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Going unnoticed

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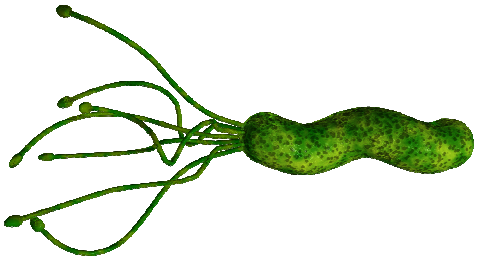
There are people who saunter through life unnoticed until something happens and reveals that they are far less ordinary than they appeared to be. The same goes for *Heliobacter pylori*. *H. pylori* is a bacterium which was discovered in the late 1800s but was forgotten for the best part of a century simply because no one had succeeded in cultivating it. Its role in causing gastric diseases was also discussed at the turn of the 19th century, only as the results were published in Polish they met with very little recognition outside Poland. And while *H.pylori* was being ignored, attempts were being made to study an enzyme which helps it to survive in the organisms it infects: urease. Like *H.pylori*, urease had to wade through waves of short-sightedness. Not only was it a common belief in those days that enzymes could not be proteins, but enzymes were also thought to exist in excessively low concentrations in plants and animals… Despite these barriers, *H.pylori* and urease finally triumphed at the end of the 20th century and both turned out to be singular entities.



Helicobacter Pylori

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Everyone has heard of stomach ulcers. Many have also heard that stomach ulcers are caused by stress. Not everyone knows, though, that many stomach ulcers are the result of *H.pylori* infection. It took a long time for the scientific community to believe that any living organism could survive within the depths of our digestive system. The environment is far too acidic. It required that a scientist drink a potion of *H.pylori* and develop gastritis which was successfully treated with antibiotics. Once it had been demonstrated that bacteria could indeed survive in our guts, the question was how?

H.pylori likes to live in the mucus gel layer which lines the stomach. It gets there by using its flagellum and is able to remain and survive there by reducing the surrounding acidity thanks to the enzyme urease. Urease achieves this by breaking down urea into carbon dioxide and ammonia. In doing so, the enzyme not only reduces the local gastric acid but also produces a source of nitrogen for itself. Concomitantly, it weakens the mucus coating. Acid is then able to reach the sensitive lining underneath and corrodes it, causing discomforts such as an ulcer.

H.pylori was first observed in humans in 1875 by German scientists. They didn't manage to cultivate them however and no one took any further notice of it. In 1899, Polish researchers mentioned in an article that a number of gastric diseases could well be due to the bacterium – but Polish, like today, was read by very few. Fortunately, in 1981, two Australian scientists – fluent in English – managed to both cultivate *H.pylori* and demonstrate that the bacterium could indeed be the cause of stomach ulcers and gastritis as opposed to stress or spicy food. However, it took a further decade before the medical community actually recognised the fact

and added antibiotics to the treatment of ulcers and gastritis.

Like *H.pylori*, it took years before urease was taken seriously. In the early 1900s, it was common belief that enzymes were not proteins and constituted a very minor part of any organism, so there was no point in trying to isolate them. Despite this, an American chemist, James Sumner, decided to ignore reasoning that only hindered the advancement of knowledge and, with the help of a coffee mill and a mortar and pestle, he took to grinding jack beans. His success was far from immediate but by 1927 he had not only demonstrated that an enzyme was a protein but he had also managed to crystallise the first enzyme ever: urease. And since we are on the subject of exploits, not only was urease the first enzyme to be crystallised but it was also the first nickel-containing enzyme to have been discovered.

In short, ureases are found in bacteria, yeast and a number of plants. This enzyme helps *H.pylori* – as well as some other bacteria – survive in our stomachs and is an assembly of heterohexamers. Most ureases are an assembly of three hexamers composed of 3 heterotrimers of alpha, beta or gamma subunits $(\alpha\beta\gamma)_3$. The *H.pylori* urease, however, is a super assembly of four hexamers of alpha and beta units $(\alpha\beta)_3$ – where the beta subunits are in fact a fusion of the alpha and the gamma subunits found in other species. The resulting complex is huge! The bigger the better it seems since it is believed that the huge size of the *H.pylori* urease may make it more stable.

This molecular stability is not good news for humans on two fronts. First, the more stable the urease is, the better *H.pylori* will be able to infect us. Second, it is always a more difficult task to design drugs to counter molecules that are sturdy. However, as always, the more we know about the structure and function of urease, the greater the chance will be of finding an adequate treatment against common ailments such as stomach ulcers, gastritis and certain forms of cancer. *H.pylori* and urease are beautiful examples of research which were confronted with scientific scepticism and narrow-mindedness, and demonstrate that what was thought to be of little interest turned out to be at the heart of groundbreaking events.

Cross-references to Swiss-Prot

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