Occasional viewpoint

Helicobacters are indigenous to the human stomach: duodenal ulceration is due to changes in gastric microecology in the modern era

Peptic ulcer disease has been considered to be a "disease of civilisation".[1] Yet *Helicobacter pylori*, which now is believed to play a critical role in this illness,[2 3] has probably been part of the human biota since time immemorial,[4] and peptic (especially duodenal) ulceration seems to have become epidemic in humans at a time when *H pylori* was loosening its firm grip on the human stomach. These phenomena seem contradictory. It is the aim of this paper to describe the elements of the apparent paradox, and to consider several alternative explanations. Resolution of this question has substantial implications for human medicine.

Microbial niches in humans

The human body is the home of countless microbes[5] which usually are called the "normal flora". Indigenous biota is a better term than normal flora, since bacteria are not plants,[6] and normal is difficult to define. The major habitats of the indigenous biota include the gastrointestinal and upper respiratory tracts, the vagina, and the skin, and each niche shares several characteristics (table 1). In each locale, multiple different ecological niches are present. For example, the lumen of the colon is characterised by notable variation in redox potential, and each niche has predominant organisms. The predominant biota of the skin is anaerobic,[7] a phenomenon that indicates the multiplicity of ecological niches present. The indigenous biota is acquired early in life, and there often is a succession of organisms as local microenvironments change. Examples of this phenomenon include the changes in the colonic and oral biota accompanying weaning and the eruption of teeth, respectively.[8] The biota are numerous, with 10^3 to 10^{11} organisms per gram at each site. The colonising microbes are diverse. Bacteria predominate, but fungi and protozoans also are present. In several locales, many different species are present, although a large number have not been grown in culture or taxonomically classified.[8 9] Much of the biota persists for years, if not for the life of the host. After an initial transient period, in which there may be a succession of colonising organisms, the climax population is stable.[9] Persistence may be considered prima facie evidence of excellent adaptation to the host. The members of the biota compete for nutrients and physical sites, yet also cooperate with one another in metabolic functions and genetic exchange, for example.[7–9] In any event, the indigenous biota includes microbes that are symbionts of humans due to their vitamin synthesis, and antagonism to transient and pathogenic microbes.[5 7–9] There is much evidence that the indigenous biota has been present in humans since well before we became humans, and that our evolution included adaptation to these organisms, and vice versa.[7–9]

Helicobacters are indigenous biota of the human stomach

Virtually all life on Earth prior to the last billion years was unicellular, and primarily bacterial.[6] Animals arose about a billion (range 0.6–1.3) years ago, and perhaps from their very beginning have carried an indigenous biota; this phenomenon can at least be traced to earthworms, which have been present for perhaps 800 million years. An acid secreting gastric epithelium (stomach) has been present in our phylogeny since before our separation (more than 300 million years) from the ancestors of present day sharks.[10] Stomachs existed well before the great mammalian radiation about 100 million years ago; thus, this potential niche for a biota is ancient. It is likely that most, and perhaps all, mammals have an indigenous biota in their gastric contents, despite acidity.[11 12] Since the identification of *H pylori*, it has become clear that many of these gastric microbes are *Helicobacter* species or closely related microaerophilic spiral organisms, and new organisms are now being identified and reported with regularity. Investigations of our closest relatives, non-human primates, show that essentially all possess an indigenous gastric biota,[13 14] often with organisms indistinguishable from *H pylori*, and with uncultivatible spiral bacteria, closely resembling *H heilmanni*. Studies of humans who have had little contact with modern civilisation indicate that virtually all carry *H pylori*, and sometimes *H heilmanni* as well[15]; by the age of 10, most people (more than 80%) in developing countries have serological evidence of carriage of *H pylori*.[16] Both the great genetic diversity of *H pylori*,[17] as well as clonal characteristics of *H pylori* strains related to their geographical origin,[18 19] are consistent with their prolonged presence in specific population groups and against their recent spread to humans. Furthermore, *H pylori* has been found in all human populations from which it has been sought.

Table 1 Characteristics of microbial niches present in humans and of their colonising biota

Macro niches contain multiple micro niches
Microbial colonisation begins early in life
Colonising organisms are numerous
Diverse organisms colonise each niche
The biota maintains an orderly and stable presence in the available niches
Within the microbial population, there is both competition and cooperation
The colonising organisms provide symbiotic functions

The hypothesis that *Helicobacter* species have been indigenous biota is strengthened by consideration of the characteristics they share with the accepted indigenous biota (table 2). The stomach seems to possess a number of niches, differing in physicochemical characteristics,[20 21] in which microbes with differing properties can be present. Much evidence indicates that *H pylori* is usually acquired early in life,[22] and then persists for decades or for life in most people. Studies in non-human primates support this observation.[23] Substantial colonisation is present; humans carry an estimated 10^4 to 10^7 *H pylori* CFU per gram of gastric mucus,[24 25] a concentration that exceeds the microbial load in many other sites that are normally colonised.[5 7 8] Carriage of more than one *H pylori* strain by a host has been well recognised but is probably under reported.[26] *H pylori* are highly diverse,[17] and ultimately may be divided into more than one species or subspecies. Cocolonisation of some hosts with *H heilmanni*[27] is another

Table 2 Characteristics of the stomach and of H pylori consistent with indigenous colonisation

The stomach contains multiple micro niches
H pylori is acquired in early childhood
Substantial numbers of *H pylori* colonise the stomach
There is notable diversity within *Helicobacter* species in humans
H pylori populations remain stable in the stomach for decades
Cocolonisation with different *Helicobacter* strains and/or with clonal variants leads to both competition and at least to genetic exchange
A symbiotic relationship between *H pylori* and humans has been postulated

example of the recognised diversity of gastric *Helicobacter* species. There is increasing evidence that phenotypic expression by *H pylori* favours persistence in human hosts. The ultra low biological activity of its lipopolysaccharide (LPS),[28] as well as expression of Lewis antigens on the cell surface,[29–32] are prime examples of this phenomenon. *Bacteroides* species, the most numerous colonisers of the human colon, also express LPS molecules with very low activity. Selection of *H pylori* strains with particular phenotypes (for example, Lewis expression) facilitates orderly succession of organisms. Competition among strains is a central facet of their coexistence.[33] There now is much evidence that the naturally competent *H pylori*[34 35] cooperate with one another, as exemplified by their genetic exchange. As befits organisms occupying a complex and dynamic niche, there is evidence that over the course of its persistent colonisation of individual hosts, genetic variation continues to emerge by both asexual and sexual means.[34–36] Although not proved, a variety of symbiotic roles for *H pylori* are currently contemplated.[4 37]

Taken together, these observations suggest that *Helicobacter* species may have been part of the indigenous gastric biota of humans and our prehuman ancestors from our earliest times; the recent finding of *H pylori* antigens in stools from South American mummies about 1700 years old is consistent with this hypothesis.[38] *H pylori* could be considered as much a part of our past as *Escherichia coli* or *Bacteroides* species. A long shared history immediately suggests that the cost of carrying *H pylori* is not too great.

Are *H pylori* pathogens, commensals, or both?

For organisms that constitute the indigenous biota, consideration of their roles in human disease are often complex. For example, *Candida albicans* lives silently in most of us for the duration of our lives, but can cause illness during pregnancy, or in people receiving antibiotics or who have diabetes mellitus. Similarly, *Bacteroides* species are well adapted for life in humans and represent our most numerous (recognised) colonisers, yet can cause life threatening infection when translocated even one millimetre because of a ruptured appendix or diverticulum. Thus, all microbes that we carry have cost to us, but there may be benefits as well, as discussed above.

The question of pathogenicity is determined by whether a microbe causes disease, or is merely carried. Disease may be defined as tissue injury, and/or clinical manifestations. Let us consider both for *H pylori*. From experimental and accidental infections of humans and animals and treatment studies it has become clear that colonisation of the stomach by *H pylori* induces infiltration of the lamina propria and epithelium with immunocytes and inflammatory cells, which is generally called chronic gastritis or chronic active gastritis.[39 40] Virtually all people carrying *H pylori* have this evidence of host recognition of the organism. Is it disease? This histological pattern clearly is the substrate from which peptic ulceration as well as adenocarcinomas of the distal stomach arise,[41] yet the vast majority of people carrying *H pylori* and who have this gastric histology, have no clinical manifestations at all. Furthermore, its presence is "normal", in that the preponderance of humans, now and presumably throughout our history, have had such a pattern, and its presence is consistent with long life.

