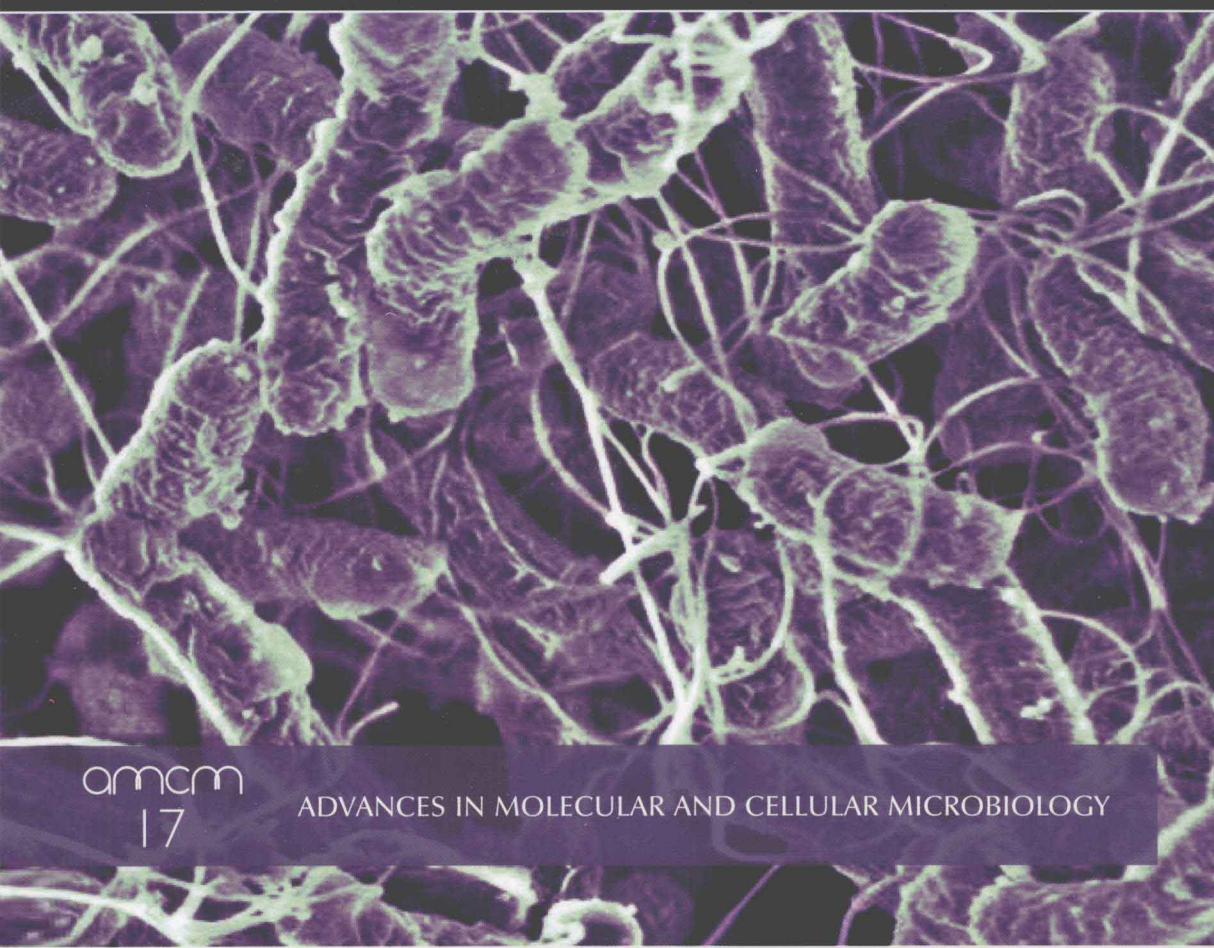
Helicobacter pylori in the 21st Century

Edited by Philip Sutton and Hazel M. Mitchell



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Advances in Molecular and Cellular Microbiology 17

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A catalogue record for this book is available from the British Library, London, UK.

