since the early 70's when he became Professor and Head of the Department of Gastroenterology at the Academic Medical Center, University of Amsterdam. His group pushed very hard and quickly



Conclusion:

(a) There is chronic gastritis with a small erosion. The quality of the surface mucus appears slightly more dense than normal in many areas, and it contains numerous bacteria in close contact with the surface epithelium. These bacteria have the morphology of Campylobacter. They appear to be actively growing and not a contaminant. I am not sure of the significance of these unusual findings, but further investigation of the patient's eating habits, gastro-intestinal function and microbiology may be worthwhile.

(b) Mild gastritis.

J.R. Warren
Pathologist

**Figure 1.** Robin Warren's original histopathology report, 1979 (reprinted with kind permission from Professor JR Warren)

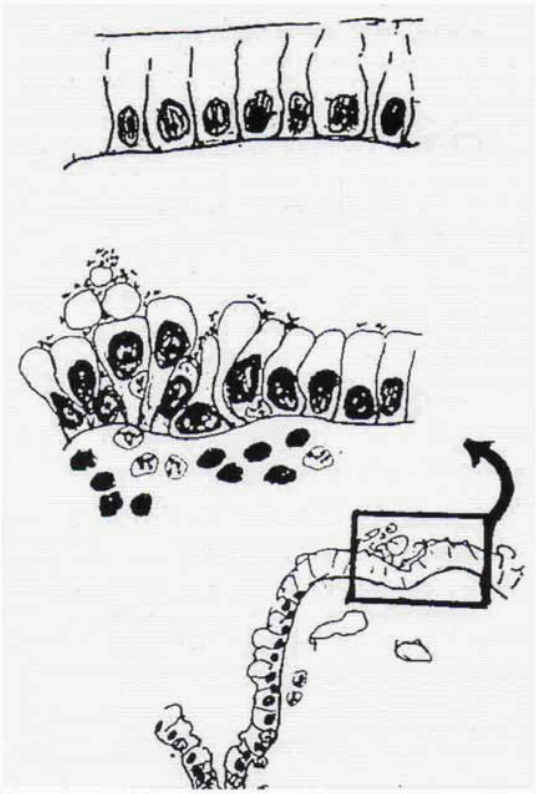


**Figure 2.** A sketch by Robin Warren of a microscopic section of a gastric biopsy showing *H.pylori*, 1979. (Reprinted with kind permission from Professor JR Warren)

in *H.pylori* research and in 1990 published their paper entitled " Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*" in the Lancet (18). In an earlier paper in 1989 with Eric Rauws as first author, Tytgat and colleagues were the first to describe resolution of gastritis on long term follow-up following successful *H.pylori* eradication (19).

## *H. pylori* and peptic ulcers

Many studies have now supported these early findings and we now know that eradication of the bacteria re-

sults in abolition of relapse of peptic ulcer disease. The older textbooks of medicine frequently state that "duodenal ulcer disease is a chronic relapsing disease which will eventually burn out with time". This is no longer true as we can now cure the disease. This is indeed a dramatic and remarkable discovery in medicine. With the great impetus to treat the infection world wide, it is not impossible to imagine that in the not too distant future, peptic ulcer disease may become a disease we read about rather than treat!

Observations of a high prevalence of *H. pylori* in patients with gastric and duodenal ulcers have been universal. We have shown in one of our studies that *H. pylori* eradication alone without continued conventional ulcer treatment, resulted in healing of ulcers (20). Zheng and colleagues (21) from China and Lam and colleagues (22) from Hong Kong, have demonstrated ulcer healing with antibiotics alone. Other studies have also shown that *H. pylori* infection preceded ulcer disease, temporally, thus making it biologically plausible that *H. pylori* is aetiologically related to ulcer disease.