When animals are raised in a germ-free state, the lamina propria and lymphoid compartments of the colon are virtually devoid of inflammatory and immune cells. When conventional bacterial flora are introduced, they rapidly colonise the gut, and induce the migration of immune and inflammatory cells to these tissue compartments. We call this phenomenon the "normal" physiology of conventionalising germ-free animals.[42] One hypothesis is that the *H pylori* colonised stomach is the "normal" stomach with the appropriate tissue response, and that large numbers of modern humans in developed countries should be considered as having "germ-free" stomachs, for perhaps the first time in human evolution. One important objection to this premise is that the presence of polymorphonuclear leucocytes is considered as representing tissue injury; this is one of the cornerstones of the science of pathology. *H pylori* clearly has a highly interactive lifestyle with its host,[43] which seems to be even greater than that for the indigenous oral and colonic flora. Yet if this is not "abnormal" in the statistical sense, by which criteria, other than precedence, can we state that the human stomach should not have neutrophils in the lamina propria and epithelium? One possibility is that in the past, neutrophils were rare, but that now the interaction has changed (see below). A difference between the stomach and the colon is that the former has a single predominant species (*H pylori*) whereas the latter has more diverse populations. Nevertheless, colonisation by bacteria throughout the gastrointestinal tract is invariably accompanied by an inflammatory infiltrate in the lamina propria, although generally not including neutrophils.[7–9] As it is clear that the presence of inflammation is strongly associated with, and probably driving, the increased risk of ulcer disease (and distal cancers) associated with *H pylori*, how can we ignore its presence?

The more important biological question is, however, whether in their colonisation of humans, *H pylori* are parasites responsible for decreased evolutionary fitness and demise of their human hosts, or potential symbionts providing services in return for shelter and nourishment. An intermediate possibility is that *H pylori* have both pathogenetic and symbiotic features and thus cost and benefit could be relatively balanced. Rosebury introduced the term "amphibiotic" to describe this type of host-microbial relationship.[7] The biological world is dynamic, and with change, one property may predominate over the other. Thus, for example, the polymorphism of the human genome that encodes for haemoglobin S is highly useful for survival of populations in environments where *Plasmodium falciparum* is hyperendemic, as in West Africa.[44] However, the movement of West African peoples to North America and elsewhere, where malaria is not holoendemic, converted a survival advantage into a characteristic in which only deleterious effects can be observed.

The presumed antiquity of the relationship between humans and *H pylori* (unlike, for example, the relatively recent relationship with *Mycobacterium tuberculosis*[45]), suggests that benefits of *H pylori* colonisation exist. Effects of *H pylori* colonisation that are protective against the development of gastro-oesophageal reflux and adenocarcinomas of the proximal stomach and distal oesophagus have already been suggested.[37 46] The critical, and as yet unanswered question is which role is more medically and biologically significant in the current postmodern era, that of the pathogen or of the symbiont? However, there may be more than one correct answer to this question because both *H pylori* strains and human populations are diverse. Careful study of the epidemiology of diseases of the stomach,

duodenum, and oesophagus may yield important clues. In any event, it is useful to take a historical perspective as well. The "natural experiment" of the twentieth century, in which *H pylori* is gradually disappearing from developed country populations,[22] suggests that under these circumstances the short term cost of *H pylori* loss is not great.

