
Differences in peptic ulcer between East and West

Shiu Kum Lam OBE, MD, FRCP, FRACP, FHKCP

Chairman of Medicine and Chief of Gastroenterology and Hepatology

Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

In general, peptic ulcer occurs at equal rates in the East and the West but with marked regional differences in both, even within the same country. In the West, the incidence of peptic ulcer, particularly duodenal ulcer, rose sharply at the turn of the century and has shown a rapid decline in the past three decades. In the East, the rise was equally impressive, but the decline appears to have been delayed, only starting in the past decade. Asians present their ulcer symptoms a decade earlier than Caucasians, and it has been suggested that this early presentation may be attributable to *Helicobacter pylori* (*H. pylori*) infection at a younger age. Interestingly, the male-to-female ratio is much higher in the East than in the West, and the duodenal-to-gastric ulcer ratio manifests a much wider variation in Asians than in Caucasians. As in Western countries, peptic ulcer occurrence in the East shows a cyclical trend, with a peak frequency in the winter months. In the West, the placebo healing rate varies widely up to 78%, whereas in the East it is rather consistent at around one-third. These variations in geographical distribution, time trends, sex and ulcer ratios, seasonal rates and behavioral response to placebo treatment indicate that while *H. pylori* is a major cause of peptic ulceration, other environmental and genetic factors contribute to ulcer formation.

The parietal cell mass and acid secretory capacity of Asian patients with duodenal ulcer are only slightly more than half of those of Caucasian patients, which may explain why Asian patients respond equally well to half the standard dose of anti-secretory agents used in Caucasians. *H. pylori* infection is generally more prevalent in the East than in the West and is more resistant to metronidazole. The response to standard triple therapies for eradication, however, appears to be as effective in the East as in the West.

It is well established that differences exist between ethnic groups such as Asians, blacks, Hispanics and Caucasians. Environmental factors, for example culture, religion, educational background, diet, body size, tradition of medical practice, etc., are well known. These may have an important bearing on the occurrence, pathogenesis and treatment of various diseases in different populations. For example, a higher dietary salt intake in Chinese and Japanese may be partly responsible for the high frequency of hypertension as well as gastric cancer in these countries, and the smaller body mass may affect drug dosage and the occurrence of side-effects. Even genetic make-up, for example having different enzymes for drug metabolism, may differ. Several enzymes, for example, those for slow acetylation (10% in Chinese, 50% in USA), the CYP2C-related poor metabolism of phenytoin, and the CYP2D6-related poor metabolism of debrisoquine (1% in Japan, 10% in USA), are polymorphically distributed in different populations.

Variations in the prevalence of disease and pathology are well described. Haemorrhagic stroke, hepatitis B and *H. pylori* infection, for example, are generally more common among Asians. The vertical transmission of hepatitis B and infection with *H. pylori* at a young age in Asians are known to have given rise to different disease behaviours. In fact, guidelines have been developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use regarding the influence of ethnic factors in the acceptability of foreign clinical data.¹ An understanding of a disease such as peptic ulcer as it occurs in the East and the West will, therefore, help towards unveiling its pathogenesis and improving its management.

It should be noted that, other than genetic factors, at least five environmental factors have laid claim to an aetiological role in peptic ulceration: *H. pylori* infection, non-steroidal anti-inflammatory drugs (NSAIDs), cigarette smoking, environmental stress and dietary factors. When dealing with epidemiological observations between East and West, the following questions should be asked: how do these environmental factors fit into the epidemiological observations?; can any single environmental factor explain all the epidemiological observations, or do we need to bring in a multitude of factors to explain these factual observations?

THE RISE AND FALL OF ULCER

Before the 19th century, peptic ulceration was uncommon, be it in East or West. The first gastric ulcer described in human history probably belongs to a Chinese man who died 2000 years ago in the Western Han Dynasty from perforated gastric ulcer and whose well-preserved body was recently discovered in Ginzhou.² In the English literature, the pathology of gastric ulcer was first described in 1935 by Jean Cruveilhier.³ In those days, gastric ulcers were occasionally seen and duodenal ulcers were rare. At the turn of the century, peptic ulcer, in particular duodenal ulcer, rose to become one of the most common medical conditions in Western countries, affecting 10% of men in their lifetime.⁴ In the East, its occurrence is equally common, and its prevalence has also been documented to be 10–11%.⁵ Midway through the 20th century, however, the incidence of peptic ulcer started to fall in Western countries⁶, while that in Asian countries such as Hong Kong and Singapore continued to rise, so that the frequency of perforated peptic ulcer in Hong Kong, for example, had been estimated to be five times that in New South Wales.⁷ However, in the past decade, although there has been no documented formal report in Asian countries, it is generally noted that the incidence of peptic ulcer has also been falling. At the same time in the West and especially in USA, the documentation of non-*H. pylori*, non-NSAID peptic ulcer appears to be on the increase, having been described as being in the region of 30% of all ulcers seen.^{8,9} Such ulcers appear to be much less common in Asia; in Hong Kong, for example, they represent only 5% of the ulcers seen.¹⁰

These ulcer trends can be explained by any of the five environmental factors. Aspirin was synthesized in 1833 by Gerhardt and was marketed in 1902. The large-scale manufacturing of cigarettes was made possible by the introduction of the Bonsack machine in the early years of this century. Industrialization, and with it environmental stress, also occurred in the early years of the 20th century in Western countries. These factors could explain the rise of ulcer frequency in the early 1900s in these countries. Aspirin and NSAIDs have also been blamed for the rise in ulcer perforation rate in the elderly in recent years¹¹, and population stress has been related to the spiky rising trend

of ulcer perforations in Hong Kong.¹² The fall in ulcer rate in recent years in advanced countries can be related to a decrease in cigarette consumption. It has also been ascribed to a change from the use of animal to vegetable oil¹³, the latter being known to be a rich source of raw materials for the synthesis of prostaglandins, which have cytoprotective properties. Although there are no supportive data, the rise and fall of ulcer frequency in this century in the West, as well as in the East, can theoretically be explained by an epidemic infection, *H. pylori* infection being a possible and serious candidate.

GEOGRAPHICAL VARIATION IN ULCER RATES

Peptic ulcer appears to be more common in Scotland than in England¹⁴, Norway and Denmark¹⁵, the USA¹⁶ and Japan.¹⁷ In Australia, the health system allows the use of H₂-antagonists in peptic ulcer only when the diagnosis has been established by endoscopy or barium meal examination. When cimetidine was first introduced into Australia, the early prescriptions thus represented index cases of peptic ulcer. This information was used to study the distribution of peptic ulcer in the country during the years 1978–81.¹⁸ A wide geographical variation in incidence was observed, the east coast in general having a higher prevalence than the west. A recent study that directly compared the incidence of peptic ulcer perforation in Hong Kong and New South Wales during 1979–85 showed that perforation was five times more common in Hong Kong, population stress, rather than NSAID or cigarette consumption, being suggested as the reason.⁷ It should also be noted that the reported frequency of *H. pylori* infection in Hong Kong is almost twice that in new South Wales.

There are also marked regional differences in India, peptic ulcer being more prevalent in southern than in northern India. High-prevalence areas stretch from the south up the west coast to Bombay, all the way up the east coast, and into the plains of Assam and Kashmir.¹⁹ It is of interest to note that the staple diet in southern India is mainly rice, whereas that in northern India is wheat, millet and pulses. It should also be noted that the south versus north difference in ulcer prevalence disappears in Indian immigrants to South Africa.²⁰ A geographical difference in peptic ulcer frequency can also be observed in China. The prevalence of peptic ulcer in cities of southern China, including Hong Kong, is twice that seen in cities of northern China.²¹ In fact, a north–south gradient of increasing duodenal ulcer rate and decreasing gastric cancer rate has been observed in China (Figure 1). It is of interest to note that, as in India, rice is the main staple diet in southern China, whereas wheat is the staple diet in the north. The regional differences in ulcer rate in India and China have been ascribed to the use of the staple diet: stored, milled rice has been shown to be ulcerogenic in Shay rats, and wheat to be gastroprotective.²² The regional differences do not appear to be related to *H. pylori* infection, which has been shown to be similar in frequency in the northern and southern regions of China.²³

Peptic ulceration is rare among south-western American Indians and among Eskimos in northern Greenland.^{24,25} It is also reported to be uncommon among Fijians, Indonesians and Australian aborigines.^{26,27,28} The rarity of peptic ulcer among South-western American Indians and Australian aborigines is a good example of ethnic differences. Ethnic differences are also well illustrated by a prospective necropsy study in 1951–56 in Uganda, where peptic ulcer occurred in 13.7% of male local Bantu, 5.4% of Nilotic immigrants and 20.6% of Ruandan immigrants.²⁹ On the island of Sumatra in Indonesia, a carefully conducted autopsy study showed that the prevalence of peptic ulcer among the Chinese was 11%, while that among the Javanese was 0.6%.²⁷ In

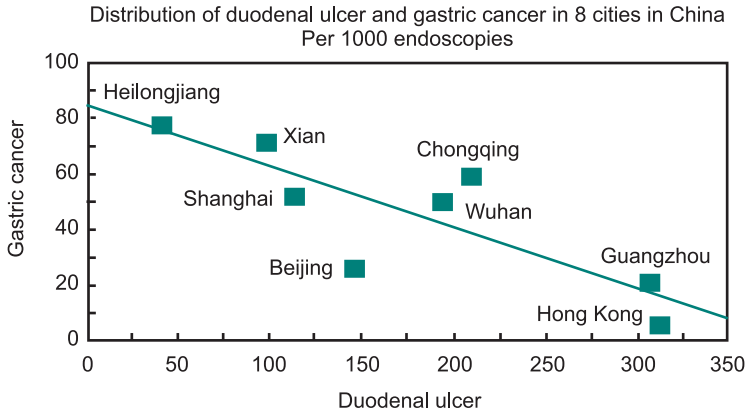


Figure 1. North–south gradient of increasing duodenal ulcer rates and decreasing gastric cancer rates in China.²¹

Singapore, the prevalence of peptic ulcer was highest among the Chinese, least among the Malays, and intermediate among the Indians.³⁰ In the USA, crude rates for duodenal ulcer prevalence and hospitalization are higher for whites than for non-whites, but age-specific mortality appears to be slightly higher in non-whites than whites up to the age of 65, thereafter becoming higher in whites.³¹ How much these ethnic differences can be ascribed to cultural practices, hygiene and other environmental factors, as well as genetic factors, is unknown.

