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The role of interleukin-1 beta in *Helicobacter pylori*-associated disease

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ABSTRACT

Helicobacter pylori **infects half the world's population and is associated with serious human diseases including peptic ulcer disease and gastric neoplasia. The clinical outcome is largely dependent on the severity and distribution of the *H. pylori*-induced gastritis. The reasons for such variable clinical outcomes remain poorly understood. Bacterial virulence factors contribute to the pathogenicity but do not explain the divergent outcomes. There is emerging evidence that host genetic factors play a key role in determining the clinical outcome to *H. pylori* infection. In particular, proinflammatory genotypes of the interleukin-1 beta (IL-1β) gene are associated with increased risk of gastric cancer and its precursors. The effects are most likely mediated through induction of hypochlorhydria and severe corpus gastritis with subsequent development of gastric atrophy. In this article we discuss the role of IL-1β and other host genetic factors in the pathogenesis of *H. pylori*-related disease.**

INTRODUCTION

It has long been established that human susceptibility to infectious agents is at least partly under genetic control. Several observations from twin, adoptee, pedigree, and candidate gene studies point to host genetic factors as key determinants of this susceptibility.[1,2] The recent explosion in genetic knowledge, accelerated by the human genome project, is helping to unravel the molecular pathways that mediate genetic susceptibility to human diseases, including infections and cancer.[3-5] While genetic susceptibility may apply to the risk of acquisition of an infectious agent, it is becoming increasingly recognised that host genes also influence the pathophysiological response to infections, which ultimately determines the clinical outcome.

The role of infectious agents in carcinogenesis has commanded significant scientific interest culminating in five Nobel prizes in the 20th century.[6,7] Infections can cause cancer by a variety of mechanisms including direct transformation of cells, induction of immunosuppression with consequent reduced cancer immunosurveillance, or by causing chronic inflammation. The last-mentioned is becoming increasingly recognised as an essential component of many epithelial cancers by virtue of its combined effects of generating genotoxic by-products and increased cellular proliferation, thus maximising the potential for DNA damage.

In this article, I hope to demonstrate how interactions between an infectious agent, host genetic makeup, and environmental factors could influence the pathogenesis of a cancer. The infectious agent in question is *Helicobacter pylori*, the world's commonest chronic bacterial infection, and the malignancy is gastric cancer, second only to lung cancer in its global incidence and impact. We demonstrate how this gastric infection could be utilised as a paradigm for gene-environment interactions in human disease, one that could help unravel a multitude of other microbially induced malignancies.

HELICOBACTER PYLORI INFECTION

The *Helicobacter* genus consists of at least 24 species found in the GI tracts of animals and humans.[8] One of these species is *Helicobacter pylori (H. pylori)*, a Gram-negative, spiral-shaped, micro-aerophilic, urease-positive bacillus, which is known to chronically infect the stomachs of over half the world's population. The infection is acquired during childhood, most probably via the faecal/oral or gastric/oral routes, and if not treated with antibiotics, will persist throughout life.[9] The organism is 2.5 to 5 micrometers long

with four to six unipolar flagellae. These flagellae are thought to allow it to move through the mucus layer within the stomach and come to reside between this layer and the gastric epithelium. Eighty percent of the bacilli are free; however the remainder are attached to epithelial cells. Once attached, the organism induces ultra-structural changes in the gastric epithelial cells. Although the bacteria mainly reside on the surface mucus gel layer with little invasion of the gastric glands, the host responds with an impressive humoral and cell-mediated immune response. This immune response is largely ineffective, however, as most infections become chronically established with little evidence that spontaneous clearance occurs.

