Phage as an antimicrobial agent: d'Herelle's heretical theories and their role in the decline of phage prophylaxis in the West

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The present report describes the presentation given by medical historian Dottore Emiliano Fruciano at the Stanier/Oxford Hygiene Symposium, held in Oxford, England, on November 10, 2004. Dr Fruciano's lecture, entitled "The failure of d'Herelle's project to consolidate the value of phage in the prevention and prophylaxis of infectious pathologies", provided a historical synthesis of the events that led to the dismissal of the amazing discoveries of Félix d'Herelle. The present article chronicles the profound works of d'Herelle, from spectacular scientific, commercial and political successes to complete obscurity. The impact of social perspectives on the outcomes of critical scientific research is revealed in this poignant account.

Key Words: *Bacteriophage; d'Herelle; Immunity; Medical history; Prophylaxis; Phage therapy; Stanier symposium*

Le phage comme antimicrobien : Les théories hérétiques d'Hérelle et leur rôle dans le déclin du phage comme agent prophylactique en Occident

Le présent rapport rend compte de la conférence prononcée par le professeur Emiliano Fruciano, historien de la médecine, à l'occasion du Symposium d'hygiène publique Stanier/Oxford, tenu à Oxford, le 10 novembre 2004. La conférence du Pr Fruciano, intitulée *The Failure of d'Hérelle's project to consolidate the value of phage in the prevention and prophylaxis of infectious pathologies* (L'échec du projet d'Hérelle de confirmer l'utilité du phage dans la prévention et la prophylaxie des infections), se voulait une synthèse historique des événements qui ont mené à la mise au rancart des étonnantes découvertes de Félix d'Hérelle. Le présent article retrace les grandes lignes des importants travaux réalisés par d'Hérelle et son cheminement, de ses fracassants succès scientifiques, commerciaux et politiques, jusqu'aux oubliettes où il est retombé. L'impact des enjeux sociaux sur l'issue de la recherche scientifique critique est révélé au grand jour dans cet émouvant compte rendu.

The Franco-Canadian microbiologist Félix d'Herelle (1873 to 1949) is credited with the discovery of bacteriophage, a bacterial virus, in 1917 at the Pasteur Institute in Paris, France (1). Through a number of trials and field experiments, d'Herelle discovered the usefulness of bacteriophage as an antimicrobial agent that was many thousand times more potent against bacteria than any agent known at the time (2). d'Herelle developed the idea of 'phage therapy', a therapeutic and prophylactic treatment designed to take advantage of phage selectivity in the cellular destruction of pathogenic bacteria while remaining completely innocuous to host cells (3). This model was poised to revolutionize the world of public health and become the 'magic bullet' described by Ehrlich. The progress of d'Herelle's research, from spectacular scientific, commercial and political successes through to complete obscurity, is followed to demonstrate the 'unique' relationship that exists between social factors within the scientific community and the outcomes of critical scientific research.

In 1917, d'Herelle and other microbiologists isolated phage able to kill then-known pathogenic bacteria, such as *Shigella dysenteriae*, *Salmonella typhi*, *Escherichia coli*, *Pasteurella multocida*, *Vibrio cholerae*, *Yersinia pestis*, *Streptococcus* species, *Pseudomonas aeruginosa* and *Neisseria meningitis* (4). These findings were the grounds for the development of specific treatments against a wide range of bacterial diseases in every part of the world, including large epidemics and epizootics that were either stopped or prevented.

Phage suspensions were administered by both topical application (5,6) and systemic administration through oral routes and/or injection (7-11). These applications were successfully used to treat staphylococcal infections of the skin, bone, eye, and others (12-14); intestinal pathologies such as typhoid, dysentery and cholera (15-18); and systemic infections such as septicemia (19-21). Also effective in disease prevention, d'Herelle's treatments were introduced into water supplies in high epidemic areas. In some cases, phage suspensions were administered to individuals. In each case, d'Herelle and his 'disciples' achieved great results, both at the individual level and at the population level.

