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Down To Earth

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Microorganisms that can kill us also help us survive. Science explains why

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Who are you?

Microorganisms explain more about us and our world than we ever imagined.

SUMANA NARAYANAN courses through rodent brain, feline gut, and the human stomach

This is not something you are likely to see in a Tom and Jerry animation.

Imagine a cat readying itself to pounce on a mouse. The mouse notes the feline but does not budge. It grooms itself and looks away. Soon, it is cat food.

Now imagine further. The cat's owner is a pregnant woman. It is possible that her unborn child would become a schizophrenic.

The parasite *Toxoplasma gondii* was looking for a definitive host (primary host where a parasite matures and in many cases reproduces sexually). Lodged inside the rodent's brain, the microbe manipulated the mouse to release dopamine, a mood regulator that gives rise to extreme emotions: euphoria, depression. Its central nervous system doped on dopamine, the mouse's survival instincts were lulled. Thereafter, life seemed pleasant, the cat friendly.

T gondii survived.

(Once inside the cat, the microorganisms made their way to the stomach, reproduced sexually and escaped via the cat's faeces. Mice that eat the faeces continue to play their part in the *T gondii* story. The microbe needs a cat to make whole its life cycle; the cat is its definitive host. As for intermediates, the microbe does not mind animals other than mice. About one in three humans carry *T gondii* in his or her head.)

Back to our story: the pregnant woman takes out the cat litter, wanders into the kitchen and bites into an apple—without washing her hands. The parasites reach her brain via the bloodstream. The dopamine spell follows, changing the woman's personality. It makes her feel guilty and duty-conscious. The microbe then makes its way to the foetus through the placenta, leaving it vulnerable to a mental disorder someday.

Most schizophrenics are known to have high levels of antibodies against *T gondii* in their blood. At the same time, some studies noted that individuals infected by *T gondii* were bound to exhibit psychiatric symptoms such as depression, anxiety and disorientation, characteristic of schizophrenia.

E F Torrey studies schizophrenia at the Stanley Medical Research Institute in

HEATHER SEBASTIAN

Toxoplasma gondii

Age: Prehistoric

Address: Rodent brain

Goal: Make cat eat rodent

Weapon of choice: Dope

Bethesda, USA. He decided to investigate a possible connection. He and his team treated infected and oddly behaving rats with anti-psychotic drugs used to suppress schizophrenia. The drugs blocked the tachyzoite formation (an asexual stage where the microbe divides and increases its number). As the microbes died, their influence on the rat brain also decreased. Dopamine levels went down subsequently and the rats were not as foolhardy.

What we have at hand is a microbe capable of messing up a rat's brain, completing its life-cycle in a cat, entering a human body, deciding the fate of an unborn child, and propelling researchers to experiment with oddly-behaving rats.

It is only wise pregnant women are told to avoid cats.

Microbe evolution

Life on earth began with microbes. As multicellular organisms evolved, their relationship with the unicellular ones became complex. Natural selection forced them to co-evolve. Several microbes made houses inside multicellular organisms.

This is how a primitive *T gondii* must have found its way into a mouse: the microbes reaching the mouse's brain would have survived. Infected mice would have made easy prey for cats and gradually the parasite managed to adapt and reproduce successfully inside the cat's body. The ones that reached other parts of the mouse's body, obviously, could not make it.

But things were not to remain as simple as a cat-mouse game. Humans entered the picture.

To colonize humans, the microbes made some lifestyle changes. They had to match the host's way of life, which was not going to be easy. They were up against one of the most complex and evolved life forms.

Early humans were nomadic—they hunted prey, gathered nuts and fruits, and collected seafood. To understand the nature of the human-microbe relationship at this stage, scientists studied a handful of such tribes left in the world, such as the Bushmen of Africa's Kalahari desert. People in these tribes wander in small, isolated groups; their contact with people from other groups is rare.