H. pylori can only proliferate on gastric epithelial cell surfaces and in the overlying mucus layer. Thus *H. pylori* has to survive in one of the harshest and least hospitable niches in the human body. Gastric acidity acts as a formidable first line of defence against food-borne pathogens, and the constant outpouring of gastric secretions, coupled with regular peristalsis, ensure that gastric contents, including microbial agents, are constantly flushed away. Despite this, *H. pylori* seems well equipped and adapted for habitation within this harsh environment. Recent studies show that *H. pylori* maintains its periplasmic pH within viable limits through possession of an acid-induced urea channel that regulates intra-bacterial urease activity.[10,11] Essential nourishment for *H. pylori* is drawn from host gastric tissue through the inflammatory exudate it induces.[12]

Since its original description and culture by Marshall and Warren in 1982,[13] *H. pylori* has been causally implicated in a variety of gastric diseases including simple gastritis, gastric and duodenal ulcer disease, and gastric cancer. While the link between *H. pylori* and peptic ulcer disease was established soon after successful culture of the bacterium, the association with gastric cancer lagged almost a decade before credible evidence was presented. The major reason for this delay was inability to demonstrate the presence of active infection in gastric tissue of cancer patients. In order to understand how this bacterium can predispose to such variable clinical outcomes, it is necessary to understand the basic pathophysiological consequences of its presence within the human stomach.

H. PYLORI AND CHRONIC GASTRIC INFLAMMATION

The key pathophysiological event in *H. pylori* infection is the initiation of an inflammatory response.[14] This response is most probably triggered by the bacterium's lipopolysaccharide, urease, and/or cytotoxins and is mediated by cytokines. Cytokines, including the interleukins, are soluble peptide molecules that mediate the interaction between immunocompetent and haematopoietic cells and between the immune and neuroendocrine systems.[15] They are produced by a variety of activated cells and exert their biological effects through binding to specific receptors on target cells. The cytokine repertoire comprises a multitude of pro- and anti-inflammatory mediators whose function is to coordinate an effective immune/inflammatory response against invading pathogens without causing undue damage to the host.

In addition to their pro- or anti-inflammatory properties, some *H. pylori*-induced cytokines have direct effects on gastric epithelial cells that have a profound effect on gastric physiology. For example, the proinflammatory cytokine interleukin-1 beta (IL-1β) is the most potent of known agents that are gastric cytoprotective, antiulcer, antisecretory, and inhibitory of gastric emptying.[16] Wolfe and Nompleggi estimated that on a molar basis, IL-1β is 100 times more potent than both prostaglandins and the proton pump inhibitor omeprazole and 6000 times more potent than cimetidine in inhibiting acid secretion.[17] Another important proinflammatory cytokine that is upregulated by *H. pylori* infection is tumour necrosis factor alpha (TNF-α), which also inhibits gastric acid secretion, but to a lesser extent than IL-1β.

In physiological terms, the stomach could be divided into two main compartments: an acidic proximal corpus that contains the acid-producing parietal cells, and a less acidic distal antrum that does not have parietal cells but contains the endocrine cells that control acid secretion.[18] *H. pylori* infection is first established in parts of the stomach that have a higher pH such as the antrum. This is most likely due to the bacterium's attempt at energy preservation, for although *H. pylori* is well equipped for survival at low pH, this is achieved at a high cost of energy expenditure. Thus, high acid production by the parietal cells probably protects the corpus mucosa from initial colonisation. Both animal and human ingestion studies suggest that successful colonisation of the gastric mucosa is best achieved with the aid of acid suppression.[19-21] Furthermore, pharmacological inhibition of acid secretion in infected subjects leads to redistribution of the infection and its associated gastritis from an antral to a corpus-predominant pattern.[22-24] Thus lack of gastric acid extends the area of colonisation and also maximises the tissue damage resultant from this colonisation.

H. PYLORI INFECTION AND THE DIVERGENT CLINICAL OUTCOMES

H. pylori infection is associated with divergent clinical outcomes that range from simple asymptomatic gastritis

to more serious conditions such as peptic ulcer disease and gastric neoplasia. The extent of this remarkable divergence is made more striking by the observation that certain outcomes of the infection, such as duodenal ulcer disease, are actually protective against others, such as gastric cancer.[25] The key determinants of these outcomes are the severity and distribution of the *H. pylori*-induced gastritis. There are three main gastric phenotypes that result from chronic *H. pylori* infection: (1) the commonest by far is a mild pangastritis that does not affect gastric physiology and is not associated with significant human disease, (2) a corpus-predominant gastritis associated with gastric atrophy, hypochlorhydria and increased risk of gastric cancer,[26] and (3) an antral-predominant gastritis associated with high gastric acid secretion and increased risk of duodenal ulcer disease.[27] The association of *H. pylori* with such variable outcomes poses a most fascinating scientific challenge, the unravelling of which will not only explain how ulcers and gastric cancer develop, but will also act as a paradigm for gene-environment interactions in most human diseases.

