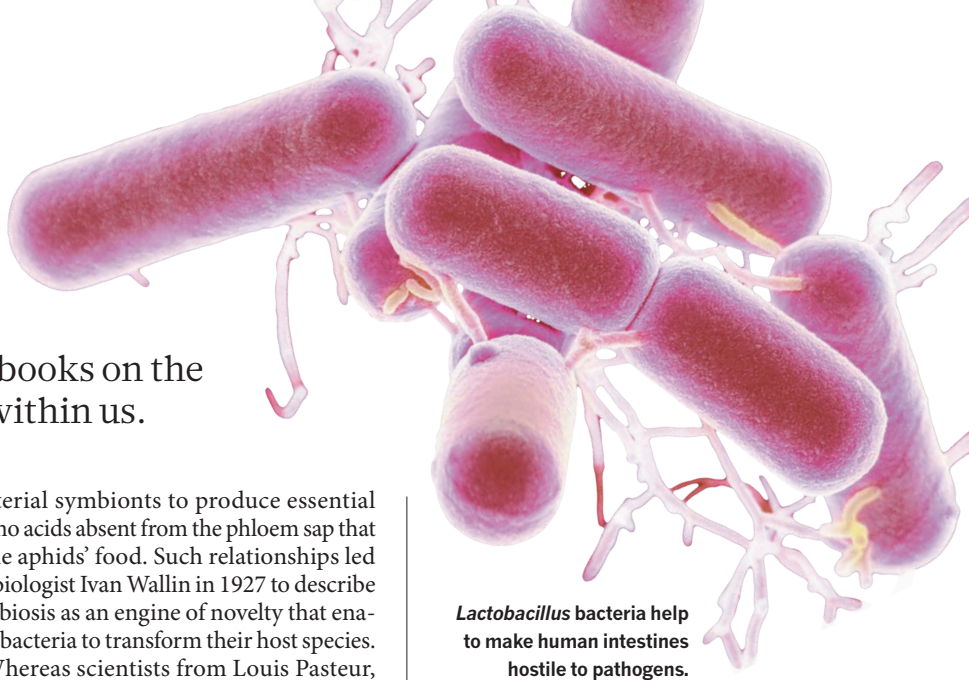
MICROBIOLOGY

Mob rule

Adrian Woolfson examines four books on the microbial universe that churns within us.



Lactobacillus **bacteria help to make human intestines hostile to pathogens.**

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In the early 1990s, molecular biologist Sydney Brenner gave a talk in Cambridge, UK, in which he espoused the merits of sequencing the human genome to fully characterize the human "gene kit". Several years later, in 2001, the first draft sequence of the human genome was released. The assumption was that human form, function and dysfunction would be reduced to a finite and tractable problem. Over time, this vision has been eroded by the discovery of successive Russian-doll-like levels of informational and regulatory complexity, from epigenetics to microRNAs. Genomic protein-encoding genes may represent the surface of a much deeper problem.

The latest assault on Brenner's model of organismal form and function has come from an unexpected quarter. It seems that, instead of being self-contained, the contents of the human gene kit are generously supplemented by a plethora of extraneous components. These riches come from the topsy-turvy world of microorganisms, symbionts whose products bolt onto the more modest collection furnished by their hosts. The implications of this extra informational dimension, and how it interweaves with our genes, are explored in four new books.

In his compelling *I Contain Multitudes*, science writer Ed Yong plunges into the Alice in Wonderland shadow world of the microbes that live in and on us. As he reminds us, the 30 trillion cells in the human body are effortlessly outnumbered by the 39 trillion or so microbial cells that lurk within it. Our own genomes muster 20,000 protein-encoding genes; our uninvited guests may collectively field an impressive 10 million. We know this thanks to metagenomics — the method of sequencing short, species-specific stretches of RNA pioneered by biophysicist Carl Woese in the late 1960s — which helps to define the genomic architecture of our microbial communities.

Bacteria confer unique properties on their hosts. Their collective genes, and capacity for rapid evolution through high rates of mutation, horizontal gene transfer and rapid replication, render them virtuosos of biochemistry, and providers of rich metabolic creativity. This gives organisms a versatility far above that afforded by their own genes. Aphids, for example, rely on *Buchnera*-strain bacterial symbionts to produce essential amino acids absent from the phloem sap that is the aphids' food. Such relationships led US biologist Ivan Wallin in 1927 to describe symbiosis as an engine of novelty that enables bacteria to transform their host species.

Whereas scientists from Louis Pasteur, pioneer of germ theory, to penicillin-developer Howard Florey have taught us to fear microbes, Yong argues that we must nurture them, appreciating that they may help us to develop into what we are. The human microbiome should be viewed as a distributed organ, performing functions as essential as those of our liver, lungs or kidneys.

