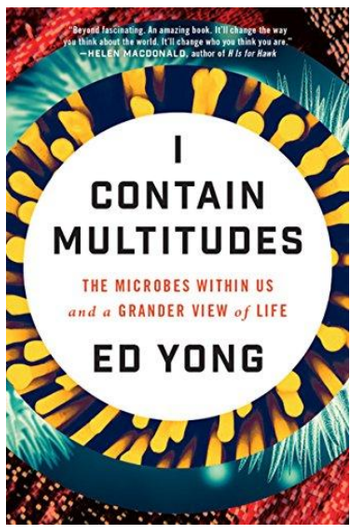



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**I Contain Multitudes: The Microbes Within Us and a Grander View of Life**

van Yong, Ed

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> Let me stress: all the visible organisms that we're familiar with, everything that springs to mind when we think of "nature", are latecomers to life's story. They are part of the coda. For most of the tale, microbes were the only living things on Earth. From March to October in our imaginary calendar, they had the sole run of the planet. During that time, they changed it irrevocably. Bacteria enrich soils and break down pollutants. They drive planetary cycles of carbon, nitrogen, sulphur and phosphorus, by converting these elements into compounds that can be used by animals and plants and then returning them to the world by decomposing organic bodies. They were the first organisms to make their own food, by harnessing the sun's energy in a process called photosynthesis. They released oxygen as a waste product, pumping out so much of the gas that they permanently changed the atmosphere of our planet. It is thanks to them that we live in an oxygenated world. Even now, the photosynthetic bacteria in the oceans produce the oxygen in half the breaths you take, and they lock away an equal amount of carbon dioxide.2 It is said that we are now in the Anthropocene: a new geological period characterised by the enormous impact that humans have had on the planet. You could equally argue that we are still living in the Microbiocene: a period that started at the dawn of life itself and will continue to its very end. Indeed,

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> After eukaryotic cells evolved, some of them started cooperating and clustering together, giving rise to multicellular creatures, like animals and plants. For the first time, living things became big – so big that they could host huge communities of bacteria and other microbes in their bodies.6 Counting such microbes is difficult. It's commonly said that the average person contains ten microbial cells for every human one, making us rounding errors in our own bodies. But this 10-to-1 ratio, which shows up in books, magazines, TED talks, and virtually every scientific review on this topic, is a wild guess, based on a back-of-the-envelope calculation that became unfortunately enshrined as fact.7 The latest estimates suggest that we have around 30 trillion human cells and 39 trillion microbial ones – a roughly even split. Even these numbers are inexact, but that does not really matter: by any reckoning, we contain multitudes.

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> There are fewer than 100 species of bacteria that cause infectious diseases in humans;8 by contrast, the thousands of species in our guts are mostly harmless. At worst, they are passengers or hitchhikers. At best, they are invaluable parts of our bodies: not takers of life but its guardians. They behave like a hidden organ, as important as a stomach or an eye but made of trillions of swarming individual cells rather than a single unified mass. The microbiome is infinitely more versatile than any of our familiar body parts. Your cells carry between 20,000 and 25,000 genes, but it is estimated that the microbes inside you wield around 500 times more.9 This genetic wealth, combined with their rapid evolution, makes them virtuosos of biochemistry, able to adapt to any possible challenge. They help to digest our food, releasing otherwise inaccessible nutrients. They produce vitamins and minerals that are missing from our diet. They break down toxins and hazardous chemicals. They protect us from disease by crowding out more dangerous microbes or killing them directly with antimicrobial chemicals. They produce substances that affect the way we smell. They are such an inevitable presence that we have outsourced surprising aspects of our lives to them. They guide the construction of our bodies, releasing molecules and signals that steer the growth of our organs. They educate our immune system, teaching it to tell friend from foe. They affect the development of the nervous system, and perhaps even influence our behaviour. They contribute to our lives in profound and wide-ranging ways; no corner of our biology is untouched. If we ignore them, we are looking at our lives through a keyhole.

