An Early History of Phage Therapy in the United States: Is it Time to Reconsider?

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Frederick William Twort and Felix d'Hérelle independently discovered bacteriophages in 1915 and 1917, respectively. This led to the early trials of using bacteriophages to treat infectious diseases worldwide. The earliest reported use of bacteriophages therapeutically in the United States was in 1922. With the subsequent discovery of antibiotics in the 1940s, and because of disappointing results of phage therapy in the next decade, use of bacteriophages as therapeutic agents declined in western countries. This paper addresses two questions in the field: what is the historical record of the successes and failures of phage therapy in the United States and, what led to abandoning phage therapy in the United States? We examined the literature from 1915 to 1965, and we present a numerical analysis of the papers published during that period. We report key historical factors leading to a decline in the use of phage therapy in the United States by the 1950s. Since bacteriophages were first used therapeutically, several changes have occurred: increased antimicrobial drug resistance and a better knowledge of the biology of bacteriophages are important examples. Early assessments leading to the rejection of phage therapy in the United States were perhaps appropriate. However, it is time to reconsider the role of bacteriophages in treatment of bacterial infections.

Keywords: Bacteriophage; Phage therapy; History, United States, Felix d'Hérelle

Bacteriophages are viruses that infect and replicate within bacteria and archaea. They may kill host cells by replicating intact new virion particles and lysing the host. This releases new viruses to infect adjacent cells. Alternatively, they may integrate their genome into the host's genome and replicate with the host for several generations (the lysogenic phase), reverting to a lytic phase under certain conditions. Bacteriophages are also referred to as phages¹ and their application to treating bacterial infections as 'phage therapy.'

Frederick William Twort² and Felix d'Hérelle³ discovered bacteriophages independently in 1915 and 1917, respectively.

Twort described a putative 'ultra-microscopic virus' from cultures of 'white micrococcus' he isolated from cultures of vaccinia virus. In hindsight, it would seem that the isolated lytic phages were bacteriophages against *Staphylococcus* species that were contaminants in a vaccinia virus culture.

F. H. d'Hérelle, on the other hand, isolated bacteriophage with activity against the *Shigella* bacillus from the stools of individuals recovering from bacillary dysentery. Abedon et al⁴ showed that even before their discovery, there were hints of the existence of bacteriophages, a period described as bacteriophage prehistory. The first clinical application of bacteriophages was by Felix d'Hérelle in 1919,⁵ with the first

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Received: July 20, 2020
1st Revision: November 30, 2020
2nd Revision: April 21, 2021
Accepted: April 22, 2021

doi:10.3121/cmr.2021.1605

reported use in the United States in 1922.⁶ The period from the early 1920s to the late 1930s saw an increasing use of bacteriophages to treat infectious diseases worldwide. This history is summarized by d'Hérelle in his 1931 paper⁷ and by Abedon et al in their review.⁸

Concurrent with the advent of commercial antibiotics in the 1940s, there was a decline in the use of bacteriophages as therapeutic agents in western countries, especially the United States. Instead, studies on bacteriophages shifted to furthering an understanding of their biology. The use of phages as therapeutic agents continued unabated, however, in Eastern Europe and Russia.

What then does history speak of the successes and failures of phage therapy in the United States? While there have been at least a couple of papers describing the history of phage therapy,^{9,10} we chose to focus this study on phage therapy in the United States to answer these questions.

Methods

We chose to examine the scientific literature from 1915 through 1965 to investigate the rise and fall of phage therapy. The date 1915 corresponded to the earlier discovery date of bacteriophages, and 1965 coincided with the year end of the

extensive bibliographies assembled by Raettig.^{11,12} We also performed an Index Medicus search on the period 1915 to 1965. We conducted a PubMed search using the MeSH keyterm 'bacteriophage' to obtain counts of articles published by year and a separate search filtering for 'human' and 'Clinical Trial'. The latter was to attempt to identify published results of clinical trials, especially in the last several decades.

