Helicobacter pylori and Gastric Cancer

Michael Rathbone and Barrie Rathbone

Abstract

Gastric cancer remains a major cause of cancer death worldwide. The discovery of *Helicobacter pylori* and its association with gastric cancer has opened up new insights into its pathogenesis. Gastric cancer pathogenesis is the result of a complex interplay between bacterial, host and environmental factors resulting in a step wise histological progression to neoplasia. *H. pylori* is a major factor in the early stages of cancer development and the mechanism of action of its virulence factors are being steadily unravelled. It is also now recognised that host genetic polymorphisms also play a complex role interacting synergistically with the bacterial virulence factors. The role of *H. pylori* in the causation of gastric cancer also raises the possibility of cancer prevention through screening and eradication, actions which may improve outcomes in high risk populations but which may not be cost-effective in areas of low risk. Ultimately, despite the vast improvements in knowledge, as yet there has not been a corresponding improvement in terms of gastric cancer survival rates.

Contents

M. Rathbone
St George's, University of London, London, UK

B. Rathbone (✉)
University Hospitals of Leicester, Leicester, UK
e-mail: barrie.rathbone@uhl-tr.nhs.uk

J. A. Z. Jankowski (ed.), *Inflammation and Gastrointestinal Cancers*,
Recent Results in Cancer Research 185, DOI: 10.1007/978-3-642-03503-6_5,

1 Introduction

Although gastric cancer rates appear to be declining worldwide, it is still a huge problem. It was estimated as the fourth most common cancer in 2002 and the second most common cause of cancer-related mortality (Parkin et al. 2005). There is considerable geographical variation in rates of gastric cancer, demonstrating higher rates in East Asia, Eastern Europe and parts of Central and South America. The lower risk areas are South Asia, North and East Africa, North America, Australia and New Zealand (Parkin et al. 2005).

The vast majority of stomach tumours are gastric adenocarcinomas (90%) which can be classified according to position (cardia or more distal tumours) and according to histological appearance (diffuse or intestinal). Tumours of the cardia are more likely to be diffuse type tumours with more distal tumours being intestinal type.

The bacterium *Helicobacter pylori* (*H. pylori*) is now known to be the predominant cause of chronic gastritis. Colonisation of the gastric epithelium by 'unidentified curved bacilli' and the association with chronic inflammation was first brought to the attention of the medical world by (Marshall 1983; Warren 1983) who also isolated the organism. Their achievement earned them the Nobel Prize in Physiology or Medicine in 2005. In addition to its role in chronic gastritis and peptic ulceration, *H. pylori* was recognised as a carcinogenic agent for gastric cancer by the International Agency for Research on Cancer (IARC 1994).

The bacterium itself is a spiral or slightly curved gram-negative rod, 2.4–4.0 μm in length, with 2–5 unipolar flagella which play a role in motility.

This microaerophilic organism colonises the gastric mucus gel and adheres to the epithelium. While generally thought to be non-invasive there is evidence that intra- and inter-cellular invasion occurs (Necchi et al. 2007). It has exceptional urease activity helping it survive in an acidic environment. The organism is mainly contracted in childhood predominantly by the gastric-oral route. The faecal–oral or the oral–oral route together with indirect transmission through contaminated food or water may be possible (Go 2002). A large study from the north of England showed that the most important factors for contracting *H. pylori* infection in the UK were worse socioeconomic conditions in childhood and number of siblings. The risk of infection rose with an increasing number of siblings (Moayyedi et al. 2002).

The prevalence of *H. pylori* infection in middle-aged adults was estimated as 74% in developing countries and 58% in developed countries (Parkin 2006). The same study suggested that 63.4% of gastric cancer cases worldwide were attributable to the bacterium, which translated to 5.5% of all cancers. *H. pylori* is most strongly associated with the non-cardia intestinal type adenocarcinoma and the rare gastric mucosa-associated lymphoid tissue-type (MALT) lymphoma (Wotherspoon et al. 1991).

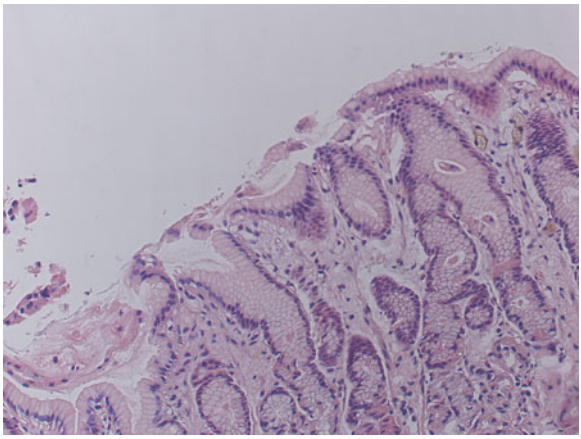

Fig. 1 Normal gastric mucosa (H & E 300× kindly supplied by Dr. Kevin West)

Other major risk factors for gastric cancer independent of *H. pylori* include pernicious anaemia, Epstein-Barr Virus (EBV) and previous gastric surgery. The following discussion relates to the complex interrelationship between *H. pylori*, inflammation and other associated risk factors in the pathogenesis of gastric adenocarcinoma.

2 Pathogenesis

Prior to the discovery of *H. pylori* it was well recognized that gastric inflammation and hypochlorhydria were associated with gastric cancer. Careful biopsy follow-up studies in high-risk populations had demonstrated the slow development of gastric atrophy over years and identified the importance of gastric body atrophy and intestinal metaplasia as risk factors for gastric cancer development (Siurala et al. 1966). Correa et al. (1975) developed the hypothesis that gastric cancer development was a slow and complex multistep process.