Library of Congress Cataloging-in-Publication Data

Helicobacter pylori in the 21st century / edited by Philip Sutton, Hazel Mitchell.
p. ; cm. -- (Advances in molecular and cellular microbiology ; 17)
Includes bibliographical references and index.
ISBN 978-1-84593-594-8 (alk. paper)
1. Helicobacter pylori infections. I. Sutton, Philip, 1965- II. Mitchell, Hazel, 1949- III. Title: Helicobacter pylori in the twenty-first century. IV. Series: Advances in molecular and cellular microbiology ; 17.
[DNLM: 1. Helicobacter Infections. 2. Helicobacter pylori. WC 200 H47533 2010]

QR201.H44H462 2010
616.3'3014--dc22

2009049449

ISBN-13: 978 1 84593 594 8

Commissioning editor: Nigel Farrar
Production editor: Tracy Head

Typeset by Columns Design Ltd, Reading, UK.
Printed and bound in the UK by CPI Antony Rowe, Chippenham.

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Through the application of molecular and cellular microbiology we now recognize the diversity and dominance of microbial life forms that exist in all environments on our planet. These microbes have many important planetary roles, but for humans a major problem is their ability to colonize our tissues and cause disease. The same techniques of molecular and cellular microbiology have been applied to the problems of human and animal infection since the 1990s and have proved to be immensely powerful tools in elucidating how microorganisms cause human pathology. This series has the aim of providing information on the advances that have been made in the application of molecular and cellular microbiology to specific organisms and the diseases they cause. The series is edited by researchers active in the application of molecular and cellular microbiology to human disease states. Each volume focuses on a particular aspect of infectious disease and will enable graduate students and researchers to keep up with the rapidly diversifying literature in current microbiological research.

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Foreword

Unlike books that have been written before about *Helicobacter pylori*, this volume, 30 years after Warren's original description of a case at Royal Perth Hospital, presents a mature understanding of how the bacterium colonizes its host and causes disease. As such, it will stay on my laboratory shelf for years to come, perhaps with a few minor details added as new signalling pathways are discovered.

Thirty years after Robin Warren first saw spiral bacteria on human gastric biopsies, Sutton and Mitchell's new book is a timely reminder that many clinical and basic aspects of *H. pylori* science are still controversial and worthy of further research. While much of our knowledge of the bacterium is a logical extrapolation of findings in other infectious diseases, the unique ability of *Helicobacter* to colonize the human gastric mucosa for many decades provides important insights into host–pathogen interactions, mucosal immunity and the whole immune system.

The editors themselves have been entrenched in *Helicobacter* microbiology for many years and are very well respected in their fields. Associate Professor Phil Sutton, an immunologist, has spent the past several years developing new animal models of *Helicobacter* infection whereby the fine details of the mucosal immune response can be isolated and teased out with the goal of designing vaccines against the organism. Similarly, Professor Hazel Mitchell is now Professor of Microbiology at the University of New South Wales, with many publications on all aspects of *Helicobacter* since she was one of the first in the world to complete a PhD on the biology and immunology of this intriguing organism.

With such eminent editors, it is no surprise that their co-authors include the leading lights in specific aspects of *Helicobacter* science. These specialists have each spent many years supervising teams of scientists and no doubt any one of them could easily produce an authoritative book on their special area of interest if they had the time. However, thanks to years of experience, every one of them has produced a concise chapter that not only emphasizes the proven facts but also mentions aspects of the disease that are unusual, controversial or defy explanation.

The chapter on epidemiology is written by Hoda Malaty, who trained in David Graham's faculty in Houston and who managed many of the seminal epidemiological studies using endoscopy, ELISA serology tests and ^{13}C-urea breath tests. There is no doubt that *Helicobacter* is less common now as the standard of living increases around the world, but questions of transmission, acquisition and spontaneous loss of the infection are not all that well understood. Clinicians treating refractory patients need to consider these puzzling aspects of the disease. Twin studies, too, have been described here, to give a taste of the ongoing controversy, which is: 'Are host factors or bacterial factors the most important in determining disease outcome?'