These therapies and prophylaxis measures captured the minds and imaginations of the collective scientific, commercial and literary world. Sinclair Lewis published a novel in 1925 entitled 'Arrowsmith' (22) based on, and inspired by, the scientific events that led to the application of phage treatments; this book won the Pulitzer Prize. Parke-Davis, Lilly, Abbott and Squibb in North America, and Robert and Carrière in Europe, all large drug manufacturing companies, began to market phage as a therapeutic preparation, and d'Herelle's treatment became a commercial success (23). Political leaders gave a great deal of attention to the work of d'Herelle and its

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potential uses throughout the 1920s and 1930s. There was support from the political and scientific community, with trials carried out in the United States and as far as the Soviet Union.

THE SOCIAL PHENOMENON AND EARLY ACCEPTANCE

The international success of d'Herelle's approach can be demonstrated by its application throughout the globe. For example, phage was used to treat dysentery in Brazil (24), and in African countries, such as Senegal and Egypt, phage was used against dysentery and plague (25-27). In Britain, Italy (28) and Greece, the effects of phage against typhoid and paratyphoid were studied. At Stanford University (Stanford, California, USA) and the Public Health Laboratory of Michigan (Detroit, Michigan, USA), antistaphylococcal phage suspensions were produced and distributed to many hospitals (29).

During World War II, the German army used phage therapy (29), and it is alleged that German troops expressly occupied Georgia in the Soviet Union to seize the phage produced at one of d'Herelle's scientific centres (30). Between 1934 and 1936, it is known that d'Herelle established three phage production laboratories in Kiev, Kharkov and Tbilisi in the Soviet Union (31) by government invitation. The Red Army physicians also used phage therapy during the war in Finland (29).

In Paris, d'Herelle founded the 'Laboratoire du bacteriophage' in 1933 for the development and production of phage therapy, which became a scientific point of reference (32). The 'Bacteriophage Inquiry', a large-scale scientific investigation, was carried out in India between 1927 and 1936 (33,34). The purpose of the study, which was commissioned by the British Indian government, was to evaluate phage properties in the treatment and prophylaxis of cholera and plague (35). Phage therapy was also used in China and Japan (36).

The study of phage and its medical applications became a real research tradition within the 'microbiological paradigm' (37), as testified by the number of publications on the topic: between 1917 and 1948, over 6000 notes and memoirs on phage were published in scientific reviews (36), and between 1917 and 1956, 800 papers on therapeutic applications of phage were published in scientific journals.

THE DICHOTOMY

d'Herelle's studies experienced great commercial and scientific success in the 1920s and 1930s, but during the 1940s, the research focusing on the medical applications of phage was abandoned in North America and western Europe. Although the utilization of phage for therapeutic and preventative prophylaxis was abandoned, it is of note that in eastern European countries, the use and development of phage technology for therapy and prophylaxis has continued to this day (38-40). This decline in the therapeutic and prophylactic use of phage research occurred despite the positive findings in earlier studies and, in some cases, demonstrated effectiveness. In fact, both phage therapy and phage prophylactic measures were shown to be strongly correlated with positive outcomes (41). The following details some of the most sensational results in phage prophylaxis that would seem to contradict the eventual dismissal of d'Herelle's works.

In 1927, an epidemic of Asiatic cholera was halted at its start in several villages with 2000 to 3000 Punjabi inhabitants via two methods of phage prophylaxis delivery: the first was the addition of potent, individually dosed phage preparations, and the second was the administration of phage prophylaxis to local water supplies. In both scenarios, the epidemic was terminated within 48 h; in the past, the same result was achieved through traditional interventions within a 26-day time period (42).

