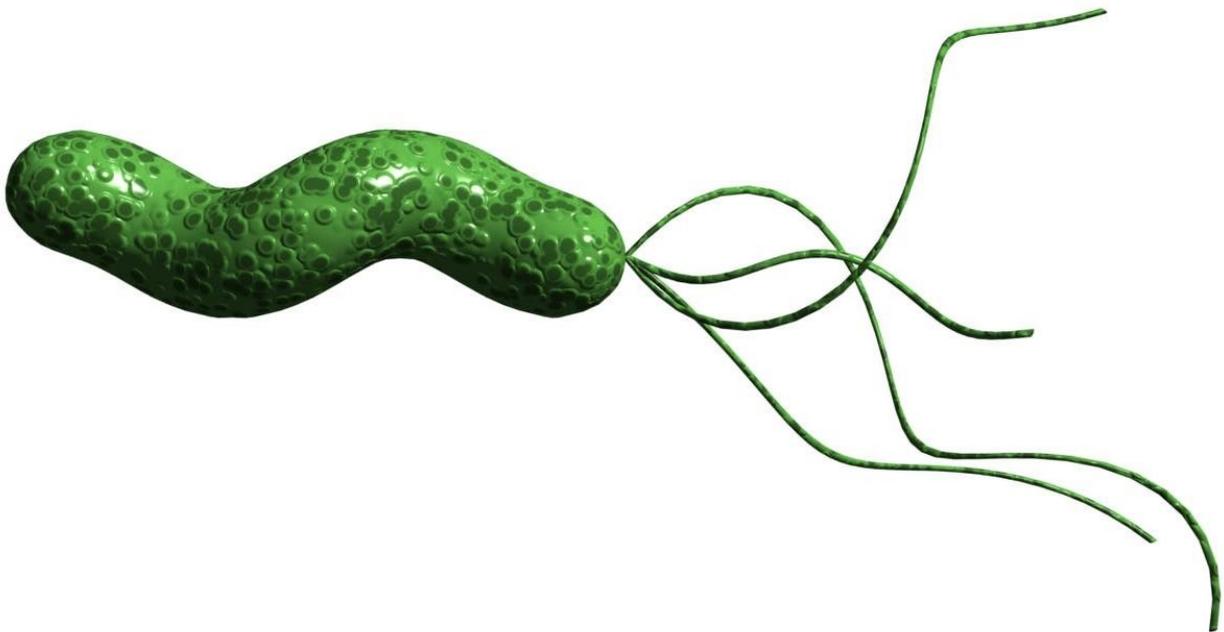


Healthcare industry BW

How cancer-causing bacteria reached the South Seas in outrigger canoes

The bacterium *Helicobacter pylori* causes gastric ulcers and gastric cancer. The prehistoric great migrations of human populations, including the expansion of the Austronesians across the Pacific and Indian Oceans, can be reconstructed in precise detail from the genetic makeup of different *Helicobacter* strains.



Helicobacter pylori
© WHO

In the 1980s, the pathologist Dr. J. Robin Warren and the gastroenterologist Dr. Barry Marshall from the Royal Perth Hospital in Western Australia showed that active chronic gastritis (which leads to gastric ulcers) is caused by a bacterium that has the unusual ability to thrive in the extremely acidic gastric juice. They identified the bacterium as *Campylobacter pylori* (later renamed *Helicobacter pylori*) and showed that this bacterium fulfilled Koch's postulates. In order to establish a causal relationship between *H. pylori* and gastritis, Koch's postulates required the researchers to 1) find *H. pylori* in abundance in gastritis patients and 2) isolate the bacterium from a diseased individual and grow it in pure culture (after 34 failures they finally succeeded). In order to test Koch's third postulate, first Warren and then Arthur Morris, a young man from New Zealand, tested on themselves whether the consumption of cultured *H. pylori* bacteria caused them to develop active and chronic gastritis. This did in fact happen, and the infection only disappeared following antibiotic treatment.



Prof. Dr. Hermann Brenner, head of the Department of Clinical Epidemiology and Ageing Research at the DKFZ
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It has long been known that ulcer-causing chronic gastritis (peptic ulcer disease) considerably increases the risk of developing gastric cancer. Shortly after Warren and Marshall's discovery, other researchers discovered that there is a close relationship between *H. pylori* infections and the development of gastric

cancer, which is the second most frequent cause of cancer-related deaths worldwide. In countries with high incidences of gastric cancer such as Peru, Columbia, Mexico and parts of East and Southeast Asia, virtually the entire population is infected with *H. pylori*. However, it also turned out that in the industrialised world, where the incidence of gastric cancer has fallen over the last decades, gastric cancer is nearly always associated with *H. pylori* infection. In Germany, the team of Hermann Brenner, an epidemiologist from Heidelberg (now at the German Cancer Research Center), carried out a study and provided proof of evidence that *H. pylori* infections led to the development of gastric cancer (Brenner H, Arndt V, Stegmaier C, Ziegler H, Rothenbacher D: Is *Helicobacter pylori* infection a necessary condition for noncardia gastric cancer? *Am J Epidemiol* 2004, 159, 252-258.).