Many of the unsolved dilemmas are then addressed further by Professor Kwong Fock from Singapore, a well-known academic and clinician with first-hand experience of the great disparities between *Helicobacter* incidence and *Helicobacter*-related diseases in the Asia Pacific region. Of particular interest is the question: 'If *Helicobacter* causes gastric cancer, why is it that some ethnic and geographic groups have one without the other?' Once again the host/cultural factors versus bacterial factors, especially various types of toxigenic *Helicobacter* strains, are carefully considered. Recent molecular/epidemiological studies of the mosaicism and phosphorylation sites of the gene encoding the cytotoxin-associated gene A product (CagA) could explain some of this variation. Presently, however, one must admit that a unifying hypothesis does not exist to explain the great disparities in disease phenotypes in Asia. Fock's chapter points out where modest efforts into carefully selected new studies are likely to pay off.

In a related chapter, the whole subject of gastric carcinogenesis, its histology, aetiology and relationship with *Helicobacter*, is placed into perspective by Pelayo Correa, a pathologist and pioneer of gastric cancer histological studies, and M. Blanca Piazuelo. With direct experience in the USA and South America, particularly the high cancer areas in Colombia, Correa and Piazuelo establish the background knowledge relating cancer risks to diets and lifestyle and then bring us up to date with new advances in the basic science of gastric carcinogenesis, particularly the exciting areas of *Helicobacter* toxin types, nitric oxide generation and oxidative stress. This well-referenced chapter is essential reading for anyone starting out in the field of gastric carcinogenesis.

Rounding off the clinical section is the chapter on antimicrobial resistance by Francis Mégraud of Bordeaux, who expertly addresses this emerging problem that is leading to global reductions in cure rate. Mégraud has authored many clinical studies of *Helicobacter* treatment and therefore has studied the resistance patterns of persisting isolates. His chapter is up to date with authoritative explanations of the pharmacokinetics of antimicrobials as they apply to the human stomach. In addition, he explains new technologies being introduced to rapidly evaluate antimicrobial resistance using molecular methods which thus avoid the several days' delay of 'old-fashioned' bacterial culture.

Bridging the clinical and basic sections, the chapter on taxonomy and extragastric *Helicobacter* infections by Hazel Mitchell, Nadeem Kaakoush and Phil Sutton will still be of great interest to clinicians. Mitchell has orchestrated a careful and impartial review of the non-gastric diseases that might be associated with *H. pylori* infection. Actually, it is very likely that some of these so-called associations are coincidental, related to socio-economic status for example. But in response to this, Mitchell has put the most robust linkages at the front of the chapter ('idiopathic thrombocytic purpura' and iron deficiency), then those with highly variable associations and likely reporting bias, most notably atherosclerosis, are discussed later. The review of the epidemiologic and basic research for each of these associations is an excellent resource for hypothesis-driven research plans. Similarly, attempts to unravel the highly variable association between *H. pylori* and atherosclerotic diseases could justify a career in clinical epidemiology. The chapter then flows easily into an expertly crafted discussion of the 'hygiene' link to allergic and 'autoimmune' disorders diseases, e.g. asthma and colitis, again using a clinical review followed by an in-depth description of hypothesis-driven basic immunological studies. Surprisingly, these have already revealed potential causative pathways that could lead to novel therapies for atopic diseases. With half the world still infected with *H. pylori*, modest increases in 'non-gastric' disease risk could actually drive numerically large amounts of morbidity, so it is very easy to justify further investigation into this emerging area of *Helicobacter* discovery.