## *H.pylori* and dyspepsia

For a while it became a norm to attribute every disease of the stomach to *H. pylori*. Non-ulcer dyspepsia (NUD) has always been a difficult clinical problem. But the causal association of this syndrome with *H. pylori* has not been established. NUD studies are difficult to perform and fraught with pitfalls. *H. pylori* has not been shown to be more common in NUD patients compared to healthy controls, there are no specific *H. pylori* related dyspeptic symptoms, there are no clear-cut pathogenic mechanisms by which *H. pylori* infection can result in dyspepsia and eradication studies have not consistently resulted in improvement in symptoms.

## *H.pylori* and gastric cancer

Current interest and "anxiety" is focussed on the role of *H. pylori* in gastric carcinogenesis. Ecological comparisons have shown that areas with high rate of gastric cancers were also areas with a high prevalence of *H. pylori*. Compelling examples can be seen in the South American countries and in certain regions in China. The first strong evidence supporting the role of *H.pylori* in gastric carcinogenesis came about in 1991. Abraham Nomura and colleagues (23) from Hawaii published results of a large nested case-control study. In this study, a group of Japanese American men who were conscripted into the military in 1942, a year after the Pearl Harbor bombing were studied. In the 1960's an extensive health survey was carried out on these men who were born between 1900 and 1919 and 8000 subjects had blood samples taken. Between 1968 and 1989, 137 of this group of men had developed gastric cancer. Nomura and colleagues focussed on a group of 109 cancer patients and studied a matched group of healthy subjects from this cohort. They found that those who were *H.pylori* positive (on bloods taken 20 years previously) were at a six-fold increased risk of developing gastric cancer. Similar studies were performed by Julie Parsonnet and her group from Stanford (24) and David Forman of the Imperial Cancer Research Fund in London (25). In both of these studies, an increased risk of cancer in the presence of *H.pylori* infection was also noted. Pelayo Correa in 1992 (26), modified and proposed a model of human gastric carcinogenesis as a multi-step, multifactorial process with *H.pylori* infection as the initiating event. In June 1994, the International Agency for Research in Cancer, an arm of the World Health Organisation declared *H.pylori* as a Class 1 (definite) carcinogen (27).

## Studies at the University Hospital, Kuala Lumpur

The news of the discovery of *H. pylori* and its possible clinical significance did not come with a "bang". In fact, for several years following its discovery, doctors continued to view it with great skepticism. We started our work at the University Hospital quite modestly, in 1985. At that time, *H. pylori* was diagnosed histologically. A preliminary report was presented at the Annual Society of Pathology Conference in 1987 (28) and I subsequently, presented our results on a larger group of patients at the Malaysia Singapore Congress in 1987 (29). Our initial observations on racial differences were published as a full a paper in 1990 (30) in the Journal of Gastroenterology and Hepatology at the same time as JY Kang and colleagues (31) from Singapore had their report published in the Gut. We performed a painstaking trial on non-ulcer dyspepsia and *H. pylori* in 1988-89 and were rewarded with its publication in the Scandinavian J Gastroenterology in 1991 (32). For many years, this paper was widely quoted. A subsequent paper on gastric emptying and non-ulcer dyspepsia has also been published (33).

In 1990, we were performing clinical trials with the new acid-suppressing drug omeprazole. We had then started to perform routine urease tests (for *H. pylori* infection) on gastric biopsies of all patients undergoing endoscopy. I observed that patients who were treated with omeprazole, always tested negative with the urease test. ASTRA Pharmaceuticals (makers of the drug, omeprazole) were skeptical of the effect of their drug on *H.pylori*, although preliminary reports from Europe had already been published. Together with my colleagues, Pitre Anderson and KK Tan, we sent a letter to the American Journal of Gastroenterology and entitled it "Omeprazole kills *H. pylori*". Martin Floch, who was editor of the journal at that time, accepted

