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EDITORIAL

Men and Microbes: War and Peace

At the turn of the century and the millennium, *Science* carried a series of essays titled *Pathways of Discovery*. An extremely readable and characteristically eloquent essay on *Infectious History* still holds a place, albeit indistinct and receding, in my memory. The author, Joshua Lederberg, was one of the most influential figures of 20th century biology and a writer of rare scholarship. In his essay, Lederberg traces the history of the relationships between men and microbes; a long history of conflict, with microbes invariably being associated with 'germs' that spread contagious disease. The 'Black Death' of the 14th century, when bubonic plague swept through Europe, and the rising tide of syphilis in the 16th century provide Lederberg the starting point for his reflections on our evolving understanding of the relationships between microbes and the environment (Lederberg, J., *Science*, 2000, **288**, 287). Viruses, bacteria, fungi and several unicellular parasites, plasmodia, the causative agents of malaria, among them, have for long been associated with disease. The war on infectious disease has had a simple objective; eliminate, by any means, the organisms that prey upon man. Microbes are, in Lederberg's words, 'moving targets'; natural variation, mutation and selection resulting in an ever changing enemy. But variation and adaptation are also at work in human hosts, over the long timescales of evolution. Many studies, most notably on malaria and tuberculosis and more recently on AIDS, illustrate the connection between infection and evolution. Lederberg is quick to point out that 'one lesson to be gleaned from this coevolutionary dynamic is how fitful and sporadic human evolution is when our slow and plodding genetic change is pitted against the far more rapidly changing genomes of microbial pathogens'.

My thoughts turned to microbiology when I was struggling to recover from a severe stomach infection. I was told cheerily, by an unsympathetic and irreverent gastroenterologist, 'Don't worry, bear it. The microbiology of your gut is changing. You will soon adjust to a new microbiome.' Having viewed with some distaste the spread of the suffixes 'ome' and 'omics' in biology, I was less than pleased that the contents of my gut now included a 'microbiome', a term describing the diverse population of organisms that inhabit the surfaces and recesses of our bodies. The 'omics' contagion began with 'genomics' in the 1990s, quickly spreading to include 'proteomics', 'metabolomics' and 'lipidomics' amongst others. In each case the term is intended to encompass all the constituents in a biological system; genes, proteins, metabolites or lipids. The 'microbiome' then evokes an image of a teeming multitude of organisms, too small to be seen, diverse in their chemistry and biology, that have colonised us with impunity. Peaceful coexistence of animals (humans amongst them) and microbes is a hallmark of biology. Our preoccupation with infectious organisms (pathogens) has often clouded our perceptions about microorganisms. Indeed Lederberg notes that 'during the early acme of microbe hunting, from about 1880 to 1940, however, microbes were all but ignored by mainstream biologists. Medical microbiology had a life of its own, but it was totally divorced from general biological studies. Pasteur and Koch were scarcely mentioned by the founders of cell biology and genetics. Instead bacteriology was taught as a speciality in medicine, outside the schools of basic zoology and botany. Conversely, bacteriologists scarcely heard of the conceptual revolutions in genetic and evolutionary theory'. Bacteriology had indeed captured the public imagination in the early years of the 20th century as it became clear that the enemy in the war on infectious disease had been identified and that a counter attack with vaccines and chemotherapeutics could now be mounted. I might add, parenthetically, that when my own institution, the Indian Institute of Science, was conceived over a century ago, a 'department of bacteriology' was envisioned and a 'school of tropical medicine' appeared a distant dream. Both did not materialize for reasons that future historians may find intriguing, despite their obvious relevance to India, then and now.

The early decades of the 20th century were a witness to the growing importance of microbiology in medicine. Generations of researchers grew up reading Paul de Kruif's 1926 classic, *Microbe Hunters*, which remains a compellingly romantic account of the golden age of bacteriology and microbiology. On the pages of this book, one encounters with a bewildering swiftness the dramatic transformation of microbiology, the birth of immunology and vaccinology and the first triumphs of medicinal chemistry as the author traces the work of Leeuwenhoek, Pasteur, Koch, Metchnikoff, Roux and Behring, Ross and Ehrlich. Should a book on science written in 1926 be recommended nearly ninety years later? Excerpts from an