In their chapter on *H. pylori*-induced acquired immunity and immunoregulation, Karen Robinson and John Atherton start off by listing the many paradoxes associated with *Helicobacter* immunology – for example, that B-cell-deficient animals can still be immunized and that some immunizations can actually increase *Helicobacter* colonization. To whet our appetite further,

they discuss tantalizing data whereby some human diseases characterized by hyperactive immune systems might be ameliorated or prevented by chronic gut infections such as *Helicobacter*.

Phil Sutton, Alison Every and Stacey Harbour's chapter on host genetic factors and susceptibility to *H. pylori* pathogenesis systematically describes the known workings of the mucosal immune system and how its components are influenced by various *Helicobacter* infections in several animal models. Since *Helicobacter* cannot usually be eradicated by even a robust serological immune response, it is important to understand the workings of the cell-mediated immune response too, as this is the component that correlates with protection from *Helicobacter* in animal models. Interaction between *Helicobacter* immunity and other pathogens, such as helminths, is discussed as part of the 'clean' versus 'dirty' human bacterial ecology hypothesis as it could affect the human propensity to develop hyperactive immune responses in autoimmune diseases, particularly atopic conditions such as asthma.

Maria Kaparakis, Cody Allison and Melanie Hutton from Richard Ferrero's group at Monash University in Melbourne start their review of innate immune initiators and effectors in *H. pylori* infection by pointing out the apparent paradox: namely that gastric epithelial cells are not usually considered to be a component of the immune system, yet colonization of this mucosa generates mucosal inflammation and a strong antibody response. However, these gastric epithelial cells are all very competent innate immune responders and this immediate part of the immune response might be used by *H. pylori* to improve its nutrition in the gastric mucus layer. The chapter then catalogues evidence for and against a major role for each of the relevant cytokines, assigning importance to the Toll-like receptors (TLR) 4 and TLR2 (from epithelia) and the neutrophil-activating protein HP-NAP (from *H. pylori*), but not lipopolysaccharide or flagellin (to which TLR5 is unreactive). Ferrero's specialty is the nucleotide-binding oligomerization (NOD) receptors, an interesting group that carries out an inflammatory role but might also trigger release of the cellular antibiotics such as 'defensins'. The authors make the point that much work is needed to further clarify this area.

Thomas Blanchard and John Nedrud have prepared a careful review of *H. pylori* vaccines, reflecting their long experience in this area. So that immunologists new to the field do not try to 'reinvent the wheel', the authors systematically explain the evolution of vaccines for *H. pylori* with tales of success and failure in various animal models, finishing with comprehensive lists of antigens, administration routes and results. They critically review the outcome of many studies, explaining results according to whether the vaccine causes protection, sterilizing immunity, or some lesser degree of effect. In each case they characterize the underlying immune response, T-helper 1 or T-helper 2 type, and consider why the results might not have been appropriate or sufficient for human use.

Going into some detail, Blanchard and Nedrud explain, similarly to the other immunological chapters, how the *H. pylori* immunity is unrelated to the serological immune response and that, in some models, antibodies actually enhance the colonization with *H. pylori* compared with a knockout mouse unable to produce antibody (μMT antibody-deficient mice). These data are reminiscent of the human situation, where *H. pylori* has never been a major pathogen in AIDS or immune-deficient patients, supporting the hypothesis that robust immunity might be necessary for conversion from the asymptomatic to the symptomatic (ulcer) phenotype. In their chapter, these authors try to make sense of a plethora of experimental data but it seems that there is much work to be done. With so many adjuvants, mouse strains, vaccination routes and even knockout animals to test these days, it is difficult to say which will mimic the human situation and be an appropriate model. Of interest is a description of some animal models whereby gastritis worsens or activates when an *H. pylori* challenge is given subsequent to a vaccine. Thoughtful consideration of this effect, which seems to resolve after *H. pylori* eradication, is worthwhile in case there are autoimmune implications to empirical attempts to eradicate *H. pylori* in humans. However, as far as we know, *H. pylori* disease is not the cause of idiopathic autoimmune gastritis.