Results

From their discovery onwards, there was a rise and fall in articles on bacteriophages published in the scientific literature between 1915 and 1965. Figure 1 shows the relative decline (light green) of phage therapy publications after about 1940. It also shows a widening gap with time between the total number of papers on bacteriophages (red line) and the papers on phage therapy (light green line) (gap indicated by double headed arrows). Figure 2 shows the number of articles indexed in *Index Medicus* by year, showing the total bacteriophages publications in each year in blue and those from the United States in red. The overall trend in number of U.S. publications was similar to that of the total number of publications in *Index Medicus*. The only difference noted was an earlier global peak in publications (in 1930) versus 1932 for U.S. publications. Table 1 compared articles grouped according to topics in the period 1915-1955 with the later period of 1956-1965. Note the significant decline in studies of phage therapy and prophylaxis (13.8% in the initial period to 1.9% in the later period). There was also a shift towards more studies on phage biochemistry increase from 14.9% to 18.2%, genetics (11.6% to 18.5%) and studies on lysogeny (increase from 8.3% to 12.5%).

Early Phage Therapy Worldwide

Very soon after discovery, d'Hérelle was probably the first to attempt to use bacteriophages therapeutically in 1919.⁵ d'Hérelle and several hospital interns at the Hôpital des Enfants-Malades in Paris ingested a *Shigella* phage cocktail to check its safety. He then administered it to a 12-year-old boy with severe dysentery. The boy's symptoms cleared up after a single dose, and he fully recovered within a few days. d'Hérelle subsequently administered a single dose each of the phage cocktail to three additional patients who also recovered within 24 hours of the administration. In 1923, d'Hérelle assisted with the founding of the Eliava Institute of Bacteriophage, Microbiology and

Figure 1. The number of bacteriophage scientific publications in the scientific literature by year according to Raettig in his bibliographies^{11,12} with the total number of papers shown in red and the phage therapy publications shown in light green. The single-headed arrow refers to the fall in numbers of scientific publications possibly from the Great Depression or World War II. The double-headed arrow show the large difference in the number of publications dealing with phage therapy compared with the total number of papers on bacteriophages

Figure 2. Graph of number of publications on bacteriophages indexed in Index Medicus showing how U.S. publications mirrored total publications. The fall in numbers of publications correspond to the Great Depression (1929 to 1941).

Virology,¹³ which became a major center for the development of therapeutic phages worldwide, and still is today. He also developed the Laboratoire du Bacteriophage in France in 1929.⁵ d'Hérelle embarked on several clinical trials of bacteriophage therapy, including a large-scale trial of phages against cholera in India,⁵ where he reported favorable results.¹⁴ In 1927, d'Hérelle and colleagues examined 33 patients. These patients were treated with the conventional treatment of fluids and salts; 13 patients died (mortality of 40%). The mortality rate was 30% (7/23) at a Calcutta hospital and

reported that 2 of the 12 children were negative for *Shigella* spp, and the number of cases was too small to justify any statement on the ineffectiveness of dysentery phage in children. Other workers in the United States were able to obtain results showing efficacy of bacteriophages.¹⁶⁻¹⁸ Spence and McKinley¹⁶ reported treating 19 cases of bacillary dysentery with 2 deaths in the treatment group versus 5 out of 12 cases in the control group. They also noted the average time of recovery was 5.8 days in the treatment group versus 12.8 days in the control group. Larkhum¹⁷ described using

approximated the 1926 cholera mortality rate of 27% at the same facility. There were 16 patients with cholera treated with a bacteriophage preparation, giving them 2 ounces of phage lysate each by mouth. None of these patients died. The study was expanded later that year. A total of 124 cholera patients did not receive the bacteriophage treatment, with a death rate of 63%. There were 74 patients who received the phage treatment, and their death rate was 8%.¹⁴

Bacteriophage History in the United States

Phage Therapy

The first use of bacteriophage therapy in the United States was in 1922⁶ by Davison; however, he concluded that the bacteriolysant (phages) had no therapeutic effect when administered to 12 children with dysentery. Morton and Engley¹⁵ reviewed the article and

Table 1. Papers published in the early and late periods in the scientific literature worldwide showing their distribution in different areas of bacteriophage study*

Topic	1917 - 1955		1956 - 1965	
	No.	%	No.	%
Reviews, studies of a general nature or contributions to the classification	858	15.2	433	7.7
Studies on the epidemiological utilization phages	699	12.4	1363	24.1
Studies of phage therapy and prophylaxis	782	13.8	106	1.9
Studies concerning the morphology of phages	192	3.4	222	3.9
Studies concerning the mechanism of reproduction of phages	756	13.4	523	9.2
Studies on the biochemistry of phages	841	14.9	1030	18.2
Studies into the immunity and serology in phages	250	4.4	117	2.1
Studies on lysogeny and bacteriocinogeny	471	8.3	705	12.5
Studies concerning phage genetics	655	11.6	1046	18.5
Studies in working techniques in phage research	151	2.7	199	3.5
TOTAL	5655	100.0	5744	100.0

*Note that between 1917-1955, papers on phage therapy made up 13.8% of all papers published on bacteriophages. This number fell to 1.9% in the period 1956-1965 (adapted from Raettig^{11,12}).

