When Australian physician Barry Marshall returned to his lab after Easter in 1982, a groundbreaking surprise awaited him. After numerous unsuccessful attempts to cultivate the helical bacterium his colleague Robin Warren had discovered, colonies had finally started to grow. The bacteria had come from biopsy samples of gastritis patients.

Marshall and Warren faced strong antagonism to their research. With only a few exceptions, the scientific community was sceptical that bacteria could colonize the harsh environment of the stomach, at a pH of somewhere between 1 and 2. The doctrine at the time was that gastritis and gastric ulcers were the result of an overly acidic stomach due to excessive stress and poor diet, which could be treated with acid-blocking drugs.

Unperturbed by this, the intrepid duo pushed ahead on their trail. When the bacterial cultures failed to cause any of the typical symptoms in lab animals, Marshall decided the only recourse was to do the experiment on himself, and he drank a beaker full of bacteria. When he came down with severe gastritis as a result, which they were able to treat successfully with antibiotics, he had proven an important cause of inflammations of the gastric mucosa. In 2005, Marshall and Warren received the Nobel Prize for their achievement.

In every second stomach

After all the doubt as to its presence in the stomach, *Helicobacter pylori* has since become one of the most well-studied chronic pathogens ever and, since 1996, has even had its own dedicated journal (“Helicobacter”, Wiley). Medical students nowadays learn completely naturally that *Helicobacter pylori*, a flagellate gram-neg-
ative bacterium, is the most important cause of type-B gastritis and of gastric and duodenal ulcers. It is also considered the most important risk factor for stomach cancer and MALT lymphoma. In 1997, the WHO even classified it among the Group I carcinogens. That makes *H. pylori* the first bacterium known to cause cancer.

According to estimates this germ, perfectly adapted to its hostile environment, colonizes every second stomach in modern man. That places it among the most common chronic infectious pathogens in the world. Yet, not every harbourer falls ill: While chronic inflammation of the gastric mucosa is detected in all those infected, gastric and duodenal ulcers requiring treatment only occur in about ten percent of cases. For one in every hundred patients, the untreated infection leads to stomach cancer.

If a sick person is found to host the pathogen, then the patient generally receives a combination of antibiotics and antacids. Given their dangerous possible side-effects and also given the problem of resistance, which is now just as much an issue for *H. pylori* (see info box ResiNet), researchers are urgently looking for alternatives to the established treatments. The researchers believe a key to sustainably treating *H. pylori* infections lies in the diverse host-pathogen relationships.

**Devious pathogen**

Since the 1990s, research groups around the world have been working on developing a vaccine against *H. pylori*. “It is a highly variable pathogen in a special ecological niche, so we cannot expect things to be simple,” says Prof. Dr. Sebastian Suerbaum, head of the Institute for Medical Microbiology and Hospital Epidemiology of Hannover Medical School. “But that is no reason to be pessimistic – new insights into bacteria and the immune system sooner or later lead to success.”

Suerbaum’s laboratory is intensively studying the pathogenicity factors, population genetics and evolution of the gastric bacterium. His experimental work in the last twenty years has revealed many adaptations of *H. pylori* to its extreme habitat as well as its high variability, thereby contributing internationally ground-breaking information to the understanding of this chronic infection.

Gamma-glutamyl transpeptidase (gGT) is essential to the successful persistence of the bacterium. This bacterial enzyme blocks T-cells, thwarting the immune response. Bacterial mutants missing gGT colonize the stomach significantly less in the mouse model. This transpeptidase also directly influences the inflammatory response in the gastric mucosa. It is found in all strains of *H. pylori* and is therefore regarded as a promising target for an alternative combat strategy.
Bacterial carcinogen

Alongside Vacuolating toxin (VacA), which destroys stomach cells and inhibits healing of the mucosa, the Ccag-pathogenicity island (Cag PAI) is considered the most important virulence factor associated with cancer. This region in the genome of *H. pylori* encodes for a type 4 secretion system (T4SS). The bacterium uses this molecular syringe to inject the effector protein, called CagA, into the stomach epithelial cells. This intervenes strongly with signal transmission and other cell functions and is therefore classed as a bacterial oncoprotein.

Suerbaum's laboratory is also studying the biogeographical distribution of these cag PAI genes [1,2]. It is not at all uniform: For instance, while only about 70–80 % of *H. pylori* isolates in the western world carry this pathogenic factor, nearly all of them in the East Asian region have it. The rate of stomach cancer is also especially high in the latter region. Possession of a functional Cag pathogenicity island is statistically highly associated with higher pathogenicity, both for gastritis and cancer. “But,” Prof. Suerbaum adds, “the effector protein CagA is also highly variable and can disrupt signal transmission in the stomach epithelium to a highly varying degree.”

Coevolution over 60,000 years

We have known about *H. pylori* infections for three decades. Yet they are hardly new. In 2003, together with an international research team, Suerbaum's lab proved that even our early African ancestors carried *Helicobacter pylori* some 60,000 years ago. [3,4] To show this, the scientists correlated the DNA of various Helicobacter strains with historical and recent migration paths from human history.

These inhabitants of the stomach had plenty of time to adapt perfectly to their extreme niche and to counter the attacks from the immune system of their only hosts – humans. “Helicobacter is a normal component of our stomach, or at least it was once,” Prof. Dr. Anne Müller is convinced. She is researching the host-pathogen relationship of *H. pylori* at the Institute for Molecular Cancer Research, Zurich. Studies show that the stomach bug’s disappearance from the human microbiota is accelerating. While there are populations in developing countries in which nearly all people are infected with *H. pylori*, epidemiologists have witnessed a radically decreasing number of infected people in industrialized countries over several years. Only around 20 to 40 % of adults, and significantly fewer children, have *H. pylori* in their stomach. The researchers attribute this decline to the use of antibiotics, generally high hygiene standards and an increasing number of caesarean births.