CYCLICAL TREND

It has long been noted that peptic ulcer and its complications tend to occur or recur during autumn and winter months and to be less observable in summer³²; this has been repeatedly confirmed.^{33–36} One study³⁶ expressed ulcer rate as a function of endoscopy rate and applied a statistical method to test whether the monthly ulcer occurrence followed a sinusoidal wave, which would confirm that the monthly occurrence was cyclical. A significant cyclical distribution of 12 months per cycle was observed, the peak rate occurring in the winter months. Interestingly, a seasonal pattern is still seen in Singapore³⁰, where the climate is tropical and varies little during the year. Although not documented, it seems generally agreed among gastroenterologists that this cyclical trend is also observed in Australia and South Africa, in that ulcers occur more commonly around the Christmas and New Year period. The seasonal occurrence of ulcers cannot be explained on the basis of cigarette smoking, NSAID use or *H. pylori* infection. Dietary changes and seasonal activity with environmental stress may fit into the picture but remain to be elucidated.

AGE AT PRESENTATION

The prevalence of peptic ulcer rises with age, the peak occurring in the sixth decade for most Western countries. The mean age at presentation appears to vary in different parts of the world (Table 1), being apparently a decade younger in Asian countries and less

Table I. Mean age of male patients with duodenal ulcer at presentation.

Country	Reference	Mean age (years)
Australia	38	50
UK	39	50
USA	40	50
Denmark	15	48
Norway	41	46
Hong Kong	42	40
India	43	40
Japan	17	40
West Africa	44	32
South Africa (blacks)	45	29

still in Africa. The tendency to an increasing age of ulcer patients has been interpreted by Susser and Stein³⁷ to indicate that, in Western societies, some environmental factor operated on a cohort of persons born near the beginning of the century and that the influence of this factor has since declined. Another possible explanation of the earlier presenting age is the earlier age of *H. pylori* infection in Asians, as described above.

GEOGRAPHICAL VARIATION IN ULCER RATIOS

The male-to-female ratio of peptic ulcer patients varies between different parts of the world. The sex ratio for duodenal ulcer has been reported as 18:1 in India¹⁹, 9:1 in Africa⁴⁴ and Bangladesh¹⁹, 4:1 in Hong Kong⁴⁶, 3:1 in Scotland⁴⁷, 2:1 in Denmark, and England and Wales^{15,48}, 1.4:1 in Sweden⁴⁹ and 1:1 in the USA.⁵⁰ Furthermore, there is evidence that, in the same country, the ratio tends to drop over the years. Thus, in Australia the male-to-female ratio of gastric ulcer has dropped from 2.5:1 in 1930 to 0.8:1 in 1960⁵¹, while in Durban, this has been observed to drop from 8:1 to 3:1 over the past 20 years.⁵² In the USA, the ratio for duodenal ulcer had been 2:1⁵³ and is now 1:1.⁵⁰ The wide geographical difference in sex ratio strongly supports once again the important aetiological role of environmental factors in peptic ulcer. The sex ratio patterns cannot be explained on the basis of *H. pylori* infection but may be explained by the pattern of cigarette smoking⁵⁰ and by the differences in lifestyle between the sexes.

The duodenal-to-gastric ulcer ratio also varies in different parts of the world. It has been reported to be 32:1 in India¹⁹, 19:1 in Africa⁴⁴, 9:1 in Bangladesh⁵⁴, about 4:1 in the UK, USA, Hong Kong, Taiwan and Singapore^{42,48,53,55,56}, 2:1 in Australia⁵¹, 1.6:1 in Shan Dong, a north-eastern province of China⁵⁷, 1:1 in Norway⁵⁸ and 1:2 in Japan.⁵⁹ The differences between Shan Dong and Taiwan, and between Australia and the UK, suggest that environmental rather than ethnic factors play a more important role. It is difficult to explain such differences on the basis of *H. pylori* infection or society stress. How much they can be ascribed to cigarette smoking and analgesic consumption, both of which are more strongly associated with gastric than duodenal ulcers^{60,61} or to dietary differences, can only be speculative.

GEOGRAPHICAL VARIATION IN PLACEBO HEALING RATES

There is a wide geographical variation in the healing rate of duodenal ulcer treated with placebo, ranging from 0% to 78% with an average of approximately one-third, as

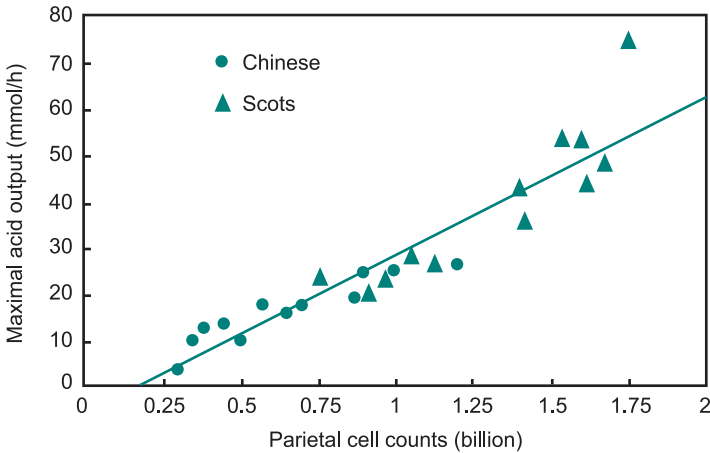


Figure 2. Parietal cell counts and maximal acid output in Chinese and Scottish patients with duodenal ulcer. (Based on data from Card and Marks, 1960³⁰ and Chen et al, 1977.⁸¹)

