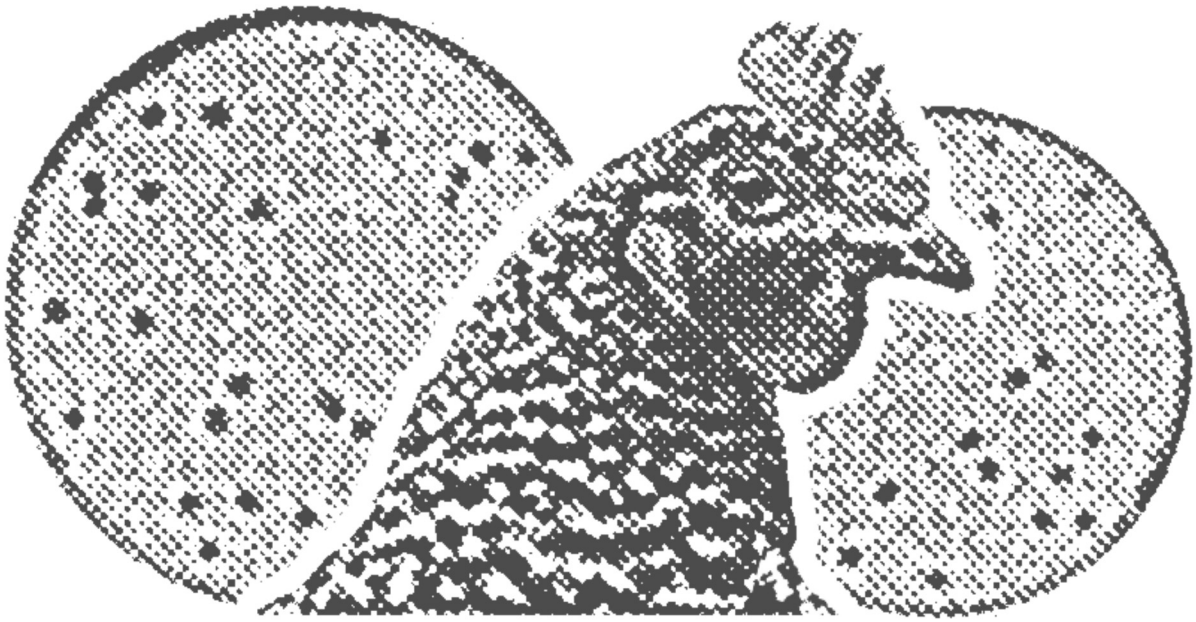
INFERENCE

BIOLOGY / BOOK REVIEW

VOL. 7, NO. 1 / **APRIL 2022**



Parallel Histories

Raghavendra Gadagkar

A Tale of Two Viruses: Parallels in the Research Trajectories of Tumor and Bacterial Viruses
by Neeraja Sankaran
University of Pittsburgh Press, 312 pp., $55.00.

I SPENT THE SECOND HALF of the 1970s at the Indian Institute of Science in Bengaluru immersed in studying the lysogenic mycobacteriophage I3.[1] One floor below my laboratory, a close friend, Arun Srivastava, was studying the Rous sarcoma virus (RSV).[2] We were both fascinated by animal and bacterial viruses, and spent our spare time reading every publication we could find about λ, T4, ΦX174, rinderpest, and Newcastle disease. We came to believe that we knew nearly everything there was to know about them.

We were wrong.

