Microbes as Menaces, Mates & Marvels

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Abstract: The conventional understanding of microbes as causative agents of disease has led us to fear them and to consider them our deadly enemies. Much less appreciated are the central roles microbes play in shaping the environment and in maintaining plant, animal, and human health. All metazoan organisms – organisms that we can see with the naked eye – exist in lifelong partnerships with vast microbial communities. These "microbiomes" supply metazoans with essential life processes that are not encoded in nonmicrobial genomes. Recent work in microbiology has revealed that microbes, like metazoans, have specific body plans and sensory systems, that they can communicate with each other, and that they orchestrate collective behaviors. Investigations of these ancient yet enduring processes are uncovering the fundamental design principles of life. Microbes are also storehouses of new molecules, biochemical pathways, and materials with medical, industrial, and agricultural relevance. Scientists are harnessing these microbial products in efforts to confront humanity's most pressing problems. This essay explores the wonder, complexity, power, and utility of microbes in the twenty-first century.

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You may think you've seen everything, but in fact, most of the world is invisible to us. It is composed of, and was constructed by, microbial organisms. Microbes are single-celled organisms too small to see with the naked eye. They include archaea, fungi, and protists, but overwhelmingly, they are bacteria. For billions of years these invisible critters, our forefathers, have been shaping the Earth and making it a suitable place for us to live. Higher organisms – all plants, invertebrates (including insects), and vertebrates (including humans) – occupy only a sliver of the world. We live exclusively within narrow ranges of temperature, air pressure, atmosphere, pH, and nutrient sources. Microbes, by contrast, have adapted to, inhabited, exploited, and tamed every niche on Earth. They thrive under extreme pressure and at high temperatures miles below the ocean surface, enveloped in the sulfurous smoke spewing from thermal vents. They live encrusted in the sediments of lakes beneath ice caps that have not thawed in more than ten thousand years. There, they exist in a world that has not seen the light of day or taken a breath from the atmosphere for millennia. Microbes flourish at the pH of battery acid, and in this hostile environment, they produce the stunning, gemstone-colored pools found in Yellowstone National Park. Unlike the human diet, which is narrow and invariant, microbes consume, well, everything. They eat the regular stuff – proteins and carbohydrates – but also radioactivity, rocks, crude oil, rust, paint, dirt, and wood. Every plant, animal, and human requires a vast community of commensal microbes working 24/7 to keep it alive and healthy.

As the foundation of nineteenth- and twentieth-century biological science, microbes enabled scientists to dismiss the possibility of spontaneous generation. They inspired Robert Koch's postulates, revealing disease causation for the first time. Microbes gave scientists a way to deduce the famous DNA double helix; they showed that heritable information is encoded in units of genes and that the essential parts of life are DNA, RNA, proteins, and lipids. Ironically, these paradigm-changing discoveries also made the microbial sciences passé. By the mid-twentieth century, microbes were generally thought to have been picked clean. Science instead focused on more "complex" problems: namely, embryonic development, neurocircuitry, and cancer.

However, much more remains to be gleaned from examining the lives and personalities of microbes. Microbiologists recently demonstrated that microbes possess the features of metazoans: they have precise body plans and sophisticated sensory mechanisms; they communicate with each other; and they amass their numbers in order to act collectively. Investigations of life's oldest organisms are teaching us how these processes operate in metazoans. Further, microbiologists are mining microbes for new genes, molecules, and biochemical pathways – work that holds great promise for medical, agricultural, industrial, and technological applications. This exciting research has coincided with the alarming rise of antibiotic-resistant microbial pathogens across the planet. New research directions, coupled with the recurrence of the microbial threat, have propelled microbiology once again to the forefront of science. This essay explores the wonder, complexity, power, and utility of microbes in the twenty-first century.

We divide all life into two categories: prokaryotes and eukaryotes. Every eukaryotic cell has a nucleus; prokaryotic cells do not. Prokaryotes are further divided into archaea and bacteria.[1] We suspect that Earth's first organisms were archaea because they thrive in habitats mirroring those of early Earth: hot, salty, anoxic, and metal-rich. Bacteria live in more temperate places. Eukaryotes include fungi, protists, plants, invertebrates, and vertebrates. Eukaryotic species are also predominantly microbial, which means that you haven't seen most of them, either.