The critical factor that determines how dangerous *H. pylori* is to us is the time of infection, as Müller explains. If infection occurs as late as adolescence or adulthood, then the immune system will fight the invader
especially fiercely. By contrast, an infection in early childhood will actually protect against the development of allergies, as epidemiological studies and her own experimental data suggest. Prof. Müller continues: “Carriers of Helicobacter have a significantly lower risk of developing allergies if they already picked up the germ as a baby. Our experimental work on miceshowes as well that permanent colonization during development is prerequisite for this protection.”

**Intervening in the immune system**

The allergy researchers can already name two effects responsible for the prevention of asthma in the case of early childhood confrontation with the bacterium: Firstly, *H. pylori* activates the so-called regulatory T-cells (Tregs) and, secondly, it re-programmes the dendritic cells (DC) so that they tolerate *H. pylori*. It is therefore classified as a strongly immunomodulating germ. For this, it employs two of the known pathogenicity factors: the VacA toxin and gGT. These ensure the immune system does not detect and attack the bacterium. As a side-effect, immune responses to other allergens are also suppressed.

It follows that, in the mouse model, the same *H. pylori* factors protecting against asthma are also responsible for ensuring permanent colonization of the stomach, and cause stomach problems. The researchers are confident that these findings on the immunomodulatory properties of the gastrophile will also reveal new paths towards preventing and treating allergies – and theoretically towards the eradication of *H. pylori* as well. [5,6]

The mouse model of *H. pylori*-mediated asthma protection established in Prof. Müller’s laboratory also experimentally supports the “disappearing microbiota” hypothesis. This is essentially a concretization of the hygiene hypothesis. In short, it means the rise of asthma and allergies in highly developed societies is a direct consequence of the disappearance of our original microbiota.

Experts these days are hotly debating whether consistent combatting of the germ is advisable in light of the newly suspected positive effects on development. The importance of human microflora, especially of the gut and lungs, has been the subject of intensive research for several years. Scientists are shedding light on the close interdependency of metabolic pathways of prokaryotes and eukaryotes and also know that transitions exist between harmless commensals and pathogenic bacteria, or pathobionts. “Understanding their role in their ecological niche is a major challenge,” Prof. Suerbaum emphasizes.
Who are “we”?

One of the leading champions of this viewpoint is Prof. Dr. Martin Blaser, professor at the School of Medicine of New York University and head of its Human Microbiome Program. According to his hypothesis, our entire microflora has been undergoing drastic change since the middle of the 20th century (see also the IR interview).

“Who are we?” was the title of his 2006 article, in reference to the fact that 90% of the cells in our body are of microbial origin. Blaser stresses the importance of autochthonous microbiota for the healthy physiology of mankind. He explicitly includes H. pylori in this consideration. He warns against a generalized fear of bacteria, which would make it difficult to differentiate between the advantages and disadvantages of our bacterial cohabitants – and which would in turn blind us to the negative consequences of their absence.

In 2011, under his leadership, New York researchers demonstrated a significant influence of H. pylori on the dietary habits of adult people: When the gastric bug was missing, the levels of the appetite regulating hormone ghrelin were significantly higher. This protein, also known as the “hunger hormone”, increases appetite and also stimulates fat production. Furthermore, the presence or absence of H. pylori also influences the protein’s antagonist leptin. The experts therefore suspect a correlation between the disappearance of this primordial gastric cohabitant and the significantly increasing obesity among children and adolescents. [7]

Good little bad germ?

We are now aware of several factors that increase the risk of contracting serious, treatment-requiring gastritis or stomach cancer from Helicobacter. These serious negative effects apply above all to adults. Prof. Müller advises: “It would be unfavourable if H. pylori were to vanish altogether because then it could no longer be inherited during earliest childhood and protect us against allergies. Its positive effects, however, only outweigh the negative up until early adulthood. After that, the negative effects of Helicobacter infection dominate.”

Prof. Suerbaum cautions: “Worldwide, H. pylori causes 550,000 to 600,000 new stomach cancer cases per year with a high rate of mortality. All discussions about potentially positive effects of H. pylori on humans must be measured against this, and must not be taken as grounds for passivity.” He therefore considers a vaccine against Helicobacter pylori indispensable.

Not too long ago, the stomach was believed to be as inhospitable to life as the moon. With the recent discovery that, alongside H. pylori, many other bacteria can be detected in the stomach (whether they truly form a stable microbiome and propagate there is still unclear), a new suspenseful road of research into the first
A known gastric bacterium has been revealed. The experts expect to find that the composition of the newly discovered gastric microbiome also influences the pathogenicity of *H. pylori*. [8,9]

Since 2001, the National Reference Centre (NRZ) for *Helicobacter pylori* of the Institute of Medical Microbiology and Hygiene of The Medical Centre – University of Freiburg has been monitoring this gastric germ’s development of resistance. With the multi-centre study ResiNet, it identifies relevant risk factors as well as trends over time. One main risk factor for resistance is prior antibiotic treatments.

The primary resistance rates of *H. pylori* are currently between 7% (clarithromycin) and 31% (metronidazole). Resistance rates rise significantly after a single failed treatment, and rise up to 80% after two failed treatments. Double and triple resistances rise sharply at the same time.

Between 2006 and 2011, a significant increase in quinolone resistance (21% to 29%) as well as resistance to metronidazole/clarithromycin/amoxicillin triple therapy (13% to 19%) can be seen.


Citations and further literature:


