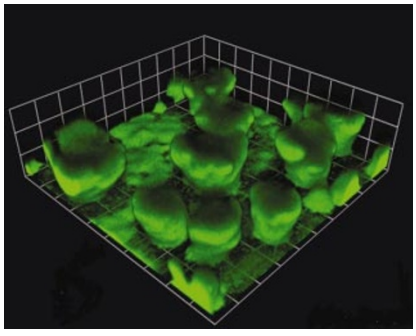
Tiny teamwork

E. Peter Greenberg

Until recently, bacteria were considered to be self-contained and self-sufficient individuals. These unicellular organisms were thought to lack the sophistication of plants and animals to organize into multicellular groups. We also assumed that they lacked the ability to communicate, a crucial function for organizing group activities. Our view has changed. Bacteria can organize into groups, they can communicate, and these abilities are important factors in the development of many diseases. Organized groups of bacteria in the form of biofilms often cause persistent infections, such as those of the middle ear, urinary tract, bone, heart valves and implanted medical devices. Because we have not considered the problem of group biology in bacteria until recently, we lack good therapeutic strategies to treat biofilm infections.

The first hints that bacteria might produce species-specific signals for cell-to-cell communication emerged more than 30 years ago from pioneering work in the laboratories of J. W. Hastings and Alex Tomasz. When critical environmental concentrations of then unidentified signalling molecules were reached, they triggered the expression of specific genes, controlling light production in a marine luminescent bacterium, and genetic competence in the pneumococcus. After a grudging acceptance of these examples, communication was viewed as a curiosity, unique to a few special bacteria. But we now know that many bacteria use cell-to-cell communication to control gene expression, a process that has become known as quorum sensing. At a high population density, there is enough signal to instruct all of the individuals to do something they won't do at lower population densities — a form of peer pressure.

Quorum sensing in *Pseudomonas aeruginosa* has attracted considerable attention because this pathogen causes many hard-to-treat infections, including chronic biofilm infections in the lungs of people with cystic fibrosis. In this bacterium, quorum sensing is a key virulence determinant — mutants that cannot communicate are seriously impaired in their ability to cause infections in lab models. *P. aeruginosa* uses quorum sensing to control hundreds of genes, many of which code for the production of secreted virulence factors that are toxic in one way or another to the host.



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Culture club: *Pseudomonas aeruginosa* can gang together to form mushroom-shaped structures.

Both the signalling molecules and the genes expressed differ between species. For example, the pneumococcus and several other bacteria use a peptide as their signal, whereas *P. aeruginosa* and the luminescent bacterium rely on acylated homoserine lactones.

The realization that many bacteria can communicate, and that there are different systems for communication, has led to what seems like a gold rush among microbiologists. But it is important to distinguish true communication from more general responses. In humans, there is an obvious distinction between communication and a startle response to a loud noise, but with bacteria the situation looks less clear-cut. There is evidence that some bacteria can measure a signal produced by most species and respond to the general bacterial population density. Is this signalling and response, but not communication? How could this have evolved?

In parallel with the new field of quorum sensing, great strides were also made in understanding surface-attached groups of bacteria — biofilms. Advances in microscope technology for imaging living biofilms allowed us to observe that bacteria growing on surfaces can develop into structured but heterogeneous groups. Even within groups of a single species, individuals in different locations have different activities. For example, when grown on a surface, *P. aeruginosa* can form a forest of mushroom-like structures and not just a uniform blanket of growth. Using fluorescent stains and micro-electrodes, investigators showed that different regions within the structures had different metabolic activities.

Finally, in 1996, the fields of quorum sensing and biofilms converged when we found that *P. aeruginosa* mutants with quorum-sensing defects failed to form the mushroom-like structures. A connection between quorum sensing and biofilm development has since been found in several other bacterial species. Quorum sensing seems to promote biofilm development in *P. aeruginosa* and some other pathogens, such as *Burkholderia cepacia*, whereas in other bacteria (for example, *Vibrio cholerae* and the photosynthetic bacterium, *Rhodobacter sphaeroides*) it might have a role in the dispersal of individual cells from a biofilm. Although the quorum-sensing–biofilm connection is evident in several bacteria, it is important not to overstate its significance. Bacterial species that are not known to communicate can form biofilms, and even *P. aeruginosa* can form biofilms, albeit abnormal ones, without quorum sensing. Perhaps the true significance of the quorum-sensing–biofilm connection is that it points to a genetic component of the development of structured biofilms.

With recent progress in understanding bacterial communication and communities has come an appreciation that biofilms are an important problem in medicine. Bacteria residing in biofilms can resist host defences, and they show a tolerance to antibiotics at concentrations that would kill them outside the biofilm. This helps to explain why biofilms can cause devastating chronic infections like the *P. aeruginosa* lung infections that plague and ultimately kill people with cystic fibrosis. A better basic understanding of bacterial group activities should lead to the development of new therapies for the treatment of lung infections in cystic fibrosis, and of other biofilm-based diseases.

With all of the promise and excitement of this new area in microbiology, there are still basic knowledge gaps about the prevalence of communication and community behaviour in bacteria, and about the evolution and diversity of these phenomena. Microbiologists need to learn from population biologists and ecologists who have been thinking of and working on communities and communication for decades. Conversely, bacteria may serve as convenient models for population biologists and ecologists to test hypotheses about the rules governing the evolution of cooperative and group activities. ■

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Bacterial communication

Recognition that bacterial cells can communicate and organize into groups has led to new ways of thinking about chronic infections.

FURTHER READING

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