Morison (43) administered phage on an individual basis. As a treatment measure, he selected two regions with the same epidemiological conditions: a population of approximately 600,000 inhabitants, cyclical epidemics of environmentally induced cholera and high rates of mortality. One region was taken as a model for classic intervention procedures involving vaccination and disinfection of the water supply with potassium permanganate, while the other region received solely phage prophylaxis. A series of flasks containing a mixture of different phage for dysentery and cholera were given to each headman, who then administered the contents of the flasks orally without considering the nature of the pathology, in the sense that diagnosis by laboratory analysis had not been made. This treatment continued until symptoms disappeared and the patient was deemed recovered. According to d'Herelle, the region where the phage had been used became progressively cholera free after phage was used for several years (42). d'Herelle (44) noted that Asheshov (a Russian bacteriologist and educator who specialized in research on phage), while conducting comparable research in Bihar, India, found that when traditional interventions were used to control cholera outbreaks, epidemics lasted an average of 26 days, whereas when phage was introduced into the well supply, the outbreak length was reduced to approximately 48 h.

Despite these instances, which are just examples of numerous other successes, d'Herelle's project was no longer embraced within the scientific community. There were claims that the trials carried out by d'Herelle and his supporters did not meet scientific standards for research, and, as such, did not produce compelling arguments to continue the use of phage therapy and prophylaxis. In this sense, the history of the 'Bacteriophage Inquiry' is exemplary: tests had not been carried out in a rigorously controlled manner and were not statistically significant (35). Contrary to the previously noted success, several eminent scientists highlighted the documented failures in the scientific research on phage and ascribed the exemplary results noted by d'Herelle and his followers to 'artifact' or positive findings resulting from limited knowledge of scientific rigueur and a predisposition to favourable conclusions, which led to meaningless speculation about the success of phage therapy (45-48). For these reasons, traditional approaches involving outbreak prevention through sanitary interventions and vaccinations remained the preferred option within the scientific community (35). There are a number of reviews that explain the failure of the scientific community to use phage as an antimicrobial agent (29,40,49-52). The reasons include methodological mistakes in research design (eg, lack of randomization, absence of control groups, careless diagnosis), and general ignorance of some biological phenomena, such as phage physiology, lack of standardization, bacterial resistance, narrow target range, process of clearance and inactivation by gastrointestinal substances. However, according to most contemporary authors, the introduction of penicillin to medical practice was the main reason for the lack of interest in d'Herelle's research.

Still, were the technical and scientific reasons enough to explain the sudden decline and antagonisms against d'Herelle's

scientific discovery? Were they enough to justify the approach of the scientific community? Probably not, when considering the exceptional qualities of phage as an antibacterial agent – that is, its activity against both Gram-positive and Gram-negative bacteria (natural penicillin had a weak activity against Gram-negative bacteria), the ability of phage to multiply exponentially when in the presence of bacteria (eg, ability to increase in titre; antibiotics, on the contrary, decrease in titre once administered), and phage's high selectivity. In addition, phage can rapidly adapt and initiate its action against bacteria (40,50,52-55). Phage also has no known side effects (except for phage encoding pathogenic genes) (56) and can be produced as a low-cost treatment (it is ubiquitous and easily available in the environment). Besides, in d'Herelle's time, effective methodology for the prevention of certain diseases was not available (for instance, in the case of cholera).

Furthermore, at the St Mary Hospital in London, England, where penicillin was first discovered, Himmelweit (57) developed a cross-therapy involving a combination of phage and penicillin to reduce the possibility of penicillin-resistant bacteria. This solution was very promising, because in vitro, it greatly reduced the rate of penicillin-resistant strains (58). Above all, the conjoined administration of phage and penicillin gave positive outcomes in clinical trials (59). It is likely that this experimental solution worked well because, as it is known today, the mechanisms by which phage and penicillin kill bacteria are different. Unfortunately, this alternative use of phage, in combination with penicillin, has been abandoned. Why has this possibility been forgotten despite the fact that antibiotic-resistant bacteria appeared as soon as penicillin was introduced (60) into medical practice?

SOCIAL FACTORS FOR DECLINING INTEREST

The potential of d'Herelle's prevention and treatment measures, as well as their initial acceptance and then sudden disregard by the political and scientific community, leads to the idea that some extrascientific factors played a fundamental role in the abandonment of d'Herelle's work. These factors can be described as social or, more specifically, as socioscientific. This notion is further reinforced by modern topical discussions regarding phage technology in contamination control and disease prevention in agriculture, food processing and hospital infection control. Renewed interest in the prophylactic application of phage in our modern society gives scientific credence to d'Herelle's research (52,61-64). The fact that prophylactic procedures with phage continued on in the Soviet Union after the 1940s further supports this theory.

Based on the return of interest, dignity and scientific plausibility to d'Herelle's findings, as demonstrated through experiments (54,65-68) and by the current commercial interests in phage treatments (56,60), it can be surmised that the social conditions that may have thwarted earlier exploitation of the possibilities no longer exist. These factors point to a socioscientific context in which d'Herelle's works were excluded from scientific research.

Summers (29), a historian of medicine who delved deeply into d'Herelle's scientific works, speaks of the "Soviet Taint" as a plausible reason for the lack of interest in phage as an antimicrobial agent. Following World War II, phage therapy research continued only in eastern European countries, and "d'Herelle's Cure" became "Stalin's Cure". According to Summers (29), phage therapy and prophylactic measures became ideological symbols of divisions and disagreements between western and eastern countries, partially explaining the lack of interest in phage as an antibacterial agent in Western medical science.

As many works in the field of social studies of science have demonstrated, acceptance of an experimental system is contingent on the credibility of the scientist, his 'persuasion ability', and the scientific, social and cultural contexts within which he is working. The consensus of other members of the scientific community must be gained so that a theory may become a 'scientific truth' or a technology can be accepted as 'effective'. The 'rhetorical' power of the scientist plays a key function in this process; to be successful, the scientist must become a 'spokesperson' of scientific, economic and social interests on behalf of powerful elements within the scientific community and society (69).

The experimental system cannot merely be explained in scientific words (70) because even randomized clinical trials, the gold standard of experimental models, are always the result of many different negotiations (71).

The technical content of a discovery does indeed have a social character, and, in conjunction with its technical-scientific content, it is critical to explore the 'social' reasons that explain the lack of interest in d'Herelle's scientific proposal, or at a minimum, evaluate the link between the scientific and social reasons for the lack of interest. In evaluating the scientific community's approach toward phage therapy and prevention measures based on phage research and utilization, the 'heretical' contents of d'Herelle's theoretical system and d'Herelle's position as an outsider in the scientific community (32) played fundamental and negative roles in the outcomes of his research; this premise is the main hypothesis of the present article.

'HERETICAL' THEORIES FOR THE FAILURE OF D'HERELLE'S PROJECT

In presenting his concepts to the scientific and world community, d'Herelle connected his phage interventions to a theoretical system that clashed with those held by institutional medical science. d'Herelle thought that the reason for natural recovery was not the humoral and cellular mechanisms activated by the immune system, but rather the presence of a virulent phage for the pathogenic bacterium in the host. His observations led him to believe that phage was a common guest of every organism from man to silkworm (2). He also believed that phage was in a state of microbiological antagonism with bacteria and was able to acquire virulence against them (3). Because he was only able to isolate virulent phage against pathogenic bacteria in convalescent patients, d'Herelle developed the theory that clinical improvement coincided with an increase in phage virulence in the organism; recovery was then attributed to the bacteriolytic action of phage. d'Herelle concluded that phage was the exogenous agent of natural recovery, leading to 'spontaneous recovery' (72).

According to his theories, the results of every infectious disease of bacterial origin could be derived from the reciprocal interaction among phage, pathogenic bacterium and host organism. Recovery was a case of the prevalence of phage over the bacterium, and death was a case of the prevalence of bacterium over phage and, consequently, over the organism. A chronic pathology by extrapolation would be a case of symbiosis between phage and bacterium and the development of a 'phage carrier mutant' bacterium d'Herelle coined 'bacterium-lichen' (3,44).