In *A Tale of Two Viruses*, Neeraja Sankaran draws parallels between the stories of the bacteriophages, a group of viruses that infect bacteria, and RSV, which infects chickens. At first glance, this might seem an odd pairing for a work of comparative history. The two viruses behave very differently: phages induce lysis, which destroys bacterial cells, while RSV builds tumors. "[T]he pairing of these two viruses might seem rather arbitrary," she writes, but "they have shared strangely parallel histories from the time of their respective discoveries in the early decades of the twentieth century until the early 1960s."[3]

In 1910, Peyton Rous, an American pathologist working at Rockefeller University in New York, observed that a highly filtered sarcoma extract from one test subject—a chicken, of course—could induce a sarcoma in a second test subject. He concluded correctly that, given the size of his filters, whatever the substance inducing the sarcoma, it could not have been a bacterium. It was for this work that he won the Nobel Prize almost half a century later. In 1915, Frederick Twort, a medical researcher in London, arrived at a similar conclusion with respect to substances that seemed to infect bacteria; in 1917, Félix d'Hérelle, a self-taught scientist working at the Pasteur Institute in Paris, announced the discovery of "an invisible, antagonistic microbe of the dysentery bacillus." Both men had discovered the bacteriophages.

Two anecdotes from the opening chapter stand out. In the first, a young Rous is advised by his distinguished mentor William Welch that, "Whatever you do, do not commit yourself to the cancer problem."[4] Rous ignored Welch's advice. In the second, Simon Flexner, the founding director of the Rockefeller Institute, in an apparent act of carelessness, later attributed the early discovery of RSV jointly to Rous and his former assistant, James Murphy. Rous wrote in protest:

> You said that Rous and Murphy demonstrated the existence of the filterable agent causing the chicken tumor. Now, the fact is that I carried out this work alone and published alone two papers that embodied its results. ... Murphy had no hand in the experimental episode.[5]

In attempting to set the record straight, Rous not only sought to reclaim the discovery for himself, but also to allay any concerns that he "defrauded a fellow worker in the beginning and [had] continued to defraud him ever since."[6]

The fact that a virus was an entirely new kind of biological entity adds drama to the story of the RSV and the bacteriophages. Scientists and doctors found it incredible that an invisible, disease-causing substance might be neither a protein nor an enzyme. Both Rous and d'Hérelle suspected that their subjects of study were viruses, and both faced pushback from the scientific community.

A Tale of Two Viruses has many good chapters, and some that are even better. The chapter concerning bacteriophages is based on Sankaran's doctoral thesis. It is material that she knows very well. Macfarlane Burnet's preeminent work on bacteriophages takes center stage.[7] Sankaran also offers a new perspective on the role played by Max Delbrück and his American Phage Group in developing the concept of bacteriophages as viruses.

The gradual embrace of bacteriophages and RSV by subsequent researchers are treated in separate chapters, which seems prudent because the contexts in which the two fields matured are quite different. On the one hand, the

work associated with bacteriophages and their host bacteria played a pivotal role in establishing the foundations of molecular biology. What Francis Crick called the central dogma of molecular biology affirmed that information can flow only in one direction: from DNA to RNA to the proteins. The work on RSV and the discovery of reverse transcriptase showed otherwise.

The penultimate chapter of *A Tale of Two Viruses* explores how new technology—ultracentrifugation, electron microscopy, and X-ray crystallography, among other techniques—helped the scientific community select among previous ideas about the nature of the substances that possessed viral properties. As striking as these innovations were, they also make the achievements of the researchers who figure in the earlier stages of Sankaran's history seem all the more impressive.

Sankaran's closing chapter, "Lysogeny as Linchpin," is perhaps the most interesting of all. Lytic bacteriophages inject their DNA or RNA into a host cell, subvert the host machinery to make copies of themselves, burst open the host cell, and escape to find more hosts. Lysogenic bacteriophages do all of this only if the host seems healthy enough to make this option profitable. If the host is impoverished, the phage will lie dormant and try later. Meanwhile, it will integrate its DNA into the host's DNA so that as the host divides, all its daughters carry a copy of the phage's DNA—the so-called prophage. When the bacterium appears to be in good health, the prophage will exit the host's DNA and switch to the lytic mode—and copy itself, attack the host, and burst open the host cell to escape and infect other bacteria.