If the microbes wanted to survive off such people, they, too, would have had to follow suit, inferred anthropologists. Since the microbes were isolated along with the people, it made no sense to overcome the host's immune system, turn virulent (the relative ability of a pathogen to cause disease) and kill the host that provided it with very few chances of moving on to another one.

There were the impatient ones that did turn virulent, leading to unfavourable consequences for them. After rapidly infecting and killing the entire group, they ran out of hosts, and disappeared themselves. The solution was harmonious co-existence. They engaged in low-intensity warfare, causing mild infections that kept coming back. Those days, killing the host was not wise.

The revolution in food security for people, agriculture, changed drastically the equation with microbes. Farming brought human groups closer. Captive food production meant people had free time on their hands. Communities grew bigger, populations denser.

A 2007 DNA study at the University of Utah, USA, confirmed the pace of human evolution increased after agriculture became widespread. It was time the microbes changed their lifestyle; they became more infectious. As the interactions between people increased, so did the degree of microbial virulence.

Half of Europe was annihilated by the Black Death in the fourteenth century. People were packed like sardines in cities with poor hygiene making conditions ideal for the bubonic plague microbe.

Every community also attracted its own set of migrants. The migrants brought new microbes with them and the community, in turn, gave its own to them. It was a unique barter system—one in which the microorganisms got to travel the globe and diversify.

Agriculture increased the demand for two things: land for farming and livestock for draught, meat and by-products like milk and leather.

More and more forests were cleared for land. This changed how people related to forest and wildlife. Wild animals carried another range of microbes. The destruction of their natural habitats increased the number of human-wildlife interactions. This, in turn, provided the microbes with ample opportunities for switching hosts.

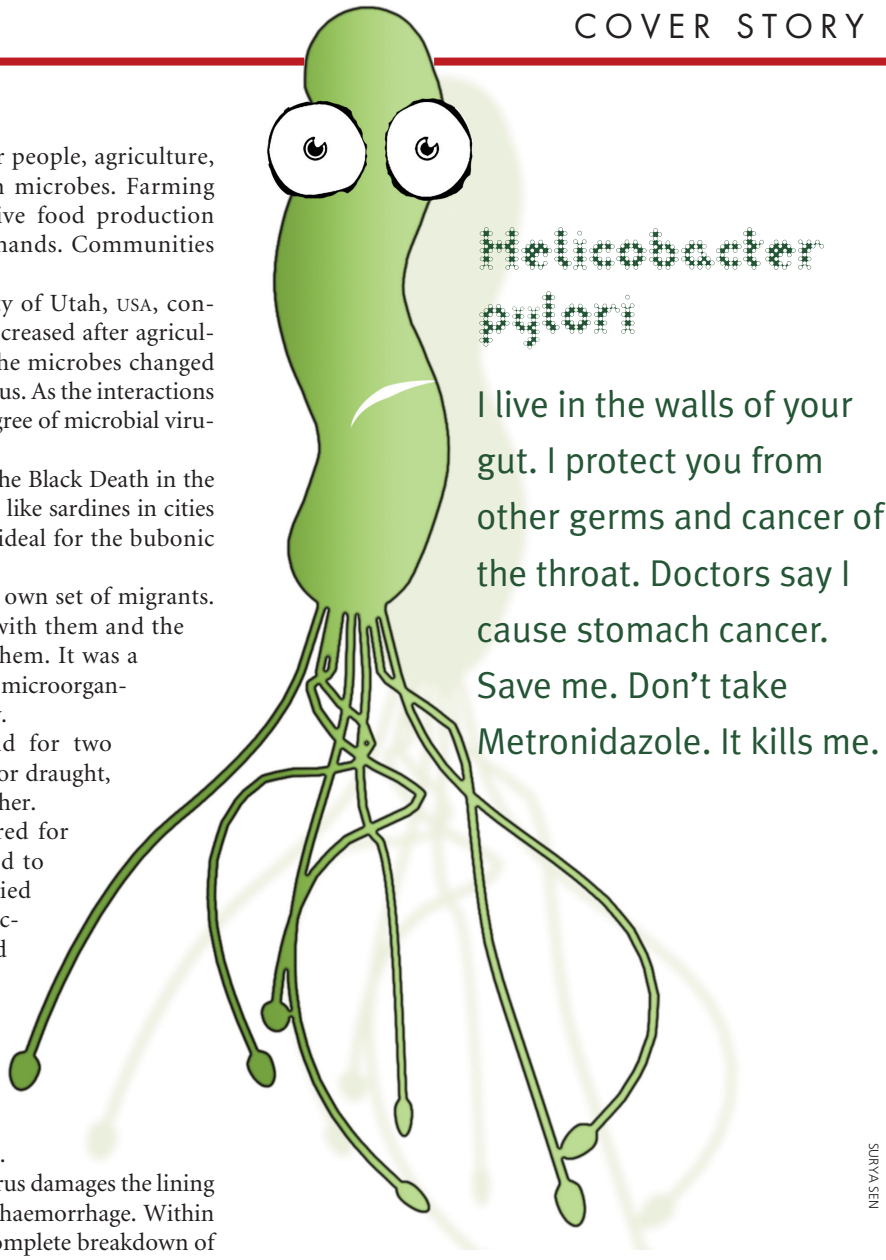
The Ebola virus first struck humans in Zaire after the rainforests were destroyed, in the 1970s. Transmitted through body fluids, this virus damages the lining of the blood vessels and causes internal haemorrhage. Within three weeks the person succumbs to a complete breakdown of body tissues. The natural cycle of the virus is still a mystery; monkeys and bats were thought to be carriers but scientists are unsure. The disease has no cure.