the letter but insisted that we change the title to "Omeprazole *may* kill *H.pylori*"! (34). Again, the discovery of the effect of omeprazole on *H.pylori* was completely serendipitous. Proton-pump inhibitors have now become the cornerstone of treatment of *H.pylori* infection. In combination with antibiotics it has proven to be highly efficacious. We published a definitive paper in 1994 in the American Journal of Gastroenterology, entitled "Omeprazole 40mg combined with amoxycillin alone or with amoxycillin and metronidazole in the eradication of *Helicobacter pylori*" (35). Since then, our GI research team has gone on to perform numerous clinical trials testing various combinations of drugs on more than 1000 patients with *H.pylori* infection. Our observations have contributed greatly to the understanding of not just the efficacy of drugs but of ulcer healing, cost-effectiveness of treatment and bacterial resistance to antibiotics particularly in the local context.

I presented our paper on zero reinfection rate at the American Digestive Disease Week (DDW) in 1995 in San Diego (36) and it attracted much attention as most workers in the Western world were skeptical that treatment was worthwhile in areas of the world where there were a high prevalence of *H. pylori* and presumably a high reinfection rate. Our definitive paper on reinfection was subsequently published in the European Journal of Gastroenterology and Hepatology (37) and subsequently several reports from the Asian-Pacific area have supported our observations. We have now followed our initial cohort of patients endoscopically, for more than 5 years and we have continued to observe a very low reinfection rate. Additionally with reports of occurrence of gastroesophageal reflux (GORD) following eradication, we looked specifically for occurrence of new symptoms particularly those related to GORD and for endoscopic evidence of oesophagitis. In a report at the American Digestive Disease Week 1999, we observed extremely low incidence of oesophagitis and GORD symptoms amongst our patient's (38).

Observations of the low prevalence of peptic ulcer disease and cancer of the stomach amongst Malays (compared to the Chinese) have been known since the 1960s. In our early observations and report in 1990 (30) as well as in Kang *et al's* (31) report of the same year, a low prevalence of *H. pylori* amongst Malays was reported. Uyub and colleagues (39) in 1994 reported on an inordinately low prevalence of *H. pylori* amongst Kelantanese Malays. As part of my Doctor of Medicine thesis (40), serum from several parts of the country were tested for *H. pylori* antibodies. In keeping with our earlier notion, Malays consistently had lower prevalence rates compared to the other major races: Indians and Chinese. In areas of high prevalence for example in Kota Kinabalu, Sabah, the prevalence in Malays is relatively higher but still the lower compared to the other racial groups. In a large prospective endoscopy survey, performed on 1060 patients, at the University Hospital, Chinese race and Indian race were found to be significant independent risk factors, following multivariate analysis using multiple logistic regression analysis (41).

## The racial cohort phenomenon

The marked differences between the three major races particularly in West Malaysia points to a racial cohort phenomenon (42). Our hypothesis of a *racial cohort* phenomenon is based on the presumption that Chinese and Indians started off originally with a large reservoir of the infection, at the time of immigration to Malaysia more than 100 years ago. This is suggested by the high prevalence of *H.pylori* in their countries of origin. The Malays, on the other hand are a relatively, "*H. pylori* free" race. The fact that the infection is confined to a racial cohort suggests that transmission of infection require close contact, as occurs within families and within racial groups. While there is many casual social interactions between races, it is pertinent to note that intermarriages between races are not commonplace in our local population. Spread of infection appears to have taken place within rather than between racial groups. The racial differences in *H. pylori* prevalence, are further underlined in a serological study in Malaysian children that we have performed, where Chinese and Indian children, were already found to have significantly higher *H.pylori* prevalence at a very young age compared to Malays (43).

Differences in incidence rates of peptic ulcer disease and cancer of the stomach between races are further intriguing (44). While Indians have as much *H.pylori* infection as Chinese does, the incidence of peptic ulcer and cancer of stomach are much lower than for Chinese. Herein lies the "Indian enigma". The differences in clinical outcome may be related to differences in infecting strains or differences in the host particularly with respect to acid-secreting capacity or differences in environmental factors between the races. A multiracial society, where three major Asian races live side by side, provides a living experimental model to further understand mechanisms of disease causation associated with *H. pylori* infection.