Figure 3. Graphical timeline showing key events in bacteriophage history with emphasis on events in the United States. The timeline for bacteriophages work is separated into that occurring in the United States (the dates in red) and Europe (the orange bar) versus that occurring in the Eastern Bloc countries (the purple bar).

bacteriophages in more than 300 cases of furunculosis, more than 50 cases of other skin infections, and osteomyelitis with success. Schultz¹⁸ described using bacteriophages successfully in treatment of dental infections.

By 1931, major U.S. companies like Eli-Lilly & Co, E.R. Squibb & Sons, and Swan-Myers (a division of Abbott Laboratories) began to produce commercial phage preparations for therapeutic use. Straub and Applebaum¹⁹ evaluated products from these three companies. Eli Lilly's product was in gel form, while the other two companies' products were fluid filtrates. The products were meant to treat infections caused by staphylococci and 'colon bacillus' (*Escherichia coli*). The products were analyzed by incubating them with host bacteria including several laboratory strains and some strains isolated from patients with bacterial endocarditis. They looked for lysis of bacteria, scoring the results in a scale ranging from 0 to 4+. Filtrates of the mixture were re-tested again in a fresh batch of bacteria. The authors' rationale was that bacteriophage propagate and were filterable. Therefore, they expected successive generations to yield the same positive results as the first incubated sample. With Eli Lilly's product, inhibition of growth of the host bacteria in the first generation was observed in some products tested, but the effect diminished with subsequent generations. This suggested to the authors that the bactericidal effect of the original preparation may have been due to something other than bacteriophage, such as a preservative.

The product of E.R. Squibb & Sons did yield positive results that improved with subsequent generations of filtrates, suggesting the presence of active bacteriophage. However, they analyzed two batches, and the results varied a great deal between them.

The *Staphylococcus* product of Swan-Meyers yielded a potent staphylococcal bacteriophage by similar testing. The fluid staphylococcus bacteriophage revealed, according to the authors, 'a genuine and potent bacteriophage which lysed only the staphylococcus' and contained no preservative. The titers measured rose from 10^{-2} in 4 hours to 10^{-7} in 24 hours and 10^{-9} in 48 hours. In contrast, their staphylococcus-colon bacillus product yielded only a 'poor colon bacteriophage.'

Figure 3 summarizes various phage therapy papers reporting work done in the United States with positive (phages cured the infection they were being used to treat) and negative (phages did not treat the infection successfully) results published in the period from 1915 to 1965. Figure 3 also shows a brief history of bacteriophages in a timeline. The U.S. history of bacteriophages is displayed in the context of bacteriophage history in general. Salient events in the U.S. history of bacteriophages encompassing both milestones in phage therapy and phage biology are shown.

In response to a growing debate on the utility of phages and the interest of industry, the American Medical Association commissioned Eaton and Bayne-Jones to report on the efficacy of phage therapy. This was published in JAMA in 1934.²⁰⁻²² The

stated purpose of the review was to 'present summaries and discussions of aspects of bacteriophages and to serve as a basis for a survey of the status of some of the commercial preparations.' The aspects the authors chose to focus on were: (1) the experimentally determined facts related to the bacteriophage phenomenon; (2) the laboratory and clinical evidence for and against the therapeutic usefulness; and (3) the relation of so-called antiviral to materials containing bacteriophages.