One hypothesis that could explain the ubiquity of *H pylori* in developing country populations is that there has been selection for its carriage. Most intriguing would be the notion that *H pylori* increases the gastric barrier during a critical vulnerable period of childhood and thus reduces susceptibility to enteric infections that are immediately lethal (for example, typhoid) or contribute to childhood mortality (for example, hookworm). Under such circumstances, the early life benefits of *H pylori* to human populations could far outweigh its late in life costs. However, with industrial development, and the provision of clean water and food, that selection (and benefit) has abated. Thus, in parallel with the model of haemoglobin S, the value of the trait to the population depends on the strength of the selective forces. There are few data that address these questions; one relevant study found that presence of *H pylori* was significantly associated with increased risk of severe cholera in people over five years old in Bangladesh.[47]

Nevertheless, even if the current balance suggests that lack of *H pylori* is beneficial (as water in developed countries is now clean and ulcers are a serious medical problem), future generations of *H pylori*-free humans could be missing a defence against diseases that arise only episodically. Nature abhors a vacuum. Worse still could be the selection of an *H pylori* mutant or a related strain with properties that allow transmission under circumstances of modern life; the emergent strain is unlikely to be as benign as *H pylori*. The selection and thus emergence of a (clonal) pathogen from a commensal population is a well described phenomenon in microbiology (for example, *E coli* pathotypes).[48] There can be no ready answer to these questions, but it is prudent to be more cautious about upsetting long term relationships than short term ones. In contrast, it is difficult to imagine many potential benefits of such clear cut pathogens of humans as the much more recently acquired rubeola or *M tuberculosis*.[45]

As *H pylori* is so well adapted to humans that its lipopolysaccharide has only marginal endotoxic activity[28] and it is covered by host (Lewis) antigens,[29–32] a final question is why it induces an acute (neutrophilic) inflammatory response in contrast to other commensals of humans. One answer may be that *H pylori* have evolved lifestyles in which inflammation is necessary for its survival,[41 49] and that the cost of this colonisation in evolutionary terms is not beyond that which humans are able to bear, especially if it may have benefits.[43]

The rise of peptic ulcer disease

One of the consequences of peptic ulcer disease is viscus perforation, another is gastrointestinal haemorrhage. The clinical presentation of perforation is easy to recognise, and the outcome (death), in the absence of surgery or antibiotics, is clear, allowing Jennings, in 1940, to review the literature on its occurrence in history.[50] In the eighteenth century, both Albertus (1725), and Morgagni (1769) considered perforation to be rare.[50] In 1803, Gerard, recording observations totalling 50 years in Paris, found only five definite cases of perforated peptic ulcer disease. In London, Travers reported in 1816 that perforations were unmistakable and rare. Beginning in the mid nineteenth century, physicians began to observe a new phenomenon, peptic ulceration, first in young women, and then in men.[51] The earliest form was gastric ulcer, which was supplanted

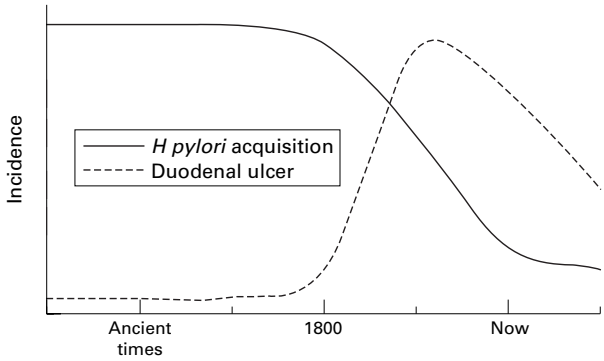

Figure 1 Schematic representation of the change in incidence of H pylori colonisation and duodenal ulcer disease among people in developed countries over time.

by duodenal ulcers.[52] The phenomenon increased more slowly on the European continent than in Britain.[53] Studies in the early twentieth century in Sweden indicated that the epidemic form involved ulcers of the duodenum and the prepylorum but not the gastric body.[51] It is unlikely that duodenal ulcers were being missed in the nineteenth century because the age distribution of perforated ulcers in England in 1857 and in Sweden in the early twentieth century are similar.[50 54]

