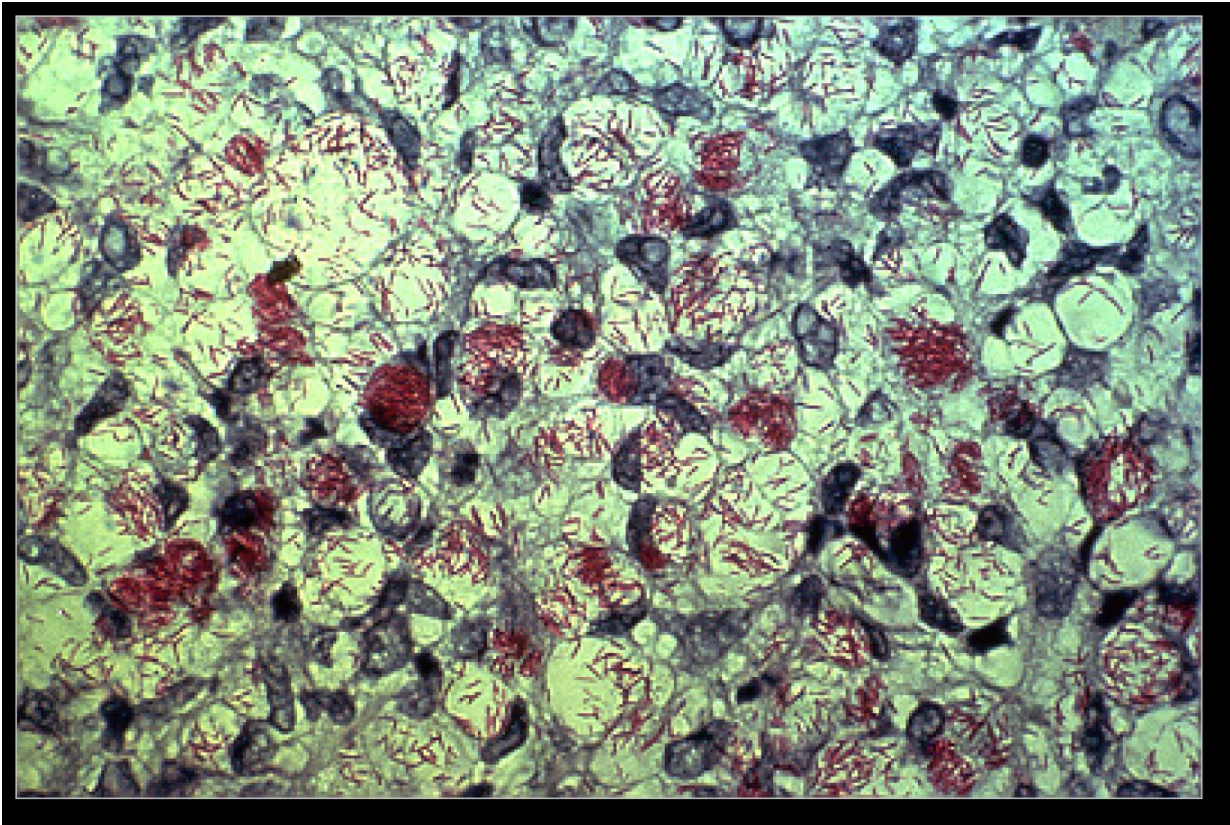


Leprosy turns the immune system against itself, study finds

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M. leprae, one of the causative agents of leprosy. Credit: Public Domain

Leprosy hijacks our immune system, turning an important repair mechanism into one that causes potentially irreparable damage to our nerve cells, according to new research that uses zebrafish to study the

disease. As such, the disease may share common characteristics with conditions such as multiple sclerosis.

Leprosy is an infectious [disease](#) that affects the skin and peripheral nerves and is caused by *Mycobacterium leprae* and, less commonly, *Mycobacterium lepromatosis*. According to the World Health Organization, there has been a dramatic decrease in the global disease burden in the past few decades: from 5.2 million people with leprosy in 1985 to 176,176 at the end of 2015.