H. PYLORI INDUCES VARIABLE GASTRIC PHENOTYPES: THE GASTRIC CANCER VERSUS DUODENAL ULCER PHENOTYPES

There is accumulating evidence that acid secretory capacity is crucial in determining the distribution and natural history of *H. pylori* infection.[18] In hosts with low secretory capacity (genetically determined or secondary to pharmacological inhibition) the organism is capable of colonising a wider niche than would be possible in the presence of high volumes of acid. Colonisation of a wider niche, including the corpus mucosa, leads to corpus gastritis with resultant functional inhibition of acid secretion. This inhibition is mediated by *H. pylori*-induced inflammatory cytokines (such as IL-1β and TNF-α) and the net effect is the establishment of a more aggressive gastritis that accelerates the development of gastric atrophy. Once atrophy develops, acid secretion is not only attenuated by the functional inhibition caused by inflammatory mediators but by a more permanent morphological change that is harder to reverse. This situation is very relevant to the subgroup of humans who develop the gastric cancer phenotype in the presence of chronic *H. pylori* infection.

In contrast to subjects who have an increased risk of gastric cancer, subjects who develop duodenal ulcer disease are known to have a large parietal cell mass that is relatively free of *H. pylori*-induced inflammatory activity. This pattern of antral-predominant gastritis with high acid output characterises the duodenal ulcer diathesis. The high acid output is associated with the development of duodenal gastric metaplasia (DGM), a protective mechanism against the persistent delivery of an increased acid load to the duodenum. The presence of gastric epithelium (DGM) in the duodenum is an invitation for antral *H. pylori* infection to colonise this new niche. The ensuing gastritis with the production of proinflammatory cytokines such as IL-1β and TNF-α greatly weakens the resistance of this mucosa, and in the presence of large volumes of acid, and a reduction in duodenal mucosal bicarbonate production,[28] ulcers develop.

As mentioned above, the effect of acid secretion on changing the distribution of *H. pylori* colonisation and gastritis is most markedly exposed in subjects in whom acid secretion is manipulated by pharmacological means. Thus *H. pylori*-infected subjects on long-term proton pump inhibitors undergo a shift in the pattern of gastritis from antral- to corpus-predominant, and they have a higher risk of developing gastric atrophy, a precursor lesion for gastric neoplasia.[23] This observation provided a clue as to the role of potential endogenous substances that could also inhibit acid secretion, such as IL-1β and TNF-α. As will be discussed later, these two cytokines were prime candidates as host genetic factors that may increase risk of gastric cancer. IL-1β is the archetypal pleiotropic cytokine being produced by many cells and exerting its biological effects on almost all cell types.[29] IL-1β is a very potent proinflammatory cytokine and is involved in the host's response to many antigenic challenges.

GENETIC POLYMORPHISMS IN THE *IL-1* GENE CLUSTER INCREASE THE RISK OF GASTRIC CANCER AND ITS PRECURSORS

The key question in *H. pylori* research is how this infection could be associated with such divergent clinical outcomes as gastric cancer and duodenal ulcer disease. A large volume of research has focused on the role of bacterial virulence factors in the pathogenesis of these diseases, and although these factors undoubtedly contribute to the degree of tissue damage, they do not distinguish between the two key outcomes.[30] This prompted us to concentrate on the host genetic factors that may be relevant to this process. The search for the appropriate candidate genes had to stem from a profound understanding of gastric physiology and how it is disrupted by *H. pylori* infection. Since *H. pylori* achieves most of its damage through induction of chronic inflammation, it was reasonable to consider genes that control this process as appropriate candidates.