has been shown in 106 randomized controlled trials.⁶² North America appears to have higher healing rates, whereas Asia (consistently around one-third) and countries in the southern hemisphere have lower healing rates. Such wide variation cannot be explained by differences in protocol and study design. While the mechanisms of placebo healing itself are unknown, one possibility is the removal, in total or in part, of the aetiological factors. There is no convincing evidence to show that abstinence from cigarette smoking or the withdrawal of NSAIDs *per se* promotes ulcer healing, although these may reduce ulcer relapse.⁶³ Evidence is scant but definitive that the eradication of *H. pylori* infection itself will lead to ulcer healing⁶⁴, although voluminous reports have shown that this very significantly reduces ulcer relapse.⁶⁵ Placebo healing, in fact, occurs in the presence of *H. pylori* infection.⁶⁶

Bedrest in hospital, however, has been shown to heal ulcers⁶⁷, the removal from environmental stress that hospitalization entails being believed to be the mechanism. Dietary manipulation, such as the use of the bland Sippy diet, appears to be a thing of the past. In practice, many patients have learned to use milk, which reduces pain and may promote ulcer healing⁶⁸, while the more health-food conscious patients may ingest more fibre, which appears to be beneficial in preventing ulcer relapse.⁶⁹ How much 'rest' and 'diet' account for the geographical variation in placebo healing remains unknown.

PARIETAL CELL MASS, ACID OUTPUT AND ACID SUPPRESSION IN DUODENAL ULCER

The parietal cell mass of Scottish patients with duodenal ulcer has been shown to be almost double that of Chinese patients (Figure 2), yet peptic ulcer occurs in about 10% in both populations. The gastric acid output following maximal stimulation is known to be higher in western patients and controls than in their Asian counterparts, by as much as 80%.⁷⁰⁻⁷² There are two known explanations. First, body weight has been shown to be closely related to maximal acid output, and body size in Asians is generally less than that in Caucasians. However, despite correction for body stature, Chinese still showed a significantly smaller maximal acid output compared with age- and sex-matched

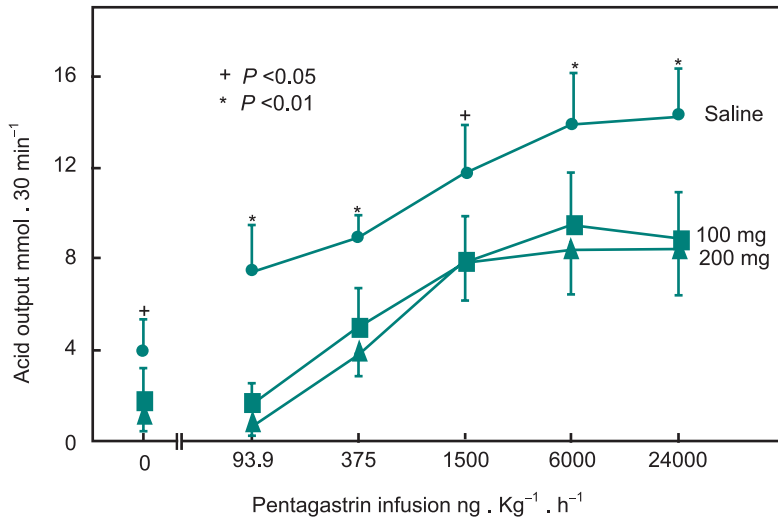


Figure 3. Effect of intravenous cimetidine, 100 mg and 200 mg, on acid response to graded doses of pentagastrin in Chinese patients with duodenal ulcer.⁷³

controls.⁷² Another explanation may be related to *H. pylori* gastritis, which is common among Asians and which may reduce the acid secretion, especially when the body and fundus are involved.

The fact that acid secretion in Asians is only about 60% that in Caucasians has an important bearing when treating Asian patients with acid-reducing agents. It has been shown that cimetidine 100 mg and 200 mg intravenously shows an identical suppression of acid secretion, as induced by graded doses of pentagastrin in Chinese patients with duodenal ulcer (Figure 3), suggesting that half the standard dose of cimetidine that is recommended for Caucasians might achieve adequate acid suppression in Chinese; this has, in fact, been substantiated by a double-blind, placebo-controlled study showing that cimetidine 100 mg and 200 mg nocte was as effective as 200 mg three times daily and 400 mg nocte for the healing of duodenal ulcer.⁷³ The requirement for antacids is also dramatically less in Chinese than in Americans.⁷⁴ This appears also to be true for proton pump inhibitors: a double-blind, controlled study showed that omeprazole 10 mg daily was as effective as 20 mg daily for the healing of duodenal ulcer.⁷⁵ Interestingly, omeprazole 20 mg daily as maintenance treatment for duodenal ulcer in Asians resulted in a relapse rate at 1 year of only 5%, as shown by a double-blind, placebo-controlled study in five Asian centres.⁷⁶ This approach may become important when the eradication of *H. pylori* fails.