## Lessons form the *H. pylori* story

The *H. pylori* story has taught us several important lessons: the cause of two important diseases-peptic ulcers and gastric cancer arose from simple observations and unsophisticated clinical studies. Lack of understanding of an observation does not mean insignificance of that observation and should instead be a

spur for more research. A disease is not conquered until its underlying cause is discovered, however well one may be able to control it - the case in point being peptic ulcer disease.

## The Future

*H.pylori* research has now moved on into an accelerated new phase with the discovery of its exact genomic sequence (45). *H. pylori* is now a major interest of molecular biologists, where exciting work is being done to identify "good" strains and bad "strains". Work continues to understand further, the host immune response and to identify environmental factors, which may modulate disease outcome. Much work has been done on the development of a therapeutic vaccine and new targets for therapy. Further work has also identified not just non-*H.pylori* gastric bacteria but Helicobacter species in other parts of the gastrointestinal tract and in the biliary tree

Internationally, *H. pylori* is a growth industry for several pharmaceutical companies. "Helicobacter" is a Journal and *H. pylori* has its own international conferences. In 1998, the Malaysian Society of Gastroenterology and Hepatology hosted the 2nd Western Pacific Helicobacter Congress in Kota Kinabalu, Sabah, which turned out to be a very successful meeting, beyond our expectations. Several international Consensus panels in North America, Europe and Asia have been convened and guidelines for diagnosis and treatment drew up. The Malaysian Society of Gastroenterology and Hepatology Working Party Report on the Management of *Helicobacter pylori* infection was published in 1998 (46).

## Epilogue

For me, my interest in *H. pylori* has stretched over 15 years. In this time it has provided me with the opportunity, not just for a scientific endeavor but also an opportunity to mature academically and professionally. I have worked for and obtained a Doctoral degree from the University of Malaya and I have learnt many research methods, which will now be invaluable, particularly to younger clinical researchers. My interest in *H. pylori* and gastric diseases continues with further work in both the laboratory and in the clinical arena.