Fundamental to the model was the progression from normal gastric mucosa to non-atrophic gastritis, multifocal atrophic gastritis,and then the development of intestinal metaplasia and dysplasia before invasive cancer (Figs. 1, 2, 3, 4, 5, 6) (Correa et al. 1975).

Helicobacter pylori gastritis is fundamentally the host immune response to the bacteria with neutrophils, lymphocytes and macrophages. Despite the pronounced host humoral and cell-mediated response, colonisation persists for decades. The immune response is thus ineffective, raising issues regarding immune evasion (reviewed by Wilson and Crabtree 2007). Although *H. pylori* is the cause of the initial gastric inflammation only a tiny proportion of infected individuals will ultimately progress to cancer. An important determinant of cancer risk relates to the phenotype of the *H. pylori* gastritis. Subjects with an antral predominant gastric

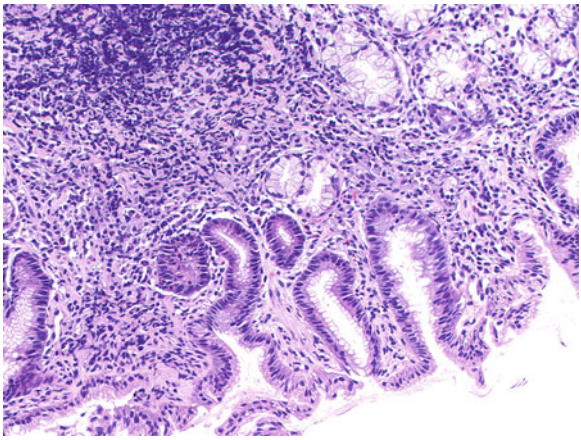

Fig. 2 *H. pylori* gastritis (H & E 300× kindly supplied by Dr. Kevin West)

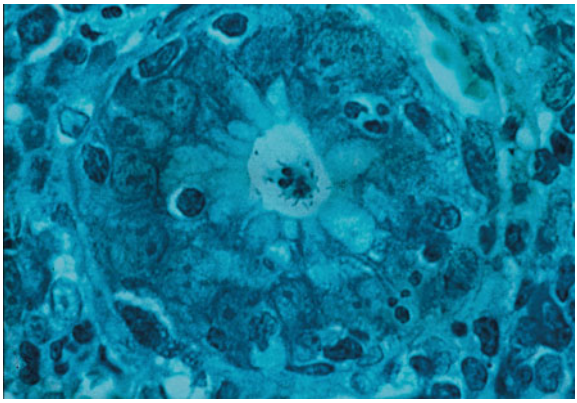

Fig. 3 *H. pylori* and polymorpholeukocyte in gastric pit (modified Giemsa stain 600× kindly supplied by Dr. Judy Wyatt)

inflammation maintain acid secretion and are not at risk of gastric cancer but are at risk of duodenal ulcer disease. Those individuals who develop an *H. pylori* pangastritis are at risk of developing multifocal atrophy, reduced acid secretion and an increased risk of gastric cancer. With decreasing acid secretion *H. pylori* colonisation may itself be lost.

Prior to the discovery of *H. pylori*, environmental factors were considered of utmost importance for gastric cancer pathogenesis. With the initial discovery of *H. pylori* the role of the bacterium took prominence. Recent studies have emphasised the importance of bacterial, host and environmental factors, and their complex interrelationship.

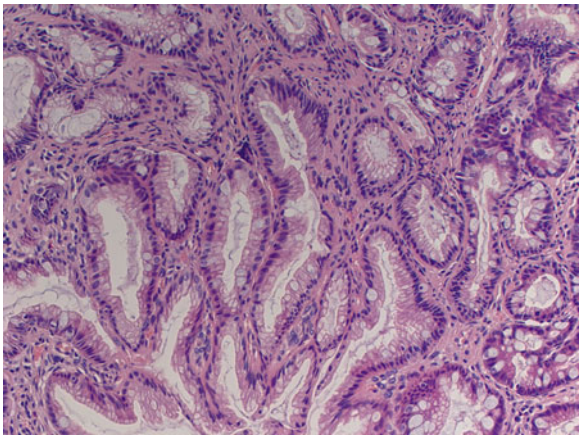

Fig. 4 Gastric intestinal metaplasia (H & E 300× kindly supplied by Dr. Kevin West)

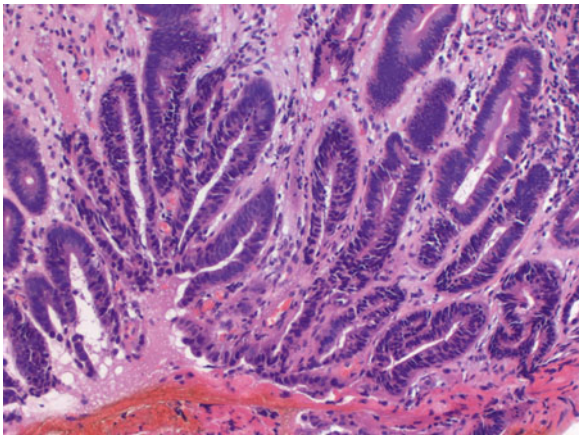

Fig. 5 Gastric low-grade dysplasia (H & E 300× kindly supplied by Dr. Kevin West)

2.1 Bacterial Factors

There is considerable heterogeneity in terms of *H. pylori* strains. A number of putative virulence factors have been identified and recently reviewed (Amieva and El-Omar 2008). Currently most interest centres on membrane proteins related to adherence, the cytotoxin associated gene A (CagA) and the cytotoxin VacA.