HELICOBACTER PYLORI AND PEPTIC ULCER IN ASIA

H. pylori infection in Asia has several characteristics. In general, the infection is more common in Asia than in most developed Western countries (Figure 4). It should be noted that the infection rate varies widely between Asians. It is low in Malays and Indonesians, in whom peptic ulcer and gastric cancer are uncommon. It is very high in India, where duodenal ulcer is common but gastric ulcer and cancer are not. The rate

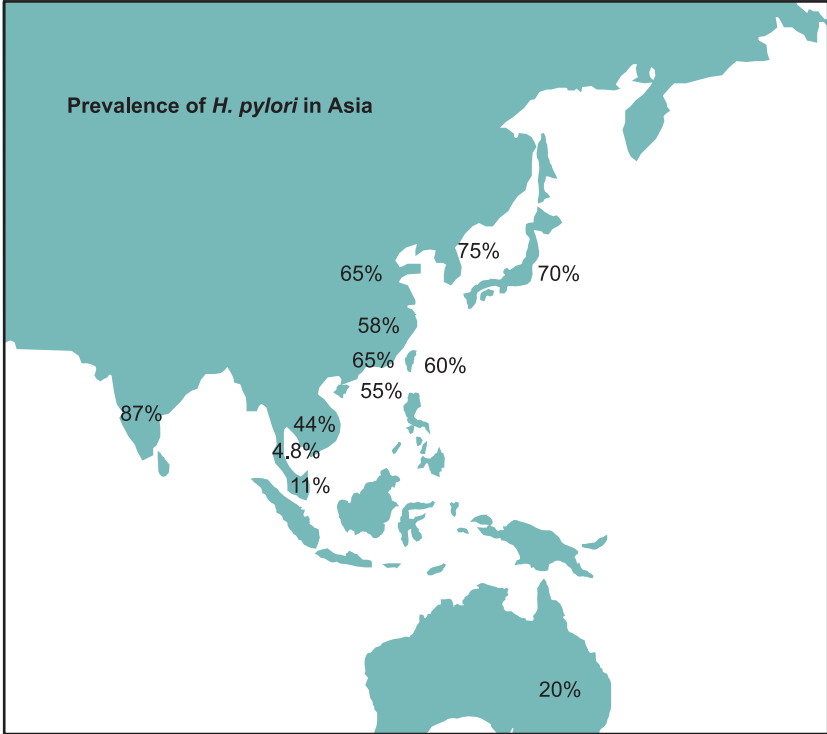


Figure 4. Prevalence of *H. pylori* in Asian populations.

in Chinese and Japanese in whom cancer is common, is high, but the Chinese appear to have a greater incidence of duodenal ulcer than the Japanese. Like other less-developed countries, early infection, i.e. infection in children, adolescents and young adults, is common.

Resistance to metronidazole is prevalent, running at between 50% and 90%, and this may lower the eradication rate of standard triple therapy that contains metronidazole, as has recently been shown.⁷⁷ Many Asians cannot afford proton pump-based and clarithromycin-based eradication regimens.

A recent meta-analysis⁷⁸ of 66 Asian studies and 115 treatment arms showed that triple therapy using proton pump inhibitors or bismuth achieved a similar per protocol eradication rate of about 90%, which is quite reasonable given the background of high metronidazole resistance. This also suggests that the expensive proton pump inhibitors can be replaced by bismuth. A recent double-blind study also showed that triple therapy with lansoprazole, amoxicillin and metronidazole had a similar eradication rate to lansoprazole, amoxicillin and clarithromycin in Asians⁷⁹, thus improving the affordability of eradication treatment in Asians by dispensing with clarithromycin.

CONCLUSION

There are significant differences between the East and the West in geographical distribution of ulcers, their time trends, sex and ulcer ratios, seasonal rates and

Table 2. Differences in peptic ulcer features between East and West.

	East	West
Prevalence (life-time, male)	10% (Chinese)	10% (Scots)
Falling incidence noted recently	Three decades (well documented)	One decade (not documented)
Regional variation in rate	Yes	Yes
Seasonal variation in rate	Yes	Yes
Age at presentation (years)	40	50
Male:female ratio	4–18:1	1–4:1
Duodenal:gastric ulcer ratio	0.8–19:1	2–4:1
Perforation	5 (Hong Kong)	1 (Australia)
Non- <i>Helicobacter pylori</i> , non-NSAID	5%	30%
Placebo healing rate	Usually 1/3	20–78%
Parietal cell mass	1/2	1
Maximal acid output, duodenal, mean mmol per hour	19	35
Maximal acid output/kg body weight	0.4	0.6
Ulcer healing dose		
Antacid per day, neutralizing capacity	200 mmol	1000 mmol
Cimetidine per day	0.5 g	1 g
Omeprazole per day	10 mg	20 mg
Metronidazole resistance	50–90%	About 30%
Eradication rate of triple therapies (per protocol)	90%	90%

NSAID = non-steroidal anti-inflammatory drug

behaviour to placebo treatment (Table 2). These indicate that while *H. pylori* is a major cause of peptic ulceration, other environmental and genetic factors contribute to ulcer formation, supporting the concept of aetiological heterogeneity.⁶⁵

The parietal cell mass and acid secretory capacity of Asian patients with duodenal ulcer is only slightly more than half that of Caucasian patients and may explain why Asian patients respond equally well to half the standard dose of anti-secretory agents used in Caucasians. *H. pylori* infection is generally more prevalent in the East than in the West and is more resistant to metronidazole. The response to standard triple therapies for eradication, however, appears to be as effective in the East as in the West.

