

Darwin and microbiomes

The year 2009 marks both the two-hundredth anniversary of Charles Darwin's birth, and the one-hundred and fiftieth anniversary of the publication of *On the Origin of Species*. Darwin did not mention microbes in his masterpiece, although Antoni van Leeuwenhoek had already reported their existence in the mid-seventeenth century; apparently, Darwin was not aware of this discovery. As Norman Pace commented in a recent talk, "*On the Origin of Species* was sterile, as it was not contaminated with bacteria." Indeed, Darwin would have been astounded to know that some of the best evidence for natural selection resided in his own gastrointestinal tract.

We should not be too hard on Darwin; if the truth be known, until recently, most of us have had a poor idea of microbes and their ubiquity. It was not until 1966 that Thomas Brock found bacteria in the hot springs of Yellowstone Park, USA; indeed, microbes define the limits of life in terms of pH, temperature, pressure, oxygen, desiccation, nutrients, metals, radiation and even longevity. After the introduction of 16S ribosomal RNA (rRNA) sequencing by Carl Woese, Pace and his colleagues showed that the surface of the Earth is populated with an enormous diversity of bacteria. For most of the past 50 years, genetic and biochemical studies of bacteria have been massively *Escherichia coli*-centric. Nonetheless, this single-minded focus has been enormously productive; it has and will continue to guide the discovery of many of the key principles of bacterial physiology. However, *E. coli* is not a good representative of soil or marine bacteria, or even of commensal populations of living organisms.

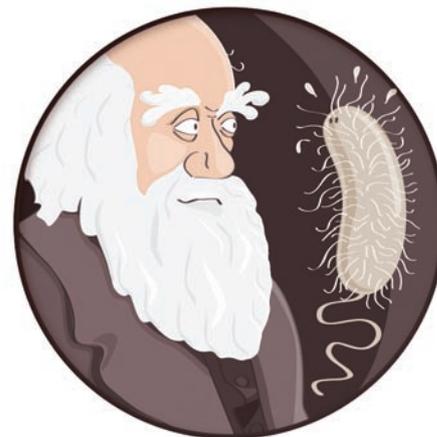
At present, the largest international life-science project of all time is taking place, based rightfully on microbes: the sequencing of all the bacterial inhabitants (microbiome) of the human body; this promises to be more significant in terms of human health than the Human Genome Project. Current estimates indicate that our bodies contain at least 10-times more bacterial cells than human cells; humans are of largely bacterial content in terms of genes and cells, and we provide a wonderfully warm home for them. Most bacteria in the body cannot be grown in the laboratory, but modern technology allows us to recognize and discriminate them based

on rRNA sequences. Knowledge of the metabolic pathways and ecology of these bugs will allow a more detailed analysis of their roles in human and animal physiology and disease. With the creation of national microbiome projects and international collaborations, we can anticipate a veritable flood of information. Microbiomics is here to stay, and microbiology and medicine will never be the same.

There have already been several important, and some startling surprises coming from the limited microbiome sequence information available so far. Early studies of various human physiologies—obesity and diabetes, for example—are providing new insights into the microbial underpinnings of these pathologies. The ways by which microbial functions can be translated into knowledge of the mammalian immune system and other responses is only now coming under scrutiny. It is safe to say that we are at the beginning of the golden age of microbiology. The near future promises a more complete understanding of the roles of microbes in our lives and a better appreciation of how living organisms depend on their microbial residents.

Despite remarkable progress in obtaining microbial genome sequences from various sources, including human pathogens, these results pale in significance when we consider that the human gastrointestinal tract contains 1,000 or more phyla, and the oral, genital tracts and skin probably double this number; in addition, we all have different flora. Environmental microbiology is an even bigger challenge: one gram of soil contains 1,000 or more phyla and it has been estimated that there are 6×10^{30} prokaryotes in the biosphere. The total number of bacterial phyla will not be known for some time.

Much of the genomic work now being carried out is producing catalogues; nonetheless, efforts to predict metabolic functions are progressing. One aspect of microbial physiology that deserves more consideration is the production of low molecular weight bioactive compounds. The world of these molecules—the *Parvome*—must be at least an order of magnitude larger than the number of bacteria in the biosphere. For one thing, bioactive small molecules are the lexicon of cell–cell communication. They modulate many aspects of bacterial community activity, including interactions with plants, humans and other organisms. Given our limited understanding of bacteria and their functions, it behooves us to develop a



more detailed understanding of cell–cell interactions in bacteria, especially within the 'superior' organisms they inhabit. Such studies will be of evolutionary significance, as the signalling and regulatory molecules found in bacteria are likely to be the precursors of similar processes in Eukarya.

Darwin focused his theory of evolution based on natural selection. But, during the past 200 years or so, it is unnatural—or, more correctly, anthropogenic—selection, which is the main force in bacterial evolution; the earth is bathed in antibiotics and countless other man-made toxic chemicals. Microbial populations have been exposed to ever-increasing concentrations of antibiotics since Fleming and Waksman discovered penicillin and streptomycin, respectively. This is nowhere more obvious than in the development of antibiotic resistance in hospitals and the community. Environmental microbes are the sources of many of the known antibiotic resistance genes; humans dump the antibiotics and nature provides the resistance.

New scientific frontiers are being breached: it is not known how many aspects of human biology are influenced either directly or indirectly by microbial symbionts. Only time and creative research will tell; human beings, supposedly the pinnacle of evolution, are dependent on the simplest, but oldest form of life. We have been described as "large, highly complex microbial communities attached to some relatively uninteresting organic matter" and are superimposed on the Bacterial Tree of Life; this would surely have appealed to Charles Darwin.

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