Intriguingly, Yong argues that human immune cells are akin more to park rangers than to xenophobes, carefully wrangling the microbial zoo, modulating its population dynamics and responding to its chatter. The degradation and collapse of coral reefs in warm, acidic waters is due not only to direct effects of global warming, but also to the disruption of relationships in microbial communities. Likewise, Yong suggests that some human diseases result from alterations to bacterial community dynamics, triggering abnormalities in internal microbial ecology and cooperativity. An example of this is obesity, which seems, in part, to result from an imbalance of gut microbes. Obese individuals have more bacteria from the phylum Firmicutes and fewer from the genus *Bacteroides* than lean ones, and a relative lack of *Akkermansia muciniphila*. It was shown in 2013 that microbes from lean mice can make obese mice lose weight (A. Everard *et al. Proc. Natl Acad. Sci. USA* **110,** 9066–9071; 2103).

Yong goes on to explain how the dialogue between cells and resident microbes may impact organismal development. Hawaiian bobtail squid (*Euprymna scolopes*) adopt their mature form only in the presence of the luminescent bacterium *Vibrio fischeri*, which colonizes the squid's light organ. Human breast milk contains indigestible oligosaccharides, the favoured food of *Bifidobacterium longum infantis*, which releases short-chain fatty acids that influence the permeability of an infant's gut cells.

In *The Human Superorganism*, immunotoxicologist Rodney Dietert goes further, asserting that *Homo sapiens* is a superorganism containing thousands of microbial species. He argues that the biology of microbes will eventually challenge our view of what it means to be human, and lead to the identification of therapeutic agents. In his vision, humans are "microbial storage machines" designed to pass microorganisms to future generations. Our "second genome" — the genes encoded by our microbiome — resides in a thriving bacterial community that he compares to the diversity of a tropical rainforest. Even in the age of genome-editing tools such as CRISPR, it remains challenging to modify the human genome. Dietert is astute, however, in suggesting that microbial genomes could be engineered to introduce functionalities and tackle human diseases. The ability of microbial metabolites to manipulate the expression of human genes has already been established: sodium butyrate, for example, helps to control the switch from embryonic to fetal haemoglobin.

Not content to cruise around their luxury human condos, microorganisms also hack into our nervous systems. In her eye-opening, entertaining and slightly disconcerting *This is Your Brain on Parasites*,

I Contain Multitudes: The Microbes Within Us and a Grander View of Life
ED YONG
Ecco: 2016.

The Human Superorganism: How the Microbiome Is Revolutionizing the Pursuit of a Healthy Life
RODNEY DIETERT
Dutton:2016.

This Is Your Brain on Parasites: How Tiny Creatures Manipulate Our Behavior and Shape Society
KATHLEEN MCAULIFFE
Houghton Mifflin Harcourt: 2016.

The Mind–Gut Connection: How the Hidden Conversation Within Our Bodies Impacts Our Mood, Our Choices, and Our Overall Health
EMERAN MAYER
Harper Wave: 2016.

journalist Kathleen McAuliffe contends that our minuscule passengers act like puppet masters, manipulating how we think, feel and act. I will think of cats differently now that I am aware that their parasite *Toxoplasma gondii* may have the ability to affect human behaviour, and is implicated in mental illnesses such as schizophrenia. Men harbouring this parasite are, furthermore, more inclined to break rules, and are more reserved and suspicious. McAuliffe ingeniously suggests that the psychoactive chemicals produced by microbes could be used to develop mind-altering medicines.

Focusing on how the microbiome may cause chronic conditions such as persistent pain and irritable bowel syndrome, gastroenterologist Emeran Mayer's *The Mind–Gut Connection* depicts the brain, the gut and its microorganisms as a unitary structure tightly knit, anatomically and chemically. He asserts, albeit with rudimentary evidence, that the enteric nervous system — the mesh of neurons that governs the gastrointestinal system — functions as a mini-brain, relaying sensory information from the gut to the central nervous system. It was fascinating to learn that microbes contain ancient versions of many signalling peptides and hormones found in the human alimentary tract, including noradrenaline, serotonin and endorphins. That may argue in favour of his thesis. Mayer speculates that early programming errors in the putative brain–gut–microbiome axis can result in medical conditions that might benefit from treatment with probiotics.

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We are descended from microbes, have evolved around them, and incorporate elements of them into our cells. Microbiome profiling is certain to become as routine as blood testing, and the extensive treasure chest of bacterial molecules will doubtless be used to change the way we are. Evidence suggests that our microbial companions may even influence our responses to important medicinal agents, such as the anti-PD-L1 and anti-CTLA4 drugs that reinvigorate the immune systems of people with cancer. Several regional initiatives, including the US Human Microbiome Project and National Microbiome Initiative, have been established to study the human microbiome. The complexities of cataloguing, mapping and characterizing this biology on a worldwide scale promise to make sequencing the human genome look easy. A global programme seems to beckon. ■

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