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The strange history of phage therapy

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Since the enlightenment, scientists have enjoyed a self-image as rational actors, guided only by reason, evidence and logic. When the Royal Society of London was founded in 1660 it chose as its motto "nullius in verba" (often translated as "on the word of no one") a reference to Horace's Epistles "Nullius addictus iurare in verba magistri…" (being not obliged swear allegiance to any master). Similar to our 21st century contemporaries who embrace the "new evidenced-based medicine," the "virtuosi" of the Royal Society proclaimed a new era in science based only on observation and direct experience.

If we are, indeed, rational decision makers, assayers of evidence, and impartial truth-seekers, how are we to understand the curious history of bacteriophage therapy? The history of phage therapy, since the discovery of phages a century ago, has been fraught with conflicting observations, misinterpretations, and incomplete understanding, all of which are part of normal science. But there is more: the history of phage therapy is rich with politics, personal feuds, and unrecognized conflicts. Understanding these extra-scientific aspects of its history can help explain the tortuous course of phage therapy over the past century.

Soon after Félix d'Herelle discovered bacteriophages in association with diarrheal illnesses, he speculated that phages were responsible for the usual recovery from such disease through their antibacterial action in vivo.[1] Furthermore, he proposed to actively employ laboratory-produced phages as both prophylactic and therapeutic agents against bacterial infections. From its first field trials as a prophylactic against avian typhosis (*Salmonella gallinarum*) in rural France in 1919 to its widespread use in humans in the pre-antibiotic 1930s, phage therapy was controversial. Some saw it as the panacea for all infectious diseases while others thought it was over-sold and probably worthless.[2,3]

While it is no doubt true that the discovery and wide-spread availability of antibiotics in the immediate post World War era undermined enthusiasm for phage therapy, that is not the whole story. It is indeed true that phage preparations did not have the convenience of antibiotics, were not "broad spectrum," and suffered greatly from the scientific controversies on the biologic nature of phages that played out in the 1920s and 30s. These are, of course, rational explanations for the decline in phage therapy beginning in the 1940s. But what of the other, more subtle reasons for this decline?

Perhaps the most telling, most detailed, and most influential nail in the coffin of phage therapy was exemplified by a passage in the introductory chapter of the very influential 1963 monograph by Gunther Stent, one of the acolytes in Max Delbrück's "Phage Church." Stent discussed the use of phage therapy against a plague epidemic in the novel *Arrowsmith* by the Nobel Prize author Sinclair Lewis as follows:

"Though Lewis wrote *Arrowsmith* as early as 1924, he allowed his hero to reach what subsequent developments showed to be a most sensible decision: in spite of twenty years' intensive work, bacteriophages never became a successful medical tool. To be sure, many physicians managed to convince themselves of the efficiency of bacteriophage therapy,

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particularly in the control of cholera, but such converts remained everywhere in the minority. Nevertheless, as late as World War II, bacteriophages were said to have found employ in the medical services of the German and Japanese armies, and even today the medical use of bacteriophages still persists in some out-of-the-way places. But ever since antibiotics have shown themselves to be far more efficacious in the control of bacterial diseases than the most fervent proponents of bacteriophage therapy had ever dared hope for their panacea, the strange bacteriophage therapy chapter of the history of medicine may now be fairly considered as closed. Just why bacteriophages, so virulent in their antibacterial action in vitro, proved so impotent in vivo has never been adequately explained. Possibly the immediate antibody response of the patient against the phage protein upon hypodermic injection, the sensitivity of the phage to inactivation by gastric juices upon oral administration, and the facility with which (as we shall see presently) bacteria acquire immunity or sport resistance against phages all militated against the success of phage therapy."[4]

In this passage, read by almost every phage biologist at the time, Stent manages to undermine phage therapy in three key ways completely unrelated to scientific evidence. First, he suggests that its advocates were scientifically sloppy: "many physicians managed to convince themselves" clearly implies that these physicians, even referred to as "converts," suggesting religious faith rather than rational analysis, were guilty of wishful thinking rather than clear-eyed scientific judgment. Second, Stent associates phage therapy with the medicine of America's World War II enemies, the Germans and the Japanese. In the immediate post-McCarthy days of the cold war, phage therapy was somehow un-American. Third, "even today" phage therapy persists, suggesting an out-dated technology found only in "out of the way places." Phage therapy was consigned to the backward and the primitive regions of the globe. That Stent refers to "the strange bacteriophage therapy chapter" of medical history places it outside the narrative of progress and scientific triumph that is conventionally told about Western medicine. With authority and not a little hubris, Stent proclaims this chapter to "be fairly considered as closed." Briefly tipping his hat, so to speak, to scientific respectability, he wonders "Just why bacteriophages, so virulent in their antibacterial action in vitro, proved so impotent in vivo..." and then suggests answers that appeal to current biological knowledge.

Stent's verdict on phage therapy had its roots in the early controversies in phage research, the lack of understanding of phage biology, and the inherent difficulties of evaluating therapies in human clinical trials. This history is as personal as it is scientific. From the very discovery of phage, this field has been seen personal attacks, disputes of priority, massive egos, and international politics. All of these are part of the rocky history of phage therapy.