In great detail Blanchard and Nedrud catalogue even more obscure factors that interact with gastric immunity, most notably the adipokine leptin. The fact that leptin influences immunization against *H. pylori* is an example to us that there may be other as yet undiscovered factors that are playing a key role in the mucosal defence, or lack thereof, against *H. pylori*. After discussing poor results from studies in monkeys and humans using live *Salmonella* vectors and various other strategies, the authors summarize by saying that there are many strategies that should work, but have yet to be properly trialled, so *H. pylori* vaccinology will remain an exciting and busy area of research for years to come.

In a personal chapter, based on a lifelong interest in the lipopolysaccharides of *H. pylori* and their importance in gastric adaptation and pathogenesis, Professor Tony Moran provides a very detailed review of the *H. pylori* lipopolysaccharide, cell wall structures, interactions with the immune systems and the intricacies of the Lewis antigen mimicry. Clearly, fundamental understanding of the bacterial cell wall structures, particularly its lipid, is essential if we are to develop new means of eradicating or immunizing against *Helicobacter*. Not just a list of references and summaries of each, Moran's well-known personal expertise in this area allows him to synthesize the data and critically review the field so that new investigators can see what has been done, what strengths, weaknesses and inconsistencies there are in the existing body of work, and what is needed to make progress in this exciting but tough scientific niche.

In a very comprehensive chapter about virulence factors of *H. pylori*, accompanied by beautiful and detailed illustrations, Steffen Backert, Hitomi Mimuro, Dawn Israel and Richard Peek from Nashville summarize current knowledge in this area. Their long experience in the field is reflected first in a relevant critique of the latest methodology, especially cell biology and new transgenic animal models. They successfully tease out the interactions between the many adhesins, cytokines, toxins and signalling proteins, with carefully linked text and illustrations. Their synthesis incorporates new information from the post-genomic/proteomic era to explain the fundamental workings of the vacuolating cytotoxin VacA and CagA. By carefully reading the text and following the numbered steps in the illustrations readers will see why, for 60,000 years, *H. pylori* has been able to successfully colonize – but not kill – its unlucky human host. This is a very detailed, heavy-duty chapter about the workings of VacA and CagA, a really great reference especially valued because of its thoughtful and expertly done illustrations.

In a related chapter on *H. pylori* adhesion to the gastric surface, authors Sara Lindén, Anna Arnqvist, Susanne Teneberg and Tony Moran represent three of the world's premier groups studying the interaction between *H. pylori* and the various carbohydrate moieties present on the gastric epithelial cells. Put simply, these structures help make *H. pylori* stick. In a complicated area, these experts have created a structured chapter starting with consideration of the oral cavity, salivary, then gastric and epithelial adhesive structures. Some of these are well studied, such as the Bab adhesins, but others remain a mystery. Clearly, however, *H. pylori* has an efficient means of reaching and then tethering itself to the gastric mucosa, and a comprehensive explanation of the current state of the art is presented here.

Hilde de Reuse, Markus Heimesaat and Stefan Bereswill provide a fast-moving and readable overview of the *H. pylori* genome, 'Helicobacteromics', emphasizing the variability and plasticity as vast bacterial numbers balance their existence against the human immune system on the quite variable environments of the human gastric mucosa. *H. pylori* does this by genome shuffling and randomly disabling or enabling its outer membrane proteins to vary their interactions with the host, aided by its rather poor DNA repair repertoire, so that small mutations continually occur whereby new variations of all its genes are constantly being tested. Understanding how the *H. pylori* genome works also explains how the bacterium imports blocks of genes such as the *cagA* pathogenicity island, a secretion system that has a distinctly different G+C content from the rest of the organism's DNA, showing that it was imported 'en bloc' from a different organism, though which one we have no idea! After finding a home in the human stomach, *H. pylori* then discarded many genes because it now lived exclusively in a rather hostile but constant environmental niche, with few competitors, and its excursions into

the outside world were probably rare and rather short-lived, as its new host was almost always in the same human family. The authors explain how tracing human migrations using polymorphisms in essential housekeeping genes (via multilocus sequence typing, MLST) has become an area of research with wide interest and general implications for the human family. These authors enhance their chapter with their own deep insights into the genomic strategies whereby *H. pylori* survives in its acidic niche.