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> These concepts can be deeply disconcerting. Independence, free will, and identity are central to our lives. Microbiome pioneer David Relman once noted that “loss of a sense of self-identity, delusions of self-identity and experiences of ‘alien control’” are all potential signs of mental illness.26 “Small wonder that recent studies of symbiosis have engendered substantial interest and attention,”. But he also added that “[Such studies] highlight the beauty in biology. We are social creatures and seek to understand our connections to other living entities. Symbioses are the ultimate examples of success through collaboration and the powerful benefits of intimate relationships.” I

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> Microbes had effectively been rediscovered, and were immediately cast as avatars of death. They were germs, pathogens, bringers of pestilence. Within two decades of Koch's work on anthrax, he and many others had discovered the bacteria behind leprosy, gonorrhoea, typhoid, tuberculosis, cholera, diphtheria, tetanus, and plague. As with Leeuwenhoek, new tools led the way: better lenses; ways of growing pure cultures of microbes on plates of jelly-like agar; and new stains that helped microscopists to spot and identify bacteria. From identification, they skipped straight to elimination. Inspired by Pasteur, British surgeon Joseph Lister started using antiseptic techniques in his practice, forcing his staff to chemically sterilise their hands, instruments, and operating theatres and sparing countless patients from raging infections. Others searched for ways of blocking bacteria in the name of curing disease, improving sanitation, and preserving food. Bacteriology became an applied science, which studied microbes in order to repel or destroy them. It didn't help that just before this wave of discoveries, in 1859, one Charles Darwin had published On the Origin of Species. "Through this historical accident, the germ theory of disease developed during the gory phase of Darwinism, where the interplay between living things was regarded as a struggle for survival, when one had to be friend or foe, with no quarter given," wrote microbiologist René Dubos.9 "This attitude moulded, from the beginning, all later attempts to control microbial diseases. It led to a kind of aggressive warfare against the microbes, aimed at their elimination from the sick individual and the community." This attitude persists. If I went to a library and lobbed a microbiology textbook out the window, I could easily concuss a passer-by. If I tore out all the pages that dealt with beneficial microbes, I could just about give someone a nasty paper cut. The narrative of disease and death still dominates our view of microbiology. While the limelight-hogging germ theorists were identifying one deadly pathogen after another, other groups of biologists were toiling on the sidelines on work that would eventually cast microbes in a very different light.

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> The cells of animals such as many sea anemones and flatworms also turned out to contain algae, while those of carpenter ants harboured living bacteria. The fungi that grow on tree roots, long thought to be parasites, were revealed as partners that provide nitrogen in exchange for carbohydrates. This type of partnership gained a new term – symbiosis, from the Greek for 'together' and 'living'.13 The word itself was a neutral one, implying any form of coexistence. If one partner benefited at the expense of the other, it was a parasite (or a pathogen if it caused disease). If it benefited without affecting its host, it was a commensal. If it benefited its host, it was a mutualist. All these styles of coexistence fell under the rubric of symbiosis.

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> These concepts emerged at an unfortunate time. In the shadow of Darwinism, biologists were talking of survival of the fittest. Nature was red in tooth and claw. Thomas Huxley, Darwin's bulldog, had compared the animal world to a "gladiator's show". Symbiosis, with its themes of cooperation and teamwork sat uneasily within this framework of conflict and competition. Nor did it fit with the idea of microbes as villains. Post-Pasteur, their presence had become a sign of sickness, and their absence a defining trait of healthy tissue. In 1884, when Friedrich Blochmann first saw the bacteria of carpenter ants, the idea of harmless resident microbes was so counter-intuitive that he performed linguistic somersaults to avoid describing them as what they were.14 "Plasma rodlets," he called them, or "very conspicuous fibrous differentiation of the egg plasma". It took him years of rigorous investigation before he finally took a stand: "One can scarcely do otherwise than declare these rodlets to be bacteria," he finally wrote in 1887. Meanwhile, other scientists had noticed that the guts of humans and other animals also contained legions of symbiotic bacteria. They caused no obvious disease or decay. They were just there – the "normal flora". "With the advent of animals . . . it was inevitable that bacteria should from time to time be caught up on their bodies," wrote Arthur Isaac Kendall, a pioneer in the study of gut bacteria.15 The human body was just another habitat, and Kendall felt that its microbes deserved to be studied, rather than crushed or suppressed. That was easier said than done. Even then, it was clear that our microbes existed in dispiritingly large communities. Theodor Escherich, who discovered E. coli, the bacterium that has become a mainstay of laboratory science, once said, "It would appear to be a pointless and doubtful exercise to examine and disentangle the apparently randomly appearing bacteria in normal feces and the intestinal tract, a situation that seems controlled by a thousand coincidences."