A long-standing question among researchers is why the host carries the prophage and bears the cost of replication despite the ever-present danger that the prophage might eventually kill it. There is growing evidence that the host benefits in many ways from harboring the prophage.[8] One advantage is that the prophage confers immunity to the host from other bacteriophages. While the prophage inhabits the host, the host is incapable of copying other infecting bacteriophages that might try to use it. The prophage might even help the host to survive conditions of low nutrition, as the death of the host would also mean the end of the prophage.

The phenomenon of lysogeny initially appeared to be the strongest argument against the theory that bacteriophages were viruses. As Sankaran writes, summarizing the Belgian microbiologist Jules Bordet, it was "impossible to imagine that the lysogenic bacteria had harbored viruses for generations without manifesting any signs of infection, and that it suddenly underwent lysis due to the action of those selfsame viruses."[9] From this perspective, Bordet claimed that "the invisible virus of d'Hérelle does not exist."[10] The ability to produce bacteriophages, he believed, was hereditary to the bacterium.

It was only after Oswald Avery, Colin MacLeod, and Maclyn McCarty demonstrated in 1944 that DNA controls heredity, that it became clear "the invisible virus" *does* exist, and in the form of a prophage. The evidence that host cells undergo lysis due to the action of viruses then became the strongest argument *in favor* of the virus theory of bacteriophages. The understanding that lysogenic bacteriophages remain dormant as prophages in the DNA of their host bacteria led to the idea that tumor viruses such as RSV could do the same—by making proviruses instead of prophages. Little wonder then that Sankaran refers to lysogeny as the lynchpin in her fascinating tale of two viruses.

DOI: 10.37282/991819.22.23

Raghavendra Gadagkar and Karumathil Gopinathan, "Inhibition of DNA Injection from Mycobacteriophage 13 by Tween-80," *Virology* 91 (1978): 487–88; and Raghavendra Gadagkar and Karumathil Gopinathan, "Bacteriophage Burst Size during Multiple Infections," *Journal of Biosciences* 2 (1980): 253–59, doi:10.1007/BF02703251. ↩

Arun Srivastava, Abraham Antony, and Thekkepat Ramakrishnan, "Molecular Mechanism for the

Specific Inhibition of Reverse Transcriptase of Rous Sarcoma Virus by the Copper Complexes of Isonicotinic Acid Hydrazide," *Biochemical Pharmacology* 27 (1978): 579–84; Arun Srivastava et al., "Studies on the Copper Complex of Isonicotinic Acid Hydrazide—A New Antiviral Drug," *Current Science* 46, no. 3 (1977): 69–71; and Arun Srivastava, "Antiviral Activity of Copper Complexes of Isoniazid against RNA Tumor Viruses," *Resonance* 14 (2009): 754–60, doi:10.1007/s12045-009-0072-y. ↩

Neeraja Sankaran, *A Tale of Two Viruses: Parallels in the Research Trajectories of Tumor and Bacterial Viruses* (Pittsburgh, PA: University of Pittsburgh Press, 2021), 3. ↩

Sankaran, *Tale of Two Viruses*, 12. ↩

Sankaran, *Tale of Two Viruses*, 18. ↩

Sankaran, *Tale of Two Viruses*, 18. ↩

See also Neeraja Sankaran, "Macfarlane Burnet: The Concept of Self," *Inference: International Review of Science* 4, no. 4 (2019), doi:10.37282/991819.19.41. ↩

Ying Chen et al., "Population Fitness and the Regulation of *Escherichia coli* Genes by Bacterial Viruses," *PLOS Biology* 3, no. 7 (2005): e229, doi:10.1371/journal.pbio.0030229. ↩

Sankaran, *Tale of Two Viruses*, 50. ↩

Sankaran, *Tale of Two Viruses*, 33. ↩

Raghavendra Gadagkar holds the Year of Science Chair Professorship at the Indian Institute of Science, awarded by the Indian Department of Science and Technology.

https://inference-review.com/article/parallel-histories
https://doi.org/10.37282/991819.22.23