Citing 151 references, the authors listed seven conclusions, stated in italics and between single quotation marks, with our comments following:

1. *'Experimental studies of the lytic agent called 'bacteriophage' have not yet disclosed its nature. D'Herelle's theory that the materiel is a living virus parasite of bacteria has not been proved. On the contrary, the facts appear to indicate that the materiel is inanimate, possibly an enzyme.'* History has proved this conclusion wrong. Bacteriophages are viruses.
2. *'Since it has not been shown conclusively that the bacteriophage is a living organism, it is unwarranted to attribute its effect on cultures of bacteria or its possible therapeutic action to a vital property of the substance.'* Once again, history has proved this conclusion wrong.
3. *'While bacteriophage dissolve sensitive bacteria in cultures and cause numerous modifications of the organisms, its lytic action in the body is inhibited or greatly impeded by blood and other body fluids.'* The authors cited several studies to support this; however, studies done after the publication of their review with better controls and purer bacteriophage preparations have contradicted their conclusion (see references 45 through 49 discussed later in this article for examples).
4. *'The materiel called bacteriophage is usually a filtrate of dissolved organisms, containing, in addition to the lytic principle, antigenic bacterial substances, products of bacterial growth and constituents of the culture medium. The effects of all these components must be taken into consideration whenever therapeutic action is tested.'* This conclusion was certainly valid at the time of the authors' publication, although, more recent studies have remedied this criticism. (Once again, see references 45 to 49 discussed later for examples of studies using highly purified bacteriophage preparations).
5. *'A review of the literature on the use of bacteriophage in the treatment of infections reveals that the evidence for the therapeutic value of lytic filtrates is for the most part contradictory. Only in the treatment of local staphylococcal infections and perhaps cystitis (due to colon bacilli and staphylococci) has evidence at all convincing been presented.'* This conclusion was an accurate assessment of the many reports reviewed by the authors. They also cited the lack of adequate controls and the impure nature of the

bacteriophage preparations used as reasons for the contradictory findings.

6. *'There is no evidence that lysis or killing of bacteriophage occurs in vivo, except possibly in the bladder and in walled-off spaces, where little exudate is present and where irrigation with large amounts of bacteriophages can be used.'* This was an accurate conclusion based on the reports the authors reviewed in their papers.
7. *'The favorable results reported may have been due to the specific immunizing action of bacterial proteins in the materiel used and to nonspecific effects of the broth filtrates.'* The conclusion was speculative but possible based on the quality of bacteriophage preparations used at the time. This was reinforced by Krueger and Scribner^{23,24} in a follow up review published 6 years later. These significant reviews coincided with a fall in interest in bacteriophages as therapeutic agents in the United States.

While interest and belief in the efficacy of phage therapy declined, there were still intermittent efforts to continue research in their use. An anti-dysentery phage was researched from 1942 onwards by the National Research Committee on Medical Research involving a collaboration between Harvard, the University of Pennsylvania, and the Overly Biochemical Research Foundation.²⁵ There continued to be some modest successes, such as the treatment of typhoid fever with type-specific bacteriophage used intravenously.²⁶ Phages were used to treat chronic staphylococcal infections in the United States as late as 1987.²⁵

Phage Biology

Interest in bacteriophages after the aforementioned papers shifted from therapeutic applications to understanding bacteriophage biology. Around 1940, future Nobel Prize laureates Max Delbrück, Salvador Luria, and Alfred Hershey founded the Phage group at Cold Spring Harbor, New York.^{27,5} Bacteriophages helped define DNA (versus protein) as genetic material.²⁸ A bacteriophage was used in the work of at least three Nobel Prizes in Physiology and Medicine (1964, 1969, and 2018). The bacteriophage genome was the first genome sequenced²⁹ and completely assembled *in vitro*.³⁰ As bacteriophages became better understood, they became employed in molecular biology laboratories and studies, evidenced by the growth in publications as seen in Figures 1 and 2 from 1945 to 1965, while simultaneously, publications on the therapeutic use of phages declined.

Analysis

Historically, the failure of phage therapy during the 1930s has been attributed to lack of knowledge on the nature of phages (whether they were microbes or enzymes).⁵ To put this into perspective, DNA was discovered in 1953, and the electron microscope was first used to visualize viruses in 1939³¹ and bacteriophage specifically in 1940.³² Without a robust understanding of the nature of bacteriophages, it should come as