Helicobacter, a class I carcinogen

As early as 1988, the Columbian pathologist Pelayo Correa from Louisiana State University, New Orleans, USA, postulated a multistep model of gastric precancerous processes caused by *H. pylori* infections. The model, which is known as Correa cascade, has been validated and is widely accepted: Chronic gastritis evolves progressively from "chronic non-atrophic gastritis" to "atrophic gastritis", "metaplasia", "dysplasia" to gastric cancer. There is evidence that the first two steps are linked to bacterial infection, with the exception of the rare genetic form of gastric cancer. Nitrosamines and free oxygen radicals have been shown to trigger the transformation of chronic gastritis into intestinal metaplasia, dysplasia and cancer. It is further assumed that *H. pylori* also plays an active role in the transformation of atrophic gastritis to metaplasia by converting nitrate that is taken up along with food into nitrosamines and other mutagenic nitroso compounds. Ascorbic acid and beta carotene block the Correa cascade and prevent the development of gastric cancer.

In 1994, the International Agency for Research on Cancer, which is part of the World Health Organisation (WHO), listed *H. pylori* as a class I carcinogen, thereby officially recognising it as the causative agent of gastric cancer. In 2005, Warren and Marshall were awarded the Nobel Prize in Physiology or Medicine for their "discovery of the bacterium *Helicobacter pylori* and its role in the development of gastritis and peptic ulcer disease".

The spread of *Helicobacter pylori* around the globe

The spectacular "career" of *H. pylori* as an important object of scientific investigation and causative agent of gastric cancer does not end here. We will go on to show you how the bacterium has unexpectedly become extremely popular in a wide variety of disciplines.

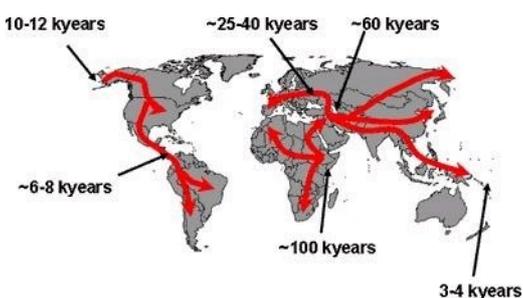
Genome analyses of *H. pylori* strains isolated from different patients, revealed the bacterium's enormous genetic variability and intraspecific differences. This "allelic diversity" is the result of a high mutation rate, a high recombination frequency between different bacterial strains that have infected the same host, and the bacterium's ability to integrate small foreign DNA fragments into its chromosome.



Professor Mark Achtman
© University College, Cork

In 1998, Prof. Mark Achtman, who then worked at the Max Planck Institute for Molecular Genetics before becoming head of a research group at the Max Planck Institute for Infection Biology in Berlin, started to focus on the genetic variability of *Helicobacter* strains in an attempt to analyse the migration of human populations. The idea is the same as that underlying molecular evolution studies: the longer two populations have diverged, the greater the genetic differences between the two, if no other factors such as natural selection change or suppress the differences. Since the bacterium's mutation and recombination rates are much higher than those of its host, Achtman hoped to be able to obtain precise information on the divergence and migration of populations that have occurred recently enough to not manifest themselves in the human genome.

Achtman and his colleagues initially found that the *H. pylori* strains of Europeans and Chinese differed considerably. They were subsequently able to show that African bacterial strains were brought to North America as a result of the slave trade while Buddhists and Muslims in North India were infected with different bacteria. In a 2007 paper, the scientists published a world map of the expansion of *Homo sapiens* across the entire globe, reconstructed from the genetic diversity of *Helicobacter* strains in the different continents (Linz B, Balloux F, Moodley Y, ... , Suerbaum S, Achtman M: An African origin for the intimate association between Humans and *Helicobacter pylori*. *Nature* 445, 915-918, 2007).



