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The only good *Helicobacter pylori* is a dead *Helicobacter pylori*

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SIR—Martin Blaser¹ suggests that microbiologists should better define markers for different *H pylori* strains associated with adverse clinical outcome and that epidemiologists should better estimate the disease risks in specific populations. Some genetic markers such as the *cagA* gene are present in about 60% of *H pylori* strains. The so-called cytotoxic strains are known to be associated with increased risk of peptic ulcer in adults and children,² and with gastric atrophy and cancer.³ Children are at increased risk of acquiring *H pylori* infection, and the earlier the acquisition the greater the risk of developing gastric cancer in adulthood.⁴ A non-invasive, low-cost test to look for specific *H pylori* antigens is needed. A western blot on saliva samples could be such a test, and we report preliminary data on 40 children who underwent endoscopy for dyspepsia.

On the morning of the endoscopy, we collected a blood sample from each child and 1 mL of saliva (the child spat in a test tube) which was immediately stored at -20°C . Histology (Giemsa) rapid urease test and ^{13}C -urea breath test showed *H pylori* gastritis in 30 children (14 boys, 16 girls, median age 12 [range 5–16] years). We also enrolled ten negative controls of similar age and sex who were not infected with *H pylori*. Serum samples and saliva were screened by western blotting after sodium dodecyl sulphate-polyacrylamide gel electrophoresis for *H pylori*-specific antigens with a commercial kit (Helori-WB, Eurospital, Italy). We tested serum samples at a 1/50 dilution and saliva samples either undiluted or at various dilutions (from 1/1.25 to 1/4) to reach a final volume of 750 μL . The marker for infection with cytotoxic *H pylori* strains was the presence of a 120 kDa (*CagA*-associated protein) band. Presence of 25 kDa band (lectin-like adhesin)⁵ indicated infection with a non-cytotoxic strain.

With these criteria, the sensitivity of the salivary test was 100% and specificity was 90% with only one false-positive test in ten controls. Undiluted

saliva samples gave the best results. The bands in serum samples and saliva were similar, although the number of salivary bands was lower. The 120 kDa band was present in saliva and serum in 20 (66%) of the children infected with *H pylori*, with a prevalence similar to that of another series of Italian children.²

The *cagA* protein expressed by *cagA*-positive strains is highly immunogenic and serum antibodies against it can be used to ascertain *cagA* expression by all *H pylori* strains that colonise the stomach; the presence of *cagA* protein in serum and mucosal secretions correlates strongly with ulcer disease and active gastritis. Indeed our patients infected with cytotoxic *H pylori* strains had the most severe gastritis: histology showed active gastritis—ie, with polymorphonuclear cell infiltration—in 11 of 20 *cagA*-positive children and in one of ten *cagA*-negative children ($p<0.02$, Fisher's exact test).

The saliva test for detection of antibodies against *cagA* is useful to identify patients at risk of developing peptic ulcer, gastric carcinoma, or both later in life. Saliva collection has the advantage of being a non-invasive, simple test. Collection is easy for patients and health-care workers and greatly reduces the risk of blood-borne infection.

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SIR—We agree with Martin Blaser¹ on the need to reserve anti-*Helicobacter* therapy for the established indications. Another important argument against mass eradication campaigns is the rapid disappearance of *H pylori* from western countries. In 1994 in the Netherlands, only 9% of children younger than 10 years,² and 17% of those under 25 years were infected with *H pylori*.³ This prevalence could mean that by 2024 it

will be under 15% in individuals younger than 45 years. Epidemiological data from other developed countries lend support to this scenario. Thus, it seems unwise to spend manpower and resources on fighting an infection on dubious clinical grounds which is already dying out.

Blaser does not discuss whether or not the different strains of *H pylori* react to antimicrobials in a similar way. Patients without peptic ulcers may need a different therapeutic approach. Previous studies showed that the cure rate for a given regimen is higher in ulcer patients than in those with functional dyspepsia or gastritis only.⁴ This difference cannot be explained by compliance alone. We have investigated the importance of the allelic variation in the gene encoding the cytotoxin (*VacA*).

We isolated DNA from biopsy samples of the stomach from patients who took part in a recent study.⁵ *H pylori* was eradicated in 59% (27/46) of the patients. One patient was excluded. Among 45 patients, *VacA* genotypes s1/m1, s1/m2, and s2/m2 were detected in 12 (26.6%), 20 (44.4%), and seven (15.5%) patients, respectively. Multiple genotypes were detected in six (13.3%) patients. *CagA* was present in 28 (62.2%) patients and was strongly associated with the type s1 *VacA* allele ($p=0.007$). Patients with peptic ulcers were more frequently positive for *cagA* and the s1 type *VacA* allele than patients with functional dyspepsia ($p=0.146$ and $p=0.012$, respectively). We found a higher cure rate for the more pathogenic *VacA* type s1 strains than the *VacA* type s2 strains ($p=0.075$). With the allelic variation in the m region of the *VacA* gene, no relation with cure rate was observed. Because strains from patients with ulcers often grow more rapidly, we postulate that the *VacA* type s1 strain, which are more commonly associated with ulcer disease, produce more toxin, induce more inflammation, grow more rapidly, and are more easy to eradicate since antibiotics achieve high concentrations in inflamed tissue, whereas bacteria in the growth phase are more readily killed. By contrast, the *VacA* type s2 strains, which are more often found in functional dyspepsia, produce no toxin, induce less inflammation, grow slowly, and are more difficult to eradicate in vivo. Such strains are usually in a stationary phase and may simply need a longer or a more aggressive treatment than the strains which cause ulcer disease. Most data on *Helicobacter* treatment are obtained from patients with ulcers, and may not, therefore, apply to functional dyspepsia. Physicians who want to treat individuals without an ulcer should expect lower cure rates than those reported in the published research. In

the coming years patients with functional dyspepsia could well need treatment for 10–14 days whereas patients with ulcers could be treated successfully in just 7 days.