Furthermore, d'Herelle hypothesized that phage was able to spread among ill people, mainly via stool; thus, a lack of hygiene, while contributing to infection, would also lead to recovery; phage would have been the reason for the end of epidemics. This characteristic made phage, the recovery agent, transmissible between individuals, just like the agent of disease. Just as the disease was a contagious process, so was the recovery (73). And just as there was always a group of pathogenic microbe carriers at the beginning of an epidemic, there was similarly a group of virulent phage carrier convalescents at the end of an epidemic (72).

In support of his theory of natural recovery, d'Herelle cited exemplary phenomena, including recovery following exposure to cholera (26). In cholera, patients generally convalesced after two or three days (sometimes within 12 h) of initial symptoms; even 'artificial' recoveries through phage therapy often occurred after 24 h. However, according to d'Herelle (26), observations from many animal diseases had demonstrated that it took many more days for immunity to become effective in the fight against infection. To explain natural recovery through the mechanisms of immunity was not possible because of the timing. Moreover, in diseases such as typhus and plague, which are characterized by strong immunity, relapses were possible during convalescence. This would mean that the patient, although convalescing, was still not immune. In these kinds of pathologies, typically typhus and plague, immunity usually lasts forever, yet immunity only comes into play 20 days following convalescence. According to d'Herelle (74), "Immunity, far from being the cause of recovery, is a consequence of recovery".

Further confirmation of d'Herelle's theory was given by the statistics of the three hospitals in Calcutta, India. Paradoxically, the lowest rate of mortality for cholera (27%) was recorded at the hospital for poor people, the Campbell Hospital, while the highest rate of mortality (86%) was recorded at a hospital for rich people, the European Hospital – a hospital recognized in 1926 for its wealthy patients and hygienic conditions. There were fewer deaths at the hospital where care and hygiene were poor, that is, where the possibility for the development and dissemination of virulent phage or the recovery agent were best (73).

According to d'Herelle, immunity and recovery were two different processes; only after the bacteriolytic action of phage could immunity be developed. Furthermore, there were two kinds of immunity: heterologous immunity, linked to the presence of phage activity against the pathogen, and homologous immunity, linked to immune system activity (72). For this reason, d'Herelle (75) purported that "Immunity is contagious as well as the disease". In d'Herelle's estimation, heterologous immunity did not replace homologous immunity because they operated at different stages of the recovery process. Besides, heterologous immunity was preponderant in sensitive animals or in those 'without' immune systems able to protect the host, and was weak in animals that had a capable immune system against specific bacterial species (72). For example, according to d'Herelle, *V cholerae* does not cause cholera in rabbits because their immune system is able to protect the host from this specific pathogen; however, man contracts cholera because his immune system is not able to neutralize the bacterium. In d'Herelle's opinion, in the case of patients with cholera, recovery occurs because of the presence of a virulent phage for *Vibrio cholerae* as a result of heterologous immunity, not because of natural or homologous immunity.

d'Herelle found that the administration of phage resulted not only in a quick recovery, but also lasting immunity. He also asserted that a suspension of phage had strong immunizing power (here in the traditional sense) because the bacterial substances dissolved by phage action induced immune system reactions (74). In addition, when it was not bacteriolytic, phage provoked bacterial mutations that favoured immune system activity (44).

d'Herelle's findings were contrary to the conclusions of Metchnikoff, Bordet and Ehrlich, the founders of immunology (76,77). d'Herelle didn't expect a 'tabula rasa' of knowledge with respect to immunity; rather, he wished to interpret and integrate classical immunology into a theoretical system he believed to be closer to fact. Above all, he sought a theoretical system that acknowledged the fundamental role of phage in the process of natural recovery (74). From this theoretical point of view, phage therapy efficacy would have required a revision of the current explanation of natural recovery:

> "... if the theory of recovery that I have deduced from the observation of diseases is correct, it must be sufficient to administer to a patient a culture of a selected hypervirulent phage to provoke suddenly in the patient the natural phenomenon of recovery ..."