The Human Immuno Deficiency Virus (HIV) is believed to have made the jump from wild monkeys to humans. The monkeys were carrying the Simian Immuno Virus that mutated into the HIV, say some researchers.

Domestication of animals into livestock expanded the microbial horizon further. Of the 1,415 pathogens infecting humans, about 863—more than 60 per cent—were originally animal pathogens.

Some of the common diseases contracted by humans from animals (zoonotic) are hitting headlines every year now. This year it was the swine flu—declared a global pandemic of the highest level by WHO. The virus from pig farms in Mexico travelled the globe. Mad cow disease, avian influenza and SARS (severe acute respiratory syndrome, caused by the coronavirus, an important pathogen of mammals and birds) haven't quite been forgotten yet.

It was believed the cholera bacterium (*Vibrio cholerae*) has one host only: *Homo sapiens*. Now, studies show it is a zoonotic disease. The evidence springs from coastal areas where outbreaks are preceded by zooplankton blooms, indicating zooplanktons like krill act as initial carriers of the bacterium. This year it infected 60,000 people and killed 3,100 in an outbreak in Zimbabwe.



SURYA SEN

From mildly infectious agents to highly virulent germs, microbes have travelled a long way to secure a home in an organism whose world population remains unrivalled; about 134 million people are born every year. And they have succeeded. A peek into the everyday life of the bacterium *Helicobacter pylori* indicates the reason. Scientists have tracked the ways of this microbe for several years now. The medical world has rarely found a person who has lived an entire life without getting infected by this microbe.

The journey within

H pylori is a species common to the human stomach. It can be passed on from the saliva of an infected to a healthy person in cases where food is shared or acquired when one consumes water or food containing contaminated human faeces. The germ colonizes the human stomach and induces chronic gastritis, a long-lasting inflammation of the stomach. More often

than not, the inflammation is low level, and half the carriers do not feel any discomfort.

Two per cent to 20 per cent of people infected by the bacterium develop gastric ulcers which might end in cancer. This makes the microbe a major risk factor for gastric cancer. In 1994, the World Health Organization declared *H pylori* a carcinogen. The medical establishment in the West decided to eradicate it from the human gut. There are signs of their success. *H pylori* is disappearing. But that does not necessarily promise our species gastric bliss. Cases of acid reflux disease and oesophageal cancer are increasing dramatically.