CagA is a 120–130 kDa protein initially identified by studies investigating the gastric humoral response to *H. pylori*. Only a proportion of colonised subjects had an immune response to this protein and the presence of such a response was associated with the degree of inflammatory activity and mucosal damage (Crabtree et al. 1991). Many studies have subsequently demonstrated that subjects with CagA positive

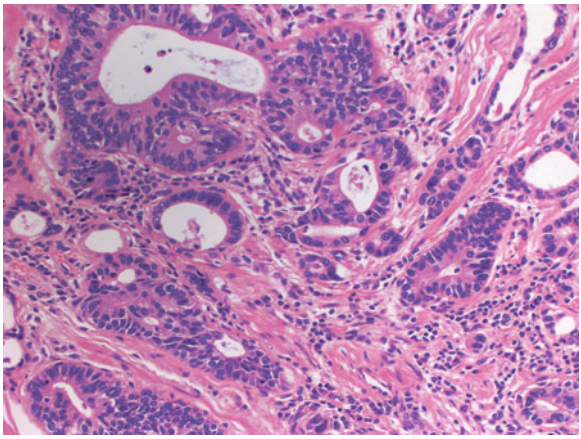

Fig. 6 Intestinal type gastric adenocarcinoma (H & E 300× kindly supplied by Dr. Kevin West)

strains are more associated with peptic ulcer disease and gastric cancer. The CagA gene is part of a large pathogenicity island (cag PAI). Genes from this island encode the CagA protein and a type IV secretion system. Following bacterial adhesion the secretion system is responsible for the translocation of CagA bacterial protein into the host cell (Segal et al. 1999; Odenbreit et al. 2000). Once translocated into host cytoplasm, CagA has complex effects on the host cell both directly and following phosphorylation.

CagA phosphorylation occurs on tyrosine residuals at its five amino acid EPIYA (Glu-Pro-Ile-Tyr-Ala) repeat region by host cell kinases. The tyrosine phosphorylated CagA interacts with a number of host proteins which can activate the ERK/MAPK pathway (Keates et al. 1999; Ding et al. 2008). The effect is to alter cellular signalling, cell proliferation and differentiation, programmed death, cytoskeletal organisation, stress and inflammatory responses (Backert et al. 2001; Chang et al. 2006).

The N-terminus of unphosphorylated CagA can complex with several junction proteins (*E*-cadherin, ZO1 and JAM) resulting in disruption of the epithelial cell apical junction complex, loss of polarity and proinflammatory and mitogenic responses (Bagnoli et al. 2005; Amieva et al. 2003). This may include the development of intestinal metaplasia (Murata-Kamiya et al. 2007).

CagA is a complex protein associated with dramatic effects on epithelial cells and associated with an increased risk of gastric cancer, yet the majority of subjects colonised with CagA positive strains will never develop gastric cancer.

The *H. pylori* bacterial cytotoxin VacA was initially described by Leunk et al. (1988) who demonstrated that *H. pylori* broth supernatents caused vacuolisation of cultured cells. The VacA gene occurs in all strains but has considerable variability in terms of cytotoxin activity. The major variations occur in the VacA signal region (types s1 and s2), the mid region (types m1 and m2) and the more recently described intermediate region (i1 and i2) (Atherton et al. 1995; Rhead et al. 2007).

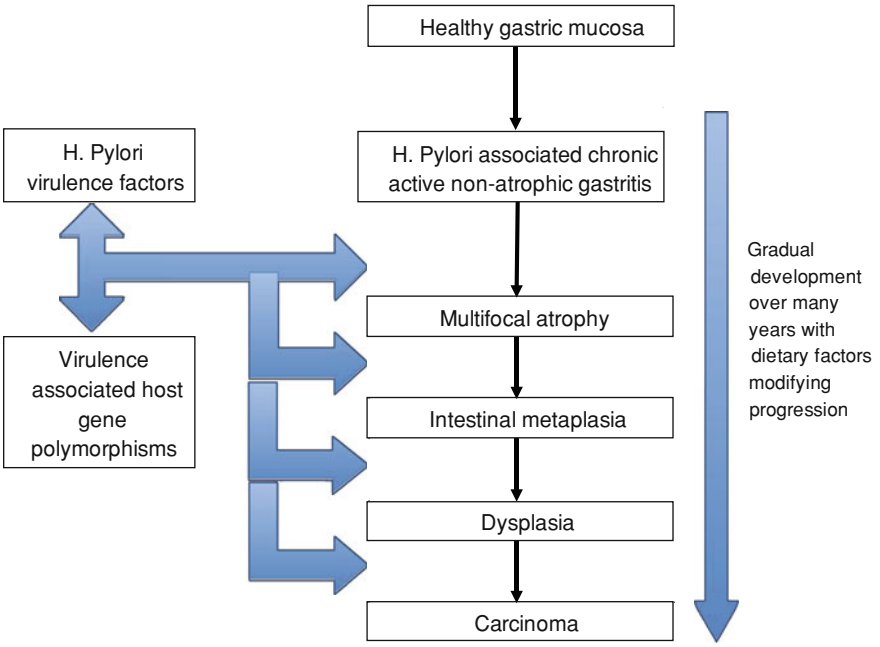

Fig. 7 Modified Correa gastric cancer pathway

When the toxin is secreted, approximately 50% remains associated with the bacterial cell surface and gains access to the epithelium with bacterial adherence (Ilver et al. 2004). The VacA toxin has multiple toxigenic properties. By affecting endosome maturation and function it causes cytoplasmic vacuolisation and impairment of antigen presentation (Molinari et al. 1998). Other effects include apoptosis, inhibition of T cell activation, disruption of tight junctions and cytochrome c release (Gebert et al. 2003; Galmiche et al. 2000; Papini et al. 1998; Willhite and Blanke 2004). The s1 m1 strains are the most toxigenic and the most associated with gastric cancer (Basso et al. 2008). Information on the intermediate type is limited although the i1 type has been associated with cancer risk in an Iranian population (Rhead et al. 2007).