REFERENCES

1. ICH Steering Committee. Ethnic Factors in the Acceptability of Foreign Clinical Data. Harmonised Tripartite Guideline. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Step 4 of the ICH Process, E5: 1–14, 1998.
2. Tien HS, Zhi XH, Wu ZB & Sung GF. Studies on the pathological changes and the cause of death. In Wu ZB (ed.) *Studies of an Ancient Corpse of the Western Han Dynasty Unearthed from Tomb No. 168 on the Phoenix Hill at Jiangling*, pp 196–219. Beijing: Cultural Relics Publishing House, 1982.
3. Cruveilhier J. *Maladies de l'estomac, de l'Anatomie Pathologique du Corps Humain*, vol. 2. Paris: Baillière, 1835.
4. Grossman MI. Peptic ulcer: definition and epidemiology. In Rotter JI, Samloff IM & Rimoin DL (eds) *The Genetics and Heterogeneity of Common Gastrointestinal Disorders*, pp 21–24. New York: Academic Press, 1980.
5. Sung JL, Wang TH, Lu TH et al. Epidemiological study on peptic ulcer and gastric cancer in the Chinese. *Rendic Gastroenterology* 1974; **6**: 111–115.
6. Langman MJS. Peptic ulcer. In *The Epidemiology of Chronic Digestive Disease*, pp 9–39. Chicago: Year Book Medical Publisher, 1979.
7. Lam SK, Byth K, Ng MMT et al. Perforated peptic ulcer in Hong Kong and New South Wales. *Journal of Gastroenterology and Hepatology* 1992; **7**: 508–511.

8. Laine L, Hopkins RJ & Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the United States been overstated? A meta-analysis of rigorously designed trials. *American Journal of Gastroenterology* 1998; **93**: 1409–1415.
9. Maher W, Jyotheeswaran S, Potter G et al. An epidemiological study of peptic ulcer disease patients in greater Rochester, New York. *Gastroenterology* 1997; **112**: A206.
- *10. Lam SK, Ching CK, Lai KC et al. Does treatment of *Helicobacter pylori* with antibiotics alone heal duodenal ulcer? A randomised double-blind placebo-controlled study. *Gut* 1997; **41**: 43–48.
11. Collier DStJ & Pain JA. Non-steroidal anti-inflammatory drugs and perforation. *Gut* 1985; **26**: 359–363.
12. Hui WM, Lam SK, Shiu LP & Ng MMT. Semi-quantitative study of negative social events, stress and incidence of perforated peptic ulcer in Hong Kong over 24 years. *Gastroenterology* 1990; **98**: A61.
13. Hollander D & Tarnawski A. Dietary essential fatty acids and the decline in peptic ulcer disease – a hypothesis. *Gut* 1986; **27**: 239–242.
- *14. Doll R, Jones FA & Bukatzsch MM. *Occupational Factors in the Aetiology of Gastric and Duodenal Ulcers with an Estimate of their Incidence in the General Population*, Medical Research Council, Special Report Series No. 276. London: Stationery Office, 1951.
15. Bonnevie O. The incidence of duodenal ulcer in Copenhagen County. *Scandinavian Journal of Gastroenterology* 1975; **10**: 385–393.
16. Kurata JH & Haile BM. Epidemiology of peptic ulcer disease. *Clinics in Gastroenterology* 1984; **13**: 289–305.
17. Kawai K, Shirakawa K, Misaki F et al. Natural history and epidemiologic studies of peptic ulcer disease in Japan. *Gastroenterology* 1989; **96**: 581–585.
18. Hugh TB, Coleman MJ, McNamara ME et al. Epidemiology of peptic ulcer in Australia. A study based on government statistics in four states. *Medical Journal of Australia* 1984; **141**: 81–85.
19. Tovey F. Peptic ulcer in India and Bangladesh. *Gut* 1979; **20**: 329–347.
20. Moshal MG, Spitaels JM, Robbs JV et al. Eight-year experience with 3392 endoscopically proven duodenal ulcers in Durban, 1972–79. *Gut* 1981; **22**: 327–331.
21. Wong BCY, Ching CK, Lam SK et al. Differential north to south gastric cancer–duodenal ulcer gradient in China. *Journal of Gastroenterology and Hepatology* 1998; **13**: 1050–1057.
22. Tovey F. Diet and duodenal ulcer. *Journal of Gastroenterology and Hepatology* 1994; **9**: 177–185.
23. Ching CK, Lam SK, Chen BW et al. North-south gastric cancer and duodenal ulcer disease gradients in China. *Gastroenterology* 1995; **108**: A8.
24. Sasaki H, Nagulesparan M, Samloff IM et al. Low acid output in Pima Indians. A possible cause for the rarity of duodenal ulcer in this population. *Digestive Diseases and Sciences* 1984; **9**: 785–789.
25. Sievers ML & Marquis JR. Duodenal ulcer among South-western American Indians. *Gastroenterology* 1962; **42**: 566–569.
26. May JM. Report on the geography of peptic ulcers. *Schweizer Zeitschrift für Pathologie und Bakteriologie* 1985; **21**: 169–209.
27. Kouwenaar W. Gastric and duodenal ulcers in Sumatra's east coast and their pathogenesis. *Transaction of the Eighth Congress Far East, Ass Trop Med* 1930; **1**: 587–597.
28. Bateson EM. Duodenal ulcer – does it exist in Australian Aborigines? *Australian and New Zealand Journal of Medicine* 1976; **6**: 545–547.
29. Raper AB. The incidence of peptic ulceration in some African tribal groups. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1958; **52**: 535–546.
- *30. Kang JY. Peptic Ulcer Disease in Singapore with Particular Reference to Racial Differences. MD thesis, University of Singapore, 1988.
31. Kurata JH & Haile BM. Racial differences in peptic ulcer disease: fact or myth? *Gastroenterology* 1982; **83**: 166–172.
32. Ivy AC. The problem of peptic ulcer. *Journal of the American Medical Association* 1946; **132**: 1053–1059.
33. Boles RS & Westerman MP. Seasonal incidence and precipitating causes of hemorrhage from peptic ulcer. *Journal of the American Medical Association* 1954; **156**: 1379–1383.
34. Ahmed SZ, Levine M & Finkbiner R. The seasonal incidence of complications of peptic ulcer. *Annals of Internal Medicine* 1963; **59**: 165–171.
35. Gibinski K, Rybicka J, Nowak A & Czarnicka K. Seasonal occurrence of abdominal pain and endoscopic findings in patients with gastric and duodenal ulcer disease. *Scandinavian Journal of Gastroenterology* 1982; **17**: 481–485.
36. Hui WM & Lam SK. Monthly variation in duodenal ulcer frequency and maximal acid output. *Journal of Gastroenterology and Hepatology* 1988; **3**: 457–463.
37. Susser M & Stein Z. Civilization and peptic ulcer. *Lancet* 1962; **1**: 115–119.
38. Kellow JE, Tao Z & Piper DW. Ventilatory function in chronic peptic ulcer. A controlled study of ventilatory function in patients with gastric and duodenal ulcer. *Gastroenterology* 1986; **91**: 590–595.
39. Watkinson G. The incidence of chronic peptic ulcer found at necropsy. *Gut* 1960; **1**: 14–31.