## References


1. Warren JR. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983; i: 1273 (letter).
2. Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983; i:1273-5 (letter).
3. Marshall B, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984; i:1311-4.
4. Editorial. Spirals and ulcers. Lancet 1984; i: 1336-7.
5. Bizzozero G. Uber die Schauchformigen Drusen des magendarmkanals und die Bezienhungren thres Epithels zu dem Oberflachenepithel der Schleimhaut. Arch. Mikrobiol Anat 1893, 42:82-152.
6. Steer HW & Colin-Jones DG. Mucosal changes in gastric ulceration and their response to carbenoxolone sodium. Gut 1975; 16:590-7.
7. Fung WP, Papadimitriou JM, Matz LR. Endoscopic, histological and ultrastructural correlations in chronic gastritis. Am J Gastroenterol 1979; 71:269-79.
8. Warren JR. "The discovery and pathology of *Helicobacter pylori*". Byk Gulden Symposium, Xth International workshop on Gastroduodenal Pathology and Helicobacter pylori, European Helicobacter pylori Study group, September 13th 1997, Lisbon, Portugal.
9. Marshall BJ, Royce H, Annear DI, Goodwin CS, Pearman JW, Warren JR, Armstrong JA. Original isolation of *Campylobacter pyloridis* from human gastric mucosa. Microbios Lett 1984; 24:83-88.
10. International Union of Microbiological Societies. Validation of publication of new names and new combinations previously effectively published outside the IJSB. List no. 17. Int J Systematic Bacteriol 1985; 35: 223-5.
11. Hartmann D & von Graevenitz A. A note on name, viability and urease tests of *Campylobacter pylori*. Eur J Clin Micribiol 1987; 6: 82-3.
12. Marshall BJ & Goodwin CS. Revised nomenclature of camplyobacter pyloridis. Int J Systematic Bacteriol 1987; 37: 68.
13. Jones DN, Curry A, Fox AJ. An ultrastructure study of the gastric Campylobacter-like organism *'Campylobacter pyloridis'*. J Gen Microbiol 1985; 131:2335-41.
14. Goodwin CS, Armstrong JA, Chilvers T, Peters M, Collins MD, Sly L, McConnell W, Harper WES. Transfer of *Campylobacter pylori* and *Campylobacter mustelae* to *Helicobacter* gen. nov. and *Helicobacter pylori* comb. nov. as *Helicobacter mustelae* comb. nov. respectively. Int J Systematic Bacteriol. 1989; 39: 397-405.
15. Marshall BJ, Armstrong JA, McGechie DB, Glancy RJ. Attempt to fulfill Koch's postulates for pyloric campylobacter. Medical Journal of Australia 1985; 142:436-9.
16. Morris A, Nicholson G. Ingestion of *Campylobacter pyloridis* causes gastritis and raised fasting gastric pH. American Journal of Gastroenterology 1987; 82:192-9.
17. Coghlan JG, Humphries H, Dooley C, Keane C, Gilligan D, McKenna D, Sweeney E, O' Morain C. *Campylobacter pylori* and recurrence of duodenal ulcers- a 12 month follow-up. Lancet 1987; ii: 1109-11.
18. Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. *Lancet* 1990;335:1233-5
19. Rauws EAJ, Langenberg W, Houthoff HJ, Zanen HC, Tytgat GNJ. (1988) *Campylobacter pyloridis*-associated chronic antral gastritis. Gastroenterology; 94:33-40.
20. Goh KL, **N** Parasakthi, Peh SC, Wong NW, Chuah SY, Chin SC. *Helicobacter pylori* eradication with short course therapy leads to duodenal ulcer healing without the need

for continued acid-suppression therapy. Eur J Gastroenterol Hepatol 1996; 8:421-4.