As first identified by Susser,[1 55 56] and then extended by Sonnenberg and colleagues,[57 58] and Svanes *et al*,[59] the temporal changes in both gastric and duodenal ulcer mortality in Western Europe, Japan, and the United States can be ascribed to a birth cohort phenomenon. This phenomenon was characterised by the steady rise in peptic ulcer mortality in successive generations born between 1840 and 1880, and by a steady fall in all subsequent generations.[57 58] Such birth cohort phenomena[60] indicate that changing environmental factors are important in the aetiology of peptic ulceration. A study of ulcer perforation incidence in Norway[59] showed that the birth cohort effect was predominant and that period effects, such as World War II, increases in use of non-steroidal anti-inflammatory drugs (NSAIDs), and the introduction of antibiotics were not associated with substantial changes in incidence. The rise and fall in incidence with year of birth found in both men and women[59] suggest a common cohort dependent aetiology. Secular trends in men and women are generally parallel,[61] especially for duodenal ulceration, but differences in gastric ulcer trends may reflect its more heterogeneous aetiologies in the modern era, such as the wide use of NSAIDs by older women.

Explanations for the rise in peptic ulceration in the nineteenth century and its fall in the twentieth century

It is important to address the phenomenon that peptic ulcer disease (PUD) was apparently uncommon when most people carried the organisms, and rose at the very time when *H pylori* colonisation of humans was beginning to wane, as illustrated in fig 1. In this representation, *H pylori* colonisation was nearly universal among adults before 1800, and then began to diminish gradually, until now when few young adults are colonised (less than 20%). In contrast, duodenal ulceration was rare before the nineteenth century and then rose dramatically, peaking in the cohorts born in the 1870s and 1880s.[1 56–58] The incidence of duodenal ulceration is now declining, a trend that follows the decline in *H pylori* incidence. Parenthetically, if the events illustrated by this figure are correct, they provide strong support for the argument that *H pylori* per se is not central to the pathogenesis of peptic ulceration. The most

Table 3 Possible reasons for the rise in duodenal ulceration in the nineteenth and twentieth centuries

Surveillance artefact
Environmental cofactors affecting acid secretion and tissue healing (e.g. nutritional changes, smoking, NSAID and aspirin use)
Introduction of new *Helicobacter* strains
Increased acquisition of *H pylori* from non-relatives
Change in multiplicity of *Helicobacter* colonisation
Improved sanitation (impediment to transmission) selected for more virulent strains
Diminished *H heilmanni* cocolonisation
Increase in *H pylori* acquisition age

obvious explanation for the rise in PUD in the last two centuries is that PUD is not new, in contrast to its recognition, but this point was addressed above.

Several hypotheses should be considered for the changing epidemiology of PUD (table 3), especially its epidemic form, duodenal ulceration. The first is that the rise in PUD is related to improved nutrition of humans beginning in the nineteenth century due to the Industrial Revolution and the mass production of food.[62] This explanation, in essence, reduces to a change in the gastric microenvironment in which both *H pylori* and host genes have remained constant. Although nutrition has continued to improve and PUD is now waning, the latter may be due to decreased incidence of *H pylori* acquisition. A related explanation for the changing epidemiology shown in fig 1 is that cofactors such as smoking, alcohol, caffeine, exposure to particular foods (for example, salt), and use of aspirin or NSAIDs, could be responsible.[63 64] This hypothesis is unlikely as many affected people have not been exposed to any of these factors; smoking, caffeine, and alcohol are not associated with increased duodenal ulcer risk in prospective studies[64 65]; and the studies of Svanes *et al*[59] indicate that the birth cohort effect is predominant. Similarly, the fall in PUD is disproportional to and not temporally related to secular changes in incidence of these cofactors.

Secondly, there is increasing evidence that *H pylori* isolates vary at the genetic level in ways that correlate with their geographical origin.[18 19] With the growth in world trade beginning in the eighteenth century, European strains could have been brought to Asia, and vice versa. If colonisation of particular population groups led to selection for *H pylori* strains with specific characteristics, then the acquisition of those organisms by people in other groups could lead to a poorer fit that might increase risk of disease.[43] This is a testable hypothesis, because it would predict that in India, isolates from patients with ulcers would be different from isolates from asymptomatic people, and might resemble British isolates, for example. Considering the scope of ulcer disease around the world, a lack of concentration in centres of trade, and the birth cohort related increase then decline, this hypothesis seems unlikely to account for much of the changed PUD epidemiology. The evidence for geographical structure to *H pylori* population distributions[18 19] and the enormous diversity within the bacterial populations are also against the recent introduction of an epidemic strain that has spread worldwide to cause ulcer disease. The apparently stable coexistence of cag^+ and cag^- strains in many countries,[66] and in non-human primates[67] also argues against shifts in *H pylori* populations being responsible for the changes in ulcer disease epidemiology.