40. Elashoff JD & Grossman MT. Trends in hospital admissions and death rates for peptic ulcer in the United States from 1970 to 1978. *Gastroenterology* 1980; **78**: 280–285.
41. Bernersen B, Johnsen R, Straume B et al. Towards a true prevalence of peptic ulcer: the Sorreisa gastrointestinal disorder study. *Gut* 1990; **31**: 989–992.
- *42. Lam SK & Ong GB. Duodenal ulcers: early and late onset. *Gut* 1976; **17**: 169–179.
43. Jayaraj AP, Tovey FI & Clark CG. Possible dietary protective factors in relation to the distribution of duodenal ulcer in India and Bangladesh. *Gut* 1980; **21**: 1068–1076.
44. Tovey FI & Tunstall M. Duodenal ulcer in black populations in Africa South of the Sahara. *Gut* 1975; **16**: 564–576.
45. Segal I, Dubb AA, Tim LO et al. Duodenal ulcer and working-class mobility in an African population in South Africa. *British Medical Journal* 1978; **1**: 115–119.
- *46. Koo J, Ngan YK & Lam SK. Trends in hospital admission, perforation and mortality of peptic ulcer in Hong Kong from 1970 to 1980. *Gastroenterology* 1983; **84**: 1558–1562.
47. Lam SK, Koo J & Sircus W. Early- and late-onset duodenal ulcers in Chinese and Scots. *Scandinavian Journal of Gastroenterology* 1983; **18**: 651–658.
48. Bernersen B, Johnsen R, Straume B et al. Towards a true prevalence of peptic ulcer: the Sorreisa gastrointestinal disorder study. *Gut* 1990; **31**: 989–992.
49. Linstrom CG. Gastric and duodenal peptic ulcer disease in a well-defined population: a prospective necropsy study in Malmö, Sweden. *Scandinavian Journal of Gastroenterology* 1978; **13**: 139–143.
50. Kurata JH, Haile BM & Elashoff JD. Sex differences in peptic ulcer disease. *Gastroenterology* 1985; **88**: 96–100.
51. Billington BP. Observations from New South Wales on changing incidence of gastric ulcer in Australia. *Gut* 1956; **6**: 121–133.
52. Moshal MG. Ethnic differences in duodenal ulceration. II: 3392 patients in Durban (1972–1979). In Rotter JJ, Samloff IM & Rimoin DL (eds) *The Genetics and Heterogeneity of Common Gastrointestinal Disorders*, pp 101–110. New York: Academic Press, 1980.
53. Elashoff JD & Grossman MT. Trends in hospital admissions and death rates for peptic ulcer in the United States from 1970 to 1978. *Gastroenterology* 1980; **78**: 280–285.
54. Hassan M, Shah MD, Ali K et al. Peptic ulcer in Bangladesh: an endoscopic survey. *Gut* 1985; **25**: A1117.
55. Sung JL, Wang TH, Lu TH et al. Epidemiological study on peptic ulcer and gastric cancer in the Chinese. *Rendic Gastroenterology* 1974; **6**: 111–115.
56. Kang JY. Mortality from peptic ulcer in Singapore 1938–1980. *Singapore Medical Journal* 1983; **24**: 333–336.
57. Zhao XC, Li JM & Peng WC. Observations on peptic ulcer in Shan Dong, China. *Journal of Gastroenterology and Hepatology* 1988; **3**: 345–348.
58. Ostensen H, Gudmundsen TE, Bolz KD et al. The incidence of gastric ulcer and duodenal ulcer in North Norway: a prospective epidemiological study. *Scandinavian Journal of Gastroenterology* 1985; **20**: 189–192.
59. Iwasake M. Nation-wide tabulation of results in gastric mass survey. *Stomach and Intestine* 1971; **6**: 745–750.
- *60. McIntosh JH, Byth K & Piper DW. Environmental factors in aetiology of chronic gastric ulcer: a case control study of exposure variables before the first symptoms. *Gut* 1985; **26**: 789–798.
61. Duggan JM, Dobson AJ, Johnson H et al. Peptic ulcer and non-steroidal anti-inflammatory agents. *Gut* 1986; **27**: 929–933.
62. Poynard T & Pignon JP. *Acute Treatment of Duodenal Ulcer: Analysis of 293 Randomized Clinical Trials*. Montrouge: John Libbey, 1989.
63. Sontag S, Graham DY, Belsito A et al. Cimetidine, cigarette smoking, and recurrence of duodenal ulcer. *New England Journal of Medicine* 1984; **311**: 689–693.
64. Hosking SW, Ling TKW, Chung SCS et al. Duodenal ulcer healing by eradication of *Helicobacter pylori* without anti-acid treatment: randomised controlled trial. *Lancet* 1994; **343**: 508–510.
- *65. Lam SK, Hui WM & Ching CK. Epidemiology, pathogenesis and etiology of peptic ulcer. In Haubrich WS, Schaffner F & Berk JE (eds) *Bockus Gastroenterology*, vol. 1, pp 700–748. Philadelphia: WB Saunders, 1994.
66. Ho J, Lui I, Hui WM et al. A study of the correlation of duodenal-ulcer healing with campylobacter-like organisms. *Journal of Gastroenterology and Hepatology* 1986; **1**: 69–74.
67. Doll R & Pygott F. Factors influencing the rate of healing of gastric ulcers. *Lancet* 1952; **1**: 171.
68. Doll R, Price AV, Pygott F & Sanderson PH. Continuous intragastric milk drip in treatment of complicated gastric ulcer. *Lancet* 1956; **1**: 70.
69. Rydning A & Berstad A. Dietary aspects of peptic ulcer disease. *Scandinavian Journal of Gastroenterology* 1985; **20** (supplement): 29–33.
70. Vakil BJ & Mulekar AM. Studies with the maximal histamine test. *Gut* 1965; **7**: 364–371.

