Gut reaction

A bacterium that causes ulcers and stomach cancer is on the decline, but not everyone is celebrating. John Whitfield talks to the experts who have misgivings about its impending extinction.

Endangered species: *Helicobacter pylori*, part of our gut flora, may offer clues to human migration.

Save the bacterium! It's an unlikely rallying cry, particularly when the microbe in question causes ulcers and stomach cancer. But *Helicobacter pylori* is in steep decline in many parts of the world, thanks to improved sanitation and the widespread use of antibiotics, and some biologists are beginning to wonder whether its disappearance is really for the best. In the West, the bacterium's demise has been dramatic — half of the US population aged 60 and over are infected with *H. pylori* compared with only 20% of those under 40.

Although most gastroenterologists view *H. pylori*'s disappearance with satisfaction, other researchers point to hints that the bacterium may help to protect against conditions such as infant diarrhoea and oesophageal disease. Some experts say that removing an important member of our intestinal flora will have unforeseen consequences for our inner ecosystem, and so our health. "We have no good sense of the microbial ecology of humans," says infectious-disease specialist Julie Parsonnet of Stanford University in California. "*H. pylori* infection revs up the immune system — what happens to our ability to respond to other infectious agents when that isn't there?" What's more, if *H. pylori* does disappear, so too will an opportunity to use studies of the bacterium to retrace the evolution and migration of human populations.

The debate over *H. pylori* begins with the question of how it got into us in the first place. Most mammals seem to have their own species of *Helicobacter* in their stomachs, leading some researchers to suggest

Helicobacter pylori may have been a success because it offers advantages to its host.

that the relationship between microbe and host predates the evolution of modern humans. But others think that *H. pylori*'s hook-up with humans, and subsequent spread around the world, was more recent.

That's the view taken by geneticist Douglas Berg of Washington University in St Louis, Missouri. Berg and his colleagues looked at more than 500 strains of the bacterium taken from people in five continents. Native Peruvians had bacteria more similar to Spaniards, they found, even though their genes are more similar to those of East Asians — the group that settled the Americas about 12,000 years ago. This led Berg and his colleagues to suggest that the conquistadors may have carried the bacterium to South America about 500 years ago¹, and that the continent's first humans arrived with virgin stomachs.

Martin Blaser disagrees. A microbiologist at New York University, he believes that *Helicobacter* has long been part of the gut flora of all humans. Late last year, Blaser and his colleagues seemed to reaffirm the ancient origins of American *H. pylori*, when they discovered strains closely related to the East Asian version of the bacterium in native people

living in remote regions of Amazonia². And in unpublished work, pathologist Marvin Allison of the Medical College of Virginia in Richmond has detected *H. pylori* in the stomachs of 1,800-year-old Chilean mummies. In areas where Europeans and Amerindians had mixed, Blaser believes, indigenous strains have fallen victim to microbial imperialism.

Berg considers the case to be unproven. Japanese and Chinese adventurers arrived in the New World about the same time as the Spanish, he points out, and they may have been the source of the Asian *H. pylori*. "It's still very controversial," he says. "How one interprets the evidence depends on one's biases."

A family affair

Knowing more about how *H. pylori* spreads would help to solve this puzzle, but so far we have only a rough sketch. Carriers usually pick up the bacterium before the age of ten and stay infected for the rest of their lives. Infected people shed large quantities of *H. pylori* in their diarrhoea and vomit³, which explains the microbe's success in regions with poor hygiene and sanitation. As a result, those at the bottom of the socio-economic scale and people in poor countries are more likely to be infected. The bug most often spreads vertically, from parents to offspring down the generations; there is very little transmission between adults.

Our tendency to keep *H. pylori* in the family means that bacterial and human histories mirror one another. A less faithful microbe that swapped between the members of a generation, a process called horizontal

Imported goods: did the Spanish introduce new bacteria to the stomachs of Amerindians?

transfer, would race around the world in a year or two, detaching itself from the genetics of its host. But *Helicobacter*, which sticks around for decades and — like genes — passes from parent to offspring, could be useful for reconstructing human evolution.