The very discovery of phage was the subject of a prolonged dispute between two camps: on one side was Félix d'Herelle,[5] the French-Canadian autodidact who first recognized phage in line with our current conception as a bacterial virus; on the other side were supporters of Frederick Twort,[6] a quirky British microbiologist who observed "tranmissible glassy transformation" of bacteria, but failed to follow up on his original observations. Twort was represented in these early controversies by an unlikely surrogate, the Nobelist Jules Bordet. This controversy, on the surface about the priority for discovery and about the biological nature of bacteriophage, had its origins, however, in hurt feelings and personal ambitions. D'Herelle was an unpaid volunteer at the Pasteur Institute in 1916 when he discovered the basic facts about bacteriophage that he observed in filtrates of dysentery fluids. He had been a peripatetic microbiologist in search of a discovery that, in his own characterization, would allow him to follow in the footsteps of Pasteur. The discovery of phage presented him with that opportunity: he immediately connected phage lysis in vitro with phage action in vivo to explain recovery of patients from dysentery. Phage became the agent of natural endogenous immunity. There was one problem, however, with this new theory. In 1919 Jules Bordet had been awarded the Nobel Prize for his work on immunity based on lysis of bacteria by antibodies, not phage. Undaunted, the iconoclast d'Herelle, in his second monograph on phage boldly challenged the famous Bordet, director of the Pasteur Institute in Brussels, by describing Bordet's work as "the history of an error."[7] This affront did not go unnoticed. Bordet and his protégé, Andre Gratia, responded with a nearly decade-long attack on d'Herelle and his work, challenging both his conception of phage as a virus (they thought it was an induced lytic enzyme) and his priority, arguing that Twort was there first. D'Herelle fought back vigorously, but lacking any real institutional base, a Nobel Prize, or a subtle nature, in 1931 he finally resorted to the Parisian courts to force the editor of the Annals of the Pasteur Institute to publish his challenge to a scientific duel between him and Bordet. As strange as it may seem to us today, most of the scientific community, including all the standard textbooks, sided with Bordet's conception of phage as a self-perpetuating lytic enzyme.

This view of phage as a lytic enzyme was strengthened by the support of another Nobelist who took up phage research in the 1930s. John Northrop of the Rockefeller Institute and a winner of a Nobel Prize for his work on digestive enzymes such as trypsin and pepsin, lent his authority to the idea that phage was another example of auto-catalytic self-activation similar to the trypsinogen/trypsin and pepsinogen/pepsin systems. It was not until the application of electron microscopy to visualize bacteriophage in the late 1930s that d'Herelle's viral conception of phage was vindicated.[8] Even then, this evidence was slow to percolate through the scientific community for an extra-scientific reason: World War II. The electron microscope was developed in prewar Germany and the first images of phage were obtained there in 1939, and published in the German literature in 1940. With the advent of the war, however, distribution of scientific literature was severely compromised. American libraries, for example, had their subscriptions mailed to Switzerland to be held

there until the war ended. In the midst of the war, German literature showing EM images of phage made its way into France where these images were republished, (with credit) in the French press.[9]

While debates, some scientific, some more personal, were raging over the nature of phage, other debates were playing out in the medical literature on the validity of phage as a therapeutic and prophylactic agent against bacterial infections. Again, the personalities of the protagonists loomed large in these debates. Assessing the effectiveness of a treatment is difficult in the best of circumstances and showing the value of prophylaxis is even harder. In these early days, standardized methods and materials, statistically controlled trials, and double-blind studies were nearly unheard of. Instead, small trials, anecdotal reports, historical controls and clinical impressions were the norm. Small wonder, then, that controversy arose. One approach to resolve ambiguity was attempted by the American Medical Association when it established a Council on Pharmacy and Chemistry which, among its other activities, routinely commissioned scholarly reviews of the literature to be published in the Association's journal. These reviews, sort of a precursor to a current "meta-analysis" were intended to balance conflicts, evaluate competing and contradictory claims and arrive at conclusions. Three such reports on bacteriophage therapy were published, the first in 1934,[10] the second in 1941[11] and the third in 1945.[12] All three agreed that the literature on phage therapy and prophylaxis was confusing and contradictory. All three reflected something of the evolving phage research of their time. All three contained strong personal biases.

The first AMA report on Bacteriophage Therapy was prepared by two Yale professors, Monroe Eaton, a young infectious disease specialist, and Stanhope Bayne-Jones, soon to become the Dean of Yale School of Medicine and an eminent bacteriologist.[10] Interestingly, Bayne-Jones had just been recruited to Yale from the University of Rochester to fill the vacancy in bacteriology left by d'Herelle's tumultuous departure for Tbilisi.

The second AMA report was published in 1941 authored by Albert Krueger, a partisan in the debate on the biological nature of phage and a protégé of John Northrop, and a young colleague, E. Jane Scribner. They emphatically supported Bordet's concept of phage as an autocatalytically activated "lytic principle" in opposition to d'Herelle's virus concept.[11] Krueger, in addition, was extending this polemic to the next generation of phage workers in his disputes with Emory Ellis and Max Delbrück, supporters of d'Herelle's position (Ellis, personal communication).