In other words, the proof of efficacy of phage therapy was equivalent to the proof of the truthfulness of d'Herelle's heretical theories. Thus, to verify the efficacy of phage therapy and prevention measures, the principles of modern medicine were at stake; this was a paradigm shift for the scientific community.

Recognizing this fact, d'Herelle could have made a 'renegotiation' of the principles of his therapy and prophylactic measures to make them theoretically compatible with the core knowledge of conventional medicine, but he did not. d'Herelle could have said that phage was a potent antibacterial agent; this would have avoided controversy through the statement that phage was the only agent of natural recovery and that the immune system could not provoke recovery. This would have been a scientifically plausible and coherent statement. Phage would have been, in this sense, 'simply' one of the many antibacterial agents available in nature. However, phage was a biological agent, as per d'Herelle's description, that could have revolutionized the principles of both theoretical and applied medicine. According to d'Herelle's followers, it was not simply a quest to develop an effective technology (phage therapy), but also to discover a secret of nature (78). They claimed that this secret of nature would have revolutionized not only microbiology, but also many other fields, including epidemiology, pathology, therapeutics and hygiene. In fact, according to d'Herelle, the real cause of natural recovery had been discovered.

Within the scientific community, there was total agreement on the fact that bacteriophagy, the disease of bacteria provoked by phage, was the cause of the dissolution of the bacterial cultures in vitro. However, the role of phage in the evolution of infectious disease, at the individual level and in the determination of the ends of the epidemic at the population level, had yet to be explained. It was a question of 'choosing' the role to give this very powerful, natural, bactericidal agent in the pathological process.

Until recently, the biomedical community had assigned a very minor role to bacteriophage in the mechanisms that determine both natural recovery and the end of epidemics; this is

witnessed, for example, by Lederberg (79), who noted that the natural history of bacterial infections, "where phage might play a role," is "a subject scarcely mentioned since d'Herelle's time". It would seem that the study of the role of phage in bacterial infections has been forgotten; however, there are some significant exceptions. Carlton (50), a scientist engaged for approximately a decade in the development of phage therapy, stated that d'Herelle may have been correct in asserting that epidemics can be checked through the spontaneous appearance of a lytic strain of phage; recent scientific studies support this statement (80-82).

But the question remains: were these findings exceptional or a recurrent phenomenon? Were these scientific refutations against phage ad hoc defenses to protect the theoretical core of modern medicine? These questions may be hypothetical in our modern times, but it is important to consider that d'Herelle believed that this infection of bacteria, provoked by phage, was the primary grounds for understanding the evolution of every kind of bacterial infection, and that this conception was at odds with the theories of modern immunology, theories that had won the Nobel Prize.

TECHNOLOGICAL AND ECONOMIC CONSEQUENCES OF D'HERELLE'S VIEWS

From d'Herelle's perspective, neither phagocytosis nor the action of antibodies was able to produce real bacteriolysis that led to the full destruction of bacteria. The only agent capable of bacteriolysis was phage (42). In fact, according to d'Herelle, the history of immunology and antibodies was a historical mistake full of "monstrosities" (42). In his opinion, no researcher had observed the lysis of a bacterium under the action of serum (75). The substances produced by the immune system would leave microbes not only alive, but with their general properties intact; this was not real bacteriolysis. d'Herelle regretted that the connection between this false bacteriolysis and immunity had become an intangible dogma accepted by everybody, a dogma hampering the development of true immunology (75).

This criticism was addressed, in general, to those "physicians in laboratory" who studied disease in unnatural conditions (42). Studies on immunity, in d'Herelle's estimation, should be carried out exclusively on animals naturally sensitive for the disease. False knowledge in immunology had been obtained by conducting research with 'artificial' or 'factitious' diseases provoked in animals naturally refractory to their effects (75). For example, the only animal naturally contracting cholera is man, and experimental cholera induced in laboratory animals would not have any relation to true cholera. He postulated that experimentally infected animals would have died due to peritonitis or septicemia as a result of imperfect procedures. During these tests, in fact, the challenged animals were infected by any microbe, and this was the real cause of their deaths. The animals did not show signs or symptoms of cholera (such as diarrhea) (42). For this reason, in d'Herelle's opinion, the conclusions that Metchnikoff attributed to an acquired immunity in the case of phagocytosis were not really attributable to an acquired immunity, but, rather, to a natural immunity (the animals studied by Metchnikoff were naturally refractory to that specific pathology). In choleric man, it was not possible to observe the reactions of the immune system typical of laboratory animals (42).