In March, molecular biologist Mark Achtman of the Max Planck Institute for Infection Biology in Berlin and his colleagues published the first global survey of the population genetics of *H. pylori*⁴. Their analysis revealed that the bacterium's genes preserve a record of human migrations both ancient and modern. Recorded through the presence of distinct genetic strains of the bacterium were the arrival of Europeans in South America, waves of migration into Europe from the near East and Central Asia, the settlement of New Zealand by Polynesians, and the influx of Africans into the Americas through the slave trade.

Researchers still debate how faithful this bacterial record of human migrations will turn out to be. Other microbes also seem to carry a record of our ancestors' movements — for example, each continent has its own strain of the human polyomavirus JC virus, another widespread, usually benign infection⁵. Studies of these microbes typically corroborate the evidence from human genetics and anthropology. But should such research suggest alternative hypotheses about our ancestry and movements — if certain strains turn up where they are not expected, for example — it may be difficult to separate misleading interpretations from important new discoveries.

"You have to be careful," says anthropologist Todd Disotell of New York University. As with language and culture, which are also mainly passed down vertically, microbes such as *H. pylori* can sometimes move horizontally, he says. "They're not a perfect record."

Even if *H. pylori* isn't ideal for anthropology, its geographical variance may help us

to understand what makes some people succumb to its harmful effects. In all carriers, *H. pylori* causes a chronic inflammation of the stomach lining; in about 10–15% of carriers this results in ulcers, and about 1–2% will develop gastric cancer, the biggest cancer killer after lung tumours. But these percentages vary around the world. Ulcers and gastric cancer are rare in sub-Saharan Africa, despite a high rate of *H. pylori* infection. In contrast, gastric cancer is most common in the Far East, where genes known to increase the bacterium's virulence are more widespread than in European strains. In India, ulcers most commonly afflict the duodenum; in Japan the stomach is hardest hit.

Tangled web

Differences in bacterial genes do not account for all of these variations. Diet and lifestyle are also important, as is the genetic make-up of the human host⁶. Several groups, including Berg's, are now working to untangle the risk factors, so that efforts to treat the infection with antibiotics can be targeted to those most likely to develop ulcers or cancer.

Poverty trap: poor sanitation in the developing world aids the transmission of *Helicobacter pylori*.

In coming years, treatments other than antibiotics may be necessary, as drug-resistant bacteria are becoming increasingly common. To this end, several research groups are working towards vaccines, some of which are already undergoing clinical trials.

But should we be in such a rush to finish *Helicobacter* off? Blaser argues that *H. pylori* may have been such an evolutionary success because it offers some advantages to its host. For one, it may protect against childhood diarrhoea⁷ — still a major killer across large parts of the developing world — by boosting the immune system and producing peptides that kill other bacteria⁸.

Blaser also notes that *H. pylori*'s wane has corresponded to an increase in acid reflux diseases — serious forms of heartburn — and cancers of the oesophagus⁹. This may be because *H. pylori* can damp down the stomach's production of acid.

But this view is controversial. Most medics view an *H. pylori* infection as an unambiguously bad thing. Some believe that infection with the bacterium may even make childhood diarrhoea worse, as the lowered acid production may allow other bacteria to survive passage through the stomach¹⁰. "*H. pylori* infection is a serious disease," says gastroenterologist David Graham of Baylor College of Medicine in Houston, Texas. "To say it has protective effects is a play on words more than anything else." Graham goes so far as to advocate pre-emptive eradication in regions where gastric cancer is common.

But even without a campaign against it, *H. pylori* seems to be doomed. "In the United States, it's disappearing faster than it would if we had a public-health drive to eradicate it," Parsonnet says.

H. pylori's fate has been easy to track, because it is by far the most dominant bacterium in the stomach. But many of the other 500 or so species of bacteria in our gut might be experiencing population changes without our knowledge. At the moment we can only guess at what the consequences will be. For instance, could shifts in our gut flora have anything to do with the Western world's epidemic of chronic conditions such as allergies and asthma? "Our indigenous organisms are part of our own physiology," says Blaser. "Their extinction may play a role in some of our post-modern diseases."

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