The third, and apparently last, AMA report on bacteriophage was published in 1945 by Harry E. Morton and Frank B. Engley Jr, which, only four years after Krueger and Scribner, in a complete reversal of prior dogma, fully accepted the viral nature of phage.[12] Indeed, a few EM pictures were worth many thousands of words.

All three reports exhibited the tension between laboratory study of phage therapy and its clinical applications, and between in vitro and in vivo action of phages on bacteria. The task of all the reviewers was not made easier by the lack of standardization of methods and materials: some trials were done with recent, patient-specific, phage isolates and some were done with one or another commercially available preparation. The commercial phage preps, often sold as polyvalent mixtures, sometimes had so much preservative in them that the phages were chemically inactivated. The composition of the preparations were unclear: one early worker recounted that while they originally prepared many different phage preps separately and then mixed them to achieve the polyvalent product, eventually they found it easier to mix the phages first, then grow them serially all together. This process, of course, assured that only the most virulent and rapidly reproducing phage were to be found in the final product (Max Delbrück, personal communication). With such uncertainties, conflicting and contradictory results were almost assured. The distinction between therapeutic and prophylactic application of phage was important, but sometimes overlooked as well.

Beyond the complexities and uncertainties of clinical trials, in the public mind bacteriophages came to occupy a murky position, as did all viruses in the late 1930s, "at the borderline of life." Their status as not quite living organisms and not quite simple chemicals intrigued both scientists and laymen alike.[13] That viruses could be crystallized, the gold standard of organic chemistry, suggested that they were "just" chemicals, yet their ability to multiply and mutate said they were somehow beyond chemistry, adding to their mysterious character. The primitive understanding of phage as biological entities was insufficient to clarify these contradictions. By contrast, the new sulfa drugs of the 1930s, simple and well-characterized organic compounds, were easy to use, quite uniformly and dramatically effective against important infections, and widely available. Antimicrobial chemotherapy was coming of age and became a challenge to phages as the answer to infectious diseases. Sulfas paved the way for the introduction of the antibiotics, potentially problematic because of their biological origin and complex chemistry, but accepted readily by a profession increasingly familiar with chemotherapy.

Medical practice in the US of this period was dominated by solo general practitioners, physicians without routine access to bacteriological laboratory resources, even for diagnosis let alone the complex support needed for effective phage therapy. Off-the-shelf medications and simple, locally compounded agents were the mainstay of general practice, and phage preparations did not fare well in this environment compared with the stable sulfas or even the new antibiotics that required only refrigeration for long-term stability. Phage therapy, even if it had been unambiguously effective, was just too complicated for the state of American medicine in the 1940s. The therapeutic niche for phage became occupied by the more "fit" antibiotics.

And then there was the political aspect of phage. D'Herelle left the US in 1934 and helped establish an institute to study phage and phage therapy in Tbilisi in the Soviet Republic of Georgia along with George Eliava, a former colleague from the Pasteur Institute. Phage therapy was developed, promoted and widely employed both in the Soviet Union and,

at least in some instances, by the German army in World War II. Such applications were not surprising since the first antibiotics were only available to the Allies and, initially at least, in very limited quantities. In the immediate aftermath of World War II, the earlier collaborations between the US and the USSR soon soured and all things "communist" became suspect in the West; that included Soviet scientific knowledge as well.[14] While there were some reasons for this attitude such as the rejection of Mendelian genetics by the Lysenko school and the discredited cancer cure of Kliueva and Roskin, much of the whole-sale rejection of Soviet science (at least until Sputnik) was political in nature. The eminent geneticist Tracy Sonneborn, for instance, was suspected of "communist sympathies" because of his interest in cytoplasmic inheritance in paramecium, a supposedly "pink" idea.[15] Any science, good or bad, embraced by "commies" was dangerous. As Gunther Stent noted, phage therapy was relegated to "out-of-the-way places" (at the time universally understood to mean the Soviet Union) and by implication was scientifically unsound because it was politically unsound.

The growth of the pharmaceutical industry in the post-war period played a role in the economic marginalization of phage therapy as well. "Big Pharma" made huge profits with the new antibiotics, the "wonder drugs." Easy to mass produce, easy to administer, and quite stable, as well as actually effective, antibiotics were seen as the way forward in dealing with bacterial infections. The last, lingering commercial phage preparations disappeared from the major pharmaceutical markets in the early 1970s. Slowly, however, as antibiotic resistance has emerged as both a clinical and public health problem, especially with the explosion in bacterial strains resistant to the basic penicillins (such strains as methicillin-resistant *Staphylococcus aureus*, MRSA), new approaches have been sought. The inherently intertwined problems of development of antibiotic resistance with widespread use opposing the failure to recover R and D investments in the face of restricted use, have made these problems even more urgent. In desperation, it seems, old prejudices may fall and new approaches may emerge. Phage therapy, of potential use in selected contexts, is being re-examined. Still, however, the debate continues.[16,17]

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