Furthermore, he maintained that cholera was studied by the "bacteriologists of the laboratory" using old vibrio strains that had become innocuous; vibrio would have kept its virulence only had it been reproduced in the intestinal mucosa. Consequently, in d'Herelle's opinion, even Koch's postulates had to be revised. It was not enough to pinpoint a microorganism as the causative agent of a disease. Rather, the following had to be demonstrated: its presence was revealed in all cases; inoculations of its pure cultures produced the disease in susceptible animals; and from these, it could be isolated again and propagated in pure cultures. Furthermore, it also had to be shown that when the agent was administered to a laboratory animal, the resultant experimental disease showed the same symptoms and the same level of contagiousness as the natural disease (42).

At stake in this debate about immunity and natural recovery was more than an accepted collection of theories of fundamental importance, or the reputation and credibility of those who promoted these ideas (eg, Ehrlich, Metchnikoff and Bordet). The technologies and economics linked to the fields of research and treatment were also at stake. Diminishing the importance of immunity mechanisms meant scaling down serotherapy and vaccines in the therapy and prophylaxis of infectious disease. This may explain the strong opposition to phage therapy at some of the most important research centres, such as the Pasteur Institute (42,83), a leader in the production of various therapies and prophylactic treatments based on the classical notions of immunology. Such a paradigm shift would have revolutionized the strategies of research, production and marketing for drug companies and prestigious research institutes.

d'Herelle and his disciples affirmed that vaccines and serotherapies did not work, at least not in accordance with the theories of conventional medicine. Sera, for example, would have been active exclusively against bacterial toxins and not the bacterium responsible for disease (3). In diseases with relapse, antibodies would be at their peak during the relapse and possibly at the time of death, demonstrating that the bacteria were not rendered impotent (42).

For instance, vaccines and serotherapy against cholera were considered by d'Herelle to be ineffective and dangerous. This was confirmed, according to d'Herelle, by the deaths in the regions where they were used. In general, every therapy and preventive measure derived from traditional immunology was a real "public danger" (42).

THE SCIENTIFIC CONTROVERSIES

The heretical nature of d'Herelle's theories may explain the attacks against him by the so-called 'Belgian group' (84) of authoritative scientists linked to Bordet, who was the director of the Pasteur Institute in Brussels and one of the founders of modern immunology. The Belgian group opposed the viral conception of phage proposed by d'Herelle (85). There was no conclusive evidence at the time because the electron microscope had yet to be discovered. Furthermore, the enzymatic theories were contrary to d'Herelle's findings, and were successful in their time due to the political and scientific weight of their proponents rather than the objectivity of proof that had been presented (86). d'Herelle purported that phage was a virus because:

- it had a corpuscular nature;
- it was a filterable agent (via porcelain filters);
- it was able to multiply infinitely; and
- it was able to maintain its infectious power against bacteria even after innumerable dilutions (1,2).

In addition, d'Herelle deemed that phage was a true living entity because of its metabolism, which was demonstrated by its ability to secrete diastases (26).

On the contrary, opponents to his theory believed that the lytic principle was linked to an anomalous working of bacterial metabolism, such that the attributes associated with phage were actually the result of an enzyme autoproduced by bacteria, causing a hereditary disease transmitted among bacteria (76). According to van Helvoort (76), the viral definition of the time would have made it possible to prove that phage was the agent of natural recovery; on the contrary, the enzymatic conception was more compatible with the explanation of natural recovery given by institutional medicine, which stated that natural recovery resulted from mechanisms of immune system defence. This fact, and the fact that Bordet's group probably studied lysogenic phage instead of lytic phage (77), may explain why the Belgian group supported the enzymatic explanation of the nature of phage, despite the evidence (42,76).