The *IL-1* gene cluster on chromosome 2q contains three related genes within a 430 kb region, *IL-1A*, *IL-1B* and *IL-1RN*, which encode for the proinflammatory cytokines

IL-1α and IL-1β as well as their endogenous receptor antagonist IL-1ra, respectively.[31] IL-1β is upregulated in the presence of *H. pylori* and plays a central role in initiating and amplifying the inflammatory response to this infection.[32-34] IL-1β is also an extremely potent inhibitor of gastric acid secretion;[35,36] on a molar basis it is estimated to be 100-fold more potent than proton pump inhibitors and 6000-fold more potent than H_2-antagonists.[37] Three diallelic polymorphisms in *IL-1B* have been reported, all representing C-T transitions, at positions -511, -31, and +3954 bp from the transcriptional start site.[38] There are conflicting data regarding the functional effects of these polymorphisms on IL-1β production.[39,40] The *IL-1RN* gene has a penta-allelic 86 bp tandem repeat (VNTR) in intron 2, of which the less common allele 2 (*IL-1RN*2*) is associated with a wide range of chronic inflammatory and autoimmune conditions.[38] *IL-1RN*2* is associated with enhanced IL-1β production *in vitro*,[40] but data regarding its effects on IL-1ra production are contradictory.[41-43] The gene also has a number of functionally relevant polymorphisms that could be correlated with high or low IL-1β production. This provided an ideal opportunity to design the appropriate hypothesis-driven epidemiological studies.

We first studied the correlation of these high IL-1β genotypes (two polymorphisms in the *IL-1B* and *IL-1RN* genes) with hypochlorhydria and gastric atrophy in a Caucasian population of gastric cancer relatives. These relatives are known to be at increased risk of developing the same cancer and have a higher prevalence of the precancerous abnormalities, but only in the presence of *H. pylori* infection. We found that the high IL-1β genetic markers significantly increase the risk of these precancerous conditions. In a logistic regression model including both genotypes, the estimated age-adjusted odds ratios for *IL-1B-511/-31)*2+* and *IL-1RN*2/*2* were 7.5 (95% CI: 1.8-31) and 2.1% (95% CI: 0.7-6.3 respectively).[44] We proceeded to examine the association between the same IL-1β genetic polymorphisms and gastric cancer itself utilising another Caucasian case-control study comprising 366 gastric cancer patients and 429 population controls. We confirmed the same positive association between these genotypes and gastric cancer. In a logistic regression model including both genotypes, the estimated odds ratios for *IL-1B-511/-31T+* and *IL-1RN*2/*2* were 1.6 (95% CI: 1.2-2.2) and 2.9 (95% CI: 1.9-4.4) respectively.[44]

Although IL-1β was the perfect candidate gene, other genes involved in the *H. pylori*-induced gastritis cascade are also legitimate targets. Our most recent search has confirmed a positive but weaker role for polymorphisms in the *TNF-A* gene that correlate with high TNF-α levels (El-Omar *et al.*, unpublished data). The TNF-α polymorphism increases the risk of gastric cancer and its precursors in a similar fashion to the IL-1β polymorphisms. This proinflammatory cytokine is also upregulated in *H. pylori* infection and has acid-inhibitory properties, albeit weaker than IL-β. So it is clear that the targeted and hypothesis-driven search for these host genetic factors will aid in unravelling the pathogenesis of *H. pylori*-related diseases.