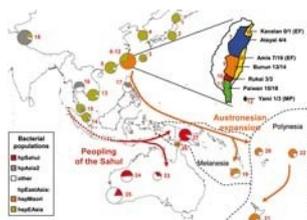
The spread of *Helicobacter* along with humans across the globe between 100,000 and 3-4,000 years ago.
© M. Achtman (modified)

The genetic distance between different *H. pylori* strains was compared with data relating to other prehistoric events and set on a time scale. The results are for

the most part identical with the results obtained by anthropologists, ethnologists, human geneticists, archaeologists, linguists, etc. from long-term investigations on the expansion of modern humans across the earth: When anatomically modern humans (*Homo sapiens*) made their way out of East Africa some 100,000 years ago to populate the world, they were accompanied by the bacterium *H. pylori*. They arrived in Southwest and Central Asia some 60,000 years ago and in Australia and New Guinea some 20 - 30,000 years ago. Around 25 to 40,000 years ago (the exact time has not yet been established), *H. pylori* colonised Southern Europe and continued its path towards Central and North Asia, from where it continued its journey to North America across the Bering Strait around 10 to 12,000 years ago. (Achtman and his colleagues have not yet come up with bacterial evidence that America was colonised much earlier, something that is still subject to fierce debate). South America was colonised around 8 - 10,000 years ago. The bacterium spread to the Pacific islands around 1,000 to 5,000 years ago and around 500 years ago, European and African *Helicobacter* strains reached America as a result of colonial expansion and the slave trade.

Sailing half of the globe on twin leeboard canoes

The story does not end here. In a recent paper (Moodley Y, Linz B, Yamaoka H, ... , Marshall BJ, Achtman M: The peopling of the Pacific from a bacterial perspective. *Science*, 23 Jan 2009), an international team of researchers led by Mark Achtman, who has since returned to his native country to continue his research at the University College in Cork, Ireland, was able to complement and fully confirm previous studies carried out by archaeologists, human geneticists and linguists, in particular. The Nobel laureate Barry Marshall provided the researchers with *Helicobacter* bacteria sampled from Australian aborigines and the Japanese scientist Yoshio Yamaoka provided them with Taiwanese samples.



The two expansions of *Helicobacter* to Oceania
© M. Achtman

The first big human expansion into the Pacific area, i.e. Australia and New Guinea, occurred during the last glacial period about 31 to 37,000 years ago across the Sahul shelf where low sea levels meant that the land masses were still connected. The descendants of these first immigrants, the Papua in the New Guinean highlands and the Australian aborigines, carry hpSahul *Helicobacter* bacteria that are not found in any other human population. The second human expansion from Taiwan 5,000 years ago, known as Austronesian expansion, is characterised by hpMaori *Helicobacter* bacteria. The hpMaori type originates from a *Helicobacter* type (hpEast Asia) frequently found in China. Archaeological finds provide evidence that Austronesians colonised Taiwan from Southern China, although Austronesian languages are no longer spoken there. Three of the four members of the Austronesian language family are only spoken by Taiwanese natives (around one per cent of the entire Taiwanese population). All other 945 languages of the Austronesian language family belong to the Malayopolynesian language group which spread from Taiwan a few thousand years ago to the Philippines and Indonesia and the Melanesian islands in the Western Pacific Ocean, and from there rapidly towards the east (to all inhabitable islands of the Pacific Ocean) and the west across the Indian Ocean to the island of Madagascar off the coast of East Africa.



Twin outrigger canoe from the Fiji islands
© J. Dumont d'Urville, "Voyage de la corvette d'Astrolabe, 1826-1829".

By air from Madagascar to the remotest island in the Pacific Ocean (Easter Island) is 23,000 km, which is more than half of the earth's circumference. Prior to colonisation by Europeans from the 16th century onwards, the Malayopolynesian language group was the most widespread language in the world. Fascinating details about this expansion are found in the wonderful book "Guns, Germs and Steel" by Jared Diamond, a book which inspired Mark Achtman. The book also focuses on the ample archaeological and linguistic evidence for this migration. In addition to archaeological and linguistic research, molecular biology has also contributed to solving the migration puzzle. All samples derived from people belonging to the Austronesian language groups contained the hpMaori *Helicobacter* type of bacteria; no single sample contained both hpSahul and hpMaori types.

So, how can the Austronesian migration be explained? Jared Diamond provides a plausible explanation, which, although speculative with regard to the early phase of this expansion, is backed by archaeological and linguistic evidence and is accepted by the majority of experts: the discovery of the outrigger sailing canoes that enabled the Austronesians to sail across the Ocean. They were unaware that they were accompanied by the bacterium *Helicobacter pylori*, which nowadays provides evidence of the great human migration which started in East Africa around 100,000 years ago.