The Belgian group also attacked d'Herelle "cruelly and viciously" because they thought he had unjustly attributed to himself the discovery of phage. Twort (87), an English microbiologist, had in fact published observations linked to the bacteriolytic action of phage two years earlier. Some historiographic studies have documented the substantial good faith of d'Herelle and the pretext of the attacks of the Belgian group against him (84). Actually, Bordet turned attention to Twort's discovery because the English scientist was inclined to the enzymatic nature of phage (84). Nonetheless, within this controversy, the Belgian group attempted to make d'Herelle appear the fool, but these were not the only obstacles diminishing d'Herelle's credibility and the destiny of d'Herelle's findings. d'Herelle also had a troubled relationship with Calmette, the Deputy Director of the Pasteur Institute of Paris from 1919 to 1933, due, once again, to his point of view on vaccination. d'Herelle considered the bacille Calmette-Guérin vaccine against tuberculosis developed by Calmette as ineffective and dangerous (42). For this reason, Calmette may have persecuted d'Herelle throughout his career and may further explain why d'Herelle suddenly left the Pasteur Institute in 1921.

It is important to note that d'Herelle was never engaged in a titular post at the Pasteur Institute, despite his important discoveries. In fact, d'Herelle's accomplishments were not limited to the discovery of phage; he also elaborated much of the constructs that became the foundation of molecular biology (32), as well as laboratory methodologies that are still used today in virology (83,88). In addition, he was responsible for a number of biological methods that continue to be used for insect control. For these discoveries, he was never rewarded fittingly inside or outside of the Pasteur Institute (36,89). The relationship d'Herelle had with the Pasteur Institute is reflective of his relationship with the whole scientific community; in fact, his move to the Soviet Union may have simply been an attempt to escape the attacks of Western scientists (30).

It appears as though d'Herelle was not considered a serious scientist by his colleagues due to his flamboyant personality and scientific style that was more inclined to hostility than persuasion (37). In some cases, he was even considered to be deceptive (90,91). His particular style created many important enemies in and out of the scientific community, because he had no patience for those who did not agree with him. Indeed, he who was not with him was against him (84).

It is also important to note that d'Herelle was an autodidact – he never ended his medical studies (32,83,88,92), nor did he have a true scientific patron (30). For these reasons, d'Herelle was both an outsider and a paradoxical figure; although his abilities as a microbiologist were well recognized, his scientific convictions, for the most part, were not (49). He occupied prestigious posts, such as Professor at Yale University and Director of Bacteriological Services for the League of Nations, and he received prestigious awards, such as the Lane Lecture (93) and honorary doctorates; however, he never did receive the Nobel Prize, despite the intrinsic value of his work and his 28 nominations between 1924 and 1937.

It is not difficult to surmise that his personality, style, credibility and approach affected his position in the scientific community and, ultimately, influenced the destiny of his discoveries about phage (94).

WHY WAS D'HERELLE'S RESEARCH ABANDONED BY THE SCIENTIFIC COMMUNITY?

Carter (37) writes that the history of phage therapy:

> "... is a notable example of the negative impact an investigator's personality can have on the outcome of a discovery. Surely the prospects of phage therapy in the historical era would have been better served if d'Herelle had possessed some of the personality traits and scientific style of Pasteur".

If d'Herelle had introduced his therapy and prophylaxis measures into an ensemble of theories that could 'fit' or be integrated with other notions of conventional medicine, would research on the therapeutic and prophylactic application have continued? Was the decline in the use of phage as an antimicrobial agent linked to d'Herelle's inability to manage and promote his discoveries in the institutional environment of science? These questions still require historical and social analysis with respect to d'Herelle's heretical theories and their role in the decline of phage prophylaxis in the West.

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