The Earth is about 4.5 billion years old.[2] At present, the oldest known prokaryotic fossil dates back 3.5 billion years. The oldest known eukaryotic fossil, a microbe, is about 1.7 billion years old. By contrast, the most ancient macroscopic fossil is only about 650 million years old.[3] Thus, the better part of the world's living history is exclusively microbial, and it is predominantly prokaryotic. Archaea had their day back when the Earth was in chaos. They have trouble living in the presence of oxygen, so when the planet became oxygenated roughly 2.5 billion years ago, archaea were relegated to the most hostile locations remaining on the planet. Bacteria, on the other hand, flourished because they adapted to both oxygenated and anoxic environments. They prevailed and made the world we know. Indeed, the vast majority of biological change and diversification has occurred and continues to occur in the unseen bacterial world.

The Gates Foundation, the National Academy of Engineering, the Plant Sciences and Environmental Sciences divisions of the National Research Council, and other groups spanning diverse scientific disciplines have proposed sets of "grand challenges" facing humanity. Strikingly, the clear consensus among leading scientists is that the microbial sciences are key to confronting the majority of these challenges.[4] In the recent National Academies report *A New Biology for the 21st Century*, for example, all four of the suggested grand challenges have significant microbiological components.[5] The overarching scientific imperative is to ensure that microbes' potential contributions to a healthy planet are fully realized. There are three main reasons why the science world is directing its focus toward microbes.

Microbes are Menaces. The top killers of humans are microbes. Chief among these are HIV (a virus), malaria (a eukaryotic microbe), and tuberculosis (a bacterium), which collectively claim more than five million lives every year. The next biggest killers are microbes that cause diarrheal diseases and pneumonias, which lead to another two million human deaths per year.[6] At present, these microbial scourges are restricted to underdeveloped regions. If you live in a developed country, there is little chance (at least for now) that you will die of an infectious disease unless you are elderly and frail. Residents of developed countries will overwhelmingly die from heart disease or cancer. Antibiotic control of bacterial pathogenicity is one of the greatest advances ever made to improve human health. This success came seventy-five years ago, and the bacterial problem was thought to be solved. Classic bactericidal drugs are excellent: they have few side effects and are broad-spectrum. Because of these qualities, only incremental improvements to existing drugs have been made in the past forty years. During this same time frame, pathogenic bacteria emerged across the globe, and many of them are resistant to conventional antibiotics. This predicament has been fueled by the widespread use of bactericidal drugs. Multidrug-resistant bacteria are now prevalent around the world, and they contribute greatly to the increasing microbial threat to human health.

Microbes are Mates. Every plant and animal (including insects and humans) depends on microbial partners for life because they provide essential functions that are not encoded in metazoan genomes.[7] Consider the human-microbe relationship: there are ten times more microbial cells than human cells and one hundred times more microbial genes than human genes in and on every person. These metrics suggest that, at best, you are 10 percent human (in terms of cells), and more realistically, you are only 1 percent human (in terms of genes).[8] The remainder of "you" is microbial. Not only do you inherit your human genome from your parents, you also inherit, during the first few months of life, your microflora. These vast communities of microbes – your "microbiome" – have effects on metabolism, immunity, and behavior[9]; and properly balanced, invisible interactions with your microbes are essential to your well-being. Microbes cover you in a thin biofilm that serves as invisible body armor protecting you from environmental insults. Microbes help digest your food, provide your vitamins, aid in the development of your blood vessels, and educate your immune system. Microbes also occupy every empty nook and cranny in and on you to make that space unavailable to pathogens that try to gain access. A profound microbial component has been shown in a growing number of ailments including allergies, asthma, obesity, cancer, and autoimmune disorders.[10]

Microbes are Marvels. Microbes hold answers to the world's most challenging issues: food, health, energy, and the environment. They represent a virtually inexhaustible source of biodiversity, metabolic ingenuity, and natural products. They are the workhorses for the production of industrial catalysts and pharmaceuticals ranging from insulin, to antibiotics, to vaccines, to probiotics. Microbes are the most promising source for the next generation of environmentally and politically neutral fuels. They provide the chassis and parts sets for synthetic biology, a new field of science devoted to developing robust, industrial-scale biological machines and processes. They are required partners for all plant growth, making microbes an untapped resource for adapting crops to grow in more places with fewer inputs. Microbes are critical drivers of Earth's biogeochemical cycles and are therefore important players in climate change, both as sentinels and, potentially, as mitigators.[11]