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> On the one hand, Metchnikoff said that intestinal bacteria produce toxins that cause illness, senility, and ageing and were "the principal cause of the short duration of human life". On the other, he also believed that some microbes could prolong life. In this, he was inspired by Bulgarian peasants, who regularly drank soured milk and lived well past the age of 100. The two traits were connected, said Metchnikoff. The fermenting milk contained bacteria, including one that he called the Bulgarian bacillus. These made lactic acid, which killed the harmful life-shortening microbes in the peasants' intestines. Metchnikoff was so convinced by this idea that he started regularly quaffing sour milk himself. Others were so convinced by Metchnikoff – a respected scientist – that they did the same. (His claims even started a fashion for colostomy, and inspired Aldous Huxley to write After Many a Summer, in which a Hollywood tycoon injects himself with carp guts to alter his gut microbes and achieve immortality.) Humans had, of course, been drinking fermented dairy products for thousands of years, but they were now doing so with microbes in mind. This fad outlasted Metchnikoff himself, who died of heart failure at the age of 71.

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> All of which makes for a very different view of immunity than the classical portrait, which is all about destroying microbes that threaten to make us sick. As I write this, Wikipedia still defines the immune system as “a system of biological structures and processes within an organism that protects against disease”. If the system activates, it is because it has sensed a pathogen – a threat that it then wipes out. To many scientists, however, warding off pathogens is just a bonus trick. The immune system’s main function is to manage our relationships with our resident microbes. It’s more about balance and good management than defence and destruction.

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> And breast milk? German was right: it’s far more than a bag of chemicals. It nourishes baby and bacteria, infant and infantis alike. It’s a preliminary immune system that thwarts more malevolent microbes. It is the means by which a mother ensures that her children have the right companions, from their first days of life.39 And it prepares the baby for life ahead.

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> An important lesson emerged: microbes matter but so do we, their hosts. Our guts, like all ecosystems, aren’t defined just by the species within them but also by the nutrients that flow through them. A rainforest isn’t just a rainforest because of the birds, insects, monkeys, and plants within it, but also because ample rain and sunlight fall from above, and bountiful nutrients lurk in the soil. If you threw the forest’s inhabitants into a desert, they would fare badly. Gordon’s team have learned that lesson several times over in the lab – and also in Malawi.

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> Scientists have long suspected a microbial culprit behind IBD, but despite extensive investigations, they haven't successfully accused any particular pathogen. It's more likely that the problem, as with Rohwer's corals and Gordon's malnourished kids, lies in a community of normal microbes gone rogue. The gut microbiomes of IBD patients certainly differ from those of their healthy peers, but the list of potential suspects seems to change with every new study – unsurprisingly, perhaps, since IBD is so diverse. Nonetheless, some broad patterns have consistently emerged. The IBD microbiome tends to be less diverse and less stable than its healthier counterparts. It lacks anti-inflammatory microbes, including fibre-fermenters like Faecalibacterium prausnitzii and B. fragilis. In their place are blooms of inflammatory species like Fusobacterium nucleatum and invasive strains of E. coli. These microbes clearly play a crucial role yet no single species makes or breaks the ecosystem. The condition looks like a disease of dysbiosis. The entire community becomes more inflammatory, dialling the host's immunostat up to the twitchiest of settings. How did these communities come about? Was it something dietary that nourished inflammatory species? Antibiotics that killed off the anti-inflammatory ones? Genetic variants that altered the host's immune system, disrupting its ability to manage its microbes? The last of these seems possible: Wendy Garrett has shown that mutant mice which lack important immune genes end up with unusual communities of gut microbes, and those communities can trigger signs of IBD when transplanted into healthy mice. This also suggests that the microbiome can contribute to the disease, rather than simply reacting to its presence. But do these microbes actually instigate inflammation, or do they simply perpetuate it once it takes hold? If they are perpetuators, what initially inflamed the gut? An infection? An environmental toxin? Some foodstuff that disrupted the lining of the gut? Genetic variants that had already made the host's immune system prone to overreacting?