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Author's reply

SIR—David Graham is unequivocal about the dangers of *Helicobacter pylori*, as he should be, since he is only considering the risks of carriage. But what if *H pylori* is more analogous to *Bacteroides* spp than to variola or *Mycobacterium tuberculosis*? *Bacteroides* spp, well-recognised as commensals, can also be pathogens—eg, their involvement in diverticulitis, peritonitis, and appendicitis. Although by current definitions commensals cannot be pathogens, and vice versa, with long-term colonisers like *Bacteroides* spp and *H pylori*, a new conceptual model is needed.

M tuberculosis has probably only infected human beings for 10 000–15 000 years, it is highly clonal and has spread in an epidemic pattern; its eradication from human beings is a worthy goal. By contrast, the hypothesis that *H pylori* and humans have coevolved over the past millions of years predicts that the loss of the organism will have harmful effects. The fall in the prevalence of *H pylori* in developed countries, as confirmed by Leen-Jan van Doorn and colleagues, has coincided with a substantial increase in

gastroesophageal reflux disease, Barrett's disease, and adenocarcinoma of the lower oesophagus and gastric cardia. If these events are related, then by eliminating *H pylori*, will we be substituting one risk (gastroesophageal reflux disease and proximal cancers) for other (ulcer disease and distal cancers)? In developed countries, adenocarcinomas of the distal oesophagus and proximal stomach are rising at a faster rate than any other cancers,¹ so that the full extent of the potential risk is not yet known.

Could variation among *H pylori* strains help explain clinical and epidemiological differences? van Doorn and colleagues seek to explain the lower *H pylori* eradication rates observed in people with gastritis alone compared with ulcer patients. Their investigations indicate that diversity in *H pylori* strains (based on *vacA* signal sequence type) correlates with the differential eradication rates, and illustrates how assessment of *H pylori* strain variation may have increasing clinical significance as diagnostic techniques become more sophisticated.

Giuseppina Oderda and colleagues suggest that testing salivary antibodies is useful for the detection of *Helicobacter pylori* in Italian children. Antibodies induced by the *cagA* protein were also detectable in saliva. Is it important to detect whether a patient carries a *cagA*-positive strain? In western populations, carriage of a *cagA*-positive strain is associated with increased gastric inflammation and increased risk of developing duodenal ulcer, adenocarcinoma of the distal stomach or both.² By contrast, among Asian populations, most people carry *cagA*-positive strains.³ Nonetheless, in both populations most carriers of *cagA*-positive strains have no clinically evident disorder. Indeed, two abstracts presented in May, 1997, at the Digestive Disease week meeting, in Washington DC, USA, suggest that *cagA*-positive strains could afford protection against oesophageal adenocarcinoma and related premalignant lesions.^{4,5} If these observations are confirmed, they would suggest that carriage of *cagA*-positive strains may be both bad (increased risk of distal gastric cancer and duodenal ulceration) and good (decreased risk of pre-malignant lesions and adenocarcinomas of the lower oesophagus and upper stomach)!

Thus, the intersection of *H pylori* and human biology is more complex than is suggested by proponents of the new dogma that the only good helicobacters are dead ones. Careful stratification of study groups in terms of age, symptoms, carriage of *H pylori*, strain types, histopathology, and host acid secretion and genotypes should allow a

better understanding of the clinical significance of particular combinations of *H pylori* and human hosts.

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Disclosing conflicts of interest

SIR—In his commentary on conflicts of interest in clinical research, Richard Horton (April 19, p 1112)¹ laments that “the research community has become extremely exercised by this issue” and argues against disclosure. Disclosure has its drawbacks² but that does not mean it is unnecessary. It is time for the discussion to go beyond disclosure and focus on whether so many scientists should have avoidable conflicting interests in the first place.

Disclosure is only possible when there is a forum for it, such as a publication or oral presentation. When investigators are restrained by industry sponsors³ from presenting their work, the sponsorship cannot be revealed. Even when studies are published, financial ties of authors are not always disclosed; Krinsky et al found that in 34% of articles in leading biomedical journals with a Massachusetts-based lead author, that author had at least one disclosed financial interest.⁴

A more important reason for actions beyond disclosure stems from a moral obligation. Researchers have an obligation to fellow scientists and to the public to do the best science possible. Professionals are accorded a great deal of trust (and economic and social status) by society, on the understanding that they will strive for excellence and hold the public's interests above personal ones.⁵ Because academic institutions receive large amounts of