A pharmacist prepares a solution of phages, viruses that can destroy bacteria.

BOOKS *et al.*

MICROBIOLOGY

The forgotten future of the phage

As antibiotic resistance soars, a journalist revisits an oft-overlooked antimicrobial strategy

By **Adrian Woolfson**

In his Nobel Lecture delivered on 11 December 1945, Alexander Fleming recounted how his pursuit of a "chance observation" of a mold contaminating a culture plate led eventually to the industrial production of penicillin, the first ever antibiotic (*1*). While anticipating the remarkable impact the drug would have on global health, Fleming also made a prescient warning: If used negligently, resistance to penicillin would inevitably "change the nature of the microbe," resulting in treatment failure.

More than 70 years later, in 2019, a report released by the United Nations predicted that antimicrobial resistance could force up to 24 million people into extreme poverty by 2030 and cause up to 10 million annual deaths by 2050 (*2*). Journalist Tom Ireland's *The Good Virus*, which recounts the intriguing history of a different type of antibiotic principle, a process by which viruses known as bacteriophages or phages destroy bacteria, is thus incredibly timely for its potential to renew interest in an orthogonal antimicrobial modality.

The Good Virus
Tom Ireland
Norton, 2023, 400 pp.

First indirectly observed in 1915 by the English physician Frederick Twort, bacteriophages are composed of a piece of DNA wrapped in a protein capsule. Their genetic instructions are entirely reliant on the hardware of their bacterial hosts, which perform all of the phage's metabolic and replicative functions. Ireland recounts how these ruthless predators penetrate bacteria like "pins in a voodoo doll," forming conduits through which they inject their genes at high pressure. When they trigger their own replication and self-assembly, bacteriophages obliterate their hapless hosts.

The antimicrobial properties of bacteriophages were first documented in 1896 by the Cambridge naturalist Ernest Hanbury Hankin, who traveled to India to investigate reports that outbreaks of cholera upstream of the river Ganges often did not spread downstream. There, he noted that "the unboiled water of the Ganges kills the cholera germ in less than three hours (*3*)." It was subsequently shown that the bacterial profusion swirling around the Ganges corresponds to an abundance of bacteriophages. When phage numbers decline, *Vibrio cholerae* proliferates, resulting in disease outbreaks.

The pugnacious "and roguishly handsome" French-Canadian autodidact Félix d'Hérelle would be the first to realize that these "invisible microbes" might form the basis of an antimicrobial therapy. He called them bacteriophages, translated from the Greek "bacteria eaters," and set about testing preparations of them on himself, family members, and attending physicians at the L'Hôpital des Enfants-Malades in Paris. In August 1919, d'Hérelle successfully treated a boy with *Shigella* dysentery using phage therapy.

After controversially suggesting that phages form part of the human immune system and being accused of plagiarizing Twort, d'Hérelle turned his back on the West. Dedicating his third book on phages to the Soviet dictator Joseph Stalin, he accepted an invitation to relocate to the USSR from the aristocrat and bon viveur George Eliava, who in 1936 set up a phage institute in Tbilisi, Georgia. Until its collapse in 1991, the use of phage therapy in the Soviet Union was widespread, with penicillin and its derivatives being largely unavailable and the use of antibiotics decried as evidence of *nizkopoklonstvo*, or "adulation of the West."

Although to date, there are still no definitive randomized clinical study data demonstrating the efficacy of bacteriophage therapy, there is sufficient reason to believe that bespoke bacteriophage treatments targeting individual strains could be successfully developed and deployed on a global scale. A "universal" antimicrobial system of this sort might comprise large, automated libraries of therapeutic phages or the point-of-care de novo synthesis of natural and artificial bacteriophages using sequence databases, synthetic genomics, and generative artificial intelligence. The astonishing prevalence of bacteriophages, which outnumber bacteria by at least 10 to 1, provides an almost limitless supply of genetic information for this purpose.

The reviewer is Executive Chairman, President, and Cofounder of Replay Holdings Inc., San Diego, CA, USA, and the author of *Life Without Genes* (HarperCollins, 2000). Email: adrianwoolfson@yahoo.com

REFERENCES AND NOTES

1. A. Fleming, "Penicillin." *Nobel Lecture*, 11 December 1945; https://www.nobelprize.org/prizes/medicine/1945/fleming/lecture/.
2. World Health Organization (2019); https://www.who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis.
3. M. E. Hankin, *Annales de l'Institut Pasteur/Microbiologie* (1896).

10.1126/science.adi5079