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> Herbert "Skip" Virgin published a case study that beautifully supports this idea.18 He worked with mice that had a genetic mutation common in people with Crohn's disease. Those rodents developed inflamed guts, but only if they were infected by a virus that knocked out part of their immune system, and were exposed to an inflammatory toxin, and had a normal set of gut bacteria. If any of these triggers was missing, the mice stayed healthy. It was the combination of genetic susceptibility, viral infection, immune problems, environmental toxin, and their microbiome that gave them IBD. This complexity helps to explain why the disease is so variable. Every case has its own convoluted history of hits. These

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> B. infantis, the infant coloniser that we nourish through breast milk, might also be in jeopardy. David Mills's team recently noticed that B. infantis is present in 60 to 90 per cent of infants from developing countries like Bangladesh or Gambia, but just 30 to 40 per cent of infants in developed nations like Ireland, Sweden, Italy, and the USA.39 Bottle-feeding can't explain this difference, since almost all the babies represented in the team's data set were breastfed. C-sections aren't responsible either, since most of the Bangladeshi infants – the ones most likely to carry B. infantis – were born through this route. In lieu of a solid explanation, Mills has a speculative one. He notes that B. infantis seems to disappear from the gut during adulthood, which means that mothers may not be able to pass it on to their children. This wasn't a problem for most of human history because women would help to raise and nurse each other's babies. "There were always small children being nursed at all times, and they were passing B. infantis between themselves and their mothers," says Mills. But as parenting became more isolated, those chains of transmission snapped. Perhaps this is why the microbe has started disappearing from Western populations, even among breastfed babies. Breast milk can't nourish it if it isn't around in the first place. Whether this is true or not, it certainly seems that B. infantis is edging towards the microbial endangered species list.

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> Have we become less healthy, as a result? There's some evidence that a diverse microbiome is better at resisting invaders like C. difficile, and that low diversity often accompanies diseases. In one study, a large European team, led by Oluf Pedersen, measured diversity by counting the number of bacterial genes in the guts of almost 300 people.41 Compared to volunteers with high gene counts, those with low counts were more likely to be obese, and to show signs of inflammation and metabolic problems. Then again, their dwindled communities may be a consequence of poor health, rather than its cause. As yet, no one has shown that people with less diverse microbiomes are more prone to acquiring disease. And there are cases where people with diverse microbiomes are more likely to carry certain intestinal parasites.42

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> There are two likely answers, and both provide valuable lessons. First, it is not enough to infuse an animal with bacteria and hope for the best. Microbes are living things. They need to eat. Oxalobacter eats nothing but oxalate, and people with kidney stones often go on an oxalate-free diet. They can ingest the bacterium, but it will instantly starve.24 Conversely, farmers are told to feed their herds on Leucaena for at least a week before drenching them in Synergistes. That way, the inoculated bacteria have enough food to digest. Substances that selectively nourish beneficial microbes are called prebiotics – a term that could include oxalate or Leucaena but normally describes plant carbohydrates like inulin, which are purified and packaged as supplements.25 These substances can increase the numbers of important microbes like F. prausnitzii or Akkermansia, and perhaps lower appetite and reduce inflammation. Whether they need to be taken as supplements is another matter. We have already seen that what we eat can substantially change the microbes in our gut, and prebiotics like inulin are in plentiful supply in onions, garlic, artichokes, chicory, bananas and other foods. HMOs, those microbe-feeding sugars

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> O’Neill marvels at how far the study of Wolbachia has come. “We were a fairly innocent lab that studied symbiosis,” he says. “It was an area of basic science, but something wonderful and applied will come out of it.” As well as thwarting dengue virus, Wolbachia stops mosquitoes from carrying the Chikungunya and Zika viruses or the Plasmodium parasites that cause malaria; a team of Chinese and American scientists has now successfully melded the microbe with the Anopheles mosquito that spreads malaria. 69 And yet more researchers are trying to use Wolbachia to control insect pests like tsetse flies, which spread sleeping sickness, and bed bugs, which spread sleepless nights. “This is just part of the whole new way of thinking, about the microbial ecology of organisms and about how that relates to disease,” says O’Neill. In

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> The legendary life-saver Florence Nightingale advocated as much some 150 years earlier. She had no explicit knowledge of the microbiome but, during the Crimean War, she noticed that patients would recover from infections more readily if she opened a window. “Always, air from the air without, and that, too, through those windows through which the air comes freshest,” she wrote. This makes perfect sense to an ecologist: fresh air brings in harmless environmental microbes that take up space and exclude pathogens. But the idea of deliberately inviting microbes into a room deeply contradicts our assumptions about how hospitals should work. “The model that we’re working with, in hospitals and also many different buildings, is to keep the outdoors out,” says Green. It’s such an ingrained attitude that when she did her study, she had to convince the hospital to let her pry some windows open – they had been bolted shut.