The twilight zones of microbiology

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Professor John Postgate, FRS, author of the well known book *Microbes and Man*, Honorary Member and former President of the Society, looks at why the 'twilight zones of microbiology' should not be ignored.

In 1674, Antoni Leeuwenhoek first described to the Royal Society his microscopic animalcules, creatures so small as to be invisible to the naked eye. His findings were received with lively interest, but they made no radical impact, because creatures close to the limits of optical resolution were already known, and his protozoa were on the margin of that limit. It was his letter of October, 1676, which astonished the Society, for the 'tiny eels' he saw, which we now call bacteria, were vastly smaller than even those earlier creatures. The subsequent story is now history. Suddenly, size-range of living things had been extended downwards by two orders of magnitude of length. It was a significant advance in our understanding of the living world, but that was all. It would be another couple of centuries before the formidable impact of those animalcules on scientific thinking began to emerge.

In the mid-nineteenth century the first hints of that impact appeared, when Robert Koch demonstrated the roles of bacteria in disease and when Louis Pasteur elucidated the function of yeasts in fermentation – and almost in passing discovered anaerobiosis. Medical and applied microbiology grew vigorously, and alongside them grew general and environmental microbiology. Long-held beliefs, such as spontaneous generation, or the roles of vapours and humours as agents of disease, withered rapidly; over the next few decades our views of ourselves and the world around us were transformed with the revelations that we eat and breathe microbes, that we are hosts both inside and outside ourselves to a menagerie of microbes; that microbes are fundamental to agriculture and many more of our economic activities; to the terrestrial cycles of the bio-elements, and even to the persistence of macroscopic life on this planet. Leeuwenhoek's letter of 1676 had seeded not just a vast explosion of both practical and scientific knowledge, but a revolution in the way we see ourselves and the biosphere.

That was the longest lag phase in the history of microbiology's intellectual impact. But within our specialized areas we can all point to recent examples of shorter lags, when an offbeat or seemingly trivial report took years, even decades, to underpin a substantial intellectual shift.

Examples feature in this issue, in which we peer into today's twilight zones of microbiology, into areas of research which seem to be out of kilter with the mainstream of thinking among microbiologists. Will their eventual illumination bring about radical revisions of our thinking?

Reflect on the history of prions. In my distant youth the scrapie agent was recognized as infectious and called a 'slow virus'; then as general virological biochemistry and molecular biology progressed it became clear that it was something exceptional. Now we are invited to regard it as a partly denatured form of a normal protein which has become infectious and catalyses or otherwise promotes further denaturation of its native form. Not happy with that? Nor am I. But the probabilities are that we shall have to come to terms with it, just as mid-twentieth-century microbiologists had eventually to accept that, contrary to the orthodoxy of the time, bacteria possessed chromosomes.

So, are prions alive? That may seem a silly question, because it has long been obvious that linguistically the borders of animate and inanimate matter are fuzzy, and that around those borders the term 'living' becomes imprecise. Yet fuzzy terminology leads to fuzzy thinking; we cannot wait for a precise definition of life, so we need an operational consensus on how elementary a biological entity can be and still be regarded as alive. Leeuwenhoek and his contemporaries had no problem here, and even when the discovery of viruses early in the twentieth century extended the size range of living things downwards yet again, there seemed to be no serious doubt that they were alive. However, in the 1930s the question became abruptly serious with the crystallization of tobacco mosaic. Well, we said, those crystals are just a special case of dormancy; or viruses are obligate parasites that have lost many of life's defining properties. On the whole viruses scored as living. But what now of viroids, fragments of infectious RNA too small to have even a plausible genome? Or self-transposing genetic elements? Are autonomous fragments of hitherto living material to be regarded as alive?

Hold it there for a moment and switch channels to another twilight area: those 'unculturable' microbes which PCR coupled with rDNA probing, and conventional c.f.u. counts on wild populations, show us are abundant in this planet, even deep beneath its surface, as well as in soils and sediments. Are they alive?

Vegetative microbes that are physiologically alive but do not multiply in conditions offered by microbiologists are commonplace in sediments, soil, old cultures and so on. As well as 'unculturable' they have been called 'non-culturable', 'dormant', 'senescent', 'moribund', 'non-viable', 'viable but non-culturable'; all names which beg questions about their physiological state. They too exist in that fuzzy zone between animate and inanimate things; therefore meticulous precision of language is needed when discussing them (especially now that interplanetary exploration is raising a serious prospect of extra-terrestrial microbiologies within the solar system). Current attempts to seek an agreed terminology for microbial cells in that state (e.g. Barer & Harwood, 1999) are laudable. Is not a rational terminology for discussing comparable non-cellular entities also needed?

The twilight zones of microbiology may seem to involve little more than biological, and sometimes philosophical, curiosities. But history tells us that, as with Leeuwenhoek's animalcules, their exploration will indeed disclose dramatic new insights, and will probably lead to scientific advances reverberating far beyond microbiology.

Further reading

Barer, M.R. & Harwood, C.R. (1999). Bacterial viability and culturability. *Adv Microb Physiol* 41, 93–137.