To be fair, microbes also contribute enormously to greenhouse gas emissions stemming from the reactions they carry out in the industrialized livestock industry.[12] For example, cattle require microbes to digest their food, and the consequence of these microbial fermentation reactions is production of methane, a greenhouse gas.[13] Further, the possibility exists that, as Earth's temperature rises, the Arctic permafrost could melt, giving microbes access to the vast stores of organic carbon trapped beneath. If this occurs, microbes could release huge amounts of greenhouse gases.[14] Frankly, however, both of these predicaments were caused by humans; and because microbes cannot resist easy access to food, the microbes are only indirectly to blame. This smudge on their reputation does not make microbes any less marvelous because microbes also have the ability to consume, sequester, and degrade greenhouse pollutants.

Finally, microbes are the ultimate model organisms for molecular and cellular biology, making possible the spectacular advances in health and biotechnology that have come from those disciplines.

Microbes are the research frontier for the twenty-first century. Two burgeoning bacterial research fields – bacterial cell biology and bacterial cell-to-cell communication – are exemplars of the progress microbiologists are making in understanding biological complexity and in generating promising possibilities for technological applications.

Keeping House: Unseen Orderliness and Complexity. For nearly all of the four hundred years that humans have known about bacteria, they have been considered amorphous bags of goop. Eukaryotes have long been known to possess a subcellular architecture in which DNA, RNA, and proteins are localized to the right place at the right time. Bacteria, on the other hand, were thought too small to be significantly organized. Consequently, cell biology, the scientific discipline that aims to understand cellular organization, was generally restricted to eukaryotes. Remarkable recent advances in imaging technology, however, have made it possible for scientists to peer into bacterial cells as they traditionally peered into bigger eukaryotic cells.[15] We see that bacteria are decidedly organized, and they are loaded with molecular machinery that is breathtaking in its design, complexity, and efficiency.[16]

Bacteria move by means of miniature motors that operate like boat engines complete with propellers.[17] These motors use the molecule ATP as fuel, and this contraption allows cells to swim through liquid at a pace that, given their size, would out-lap Olympian Michael Phelps ten to one. Bacteria propel themselves more than ten body-lengths per second.[18] Phelps, during his world-record-setting Olympic freestyle swim, moved at about one body-length per second. When bacteria settle out of their liquid world onto a surface – including ocean sediments, oil slicks, and the bodies of larger organisms – they sense that they need another form of transportation. They then sprout thousands of appendages allowing them to crawl spider-like across surfaces. When they leave the surface to return to the liquid environment, these legs fall off and the boat propeller reengages.[19] They are the perfect amphibious vehicles.

Bacteria possess similarly stunning equipment to control information flow, inheritance, and reproduction. Marvelous multipart machines are constructed from component protein building blocks. One such apparatus can rapidly copy the millions of nucleotide bases that compose the genome.[20] Accuracy in this task is essential, and so in the midst of copying, this biological machine proofreads every letter. How accurate is this proofreader? If a typist transcribed at a reasonable rate – say, forty words per minute – and that typist worked continuously eight hours a day, five days a week (with two weeks off for vacation), it would be as if he or she made one mistake every forty years.

Accurately copying the genetic code from generation to generation is one requirement for life to happen. Additionally, the biological machinery of a cell must convert the one-dimensional information embedded in the DNA molecule into a complete three-dimensional organism. The cellular components are not swishing around willy-nilly. Rather, there is a precise spatial organization to each part that provides asymmetry, another feature that we now understand is essential for life, even in bacteria. Without asymmetry, no embryo could develop, our neurons could not convey information, our intestines could not absorb nutrients, and bacteria could neither swim nor crawl. Indeed, all cells, even bacterial cells, possess subcellular architectures in which the component parts are put in very specific places at specific times. Dare I say, molecular *feng shui*?

How do bacteria accomplish such feats? Bacteria do it like eukaryotes do it; or, to put things in proper perspective, eukaryotes perform these tasks in the same way as bacteria. In eukaryotes, cellular organization is largely established through a so-called cytoskeletal network – your molecular skeleton – made up of three different types of filament proteins. We have recently learned that bacteria have their own versions of each filament that together organize the cell.[21] In addition, bacteria construct miniature assembly lines containing ordered arrays of enzymes that function sequentially in biochemical pathways to ensure the stepwise and efficient production of products.[22] (Perhaps Henry Ford got the idea for mass production of automobiles from his microbiome.) This molecular assembly-line capability, which was discovered only a few years ago, appears conserved from bacteria to humans.