But how do these IL-1β/TNF-α polymorphisms explain the divergent outcome to *H. pylori* infection? We speculate that the effect of these polymorphisms operates early in the disease process and requires the presence of *H. pylori* infection. When *H. pylori* infection challenges the gastric mucosa, a vigorous inflammatory response with a high IL-1β/TNF-α component may appear to be beneficial, but it has the unfortunate side effect of switching acid secretion off, thus allowing the infection to extend its colonisation and damaging inflammation to the corpus mucosa, an area that is usually well protected by secretion of acid. A decreased flow of acid will also undermine attempts to flush out these toxic substances, causing further damage to the mucosa. More inflammation in the corpus leads to more inhibition of acid secretion and a continuing cycle that accelerates glandular loss and onset of gastric atrophy. It is apparent that this vicious cycle ultimately succeeds in driving the infection out, but at a very high price for the host. This is amply demonstrated by the finding that *H. pylori* density becomes progressively lower with the progression from mild gastritis through severe gastritis, atrophy and intestinal metaplasia. Indeed, by the time gastric cancer develops, it is extremely hard to demonstrate any evidence of the infection.[45]

ROLE OF ENVIRONMENTAL FACTORS IN GASTRIC CARCINOGENESIS

A very obvious question at this juncture is why only a few *H. pylori*-infected subjects with these polymorphisms develop gastric cancer. Why isn't everyone with such a genetic makeup at risk of this outcome? The answer lies in the polygenic and multifactorial nature of most complex human diseases. These genetic factors operate only in the presence of an infectious agent and lead to the development of an atrophic phenotype. Progression of atrophy towards cancer depends on other components of the host genetic constitution acting epistatically, as well as dietary and other factors in the environment. While *H. pylori* infection and host genetics interact to initiate a hypochlorhydric and atrophic phenotype, environmental co-factors may mediate subsequent neoplastic transformation, even after disappearance of the infection. Diet may be particularly relevant, with greater consumption of fresh fruits and vegetables shown to protect against the risk of gastric as well as several other cancers. Dietary vitamin C reduces the formation of

N-nitroso-compounds and scavenges mutagenic reactive oxygen metabolites generated by gastric inflammation,[46] and supplemental vitamin C is associated with significantly lower risk of noncardia gastric cancer.[47] Furthermore, vitamin C concentrations and bioavailability are reduced in the presence of *H. pylori* infection.[48,49] Another important co-factor is cigarette smoking, which was found to nearly double the risk of transition from atrophic gastritis to dysplasia in a high-risk population.[50] Thus, cytokine gene polymorphisms represent only one component of a complex interplay among host, pathogen, and environmental factors involved in gastric carcinogenesis.

These proinflammatory polymorphisms, therefore, can distinguish between subjects who will develop the hypochlorhydric atrophic phenotype in response to *H. pylori* infection and those who will manage to limit the infection to a smaller area and offer relatively better protection of their corpus function. Another valid question is whether these proinflammatory polymorphisms actually offer protection against the other extreme clinical outcome, namely, duodenal ulcers. Could it be that a low IL-1β/TNF-α response to *H. pylori* infection, and a consequently lower inhibition of acid secretion, is the determinant of the antral-predominant, corpus-sparing gastritis pattern seen in duodenal ulcer patients? To date, no reports have been published addressing this specific question. It would be tempting to speculate that this would be the case, but my gut feeling is that the large parietal cell mass frequently seen in duodenal ulcer patients is determined by other genetic factors, hitherto undescribed, that relate to parietal cell development and the endocrine receptors they express. This genetically determined capacity to secrete large volumes of gastric acid will probably neutralise any subtle contribution of a genetic polymorphism in a cytokine gene.

CONCLUSIONS AND A LOOK TO THE FUTURE

IL-1β is a very important proinflammatory cytokine with profound effects on gastric physiology. Its acid-inhibitory properties uniquely qualify it as a major player in the host's response to *H. pylori* infection and the diseases associated with it. Polymorphisms in the gene for IL-1β that correlate with higher levels of this cytokine have been found to increase the risks of hypochlorhydria and gastric atrophy in response to *H. pylori* infection and to increase the risk of gastric cancer itself. These host genetic factors that affect IL-1β may determine why some individuals infected with *H. pylori* develop gastric cancer while others do not. Future research should focus on identifying the molecular pathways that mediate this increased risk. The search for other host genetic factors that contribute to the pathogenesis of the disease should continue, particularly in view of the wonderful new opportunities made possible by the human genome project. A special effort should be directed at understanding these host genetic factors in non-Caucasian populations, and in populations with high and low incidences of gastric cancer. We should also target other upper GI diseases that may be linked indirectly to these genetic polymorphisms that alter gastric physiology. Prime amongst these are oesophageal cancers and gastro-oesophageal reflux disease.