The bacterium has beneficial effects on the human body, said microbiologist Martin Blaser in 1996. It produces alkaline chemicals to neutralize stomach acids, protecting against acid reflux disease, explained Blaser, who works at the New York School of Medicine in the US. He is best known for his work with this spiral-shaped bacterium and how it relates to the human gut. Acid reflux is not an insignificant problem; it can trigger asthma (90 per cent of acid reflux patients have it) and 60 per cent of the oesophageal cancers.

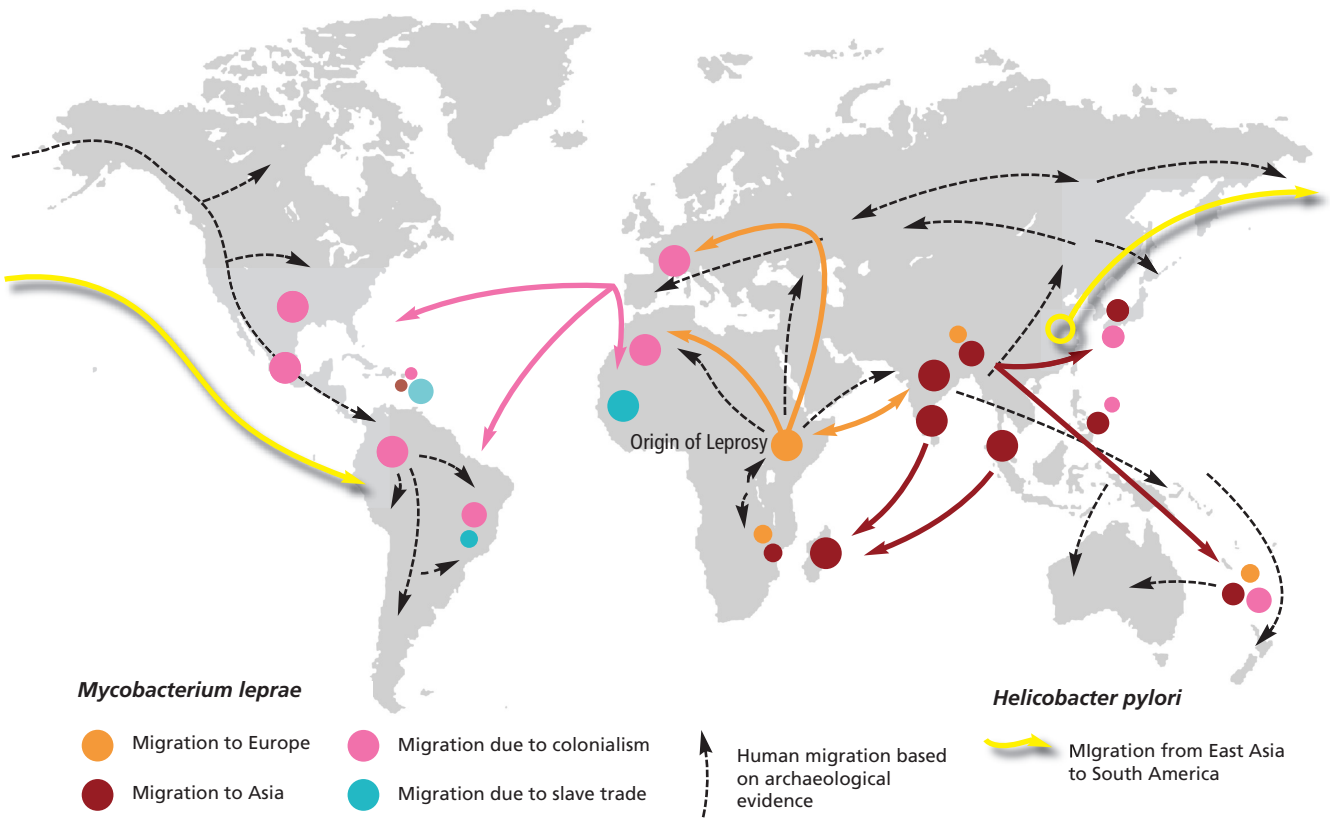
The choice then is between a 60 per cent chance of oesophageal cancer versus less than 20 per cent chance of gastric ulcers. Besides, *H pylori* has a wider role as an essential part of human gastric physiology: it regulates the hormones that control hunger pangs. Namely, ghrelin, which increases appetite, and leptin, which signals the presence of fat to the brain. If leptin malfunctions, one would not know when to stop eating.