Adherence seems a critical step with regard to *H. pylori* virulence with the highest density of adherence around intercellular junctions (Steer 1984). Several outer membrane proteins appear to act as adhesins. One of the most studied is BabA which is a 78 kDa outer membrane protein which binds through Lewis b blood antigens on the gastric epithelium (Ilver et al. 1998). Subjects expressing BabA have a higher density of colonisation which is associated with an enhanced mucosal inflammatory response (Rad et al. 2002). Two genes are associated with the encoding of BabA, although only BabA2 is functionally active. The expression of BabA2 is associated with the s1 VacA subtype and when associated with CagA it is associated with an enhanced risk of cancer formation (Gerhard et al. 1999).

The bacterial virulence factors described above are byzantine and intriguing in terms of benefit to the bacteria and cancer risk for the host. Adherence would appear to be a necessary prerequisite for significant mucosal damage. The BabA2, CagA and s1/m1 VacA virulence factors appear to act synergistically in promoting inflammation and the development of intestinal metaplasia (Zambon et al. 2003). An attempt to quantify the relative risk of the CagA and VacA bacterial factors confirmed the previously described CagA and VacA polymorphisms with disease but found that the single most important factor was the number of EPIYA-C segments and hence the magnitude of CagA phosphorylation (Basso et al. 2008).

The risk factors described above are all associated with an increased risk of gastric cancer and detailed studies are unravelling the mechanisms of increased risk.

Subjects colonised with the highest risk bacterial genotype are still unlikely to develop gastric cancer, again emphasising the multifactorial nature of this disease.

2.2 Host Factors

Helicobacter pylori colonisation is responsible for the increased mucosal expression of many cytokines, including several interleukins (IL-1β, IL-6, IL-8), tumour necrosis factor-α (TNFα) and interferon-γ (IFN-γ) (Calam 1999). These have all been described as affecting the parietal cells of the stomach, inhibiting acid secretion. There are multiple polymorphisms in inflammation-associated genes, for example in the IL-1 gene cluster that results in an increased expression of IL-1β, and in the TNF-A gene, resulting in increased expression of TNF-α (Kusters et al. 2006). Polymorphisms present in the interferon-γ receptor 1 (IFNGR1) gene have been found to increase host susceptibility to *H. pylori*-associated gastric cancer development (Canedo et al. 2008), and it was postulated that an increased receptor presence would result in increased number of proinflammatory cytokines. IL-8 is an important cytokine responsible for activating and attracting neutrophils and lymphocytes and for the induction of proinflammatory cytokines. The IL-8-251 gene polymorphism is associated with increased IL-8 production in *H. pylori*-associated gastric mucosa with an increased risk of premalignant change (Li et al. 2010). The presence of three or four proinflammatory gene polymorphisms in association with *H. pylori* infection has been shown to increase the risk of gastric cancer substantially (El-Omar et al. 2003).

In addition to the cytokine polymorphisms described above, other polymorphisms have been associated with an increased risk of gastric cancer in association with *H. pylori*. These include polymorphisms of the Toll-like receptor TLR4, a type I transmembrane protein expressed in the gastric epithelium which acts as a lipopolysaccharide (LPS) receptor and activates proinflammatory pathways. Certain polymorphisms in TLR4 have been shown to increase the risk of premalignant and malignant change in *H. pylori* colonised individuals (Hold et al. 2007; Hishida et al. 2009). The gene selenoprotein S (SEPS1) encodes a protein in

the endoplasmic reticulum which protects cells from oxidative damage and has a role in cytokine release (Curran et al. 2005).

A promoter polymorphism which results in reduced expression of SEPS1 has recently been associated with gastric cancer in a Japanese population (Shibata et al. 2009).

There is increasing interest in the potential role of bone marrow derived cells (BMDCs) as cancer stem cells in gastric neoplasia, reviewed by Correa and Houghton (2007). The bacterial and host factors resulting in ongoing inflammation and atrophy theoretically produce a situation where local stem cells are depleted. Mouse studies have demonstrated tissue stem cell depletion with ongoing inflammation and injury, and recruitment of bone marrow cells into the tissue stem cell niche. With continued inflammation and injury the BMDC-derived gastric mucosa developed metaplasia and dysplasia and subsequent invasive neoplasia (Houghton et al. 2004). The relevance and implications of these studies for human disease are as yet unclear.

2.3 Environmental Factors

Similar to other parts of the GI tract, the stomach has prolonged contact with ingested food material. The varying rates of gastric cancer geographically and chronologically have promoted an interest in the potential role of diet. Characteristically populations at high risk of gastric cancer have diets low in animal fats and proteins, low in fresh fruit and vegetables, high in starches and carbohydrates and high in salt and nitrates (Judd 1988). Particular interest has been paid to N-nitroso compounds as these have been found to induce tumours in the glandular stomachs of experimental animals and to the antioxidant vitamin C (ascorbic acid) as a potential protective factor.