no surprise that there was large variation in preparations of bacteriophages and, consequently, inconsistent results of phage therapy experiments and trials. The concurrent emergence of well-defined and better-understood antibiotics in the same period led to their logical choice as antimicrobials. The period of 1939 to 1945 was a period of declining scientific publication (see Figures 1 and 2), largely due to the disruptive effects of World War II. It was also a period of increased use of antibiotics to treat war infections. The award of the 1945 Nobel Prize in Physiology or Medicine to Fleming, Chain, and Florey for penicillin signaled recognition of the impact of chemical antimicrobials over bacteriophages. There were several reasons for the rejection of phage therapy in the United States by the 1950s: (1) reports of failed therapy often due to inconsistent technique and skill in phage cultivation³³ (see figure 3); (2) commercial U.S. bacteriophage preparation with little or no bacteriophage content and inconsistent performance;¹⁹ (3) an incomplete understanding of bacteriophage biology; and (4) lack of rigorous clinical trials with adequate controls. Thus, history tells us that bacteriophages were rejected for reasons that were valid in 1950 but not in 2020. Modern bacteriophage trials use adequate controls, purified bacteriophage preparations, and sophisticated data analyses. Current National Institutes of Health (NIH) funded clinical trials of bacteriophages as potential therapeutic agents can be found at the NIH website (<https://clinicaltrials.gov/ct2/results?cond=&term=bacteriophage&cntry=&state=&city=&dist=>). The reader is also referred to the excellent literature review and analysis by Sulakvelidze et al.³⁴

The 21st century saw an improved understanding of bacteriophage biology and standardized methods to utilize them. Bacteriophages have been demonstrated to be constituents of normal human flora of the anterior nares,^{35,36} oral cavity,³⁷ urogenital tract,³⁸ and gut.³⁹ Several recent studies have suggested that bacteriophages are part of microbiomes in humans. Maqsood et al⁴⁰ showed transmission of bacteria from mothers to infants in the formation of their gut microbiome is affected by bacteriophages. Verbanic et al⁴¹ showed through deep sequencing that bacteriophages are part of wound microbiomes. Wang et al⁴² showed bacteriophages were part of the skin microbiome and there was differential bacteriophage composition noted between the microbiomes of normal and psoriasis skin. Finally, Ly et al⁴³ showed mouth and gut microbiomes are often shared by members of the same family and bacteriophages make up a sizeable portion of these microbiomes.

The increasing bacterial resistance to antibiotics, recognition of the importance of the microbiome, and that bacteriophages make up a part of these microbiomes have led several scientists and physicians to wonder if bacteriophages could be used as therapeutic agents. Attesting to their safety and providing anecdotal evidence of efficacy is their long-standing use as therapeutic agents in Poland, Georgia, and several other Eastern Bloc countries. The *Journal of the American Medical Association (JAMA)* also recently published the announcement of the first FDA approved U.S. clinical trial of intravenously administered

bacteriophage therapy on February 19, 2019.⁴⁴ There are also now several U.S. companies marketing phages for therapeutic use in animals and investigating future use in humans. Bacteriophages are once again being evaluated as potential therapeutic agents. The initial results⁴⁵⁻⁴⁹ from recent trials suggest a much more positive reception this time around than in the early trial of phage therapy. In the PHAGE study (n=43), Febvre et al⁴⁵ used a commercial cocktail of *E. coli*-targeting bacteriophages in a double-blinded, placebo-controlled crossover trial, in which normal to overweight adults consumed bacteriophages for 28 days. They demonstrated reductions in fecal *E. coli* loads with phage consumption. Leitner et al⁵⁰ reported in their randomized, placebo-controlled double-blind clinical trial (n=474), that intravesical bacteriophage therapy was non-inferior to standard-of-care antibiotic treatment for treating urinary tract infections in patients undergoing transurethral resection of the prostate. Schooley et al⁴⁷ reported on a method used to produce a personalized bacteriophage-based therapeutic treatment for a 68-year-old diabetic patient with necrotizing pancreatitis complicated by a multi-drug resistant *Acinetobacter baumannii* infection. They showed how administration of bacteriophages intravenously and percutaneously into the abscess cavities was associated with reversal of the patient's downward clinical trajectory, clearance of the *A. baumannii* infection, and a return to health.

Conclusion

Despite the discovery of phages in 1915, phage therapy was rejected after early use. Reasons for this included lack of early success in treating bacterial infections, discovery of antimicrobials in the 1940s, lack of high quality phage preparations in the 1930s, and a lack of understanding of phage specificity and phage resistance. With emergence of antibacterial resistance in clinically important pathogens, a better understanding of phage genomics, specificity, and their therapeutic power convinces us that there is a need to revisit phages as therapeutic agents.

Acknowledgments

We gratefully acknowledge the contributions of Barbara Bartkowiak, research librarian at the Marshfield Clinic Library in the collection of material for this paper. An early version of this paper was first presented as a poster at the American Society of Microbiology Meeting in 2014.

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