The 'African enigma' – another explanation

To the editor—Fox *et al*.[1] provide evidence that an enteric helminth infection concurrent with a *Helicobacter felis* infection changes the T-helper (Th)-cell immune response from a predominantly Th1-type to a Th2-type. The response is characterized by the release of the non-inflammatory cytokines IL-4, IL-5, IL-6 and IL-10. The observed switch in Th-cell activity was associated with a reduction in helicobacter-associated gastritis and gastric atrophy. The authors use the data from their animal study to explain the 'African enigma'[2]. They attribute the divergent occurrence of gastric cancer in countries with poor socio-economic conditions—where *H. pylori* infection and gastric cancer could be expected to occur at a similar mean age—to variations in the immune responses of the hosts, which are in turn affected by concurrent infections by intestinal helminths[1]. In contrast, we propose that factors other than intestinal helminths may contribute the difference in gastric cancer rates in countries such as Nigeria and Peru.

The main factor determining the outcome of *H. pylori* infection is the ability of the stomach to secrete acid. After infection, *H. pylori* is found throughout the stomach, but inflammation is frequently confined to the non-acid-secreting mucosa of the antrum, cardia and even the corpus[3]. This inflammation further suppresses acid secretion and thus initiates a vicious cycle eventually leading to gastric atrophy[4]. Any prolonged suppression of gastric acid secretion should favor the development of gastric atrophy and subsequent cancer, particularly in individuals who become infected at a very young age.

Throughout the Andean countries, chewing of coca leaves is a widespread habit. By some estimates, 20% of certain population groups chew coca leaves regularly[5]. Cocaine, the active ingredient and primary alkaloid of the coca leaf, becomes biologically active only when released from plant molecules through reaction with strong alkalines[6]. To activate the cocaine, coca chewers add slaked lime or ash from the Quinoa plant to coca leaves, and the released cocaine and free base will then buffer gastric acid and generate an alkaline pH in the stomach lasting hours. In this way, coca chewing may assist *H. pylori* infection in several ways.

First, coca chewers should be more prone to infection with *H. pylori* due to their low stomach acidity. Second, continuous suppression of gastric acid secretion should facilitate the rapid spread from antrum and cardia to the corpus enabling development of corpus gastritis and subsequent atrophy. Third, if systematic suppression of acid secretion through coca chewing is present in adolescence, an increased occurrence of gastric atrophy in the population of young adults should coexist with a low prevalence of duodenal ulcer and gastric metaplasia in the duodenal bulb. In fact, such a pattern has been observed in Peru[7].

Because regular consumption of fresh fruits and vegetables seems to delay the onset of atrophic gastritis[8,9], the difference in gastric cancer rates between African and Andean countries may also be related to differences in intake of these foods. Whereas in sub-Saharan Africa fresh fruits and vegetables are available throughout the year, especially in the higher altitude areas of the Andean countries, these foods are either seasonally restricted or not available.

As with other infections, the natural history of *H. pylori* infection is determined by a range of parasite, host and environmental factors[4]. For example, diversity in parasite genotypes can lead to differences in virulence[10] and polymorphism in the host of the IL-1-β–promotor allele leads to increased release of the pro-inflammatory cytokine IL-1-β in gastric mucosa[11]. Genetic polymorphism is, however, neither a necessary nor a sufficient cause for gastric cancer[11]. The presence of different strains of *H. pylori* circulating in different regions has provided only confusing data regarding the role of potential virulence factors[12].

The outcome of an *H. pylori* infection is probably determined by environmental factors. Risk factors such as young age of infection, childhood malnutrition, socio-economic conditions and intestinal parasitosis being equal in the countries under consideration, the African enigma might be explained by behavioural factors such as coca chewing and lack of fresh fruits and vegetables in the diet, commonly seen in Andean but not in African countries.

Our hypothesis also fits a recent model of a dynamic equilibrium between the colonising microbes and the host, in which the host environmental determines the nature and extent of *H. pylori*-associated pathology[13]. In this model, coca chewing and lack of fresh fruits and vegetables would constitute strong environmental stimuli affecting the gastric equilibrium and promoting the progression from superficial gastritis to atrophy and cancer.

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Fox and Wang reply—In our paper, we have provided the first experimental evidence in a mouse model of the influence of an intestinal parasite on gastric helicobacter-induced disease; this data may partially explain the African enigma. The majority of epidemiologic studies have reported a decreased incidence of gastric cancer in Africa compared to other countries where *H. pylori* infection is endemic. The one reference cited by Feldmeier and Krantz[14] is a retrospective literature review of endoscopic-based studies of highly selected groups of patients. This one study does not, on its own, justify discounting all the literature that supports the concept of an 'African enigma'. In a recent paper presented at the international Helicobacter meeting in Rome[15] the authors compared *H. pylori* immune responses in infected individuals from developing countries (South Africa) to those from developed countries (Australia and Europe). Using an Ig-subclass analysis, they specifically investigated whether differences in the IgG1/IgG2 ratio may in part explain the African enigma. In examining Th1 and Th2 profiles the authors found preliminary evidence that a Th2 (Ig1) profile was more common in Africans with a low incidence of serious GI disease versus others with *H. pylori* infection from developed countries which have a proinflammatory Th1 response. Indeed, *H. pylori* infection in Soweto (Th2-type) apparently differs from that of individu-