The question, though, is: why would the microbe cross the threshold and start helping the host?

Altruism, redefined

Thousands of years ago, when *H pylori* infected people, it would have encountered the body's immune system. Unprepared, the human body would have succumbed to fatal infections initially. This would have resulted in wide-scale deaths—of people and the microbe. Over the years, though, the bacterium would have developed strains that struck truce

Human transport: the means for microbes to travel the world



DNA strands comprise a series of four units (nucleotides). During replication, a stray mutation may cause a unit to replace another. Each individual has many of these single nucleotide polymorphisms (SNPs), as they are called, and this helps create a unique DNA sequence. Hence the SNPs can be used as markers to trace a species' evolution.

The map traces the routes of two microbial species: *Helicobacter pylori* and *Mycobacterium leprae*. The routes corroborate the archaeological evidence of human migration. The SNPs in the DNA of *M leprae*—the leprosy-causing bacterium—showed three strains taking four routes to spread across the world. The findings proved leprosy did not arise in India, as was believed. Of the two common strains of *H pylori*—East Asian and European—the East Asian strain was found in indigenous Venezuelans.

with the immune system. It found safety and shelter in the stomach's mucosa (the organ's inner lining of tissues covered in a thick, sticky fluid called mucus), and returned the favour by preventing the acid reflux disease. But why? Was it altruism? Are microorganisms capable of the kind of altruism that requires expending energy for helping the host? Scientists think not.

Here's the answer they found: the chemicals the microbe produces serve two functions. One, they help the host survive; two, they prevent other pathogens from lodging in the digestive system. This is how *H pylori* tries to monopolize the microbial space available inside the digestive system, furthering the survival of its progeny.

Even among the most beneficial of germs are renegade individuals. They rebel against the existing order. They refuse to perform the beneficial functions. They concentrate their energy on reproduction; their number increases. The day they get the upper hand, the host develops a gastric ulcer. This explains why *H pylori* causes a mild infection in several people and, at the same time, an ulcerous infection in quite a few.

But *H pylori* is not the only microbe that strategizes to own microbial space within the gut. Therefore, try as it might, it cannot always succeed in its game of monopoly.

It's a jungle in there

Nature has billions of microbes and thousands of them inhabit the human gut. The digestive tract is a theatre of intense microbial drama. There is competition within a microbe species as well as between species. Then there is the immune system to watch.

At one moment *H pylori* is in majority, the next it loses to stronger species. And yet a fine balance is maintained—otherwise stomach infections would be an everyday affair. Even cholera epidemics do not happen everyday. What is it that tells the microbes that a truce with the host's immune system is better than virulence? What is it that ensures the host's immune system is always on the alert—from the virulent as well as the non-virulent species?

Natural selection.

Survivor

The host immune system is constantly evolving. It restricts gut microbes within the gut, preventing them from infecting other body parts. More often than not, the rebels within the system are squashed. Over the years, natural selection has favoured the evolution of helpful microbes. Take, for example, species of the *Eubacterium* and *Bifibacterium* groups. They help in the digestion of plant-based foods.

Natural selection also makes sure each strain keeps evolving to carry out the same function in different ways. This is to keep the community going even when the weak bacteria are destroyed by other pathogens, including by viruses that eat bacteria (bacteriophages).