From moment to moment, bacteria assess and adapt to what is happening around them. If a nutrient or a poison wafts by, bacteria move in the direction of a food source while they swim away from a toxin. If the environment is too salty, putting the bacteria in danger of shriveling up and dying, they install pumps in their membranes to actively squirt ions out of the cytoplasm. If the pH becomes acidic, bacteria synthesize buffer molecules that bind to and sop up excess protons. To monitor the environment, bacterial membranes are decorated with antenna-like apparatuses called receptors, which connect the outside world to the inside of the cell.[23] When bacteria encounter an environmental change, the receptors sound a sensory alert in the cytoplasm where information in the DNA can be extracted to instantaneously make appropriate biomolecules to deal with the situation. Remarkably, bacterial receptors look and work essentially the same way as receptors in plants and animals. Indeed, our cell surfaces are likewise adorned with membrane-spanning receptors that monitor and react to hormones, that tell our cells to go to sleep or wake up, and that alert our cells to react to heat, cold, and pain. In all cases, bacterial or human, the receptor's job is to monitor changes in the outside world and shuttle that information internally so that cells can do the right thing at the right time. Bacteria invented this solution for adapting to a changing world billions of years ago. Eukaryotic cells subsequently co-opted these biochemical mechanisms and biological design principles to robustly convey extracellular information into cells.

We have long known that some bacterial parts (DNA, RNA, lipids, and some important proteins) are essential for bacterial life. The new field of microbial cell biology has demonstrated that viability depends on these bits being precisely located within the bacterial cell in space and in time.[24] This revelatory finding offers scientists exciting new ways to imagine combating pathogenic bacteria. The hope is to identify new antibacterial compounds that do not target the essential molecules of life, such as DNA and RNA, but rather, that disrupt how bacteria distribute particular components to defined subcellular destinations at the correct times. We can exploit this new knowledge of cell biology for beneficial and industrial purposes. We are becoming able to logically string together preexisting biological units and induce them to perform new functions. We can now engineer mini-assembly lines to build organisms that do or produce useful things. We can construct miniature scaffolds to use as new materials or tissues or building platforms. Such research holds tremendous promise for the future of renewable energy, new material synthesis, environmental sustainability, food production, and medicine.

Mob Psychology: Bacteria Talk to Each Other and Orchestrate Group Activities. Bacteria are miniscule. They are five hundred times smaller than human cells, which are also microscopic. Most of the interesting things that bacteria encounter are comparatively enormous. How then is it possible for bacteria to influence their environment? New research shows that the principal reason bacteria are so successful is that they rarely act alone. Rather, bacteria keep track of the number of cells in the vicinity; when there are enough present, they cooperate to synchronously undertake tasks that would be unproductive if carried out by an individual bacterium acting alone. We call this phenomenon *quorum sensing*.[25]

Quorum-sensing bacteria count their cell numbers by communicating with one another. They use chemical molecules, called autoinducers, as their "words."[26] As quorum-sensing bacteria multiply, each cell releases autoinducer molecules into the surroundings. Because each bacterium contributes a share of autoinducer to the environment, the quantity of the extracellular autoinducer increases in step with the increasing bacterial cell number. When the autoinducer accumulates above a threshold level, receptors on the bacterial cell surfaces become capable of efficiently detecting the molecules' presence. The receptors relay information into the cytoplasm, specifying, in effect, that the number of neighbors present has exceeded the minimum needed to accomplish some task. The bacterial group then responds with a population-wide, synchronous change in activity. In essence, quorum sensing is a bacterial voting procedure.

The bacteria cast chemical votes, they tally the vote, and all the members of the community go along with the outcome.

Quorum sensing controls collective behaviors including the release of toxins and other virulence factors, biofilm formation, and DNA exchange. These types of tasks are effective only when undertaken en masse. Say, for example, you eat contaminated food and a few bacterial pathogens are lucky enough to come along for the ride. The amount of a toxin that a few bacteria could manage to dribble out would be inconsequential in terms of establishing an infection. The more cunning strategy is for the bacteria to wait, to multiply, and to recognize when they have enough cells that can, together, launch an attack that will successfully overcome your host defenses. Thus, bacteria require quorum sensing to be virulent. The good news is that they also require quorum sensing to perform the many beneficial jobs they routinely do for us to keep us healthy.