To sum it up then, this is an industrial-strength book containing up-to-date reviews on *Helicobacter* science, each presented by a world expert in that particular area. The first third of the book contains reviews of the issues of interest to clinicians, i.e. epidemiology, microbiology, pathophysiology and therapeutics. The rest of the book delves minutely into a diverse range of fundamental issues arising in the bacterium itself (carbohydrates, lipids and toxins) and their effects on the host's immune systems, innate and adaptive. This book is action-packed, fact-filled and thoughtfully assembled. I look forward to having it on my laboratory shelf for years to come.

Barry Marshall
December 2009

Contents

1 Epidemiology of *Helicobacter pylori* Infection

H.M. MALATY

1.1 Introduction

Helicobacter pylori infection is now recognized as a worldwide problem. *H. pylori* infection is the most common cause of chronic gastritis, and has been strongly linked to peptic ulcer disease and gastric cancer. *H. pylori* is estimated to infect one-half of the world's population. The epidemiology of infection reveals that given the right circumstances it is readily transmissible. Infection is generally acquired in childhood, but disease manifestations typically do not appear until adulthood and often only after long periods of latency. The infection has a high morbidity rate, but a low mortality rate, and is curable with antibiotic therapy.

1.2 Relationship between *H. pylori* Infection and Associated Diseases

H. pylori infection is causally related to chronic gastritis and peptic ulcer disease, and indirectly related to gastric adenocarcinoma and primary gastric B-cell lymphoma (Forman *et al.*, 1990, 1991; Tytgat *et al.*, 1993; Peura and Graham, 1994). Infection with *H. pylori* leads to the development of gastric damage, and of those infected approximately 25% may ultimately develop low gastric acid production (achlorhydria), which is associated with an increased susceptibility to the development of gastric cancer (see Correa and Piazuelo, Chapter 3, this volume; Graham *et al.*, 1988). Approximately 17% of infected patients develop peptic (gastric and duodenal) ulcers, and one-quarter of such patients experience an ulcer complication (Tytgat *et al.*, 1993). Numerous trials have shown that ulcer relapse is prevented after cure of the infection (Graham *et al.*, 1992). Histological and serological studies have also shown that infection precedes the ulcer and thus *H. pylori* infection is now accepted as one of the two major causes of peptic ulcers, the other being use of non-steroidal anti-inflammatory drugs (NSAIDs). In an evaluation of 100 consecutive duodenal ulcer and 154 gastric ulcer patients in a Veteran Affairs population in Houston, Texas, 99% of those with duodenal ulcers were found to be positive for *H. pylori*, 30% of whom were also found to be using NSAIDs (Al-Assi *et al.*, 1996), and 92% of patients with gastric ulcers were infected with the bacterium, 58% of whom were also taking NSAIDs. These findings were confirmed in a recent study by Gisbert and Calvet (2009) that reviewed the real prevalence of *H. pylori*-negative duodenal ulcer and its possible causes. This study reported that, in truly *H. pylori*-negative patients, the single most common cause of duodenal ulcer is, by far, the use of NSAIDs.

More sophisticated approaches looking for evidence of cyclooxgenase-1 inhibition

have shown that NSAID use is much more common than expected in peptic ulcer patients (Al-Assi *et al.*, 1996) and probably accounts for a sizeable proportion of cases. Additional possibilities include other infections such as herpes simplex virus and other drugs such as alendronate (Gisbert and Calvet, 2009), as well as misdiagnosis by the endoscopist. Peptic ulcer disease is a chronic relapsing disorder, with typical morphological and endoscopic appearances. One important reason for the observed differences in the ulcer prevalence and ulcer recurrence rates in clinical trials is the interpretation of the findings by endoscopists, who are possibly the most likely source of variability in such studies.