The math adds up to what is called homoeostasis: maintaining a stable metabolism by making minute adjustments to the internal environment. Natural selection makes sure homeostasis prevails—amidst constant ups and downs brought on by competition, changes in the environment, changes in the host's diet, changes in the immune system and pathogen attacks that come and go. They live. We live.

FLORIAN CALMER

Jungle code

The human gut. Theatre of a a microbial war of attrition for gut domination. But, in the end, the gastric universe maintains a fine balance: homoeostasis

Gastric chemistry is one part of the relationship people have with microbes. Scientists are constantly uncovering some fact or the other that emphasizes the role of microbes in human lives.

Stomach microbes, for example, also decide whether or not one will turn out to be fat.

Far-reaching effects

Jeffrey Gordon is a molecular biologist who studies obesity at the Washington University School of Medicine in the US. His research might turn on its head our understanding of obesity. In an experiment in 2006, Gordon introduced microbes from the stomach contents of a fat mouse into a sterile, germ-free rodent; it caused the sterile rodent to rapidly put on weight. When microbes from a lean mouse were introduced into another sterile mouse, it did not gain weight. This is just one of the ways microbes have an impact on human lives.

The human body wears an external suit of millions of microbes. As we change our clothes, our invisible attire of skin microbes changes too. Different fibres—cotton, wool—mean a different set of bacteria. Some skin areas maintain a core microbial population that does not vary over time, like the ears, the nostrils and the creases on either side of the nose. In between the toes alone, there could be as many as 10 million microbes in a square centimetre.

Kevin Lafferty, a marine ecologist with the US Geological Survey goes so far as to suggest that these single-celled creatures may very well be controlling the cultural differences between people. Because cultures arise from the average personality of a community and individual personalities are affected by microbes. In medieval Europe, people who acted strange were accused of being werewolves and sentenced to death. Perhaps they had a spot of *T gondii* or microbes that cause dopamine-induced behavioural changes.

Irritation caused by sexually transmitted diseases, like gonorrhoea, may be responsible for increase in the desire for sex, it has been suggested.

To understand human behaviour, scientists are increasingly looking under the microscope.

We are the microbes we carry

Using genetic analysis, researchers are now busy creating a comprehensive inventory of microbes that come with humans. They are gathering the information under the Human Microbiome Project, an offshoot of the Human Genome Project that mapped the human DNA.

When the human genome map was created, scientists found we have about 20,000 functioning genes, putting us roughly in the same category as worms. Then they realized they had forgotten the trillions of microbes in and on us.

The new exercise can be defined as a 'them-plus-us genome project', one that makes it evident that humans cannot understand themselves fully if they do not know microorganisms that make them who they are. By textbook definition, of course, that implies humans are *Homo sapiens* belonging to the tribe of hominines from a family of hominids in the kingdom of animals.

But is that enough? Could it be people reading this magazine are doing so at the behest of a microbe in their brain?

The bigger picture

Coughing, sneezing and nasal discharge are ways of ridding the body of unwanted matter, it is believed. But maybe not. Maybe these are ways of ensuring the microbe spreads far and wide. A common cold virus can never be lost for good. It is the ability of this virus to manipulate its identity genetically and fool the host's immune system every time it attacks. Researchers across the globe have been trying to overcome this. HIV operates in similar ways.

Both viruses contain an RNA strand instead of DNA; genetic manipulation becomes easier with RNA, scientists say. An HIV positive person can die of a common cold that is a minor inconvenience for an uninfected person.

With science learning about microbes everyday, the idea of human agency will undergo corrections. It will lead to re-examination of the motives of our action. It will also change the way we look at microbes. From seeing them as germs that infect us, we might come to a deeper appreciation of the intrepid microscopic travellers around us, inside us. ■

Fat boy slim

Want to lose some flab? If you are looking for some quick weight loss, the 'Fat Boy Takes It All' is the best option for you. Contact info: I am found in the guts of thin people