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Discussion following lecture by E.M. El-Omar

Van der Meer: Being a person who performs research with interleukin-1, I would be interested to hear why you left interleukin-1α out. Conceptually, IL-1α would also be an interesting candidate. I wonder if you did consider that and if you have data on it?

El-Omar: It is a very good point. We did not ignore interleukin-1α. IL-1α does not have any effect whatsoever on this particular model.

Kimman: Your genetic data appear very convincing, but are they supported by physiological data? Do people with a proinflammatory genotype really have higher IL-1β levels in their gastric lesions than people with a less inflammatory genotype?

El-Omar: Polymorphism has to be functional. There are some data showing these proinflammatory genotypes to be associated with higher IL-1β levels, but it is pretty weak. The IL-1 receptor antagonist is probably the strongest. Allele 2 of that VNTR polymorphism is probably the strongest that we have. It is actually very difficult to measure the cytokine content and correlate that with genetic polymorphisms. In the presence of the infection, depending on the severity, it may be quite difficult to correct for the degree of inflammation in that particular locus. We lack tools to address this question appropriately and we are lagging behind in terms of explaining the physiological effects of these polymorphisms, but the epidemiological data are pretty powerful.

Netea: IL-1 receptor antagonist is approved for treatment of rheumatoid arthritis and anti-TNF treatments have already been in use for a couple of years. Is there anything known about whether this pattern of gastric pathology is changing in some of the patients who also have *Helicobacter* infections?

El-Omar: A very interesting question. We have not been studying this. Rheumatologists are probably not going to look for changes in the stomach. It is a very worthy experiment to perform, perhaps in an animal model.

Netea: Would patients with a duodenal ulcer, who receive anti-TNF for rheumatoid arthritis, get worse as a result of the treatment?

El-Omar: Nothing is known about that, but people with rheumatoid arthritis who get ulcers usually get them because of nonsteroidal anti-inflammatory drugs. So you are dealing with two different issues, which makes it difficult.

Van der Meer: The nonsteroidal anti-inflammatory drugs should inhibit prostaglandins and thereby upregulate cytokine production. So you get into complicated counter-regulatory mechanisms.

El-Omar: And the link between the effect of NSAIDs and *H. pylori* is very controversial.

Van Deuren: It is even more complicated, because IL-1 upregulates cortisol. High IL-1 producers may have higher cortisol levels and therefore a higher acid secretion. On the other hand IL-1 would decrease acid secretion. Physiological tests would be decisive, I think.

El-Omar: I do not think experiments have been conducted that address these questions.

Van Deuren: We are often considering whether we should perform a repetitive gastroscopy in patients with atrophic gastritis and if so, how many times – once every three years, once or twice a year? Do you envisage that in the future, genetic make-up will be decisive in the scheme for endoscopic control?

El-Omar: It is of course much simpler to test for HP infection and if you find it, get rid of it. The genetic make-up becomes unimportant. The value of these genetic studies and genetic markers, from my point of view, is in understanding the pathogenesis.

Kusters: Clearly there are markers for severity and for susceptibility. Could it be that your population is biased regarding the susceptibility to infection with *H. pylori* and how would that affect your data?

El-Omar: What I have shown is that these markers influence the severity and the outcome of the infection, not necessarily the susceptibility. We looked at susceptibility originally and found that high IL-10 genotypes will increase the risk of contracting a chronic *H. pylori* infection. This suggests that an anti-inflammatory Th2-driven response allows this infection to persist. We found this in two populations in two studies, but in a third, much larger study I could not reproduce the same data, and that made me reluctant to claim that high IL-10 genotypes increase the risk of acquiring the infection. However, mice that consecutively produce more IL-10 have persistent *Helicobacter* infection, while mice with a vigorous Th1-driven cytokine response clear the infection.