21. Zheng ZT, Wang ZY, Chu YX, Li YN, Li QF, Lin SR, Xu ZM. (1985) Double blind short-term trial of furazolidine in peptic ulcer. Lancet; i:1048-9 (letter).
22. Lam SK, Ching CK, Lai KC, Wong BCY, et al. Does treatment of Helicobacter pylori with antibiotics alone heal duodenal ulcer? A randomised double blind placebo controlled study. Gut 1997; 41: 43-8.
23. Nomura A, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. N Eng J Med 1991; 325:1132-36.
24. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, Sibley RK. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med 1991; 325:1127-31.
25. Forman D, Newell DG, Fullerton F, Yarnell, JWG, Sracey AR, Wald N, Sitas F. Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *BMJ* 1991; 302:1302-5.
26. Correa P. Human gastric carcinogenesis: A multi-step and multifactorial process — First American Cancer Society Award Lecture on Cancer Epidemiology. Cancer Research 1992; 52:6735-40.
27. International Agency for Research on Cancer. Schistosomes, liver flukes and *Helicobacter pylori*. IARC monographs on the Evaluation of Carcinogenic Risks to Humans. 1994; Vol 61. Lyon, France: IARC.
28. Goh KL, Peh SC, Jalleh R, Wong NW, Tan HS. Non-ulcer dyspepsia and Campylobacter infection. Proceedings, Malaysian Society of Pathologists, 12th Annual Scientific Meeting, 7-9th August 1987.
29. Goh KL, Peh SC, Jalleh R, Wong NW.. Campylobacter infection and Dyspepsia. Proceedings, 21st Malaysia-Singapore Congress of Medicine, 1987.
30. Goh KL, SC Peh, NW Wong, N. Parasakthi, SD Puthucheary. *Campylobacter pylori* infection - Experience in a Multiracial population. J Gastroenterology and Hepatology 1990; 5:277-80
31. Kang JY, Wee A, Math MV, Guan R, Tay HH, Yap I, Sutherland IH. *Helicobacter pylori* and gastritis in patients with peptic ulcer and non-ulcer dyspepsia: ethnic differences in Singapore. Gut 1990; 31:850-3.
32. Goh KL, Parasakthi N, Peh SC, Wong NW, Lo YL, Puthucheary SD. *Helicobacter pylori* infection and non-ulcer dyspepsia: the effect of treatment with colloidal bismuth subcitrate. Scand J Gastroenterol 1991.26:1123-31.
33. Goh KL, Paramsothy M, Azian M, Parasalkthi N, SC Peh, Bux SI, Lo YL, Ong KK. Does *Helicobacter pylori* infection affect gastric emptying in patients with functional dyspepsia ? J Gastroenterol Hepatol 1997; 12:790-4.
34. Goh KL, Tan KK, Anderson PE. Omeprazole may kill *Helicobacter pylori*. Am J Gastroenterol; 1991: 86:124 (letter).
35. Goh KL, Peh SC, Parasakthi N, et al. Omeprazole 40mg om combined with amoxicillin alone or with amoxicillin and metronidazole in the eradication of *Helicobacterpylori:* results of a prospective, controlled and randomized trial with long-term follow-up. Am J Gastroenterol 1994; 89:1789-92.
36. Goh KL, Parasakthi N, Peh SC, Chin SC. Reinfection and ulcer relapse in South - East Asian patients- A 2 year follow-up of patients. Gastroenterology 1995; 108:A103
37. Goh KL, N Parasakthi, SC Peh . Reinfection and ulcer relapse in South-East Asian patients following successful eradication: Results of a two year follow-up. Eur J Gastroenterol Hepatol 1996; 8:1157-60.
38. Goh KL, Parasakthi N, Peh SC, R Prabhakeran, Chin SC. No occurrence of reflux oesophagitis following Helicobacter pylori eradication in duodenal ulcer patients- A 5 year endoscopic follow up in South East Asian patients. Gastroenterology 1999; 116:A 173 (Abs)
39. Goh KL. *Helicobacter pylori* infection in Malaysia. Doctor of Medicine Thesis, 1996, University of Malaya.
40. Uyub AM, Raj SM, Visvanathan R, Nazim M, Aiyar S, Anuar AK, Mansur M. *Helicobacter pylori* infection in North-Eastern Peninsular Malaysia-evidence for an unusually low prevalence. Scand J Gastroenterol 1994; 29:209-13.
41. Goh KL. Prevalence of and risk factors for *Helicobacter pylori* in a multiracial population undergoing endoscopy. J Gastroenterol Hepatol 1997. 12: S29-35.
42. Goh KL, Parasakthi N. The racial cohort phenomenon: Seroepidemiology of Helicobacter pylori infection in a multiracial South-East Asian country. Eur J Gastroenterol Hepatol. 2001; 13 :177-83.
43. Boey CCM, Goh KL, Lee WS , Parasakthi N. Seroprevalence of *H.pylori* in Malaysian children- evidence for ethnic differences. J Paedtr Child Health 1999; 35(2):151-2.
44. Goh KL. Epidemiology of *H.pylori* infection, peptic ulcer and gastric cancer: experience in a multiracial South East Asian country. Helicobacter Research 2000; 4: 34-40.
45. Tomb JF, White O, Kervalage AR, et al. The complete genome sequence of the gastric pathogen *Helicobacter pylori. Nature* 1997; 388:539-47.
46. Goh KL, Mahendraraj S, Parasakthi N, Kew ST, Kandasami P, Mazlam Z. Management of Helicobacter pylori infection: Working Party Report of the Malaysian Society of Gastroenterology and Hepatology. Med J Malaysia 1998; 53:302-10.