Quorum sensing is the norm in the bacterial world, and in each bacterial species, hundreds of traits are controlled by this chemical discourse.[27] Bacteria count to different numbers depending on the task at hand. Some collective jobs require the concerted effort of only a modest number of cells, while other duties require significantly more team members. Evolution has apparently optimized quorum sensing so that correctly sized battalions undertake appropriate missions.

Every quorum-sensing bacterium has multiple quorum-sensing circuits. That is, bacteria are multilingual, and they converse using a rich chemical lexicon.[28] Beyond simply counting, bacteria use different quorum-sensing molecules to distinguish between self and non-self, and they decode blends of autoinducer molecules to extract information about the ratios of different species present. In turn, they tailor their collective behaviors depending on who is in the majority and who is in the minority of a mixed-species bacterial consortium (that is, friend or foe). To accomplish this feat, bacteria employ a chemical vocabulary composed of molecules that identify self, non-self but closely related, and non-related.[29] In essence, they can determine "you are my sibling," or "you are my cousin," or "you are not family."

Research into the social lives of bacteria is providing the first understanding of the origins of cell-to-cell communication, self versus non-self recognition, how synchronicity is achieved in collective processes, and the evolution of cooperation.[30] Given that life began with bacteria, there is a high likelihood that discovering the principles underpinning nature's earliest command-and-control centers will provide insight into analogous processes in eukaryotic organisms. The second outcome of this research is practical: we now know that quorum sensing is intimately linked to biofouling and pathogenesis. Interfering with quorum sensing opens up new ways to control bacteria that erode industrial processes, and it offers a fundamentally new approach to antibiotics to battle virulent bacteria.

Anti-quorum-sensing antibiotic strategies should be especially difficult for bacteria to bypass by mutation. If collective action is required for virulence to be effective, then a single cell that fortuitously acquires a mutation making it blind to a quorum-sensing drug does not gain an advantage from the mutation. The "resistant" bacterium will switch into quorum-sensing mode at the appropriate time; however, other nearby bacteria that remain susceptible to the drug will not. In all likelihood, the resistant mutant will have decreased fitness because it will undertake energy-expensive quorum-sensing behaviors without reaping the benefits of collective action.[31] This quorum-sensing resistance scenario is fundamentally unlike the development of resistance to traditional antibiotics, in which the resistant mutant and its offspring receive an immediate growth advantage. The use of traditional antibiotics fuels the growth and spread of antibiotic-resistant bacteria whereas anti-quorum-sensing therapies are not predicted to contribute to resistance.

Equally interesting in terms of future quorum-sensing research is the development of pro-quorum-sensing strategies that make bacterial "chit chat" more effective. The goal is to enhance quorum sensing to encourage beneficial collective behaviors and improve production of compounds or processes of value to society. For example, we could intensify microbial conversations to encourage bacteria that produce modest amounts of interesting natural products to make considerably larger amounts. We could convert bacteria that are inefficient at bioremediation or at biofuel production into powerhouses. Developing potent pro-quorum-sensing molecules could enable these and other applications to occur at industrial scales.

Microbes are the repositories of 3.5 billion years of evolutionary secrets that have enabled life and shaped a planet. They can kill us and they can rescue us. To ensure the latter fate, we need a concerted effort toward understanding and harnessing the power of microbes. A vanguard of scientists from biology, chemistry, physics, computation, evolution, and engineering have entered the fray. Our objective is to deliver to society a comprehensive understanding of microbial complexity so that humans can effectively conquer the bad microbes, enslave the useful microbes, and reward the good microbes that devote their tiny lives to keeping us alive.

Microbial diversity surpasses everything else on the planet. Scientists have studied only a handful of microbial species; we know there are millions more. That means there are thousands of millions of microbial genes that produce molecules, ingenious pathways, biological machines, and structures that can be discovered and exploited for medical, industrial, and agricultural purposes.[32] Microbes are our planet's only limitless renewable resource, and this cache remains virtually untapped. We can look to the accumulated smarts of eons of evolution, expertly preserved inside microbes, for timely approaches and solutions to problems of global significance.

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