introduction to a reissue of the book in 1996 provide an answer. 'It is thus no small praise to say of Paul de Kruif's *Microbe Hunters* that, well over half a century after it first saw the light (1926), it manages to delight, and frequently to entrance, old and new readers – those who have kept a more or less blurry recollection of its pages from adolescence … and those for whom its vivid images and portrayals are a fresh experience…. Survival of this magnitude is uncommon for any book, but especially for one aptly regarded as a work of "scientific popularization" and that deals with facts and personalities whose description has been reiterated ad nauseam' (Gonzalez-Crussi, F., Introduction to the 1996 reissue of *Microbe Hunters*, Harcourt Brace & Company, Florida). De Kruif's narrative style may be a part of the magic which has sometimes drawn student readers to the practice of science. Gonzalez-Crussi quotes de Kruif: 'A scientist, a really original investigator of nature, is like a writer, or a painter or a musician. He is part artist, part cool searcher.' Is science, especially a subject of such practical utility as microbiology, a product of the creative imagination of those who have advanced the field? De Kruif provides a simple answer; one which merits some reflection: 'Great advances of science so often start from prejudice, on ideas got not from science, but straight out of the scientist's head, on notions that are only the opposites of the prevailing superstitious nonsense of the day.'

Modern genomics has unified biology. The founders of bacteriology, who so vividly come to life in de Kruif's book, may not have been really surprised by the resurgence of their disciple, albeit in a vastly altered form, with the recent excitement on the analysis of 'human microbiomes'. Attention has been focused on an entirely different aspect of the relationship between microbes and man; their necessity to coexist. The *Human Microbiome Project* has subjected the microbial populations found in different niches in the human body to a detailed scrutiny using DNA analysis, specifically a taxonomic marker the 16s rRNA gene, employing the recently developed techniques of 'next generation' sequencing to probe the 'structure, function and diversity of the human microbiome' (The Human Microbiome Project Consortium, *Nature*, 2012, **486**, 207 and 215). The methodology used permits a sampling of organisms 'from the skin, nose, mouth, throat, vagina and faeces (to represent the gastrointestinal tract)' using DNA samples from '242 healthy adults in the United States'. The analysis of the marker molecule in 5177 samples permits a broad characterization of the nature of the organisms that colonise specific sites in the human body. David Relman in a News & Views piece notes that 'studying the human microbiome has so far been an exercise in humility' (*Nature*, 2012, **486**, 194). Microbiome analysis will be confronted with many issues in the future as individual habitats vary widely and the selective pressures of the environment can be vastly different. The microbiome will be a dynamically changing, evolving community of invisible colonisers. Relman notes that 'many areas of human microbiome research warrant further investigation, but viruses and small non-bacterial organisms such as fungi deserve special attention, as do questions regarding the functions of the microbiome. We are essentially blind to many of the services that our microbial ecosystems provide – and on which our health depends – and investigators desperately need new approaches for studying interactions between members of the microbial community and their human hosts'. Indeed, the *Nature* reports suggest that 'some of the microbiome's functions are likely to be performed by rare community members or to involve genes that are expressed at low levels', a feature that 'will complicate attempts to decipher their influence' (Relman, D. A., *Nature*, 2012, **486**, 194). The gut microbiome is rapidly emerging as the community which is being most extensively investigated, with microbial ecology and evolution of the human–microbe symbiosis attracting great attention (*Science*, Special Section, 8 June 2012). At birth, the human gastrointestinal tract is sterile, slowly acquiring a stable and valuable microbial community that vastly enhances the gene complement that produce the protein catalysts that perform the necessary chemistry. This process appears analogous to the strategy adopted by corporations which enhance their competitive fitness by mergers and acquisitions. A recent review concludes, rather sombrely, drawing a connection between the evolution of human lifestyles and chronic disease: 'It is almost inevitable that the characteristics of the modern lifestyle, such as antibiotics, Caesarian sections, hygiene, refined diets, formula feeding and small households, would introduce hurdles into symbiont transmission with consequences for the functional development of the gut microbiota. This is one way in which the modern lifestyle might contribute to the rise in chronic diseases recently associated with the gut microbiome in westernized societies' (Walter, J. and Ley, R., *Annu. Rev. Microbiol*., 2011, **65**, 411).

The human microbiome may soon be dwarfed by an attempt to map the *Earth Microbiome*; an effort to understand the most populous, but invisible, inhabitants of our planet. This enterprise may turn out to be a new mega project for biology which will generate vast amounts of data. Turning that flood of information to useful knowledge will be a major challenge (Hood, L., *Science*, 2012, **336**, 1209). Lederberg anticipated a great deal of current discussions on the microbiome when he argued that we must abandon 'our manichaen view of microbes – we good, they evil'. He underscored the need for abandoning the 'metaphor of war' in favour of 'a more ecologically informed metaphor'. The human microbiome project is a major step in transforming our view of the relationships between men and microbes. The metaphor of war may soon be replaced by the more informed metaphor of peaceful coexistence.

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