Appelmelk: I can understand how inflammation shuts down acid production, but I am puzzled how a shutdown of acid would act the other way around. In your view, the cause is the shift of the bacteria from antrum to corpus, but what is the evidence? In the mouse colonisation is exclusively localised in the antrum. Yet there is strong atrophy in the corpus. Could you envisage a model where the bacteria are not needed and still an acid-induced increased inflammation occurs in the corpus?

El-Omar: There are only two experiments where people have either ingested or acquired acute *H. pylori* infection. When Marshall and Morris just took a preparation and swallowed it, there was colonisation only when they took acid inhibitors. So it looks as though you have to switch off the acid secretion to allow the bacteria to take hold in the stomach. The other fact is that when *H. pylori* is first acquired, it tends to settle in the less acidic parts of the stomach. That is why you get maximal colonisation in the antrum. Although *Helicobacter* is unique in surviving in an acidic environment, it is at the cost of high energy expenditure. It has to use a lot of its machinery to try and protect itself from the acid exposure. Acid secretion seems to determine how extensive the colonisation in the stomach will be. Now, if interleukin-1β is poured out to fight this infection and at the same time acid secretion is switched off, the infection does extend from the antrum to the corpus leading to a more severe corpus gastritis. But the counts are probably even slightly reduced in both areas. What is happening here is a pouring out of acid from the glands trying to flush out all the toxins and all the mediators. If the acid secretion is switched off, you have basically got a dry part of the stomach where maximal concentrations of these damaging genotoxic substances can exert their effect.

McAdam: In West Africa the babies seem to be getting infected at weaning or before. By the age of one, using noninvasive tests, we have a *Helicobacter* infection rate of approximately 80%. This has been ascribed to all sorts of things, but certainly to malnutrition. Around the age of weaning these children start losing weight. What is the natural history when *Helicobacter* infects people from the age of one for the rest of their lives?

El-Omar: Theoretically, if the infection is acquired at a much earlier age, at the time when the stomach is not fully developed in terms of its acid secretion, the phenotype should be more in keeping with the gastric atrophy and low acid secretion and that should increase the risk of developing gastric cancer. In addition, the Africans tend to have a so-called proinflammatory genetic make-up. Yet we do not see such a dramatic increase in gastric cancer. Whether they do not live long enough to develop it, or whether there are other conditions that are modifying the inflammatory response, has not been addressed. One very interesting experiment came from Fox *et al.*[1] They looked at the role of co-infection with helminths. It showed that in an animal model, if you co-infect with a helminth the system tries to switch the immune response from a Th1 to a Th2, which attenuates your inflammatory response and prevents gastric atrophy. It may be that in these populations, where you have such a high prevalence of *H. pylori*, yet you have very little clinical disease, there are other factors, other bacteria that may be modulating this inflammatory response.

Peña: There is a great difference between duodenal ulcer and gastric ulcer. There are families that either develop gastric ulcers or duodenal ulcers. Did you study this kind of polymorphism?

El-Omar: It is fascinating that in the West duodenal ulcer and gastric cancer so seldom both strike in one patient. Classically, the people who develop gastric cancer are the ones in whom there has been manipulation of acid secretion: they either have had a vagotomy or surgery that basically attenuates their acid production. Some people would argue that inhibition of gastric acid over many years could be the reason why these people basically switch from being protected towards being at risk. Some fascinating data from Japan[2] recently showed that regarding the proinflammatory genotype, this genetic constitution in people who have DU disease at the beginning, at an early age, when they are in their teens or in their early twenties, if you follow them long enough, you will see very few people with this proinflammatory genotype actually having duodenal ulcer disease or a relapse of duodenal ulcer disease. So it may increase the risk at an early age, but it burns out, and the reason it burns out is presumably because of the effects on the corpus mucosa, discontinued inflammation, the onset of atrophy, and eventually they basically become less protected against gastric cancer and more likely to show the hypochlorhydria atrophic phenotype. The question of looking at gastric ulcers *vs* duodenal ulcers has not been addressed properly and there is one study looking at the effect of these polymorphisms on peptic ulcer disease.[3]

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