Thirdly, for certain infectious diseases, acquisition of the microbial agent from a household member results in different characteristics than acquisition from an unrelated person.[68] This phenomenon may be due to selection for host adapted organisms, which affects transmission characteristics to other hosts.[69] The falling family and household sizes associated with economic development,[70 71] and increasing urbanisation over the past 200 years would increase the likelihood that the *H pylori* strain acquired by an individual would not be from a related person.

Fourthly, individuals may be simultaneously colonised by more than one *H pylori* strain.[26] This phenomenon may be more common among populations of low socioeconomic status,[72] suggesting that with economic development and associated effects on hygiene, the multiplicity of colonisation in an individual host has decreased. *H pylori* strains compete among themselves to establish and maintain colonisation.[73 74] The (unopposed) colonisation of a niche with a single strain may have different sequelae than colonisation by a community of competing and cooperating organisms, as occurs in the mouth, colon, or vagina. This hypothesis could be tested by careful microbiological studies to compare strain multiplicity in people with PUD or who are asymptomatic.

A corollary to this hypothesis is that improving sanitation and falling family size selected for a subset of *H pylori* strains that were most readily transmissible. Such a phenomenon has been observed for transmission of *Shigella* species during the last century.[75] More virulent *H pylori* strains, for example those colonising at highest density, might be selected under such circumstances. Among US and European populations, we know that $cagA^+$ strains are most highly associated with duodenal ulceration,[76] and colonise the host more densely than $cagA^-$ strains.[24] However, we can find no evidence of an increasing proportion of carriage of $cagA^+$ strains among successive age cohorts,[66] and in Asian countries cagA positivity is not associated with ulceration.[77 78]

Fifthly, *H heilmanni* are present in the stomachs of humans and non-human primates,[13 27] and may in fact represent more than one species.[79] These organisms are especially common among monkeys,[13] but less so among people in developing countries,[80] and among people in developed countries.[81–83] Current evidence suggests that humans may acquire these organisms from our domesticated animals, including pets.[83] With changes away from an agrarian life, *H heilmanni* may be acquired proportionately less frequently in human populations than is *H pylori*. *H heilmanni* induce less tissue response in hosts than do *H pylori*,[13] and seem to be less commonly associated with disease.[13] Cocolonisation by both *H heilmanni* and *H pylori* may produce a different interaction with the host compared with colonisation by *H pylori* alone, with different effects on acid secretion and tissue histology. This hypothesis, which is similar and possibly additive to the previous hypothesis, could potentially be studied in non-human primates.

The most attractive hypothesis is that changes in the age at which *H pylori* is acquired had the largest bearing on risk of ulcer disease, especially duodenal ulceration, which has been the epidemic form. Specifically, this hypothesis holds that the acquisition of *H pylori* very early in life increases risk of distal gastric cancers and gastric ulcers, which have similar epidemiological characteristics,[84] but protects against duodenal ulceration. Conversely, the later acquisition of *H pylori* increases duodenal ulcer risk but decreases risk of gastric ulcers and cancer. The birth cohort effects cited above,[1 55–59] are consistent with changes in environmental exposures early in life. Sonnenberg showed that environmental factors clearly exert an aetiological influence on gastric ulcer by the age of five years, whereas for duodenal ulcer, it is not until 15 years.[85 86] Among Japanese-American men in Hawaii, evidence favours the hypothesis that acquisition of *H pylori* early in life increases the risk of development of gastric ulcers (and gastric can-

cer), but not duodenal ulcers.[87] Such data support the hypothesis that variation in the *H pylori* acquisition age influences gastric or duodenal ulcer risk. Susser and Stein suggested that duodenal ulceration could be a disease of the early phase of urbanisation,[1] at a time when hygienic conditions were progressively but incompletely improving from rural life. Its decline in recent years indicates that PUD is not strictly a disease of civilisation, but it does not eliminate the idea that urbanisation was an amplifying event.[55]