Dietary N-nitroso compounds are typically found in cured meat, fish and beers, and have been associated with populations at an increased risk of gastric cancer (Judd 1988). There is also the potential for the formation of N-nitroso compounds in the stomach itself with gastric nitrate-reducing bacteria acting on dietary nitrates. *H. pylori* is not nitrate reducing, but if the *H. pylori* related inflammation involves the gastric body and results in decreased acid secretion, progressive atrophy can occur, raising the gastric pH. In these circumstances a range of other bacteria can colonise the stomach including nitrate-reducing bacteria and as a result higher levels of potentially carcinogenic N-nitroso compounds can be detected in gastric juice.

The recent EPIC-EUROGAST study demonstrated an association between endogenous formation of N-nitroso compounds and gastric cancer risk (Jakszyn et al. 2006). Paradoxically as the gastric pH rises, *H. pylori* colonisation is often lost, which could be due to a less favourable environment or competition from other bacteria. In practice *H. pylori* is absent from the stomach in most patients at the time when their cancer is diagnosed, emphasising the potential for varying factors to be important at different points in the natural history of gastric cancer.

Dietary ascorbic acid as an antioxidant has the potential to reduce carcinogenic *N*-nitrosamine formation in the stomach. Studies looking at gastric juice vitamin C levels demonstrated higher concentrations than would be expected from simple oral intake. These high levels are due to active gastric secretion of vitamin C. The mechanism for the secretion is unclear but like acid secretion it decreases with inflammation and atrophy (Rathbone et al. 1989; Sobala et al. 1989). Furthermore as the gastric luminal pH rises the proportion of the vitamin C available in its active form decreases thus increasing the risk of potentially carcinogenic N-nitroso compounds formation.

Another often overlooked environmental factor for gastric cancer is smoking with the EPIC study estimating that 17.6% of gastric cancer is related to smoking (González et al. 2003). A study looking at *H. pylori* status and smoking demonstrated a strongly increased risk of gastric cancer in those patients who were infected with CagA positive *H. pylori* and smoked, although the mechanism is unclear (Brenner et al. 2002).

3 Treatment

Both gastric cancer incidence and *H. pylori* infection rates are declining in many countries with the most probable reasons relating to improved living conditions. Important factors for this almost certainly include improved sanitation, water quality, food hygiene and a reduction in smoking. Despite the well-described association of gastric cancer risk with diets poor in vegetables and fruit, related intervention studies have failed to show a convincing benefit (Forman and Burley 2006).

A Cochrane analysis of randomised trials of anti-oxidant supplementation failed to demonstrate any evidence for a preventative effect against gastric cancer (Bjelakovic et al. 2008).

One of the sad facts regarding gastric cancer is the poor improvement in survival figures with treatment over the past 50 years. Clinical symptoms of gastric cancer generally occur late when the tumour is advanced and treatment options are limited. In the USA, Europe and China survival rates are only 20–25% whereas in Japan the equivalent survival rate is 52% (Parkin 2001). This difference is largely attributable to Japanese screening programmes to detect early disease. The current position regarding different treatment modalities has recently been well reviewed by Hartgrink et al. (2009).

With the important role *H. pylori* has in the early stages of the pathogenesis of gastric cancer it is compelling to believe that eradication programmes would be beneficial. The major problem here is that approximately 50% of the world's population is infected with *H. pylori*, and only a tiny minority of these are at risk of gastric cancer. Certainly in low-risk populations such as the UK and most of Europe, broad-based screening and treatment programmes are unlikely to be cost effective. In high-risk populations such as Japan and Columbia the cost benefit ratios are much better and the Asia–Pacific consensus guidelines on gastric cancer

prevention recommend screening and eradication in high-risk populations (Fock et al. 2008).

Current treatment regimens are not perfect with major problems regarding drug resistance which dramatically alters eradication rates. Where population treatment intervention studies have been carried out the results have been conflicting (Fuccio et al. 2007; Ito et al. 2009). For those with established atrophy and intestinal metaplasia, eradication is not so reliable in reducing cancer risk and endoscopic-histological screening is necessary to detect progression. This is demonstrated in a study on early gastric cancer patients treated by endoscopic mucosal resection and then treated with *H. pylori* eradication or placebo. At three years 3.3% of the eradicated patients had developed a metachronous gastric cancer compared to 8.8% of the placebo-treated patients (Fukase et al. 2008).

Clearly, advances in treatment regimens may alter the cost effectiveness of potential population treatment strategies but the development of an effective vaccine would be the best option for the future, but concerns remain regarding *H. pylori*'s immune evasion.

4 Conclusion

Gastric cancer remains a major health problem and is paradigmatic of a cancer which develops from inflamed mucosa. There is a clear pathway of development with many different factors operating. Despite a steady decline in the western world it remains a very significant cause of cancer deaths worldwide. Our understanding of the pathogenesis as described above has improved dramatically over the past thirty years however this has not translated into improved outcomes as yet.