The exact prevalence of *H. pylori* infection in gastric cancer patients remains difficult to estimate, because infection can be lost from individuals with cancer or its precursor conditions (see Correa and Piazuelo, Chapter 3, this volume). In a study by Yamaji *et al.* (2002), sera from 10,234 consecutive Japanese individuals who participated in a health examination programme were tested for the presence of antibodies against *H. pylori* by immunoglobulin G (IgG) ELISA. While this study confirmed the relationship between serum positivity and gastric cancer, these authors pointed out that, particularly in the elderly, a weak *H. pylori* antibody response carried a high risk for gastric cancer. A Swedish population-based case–control study, using an immunoblot for the cytotoxin-associated gene A protein (CagA) (rather than an IgG ELISA) to detect infection, showed the CagA immunoblot to be a more sensitive assay for detecting past infection. The study reported that the estimated proportion of non-cardia adenocarcinoma attributable to *H. pylori* was 71% for both histological subtypes (odds ratio (OR) = 21, 95% confidence interval 8.3, 53.4), ranking with the association reported between smoking and lung cancer (Ekstrom *et al.*, 2001).

Atrophic gastritis and intestinal metaplasia are well-established precursor lesions of the intestinal type of gastric cancer (see Correa and Piazuelo, Chapter 3, this volume). A study from Japan followed up 1526 patients with duodenal ulcers, gastric ulcers, gastric hyperplasia or non-ulcer dyspepsia, of whom 1246 had *H. pylori* infection and 280 did not, for a mean period of 7.8 years (Uemura *et al.*, 2001). Gastric cancer was shown to develop in 36 (2.9%) of the infected subjects compared with none of the uninfected patients. Among the patients with *H. pylori* infection, those with severe gastric atrophy, corpus-predominant gastritis and intestinal metaplasia were at significantly higher risk for gastric cancer. The authors detected gastric cancers in 21 (4.7%) of the 445 patients with non-ulcer dyspepsia, ten (3.4%) of the 297 with gastric ulcers, five (2.2%) of the 229 with gastric hyperplastic polyps, and none of the 275 with duodenal ulcers. The study concluded that gastric cancer develops in persons infected with *H. pylori* but not in uninfected persons. Another study from Japan reported the results of a multicentre study to evaluate the relationship between *H. pylori* infection, atrophic gastritis and intestinal metaplasia (Asaka *et al.*, 2001). The study reported that the prevalence of atrophic gastritis increased from 9.4% in individuals less than 20 years of age to >70% in those aged 60 years or older, and was strongly associated with *H. pylori* infection. The overall prevalence of atrophic gastritis in *H. pylori* infection was 82.9%, compared with 9.8% among those uninfected (OR = 44.8). Intestinal metaplasia was present in 43.1% of *H. pylori*-positive persons compared with 6.2% among the uninfected (OR = 11.5). The authors concluded that atrophic gastritis and intestinal metaplasia were strongly associated with *H. pylori* and not with ageing. These data suggest that the risk of development of early gastric cancer will continue to remain high in Japan.

1.3 Geographical Distribution of the Prevalence of *H. pylori* Infection

The prevalence of *H. pylori* infection varies from country to country, with the largest differences being observed between developed and developing countries (Megraud *et al.*, 1989; Graham *et al.*, 1991a; Taylor and Blaser, 1991; Bardhan *et al.*, 1998; Redlinger *et al.*, 1999) (Fig. 1.1). The epidemiology of *H. pylori* infection in developing countries such

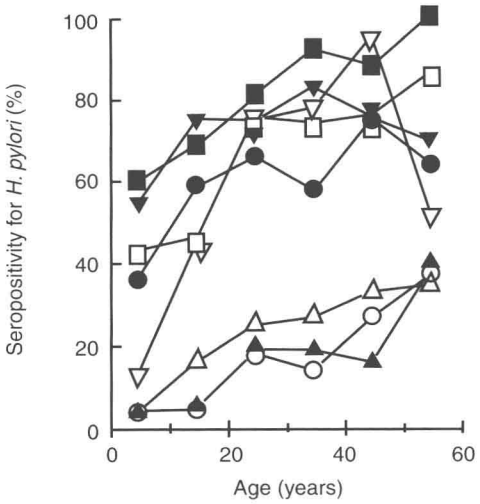

Fig. 1.1. Comparison of the prevalence of *Helicobacter pylori* infection in industrialized and non-industrialized countries (■, India; □, Saudi Arabia; ▼, Ivory Coast; ●, New Guinea; ▽, Vietnam; ▲, UK; ○, Australia; △, France), as indicated by the presence of serum immunoglobulin G antibodies to *H. pylori* antigens. In both regions acquisition takes place primarily in childhood, and the higher rate of acquisition among children in developing countries accounts for the large difference in the prevalence between industrialized and non-industrialized countries. (Adapted from Graham *et al.*, 1991a.)

as India, Saudi Arabia and Vietnam is characterized by a rapid rate of acquisition of infection such that approximately 80% of the population is infected with the bacterium by the age of 20 (Megraud *et al.*, 1989; Al-Moagel *et al.*, 1990; Graham *et al.*, 1991a). Because the infection is most often acquired in childhood (Mitchell *et al.*, 1992; Malaty *et al.*, 1996a, 1999, 2001, 2002), unless the infection is treated, it persists during adulthood. The prevalence of infection varies between and within countries and within subpopulations within the same country (Pateraki *et al.*, 1990; Perez-Perez *et al.*, 1990; Graham *et al.*, 1991b; EUROGAST Study Group, 1993; Breuer *et al.*, 1996). For example, a study conducted in Houston, Texas, of 485 asymptomatic individuals (50% black and 50% white) aged 15–80 years of age showed that the prevalence of *H. pylori* infection increased with age (Graham *et al.*, 1991b). These results are similar to patterns observed in other developed countries such as the UK, Australia and France where an increasing prevalence of infection with age has been observed. The increase in prevalence of infection with age can be attributable either to new acquisition of infection among the adult population or to the presence of different birth cohorts, each with a different rate of acquisition in childhood, within the population. Current data suggest that the increase with age is actually related to different birth cohorts, and reflects that each successively younger cohort has had a lower rate of acquisition of infection than those born earlier (Parsonnet *et al.*, 1992; Banatvala *et al.*, 1993). *H. pylori* infection has been shown to follow the routes of human migration by their geographical origin, and several studies have examined the effect of immigration on the prevalence of the infection. One recent study examined *H. pylori* strains among three major ethnic groups in Malaysia (namely the Malay, Chinese and Indian populations), reporting that while the majority of the Malay and Indian *H. pylori* isolates share the same origin, the origin of the Malaysian Chinese *H. pylori* is distinctive (Tay *et al.*, 2009). The study concluded that the Malay population was likely to have been initially *H. pylori*-free and gained the pathogen recently from cross-infection from other populations.

It has been also established that the prevalence of *H. pylori* is inversely related to socio-economic status (Graham *et al.*, 1991b; Malaty *et al.*, 1996a,b, 2001) with the major variable being the status during childhood, the period of highest risk of acquisition. Attempts to understand the different rates of infection in defined groups have focused on differences in socio-economic status as defined by occupation, family income level and living conditions. Each of these variables measures a different component of the socio-economic complex. Within the USA, studies in a cohort of blacks and white Hispanics examined the relationship between current and childhood socio-economic status and the prevalence of *H. pylori* infection (Malaty *et al.*, 1992). The study showed that there was an inverse correlation between low socio-economic status during childhood and the prevalence of *H. pylori* infection, irrespective