the complete genome of the phage ΦX174 in 1977, decades before any cellular genome was completed. As additional phage genomes accumulated, it became apparent that phages exchange genes and large sections of DNA between individuals[4]. This discovery of horizontal gene transfer changed our understanding of how genetic variability is produced. Marine phage communities were the first to be 'shotgun sequenced', leading to the rise of metagenomics — the sequencing en masse of all members of a community[5].

Understanding phages has contributed to our fundamental understanding of host cells and disease (Fig. 1). When phages integrate into bacterial genomes, they can dramatically change the characteristics of their bacterial hosts — many of the most deadly bacterial pathogens, including *Vibrio cholerae* and *Shigella* and *Salmonella* species, acquire virulence factors through this mechanism. Dissecting the biology of phage replication also uncovered several key host-encoded factors that are needed for the phage life cycle, such as the enzyme DNA gyrase[6] and the 'chaperone' protein complexes GroEL and GroES[7].

When the 'war on cancer' was declared by then US President Richard Nixon in 1971, phage biologists were actively recruited into research on human biology. Building on the knowledge that phages encode some proteins that are similar to those of the host, these scientists looked in the human genome for analogous genes from other viruses. Not only did they find such genes, but they also developed the idea of 'proto-oncogenes' present in our genome that, when mutated, are key drivers of cancer.

Other phage researchers moved into the fields of DNA mutagenesis, repair and recombination, providing the basis for our understanding of cancer today. For example, the understanding[8] that pre-existing mutations can give individual cells growth advantages under different environmental conditions led to the idea that cancer cells harbour dozens of pre-existing mutations that may or may not be related to the actual tumour[9]. With the advent of the AIDS epidemic, phage researchers opened the door to our understanding of how retroviruses integrate into the human genome, and what host proteins are involved[10].

The downside of phage scientists moving into different arenas was a massive decline in phage research from the 1970s onwards. Given that phages are such great anvils for the hammers of biologists, why do many researchers pay them so little attention? One reason might be that, as frequently occurs in any old discipline, the literature is dense and filled with acronyms and a changing nomenclature. To help counter this, we provide some guiding principles on phages.

A first key point is the contribution of phages to biological diversity. There are probably more than 10^{31} phage particles on the planet, with approximately 10 phage particles for every bacterial cell[11]. In humans, the main genetic difference between two individuals is the phages in their gut[12]. Among other roles, these viruses form an adaptable immune system that makes use of hypervariable, immunoglobulin-like protein domains similar to those used by antibodies[13].

The second concept is that phages carry genes encoding proteins that modulate the fundamental physiology of the host, such as metabolism and antibiotic resistance. One fascinating example occurs in photosynthesis by oceanic cyanobacteria[14]. The components of the light-gathering antenna complexes produced by these bacteria are highly labile and decay during phage infection. But the phages can carry genes that encode replacement of the damaged proteins, allowing the bacteria to continue to produce biomass and the phages to produce larger bursts of progeny. Thus, these marine phages contribute to the vast turnover of carbon in the oceans by increasing the efficiency and output of photosynthetic processes.

When phages integrate into bacterial genomes, they can dramatically change the characteristics of their bacterial hosts.

A third phage lesson is that the niche space of any bacterial cell is determined by its phages. The main genomic differences between closely related bacteria derive from integrated phages (prophages) and genomic features, ranging from indels to major rearrangements, that help to guard against phage infection. This never-ending selective pressure exerted on bacteria by their phages is the best-characterized example of the Red Queen hypothesis — that predator and prey species must constantly evolve.

What will the phage future look like? These viruses are relatively easy to synthesize, and their genomes have modular characteristics that appeal to synthetic biologists for engineering biological functions. One hundred years after their discovery, we think that it is time for our fellow biologists to throw off their cell-centric habits and embrace the phage. ■

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NATURE

50 Years Ago

The Architecture of Molecules. By Prof. Linus Pauling and Roger Hayward — "We are now living in an atomic age. In order to understand the world, every person needs to have some knowledge of atoms and molecules." This is the beginning paragraph of a fascinating work of art … The question as to how some understanding of science, however superficial, can be brought to the man and woman in the street has exercised many organizations as well as individuals. At a practical level, of course, it is unnecessary to know anything about electric currents in order to turn a switch and bring on the light. Babies love to do it before they are one year old. But for all too many people science is still magic even when they are twenty-one … Linus Pauling worries. He thinks, quite rightly, that young people ought to want to know why the 'lead' of a pencil comes off on to the paper, what an atom of hydrogen or uranium 'looks like' … Undoubtedly many an arts sixth-former will pick the book off the school library shelf and will learn a great deal by browsing through it.
From *Nature* 4 December 1965

100 Years Ago

The nation's attitude towards science is, I think, largely due to the popular idea that science is a kind of hobby followed by a certain class of people, instead of the materialisation of the desire experienced in various degrees by every thinking person to learn something about innumerable natural phenomena still unsolved; and, having learned, to control and apply them intelligently for the benefit of the human race … It is to the new generation now being educated that we must look for betterment of our position … We must make all education more scientific.
From *Nature* 2 December 1915