Despite the disease having been known about for thousands of years - many people will have first heard about it through references in the Bible—very little is understood about its biology. This is in part because the bacteria are difficult to grow in culture and there are no good animal models: *M. leprae* can grow in the footpads of mice, but do not cause [nerve damage](#); the disease causes nerve damage in armadillos, but these animals are rarely used in research.

Now, an international team led by researchers at the University of Cambridge, UK, and the University of Washington, the University of California Los Angeles and Harvard University, USA, have used a new animal model, the zebrafish, to show for the first time how *M. leprae* damage nerves by infiltrating the very [cells](#) that are meant to protect us. Zebrafish are already used to study another species of mycobacteria, to help understand tuberculosis (TB).

Scientists have previously shown that the nerve damage in leprosy is caused by a stripping away of the protective insulation, the [myelin sheath](#), that protects [nerve fibres](#), but it was thought that this process occurred because the bacteria got inside Schwann cells, specialist cells that produce [myelin](#).

In new research published today in the journal *Cell*, researchers used

zebrafish that had been genetically modified so that their myelin is fluorescent green; young zebrafish are themselves transparent, and so the researchers could more easily observe what was happening to the nerve cells. When they injected bacteria close to the nerve cells of the zebrafish, they observed that the bacteria settled on the nerve, developing donut-like 'bubbles' of myelin that had dissociated from the myelin sheath.

When they examined these bubbles more closely, they found that they were caused by *M. leprae* bacteria inside of macrophages - literally 'big eaters', immune cells that consume and destroy foreign bodies and unwanted material within the body. But, as is also often the case with TB, the *M. leprae* was consumed by the macrophages but not destroyed.

"These 'Pac-Man'-like immune cells swallow the leprosy bacteria, but are not always able to destroy them," explains Professor Lalita Ramakrishnan from the Department of Medicine at the University of Cambridge, whose lab is within the Medical Research Council's Laboratory of Molecular Biology. "Instead, the macrophages—which should be moving up and down the nerve fibre repairing damage—slow down and settle in place, destroying the myelin sheath."

Professor Ramakrishnan working with Dr Cressida Madigan, Professor Alvaro Sagasti, and other colleagues confirmed that this was the case by knocking out the macrophages and showing that when the bacteria sit directly on the nerves, they do not damage the myelin sheath.

The team further demonstrated how this damage occurs. A molecule known as PGL-1 that sits on the surface of *M. leprae* 'reprograms' the macrophage, causing it to overproduce a potentially destructive form of the chemical nitric oxide that damages mitochondria, the 'batteries' that power nerves.

"The leprosy bacteria are, essentially, hijacking an important repair mechanism and causing it to go awry," says Professor Ramakrishnan. "It then starts spewing out toxic chemicals. Not only does it stop repairing damage, but it creates more damage itself."

"We know that the immune system can lead to nerve damage - and in particular to the myelin sheath - in other diseases, such as multiple sclerosis and Guillain-Barré syndrome," says Dr Cressida Madigan from the University of California, Los Angeles. "Our study appears to place leprosy in the same category of these diseases."

The researchers say it is too early to say whether this study will lead to new treatments. There are several drugs being tested that inhibit the production of nitric oxide, but, says Professor Ramakrishnan, the key may be to catch the disease at an early enough stage to prevent damage to the nerve cells.

"We need to be thinking about degeneration versus regeneration," she says. "At the moment, [leprosy](#) can be treated by a combination of drugs. While these succeed in killing the [bacteria](#), once the [nerve damage](#) has been done, it is currently irreversible. We would like to understand how to change that. In other words, are we able to prevent damage to nerve cells in the first place and can we additionally focus on repairing damaged [nerve cells](#)?"

More information: Madigan, CA et al. A Macrophage Response To Mycobacterium leprae Phenolic Glycolipid Initiates Nerve Damage In Leprosy. *Cell*; 24 Aug 2017; [DOI: 10.1016/j.cell.2017.07.030](https://doi.org/10.1016/j.cell.2017.07.030)

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