Change in acquisition age is attractive for explaining outcome differences, since it is well documented that the age of primary infection with a number of microbial agents affects clinical consequences. For example, early life acquisition of hepatitis B virus leads to asymptomatic infection but a high likelihood of chronic carriage and later development of cirrhosis and hepatic adenocarcinoma; whereas acquisition during late childhood or adulthood most often leads to acute illness with jaundice, but chronic carriage is much less common.[88 89] Parallel phenomena have been observed for Epstein-Barr virus infection and varicella, among other infections. A declining incidence of *H pylori* colonisation as we believe to have occurred,[22] is consistent with an increase in median acquisition age. Similarly, since presence of siblings seems to be a major risk factor for acquisition of *H pylori*,[90–92] and acquisition age for childhood infections generally rises in children with no older siblings,[93] the falling birth rate[94] and family size[70 71] associated with socioeconomic development is consistent with later *H pylori* acquisition. Recently, Goodman *et al*, studying a Colombian village, showed that for a child, the presence of siblings less than five years older notably elevated the risk of *H pylori* acquisition compared with a larger age difference or the absence of older siblings.[95] These data suggest that most *H pylori* transmission is from child to child, and explain how falling family size can notably affect *H pylori* prevalence.

The mechanisms for changes in host response related to age are incompletely understood, but may be divided into immunological and non-immunological phenomena. The former may include the influence of maternal antibody, breast feeding, and the age related maturation of immunological responses. In particular, neonates exposed to novel antigens may become tolerant to them, whereas for older children or adults the same exposure may lead to immunising responses.[96–98] Increased resistance to acquisition of *H pylori* associated with older exposure age may also help to explain the decline in its incidence during the past century[22] (see fig 1). Thus, the timing of the window of exposure becomes critical in the host's immune response to the organism (for example, hepatitis B virus) and can help determine events that occur decades later.[88 89] Age related non-immunological factors include the nature of the competing microflora, expression of particular receptors for adherence, and effects of changes in gastric acid physiology on *H pylori* colonisation characteristics.[99] A parallel phenomenon of increasing acquisition age associated with an enhancement in disease has recently been proposed for malaria due to *Plasmodium falciparum*.[100] The differences in acquisition age that may lead to outcome differences are not defined. Undoubtedly it is a continuous function, but differences in mean *H pylori* acquisition age from 12 months to 24 or 36 months—for example, could be immunologically, and thus ultimately clinically, significant. Similarly, gastric acid secretory physiology may reflect the immunological balance that develops between host and microbe.

Conclusions

The available evidence suggests that *H pylori* has been part of the indigenous gastric biota since time immemorial, but is being gradually eliminated as a consequence of the changes in modern life. As such, the histological findings that are currently called chronic gastritis represent the host response to the resident gastric biota, parallelling, but not mimicking, the responses observed in the colon. Much evidence indicates that we have coevolved with our indigenous biota over (probably hundreds of) millions of years, and have reached a dynamic equilibrium. Changes in the ecology of our microflora are likely to affect disease risk, as investigation of *H pylori* illustrates.

Peptic (especially duodenal) ulceration was apparently rare when *H pylori* colonisation was nearly universal, and rose in the nineteenth century as colonisation rates were beginning to fall. Reasons for the rise in duodenal ulceration include such changes in gastric microecology as those related to improved nutrition, changes in the nature of the *H pylori* colonisation including source and multiplicity of strains, as well as in the immune response to the organism related to acquisition age. While the presence of *H pylori* contributes to the pathogenesis of lesions of the distal stomach, including peptic ulceration and distal gastric cancer, there is increasing evidence that its absence is associated with more proximal diseases, such as adenocarcinomas of the gastric cardia and oesophagus, and reflux oesophagitis and Barrett's oesophagus.[37 46 101] Thus, the natural removal of *H pylori* during the modern era has diminished risk of peptic ulceration, but seems to be accompanied by new disease risks. Lest we physicians amplify these risks without providing substantial benefits to our patients, we must better understand our interactions with *H pylori*; an ecological perspective should be a part of this process.

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