71. Guo FL, Chen GZ, Liu SQ et al. The effects of smoking and nicotine on the parietal cell mass of human beings and rats. *Journal of Gastroenterology and Hepatology* 1986; **1**: 45–54.
72. Lam SK, Hasan M & Sircus W. Comparison of maximal acid output and gastrin response to meals in Chinese and Scottish normal and duodenal ulcer subjects. *Gut* 1981; **21**: 324–328.
73. Lam SK & Koo J. Accurate prediction of duodenal-ulcer healing rate by discriminant analysis. *Gastroenterology* 1983; **85**: 403–412.
74. Lam SK. Antacids: past, present and future. *Clinics in Gastroenterology* 1988; **2**: 641–654.
- *75. Hui WM, Lam SK, Lau WY et al. Omeprazole and ranitidine in duodenal ulcer healing and subsequent relapse – a randomized double-blind study with weekly endoscopic assessment. *Journal of Gastroenterology and Hepatology* 1989; **4** (supplement 2): 35–43.
- *76. Goh KL, Boonyapisit S, Lai KH et al. Prevention of duodenal ulcer relapse with omeprazole 20 mg daily: a randomized double-blind, placebo-controlled study. *Journal of Gastroenterology and Hepatology* 1995; **10**: 92–97.
77. van der Hulst RWM, van der Ende A, Homan A et al. *Gut* 1998; **42**: 166–169.
78. Wang WH, Wong BCY & Lam SK. Pooled analysis of *Helicobacter pylori* eradication regimes in Asia. Unpublished data, 1999.
79. Lam SK & Wong CY. Prospective double-blind randomized placebo-controlled study comparing two lansoprazole-based triple therapy and one dual therapy for *Helicobacter pylori*-related duodenal ulcer: an Asian multicenter study. *Gastroenterology* 1999; **116**: G1562.
80. Card WI & Marks IN. The relationship between the acid output of the stomach following 'maximal' histamine stimulation and the parietal cell mass. *Clinical Science* 1960; **19**: 47–63.
- *81. Cheng FCY, Lam SK & Ong GB. Maximal acid output to graded doses of pentagastrin and its relation to parietal cell mass in Chinese patients with duodenal ulcer. *Gut* 1977; **18**: 827–832.