Microbiology: past, present and future

Advances in microbiology are largely driven by improvements in technology. The awe-inspiring size of the experiments performed today — such as studies of entire microbial communities — is the result of a centuries-long path of discovery, one advance built on the next. Current technologies have provided us with new insight into entire communities and biomes, and promise to unravel many secrets of the microbial world.

The microscopic world became visible with Antonie van Leeuwenhoek's improved lenses; he revealed a new world filled with 'animalcules', single-celled organisms that swim and tumble in water. When the Italian scientist Lazzaro Spallanzani discovered that microorganisms are killed by boiling and can travel through the air, he paved the way for Pasteur's experiments, which finally laid to rest the notion that life could be spontaneously generated. Spallanzani was also the first to isolate a bacterium. He watched one bacterium swim from a drop of water full of organisms across a narrow bridge into a drop of sterilized water. When he removed the bridge with a camel-hair brush, he had isolated the first bacterium — a rod. Minutes later, the bacterium divided, forming smaller, but otherwise perfect, replicas of itself, disproving the notion that the 'breaking' of organisms that van Leeuwenhoek had observed was the result of violent collisions between the animalcules. Further improvements were made in bacterial isolation and culturing: for example, Joseph Lister's isolation of the bacterium that spoils milk by serial dilution and Robert Koch's attempts to grow bacteria on sterilized potato slices. But it was the adaptation of the agar used in a dessert made by one of the members of Koch's laboratory to make a solid growth medium that ushered in an era in which bacteria could be studied in isolation. The invention of a simple dish to hold the medium, by Julius Petri, a researcher in Koch's laboratory, in 1887, produced a tool that is still in use today, virtually unchanged — the Petri dish.

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Also still in use today is the ultracentrifuge. Invented by Theodor Svedberg in 1927, the ultracentrifuge made possible the classic Meselson and Stahl experiment in 1958, which showed that DNA is synthesized through semi-conservative replication. With the production of the first commercial electron microscope in 1939, the limits of visible light were left behind and microorganisms could be observed in much greater detail than ever before. The description of fluorescence microscopy by Coons and colleagues in 1942 allowed specific visualization of microorganisms and even parts of microorganisms, and the discovery and subsequent application of the green fluorescent protein and its various derivatives allowed proteins to be detected in live cells.

In parallel, a steady stream of discoveries of the molecular biology of bacteria and phages provided an increasingly detailed view of what goes on inside a cell — DNA was discovered as the hereditary molecule, its structure was unravelled and semi-conservative replication, transcription, translation and the three-letter genetic code were all discovered, for example. These discoveries were harnessed using restriction enzymes, which were first purified in 1968 and quickly adapted, together with ligase, discovered in 1966, to establish recombinant DNA technology. The first sequencing protocols were produced in the 1970s, revealing the exact sequence of the cloned DNA, and in 1976, the first full genome, of the bacteriophage MS2, was sequenced. Advances in sequencing technology, together with the invention of PCR, provided the power to sequence the entire genome of a bacterium, *Haemophilus influenza*, in 1995, which was followed by sequencing of the *Escherichia coli* genome in 1997.

Sequences led to gene arrays and transcriptional profiling and then proteomics technology, which revealed the many protein products present in one organism. Ocean samples and other biomes were sequenced, allowing a view of the tremendous diversity of the species that live together in one environment. Further improvements in technology now allow bacterial genomes to be sequenced in a day. As described in this issue by VerBerkmoes and colleagues, as part of our ongoing series on systems microbiology, thousands of species can now be identified in one experiment, and even variation within a species can be detected. Improvements in these technologies provide a clearer picture not just of single bacterial species, but also of entire communities.

In 300 years, we have gone from observing mixed species in a drop of pond water to isolating and studying individual bacteria to sequencing all species in a sample of seawater. In the process, we have still only discovered perhaps 1% of all bacteria, and possibly an even lower percentage of phages and viruses. Microbiology has come a long way, and has a longer way to go. It will be fun.