The Correa pathway was an important concept in understanding the stepwise histological progression leading to invasive gastric cancer. Since this was described, the most fundamental breakthrough was the discovery of *H. pylori* and its role in causing histological chronic gastritis. Intensive research across the world has uncovered an astonishingly complex host–bacterial interaction and identified a number of interrelated factors pertinent to cancer risk (Fig. 7). The presence of *H. pylori* causes chronic mucosal inflammation early in the pathway. In the stepwise histological progression there appears to be a point of no return after which *H. pylori* plays no role and indeed colonisation is often lost. Eradication of or vaccination programmes against *H. pylori* in high-risk populations potentially offer a reduction in gastric adenocarcinoma and therefore the worldwide burden of cancer.

References

Amieva MR, El-Omar EM (2008) Host-bacterial interactions in *Helicobacter pylori* infection. Gastroenterology 134(1):306–323

Amieva MR, Vogelmann R, Covacci A, Tompkins LS, Nelson WJ, Falkow S (2003) Disruption of the epithelial apical–junctional complex by *Helicobacter pylori* CagA. Science 300(5624):1430–1434

Atherton JC, Cao P, Peek RM Jr, Tummuru MK, Blaser MJ, Cover TL (1995) Mosaicism in vacuolating cytotoxin alleles of *Helicobacter pylori*. Association of specific vacA types with cytotoxin production and peptic ulceration. J Biol Chem 270(30):17771–17777

Backert S, Moese S, Selbach M, Brinkmann V, Meyer TF (2001) Phosphorylation of tyrosine 972 of the *Helicobacter pylori* CagA protein is essential for induction of a scattering phenotype in gastric epithelial cells. Mol Microbiol 42(3):631–644

Bagnoli F, Buti L, Tompkins L, Covacci A, Amieva MR (2005) *Helicobacter pylori* CagA induces a transition from polarized to invasive phenotypes in MDCK cells. Proc Natl Acad Sci USA 102(45):16339–16344

Basso D, Zambon CF, Letley DP, Stranges A, Marchet A, Rhead JL, Schiavon S, Guariso G, Ceroti M, Nitti D, Rugge M, Plebani M, Atherton JC (2008) Clinical relevance of *Helicobacter pylori* cagA and vacA gene polymorphisms. Gastroenterology 135(1):91–99

Bjelakovic G, Nikolova D, Simonetti RG, Gluud C (2008) Antioxidant supplements for preventing gastrointestinal cancers. Cochrane Database Sys Rev 16(3):CDO04183

Brenner H, Arndt V, Bode G, Stegmaier C, Ziegler H, Stümer T (2002) Risk of gastric cancer among smokers infected with *Helicobacter pylori*. Int J Cancer 98(3):446–449

Calam J (1999) *Helicobacter pylori* modulation of gastric acid. The Yale J Biol Med 72(2–3):195–202

Canedo P, Corso G, Pereira F, Lunet N, Suriano G, Figueiredo C, Pedrazzani C, Moreira H, Barros H, Carneiro F, Seruco R, Roviello F, Machado JC (2008) The interferon gamma receptor 1 (IFNGR1) -56C/T gene polymorphism is associated with increased risk of early gastric carcinoma. Gut 57(11):1504–1508

Chang YJ, Wu MS, Lin JT, Pestell RG, Blaser MJ, Chen CC (2006) Mechanisms for *Helicobacter pylori* CagA-induced cyclin D1 expression that affect cell cycle. Cell Microb 8(11):1740–1752

Correa P, Houghton J (2007) Carcinogenesis of *Helicobacter pylori*. Gastroenterology 133(2):659–672

Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M (1975) A model for gastric cancer epidemiology. Lancet 2(7924):58–60

Crabtree JE, Taylor JD, Wyatt JI, Heatley RV, Shallcross TM, Tompkins DS, Rathbone BJ (1991) Mucosal IgA recognition of *Helicobacter pylori* 120 kDa protein, peptic ulceration, and gastric pathology. Lancet 338(8763):325–332

Curran JE, Jowett JB, Elliott KS, Gao Y, Gluschenko K, Wang J, Abel Azim DM, Cai G, Mahaney MC, Comuzzie AG, Dyer TD, Walder KR, Zimmet P, MacCluer JW, Collier GR, Kissebah AH, Blangero J (2005) Genetic variation in selenoprotein S influences inflammatory response. Nat Genet 37(11):1234–1241

Ding SZ, Smith MF Jr, Goldberg JB (2008) *Helicobacter pylori* and mitogen-activated protein kinases regulate the cell cycle, proliferation and apoptosis in gastric epithelial cells. J Gastroenterol Hepatol 23(7 Pt 2):e67–e78

El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, Stanford JL, Mayne ST, Goedert J, Blot WJ, Fraumeni JF Jr, Chow WH (2003) Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology 124(5):1193–1201

Fock KM, Talley N, Moayyedi P, Hunt R, Azuma T, Sugano K, Xiao SD, Lam SK, Goh KL, Chiba T, Uemura N, Kim JG, Kim N, Ang TL, Mahachai V, Mitchell H, Rani AA, Liou JM, Vilaichone RK, Sollano J (2008) Asia–Pacific consensus guidelines on gastric cancer prevention. J Gastroenterol Hepatol 23(3):351–365

Forman D, Burley VJ (2006) Gastric cancer: global pattern of the disease and an overview of environmental risk factors. Best Pract Res Clin Gastroenterol 20(4):633–649

Fuccio L, Zagari RM, Minardi ME, Bazzoli F (2007) Systematic review: *Helicobacter pylori* eradication for the prevention of gastric cancer. Aliment Pharmacol Ther 25(2):133–141

Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, Terao S, Amagai K, Hayashi S, Asaka M (2008) Effect of eradication of *Helicobacter pylori* on incidence of metachronous

gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 372(9636):392–397

Galmiche A, Rassow J, Dove A, Cagnol S, Chambard JC, Contamin S, de Thillot V, Just I, Ricci V, Solcia E, Van Obberghen E, Boquet P (2000) The *N*-terminal 34 kDa fragment of *Helicobacter pylori* vacuolating cytotoxin targets mitochondria and induces cytochrome c release. EMBO J 19(23):6361–6370

Gebert B, Fischer W, Weiss E, Hoffmann R, Haas R (2003) *Helicobacter pylori* vacuolating cytotoxin inhibits T lymphocyte activation. Science 301(5636):1099–1102

Gerhard M, Lehn N, Neumayer N, Borén T, Rad R, Schepp W, Miehlke S, Classen M, Prinz C (1999) Clinical relevance of the *Helicobacter pylori* gene for blood-group antigen-binding adhesion. Proc Natl Acad Sci USA 96(22):12778–12783

Go MF (2002) Review article: natural history and epidemiology of *Helicobacter pylori* infection. Aliment Pharmacol Ther 16(Suppl 1):3–15

González CA, Pera G, Agudo A, Palli D, Krogh V, Vineis P, Tumino R, Panico S, Berglund G, Simán H, Nvrén O, Agren A, Martinez C, Dorronsoro M, Barricarte A, Tormo MJ, Quiros JR, Allen N, Bingham S, Day N, Miller A, Nagel G, Boeing H, Overvad K, Tionneland A, Bueno-De-Mesquita HB, Boshuizen HC, Peeters P, Numans M, Clavel-Chapelon F, Helen I, Agapitos E, Lund E, Fahey M, Saracci R, Kaaks R, Riboli E (2003) Smoking and the risk of gastric cancer in the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer 107(4):629–634

Hartgrink HH, Jansen EP, van Grieken NC, van de Velde CJ (2009) Gastric cancer. Lancet 374(9688):477–490

Hishida A, Matsuo K, Goto Y, Mitsuda Y, Hiraki A, Naito M, Wakaj K, Tajima K, Hamajima N (2009) Toll-like receptor 4 +3725 G/C polymorphism, *Helicobacter pylori* seropositivity, and the risk of gastric atrophy and gastric cancer in Japanese. Helicobacter 14(1):47–53

Hold GL, Rabkin CS, Chow WH, Smith MG, Gammon MD, Risch HA, Vaughan TL, McColl KE, Lissowska J, Zatonski W, Schoenberg JB, Blot WJ, Mowat NA, Fraumeni JF Jr, El-Omar EM (2007) A functional polymorphism of toll-like receptor 4 gene increases risk of gastric carcinoma and its precursors. Gastroenterology 132(3):905–912

Houghton J, Stoioy C, Nomura S, Rogers AB, Carlson J, Li H, Cai X, Fox JG, Goldenring JR, Wang TC (2004) Gastric cancer originating from bone marrow-derived cells. Science 306(5701):1568–1571

Ilver D, Arnqvist A, Ogren J, Frick IM, Kersulyte D, Incecik ET, Berg DE, Covacci A, Engstrand L, Borén T (1998) *Helicobacter pylori* adhesion binding fucosylated histo-blood group antigens revealed by retagging. Science 279(5349):373–377

Ilver D, Barone S, Mercati D, Lupetti P, Telford JL (2004) *Helicobacter pylori* toxin VacA is transferred to host cell via a novel contact-dependent mechanism. Cell Microbiol 6(2):167–174

International Agency for Research on Cancer (1994) IARC monographs on the evaluation of carcinogenic risks to humans: Schistosomes, liver flukes and *Helicobacter pylori*, vol 61. Lyon, IARC

Ito M, Takata S, Tatsugami M, Wada Y, Imagawa S, Matsumoto Y, Takamura A, Kitamura S, Matsuo T, Tanaka S, Haruma K, Chayama K (2009) Clinical prevention of gastric cancer by *Helicobacter pylori* eradication therapy: a systematic review. J Gastroenterol 44(5): 365–371

Jakszyn P, Bingham S, Pera G, Agudo A, Luben R, Welch A, Boeing H, Del Giudice G, Palli D, Saieva C, Krogh V, Sacerdote C, Tumino R, Panico S, Berglund G, Simán H, Hallmans G, Sanchez MJ, Larrañaga N, Barricarte A, Chirlaque MD, Quirós JR, Key TJ, Allen N, Lund E, Carneiro F, Linseisen J, Nagel G, Overvad K, Tionneland A, Olsen A, Bueno-de-Mesquita HB, Ocké MO, Peeters PH, Numans ME, Clavel-Chapelon F, Trichopoulou A, Fenger C, Stenling R, Ferrari P, Jenab M, Norat T, Riboli E, González CA (2006) Endogenous versus exogenous exposure to *N*-nitroso compounds and gastric cancer risk in the European prospective investigation into cancer and nutrition (EPIC-EURGAST) study. Carcinogenesis 27(7):1497–1501

Judd PA (1988) Dietary factors in the aetiology of gastric cancer. In: Gastric carcinogenesis, proceedings of the 6th annual symposium of the European organisation for cooperation in cancer prevention studies. Amsterdam, Excerpta Medical

Keates S, Keates AC, Warny M, Peek RM Jr, Murray PG, Kelly CP (1999) Differential activation of mitogen-activated protein kinases in AGS gastric epithelial cells by cag+ and cag− *Helicobacter pylori*. J Immunol 163(10):5552–5559

Kusters JG, van Vliet AH, Kuipers EJ (2006) Pathogenesis of *Helicobacter pylori* infection. Clin Microbiol Rev 19(3):449–490

Leunk RD, Johnson PT, David BC, Kraft WG, Morgan DR (1988) Cytotoxic activity in broth-culture filtrates of *Campylobacter pylori*. J Med Microbiol 26(2):93–99

Li ZW, Wu Y, Sun Y, Liu LY, Tian MM, Feng GS, You WC, Li JY (2010) Inflammatory cytokine gene polymorphisms increase the risk of atrophic gastritis and intestinal metaplasia. World J Gastroenterol 16(14):1788–1794

Marshall B (1983) Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1(8336):1273–1275

Moayyedi P, Axon AT, Feltbower R, Duffett S, Crocombe W, Braunholtz D, Richards ID, Dowell AC, Forman D (2002) Relation of adult lifestyle and socioeconomic factors to the prevalence of *Helicobacter pylori* infection. Int J Epidemiol 31(3):624–631

Molinari M, Salio M, Galli C, Norais N, Rappuoli R, Lanzavecchia A, Montecucco C (1998) Selective inhibition of Ii-dependent antigen presentation by *Helicobacter pylori* toxin VacA. J Exp Med 187(1):135–140

Murata-Kamiya N, Kurashima Y, Teishikata Y, Yamahashi Y, Saito Y, Higashi H, Aburatani H, Akiyama T, Peek RM Jr, Azuma T, Hatakeyama M (2007) *Helicobacter pylori* CagA interacts with E-cadherin and deregulates the beta-catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. Oncogene 26(32):4617–4626

Necchi V, Candusso ME, Tava F, Luinetti O, Ventura U, Fiocca R, Ricci V, Solcia E (2007) Intracellular, intercellular, and stromal invasion of gastric mucosa, preneoplastic lesions, and cancer by *Helicobacter pylori*. Gastroenterology 132(3):1009–1023

Odenbreit S, Püls J, Sedlmaier B, Gerland E, Fischer W, Haas R (2000) Translocation of *Helicobacter pylori* CagA into gastric epithelial cells by type IV secretion. Science 287(5457):1497–1500

Papini E, Satin B, Norais N, de Bernard M, Telford JL, Rappuoli R, Montecucco C (1998) Selective increase of the permeability of polarized epithelial cell monolayers by *Helicobacter pylori* vacuolating toxin. J Clin Investig 102(4):813–820

Parkin DM (2001) Global cancer statistics in the year 2000. Lancet Oncol 2(9):533–543

Parkin DM (2006) The global health burden of infection-associated cancers in the year 2002. Int J Cancer 118(12):3030–3044

Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics 2002. CA Cancer J Clin 55(2):74–208

Rad R, Gerhard M, Lang R, Schöniger M, Rösch T, Schepp W, Becker I, Wagner H, Prinz C (2002) The *Helicobacter pylori* blood group antigen-binding adhesion facilitates bacterial colonization and augments a nonspecific immune response. J Immunol 168(6):3033–3041

Rathbone BJ, Johnson AW, Wyatt JI, Kelleher J, Heatley RV, Losowsky MS (1989) Ascorbic acid: a factor concentrated in human gastric juice. Clin Sci 76(3):237–241

Rhead JL, Letley DP, Mohammadi M, Hussein N, Mohagheghi MA, Eshagh Hosseini M, Atherton JC (2007) A new *Helicobacter pylori* vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. Gastroenterology 133(3):926–936

Segal ED, Cha J, Lo J, Falkow S, Tompkins LS (1999) Altered states: involvement of phosphorylated CagA in the induction of host cellular growth changes by *Helicobacter pylori*. Proc Natl Acad Sci USA 96(25):14559–14564

Shibata T, Arisawa T, Tahara T, Ohkubo M, Yoshioka D, Maruyama N, Fujita H, Kamiya Y, Nakamura M, Nagasaka M, Iwata M, Takahama K, Watanabe M, Hirata I (2009) Selenoprotein S (SEPS1) gene -105G > A promoter polymorphism influences the susceptibility to gastric cancer in the Japanese population. BMC Gastroenterology 9:2

Siurala M, Varis K, Wiljasalo M (1966) Studies of patients with atrophic gastritis: a 10–15 year follow-up. Scand J Gastroenterol 1(1):40–48

Sobala GM, Schorah CJ, Sanderson M, Dixon MF, Tompkins DS, Godwin P, Axon AT (1989) Ascorbic acid in the human stomach. Gastroenterology 97(2):357–363

Steer HW (1984) Surface morphology of the gastroduodenal mucosal in duodenal ulceration. Gut 25(11):1203–1210

Warren JR (1983) Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1(8336):1273

Willhite DC, Blanke SR (2004) *Helicobacter pylori* vacuolating cytotoxin enters cells, localizes to the mitochondria, and induces mitochondrial membrane permeability changes correlated to toxin channel activity. Cell Microbiol 6(2):143–154

Wilson KT, Crabtree JE (2007) Immunology of *Helicobacter pylori*: insights into the failure of the immune response and perspectives on vaccine studies. Gastroenterology 133(1):288–308

Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG (1991) *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. Lancet 338(8776):1175–1176

Zambon CF, Navaglia F, Basso D, Rugge M, Plebani M (2003) *Helicobacter pylori* babA2, cagA, and s1 vacA genes work synergistically in causing intestinal metaplasia. J Clin Pathol 56(4):287–291