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On the history of the discovery of bacteriophages

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The article is devoted to an analysis of the significance of bacteriophages' discovery in the subsequent development of medicine: from the prevention and control of infectious bacterial diseases to the study of global evolutionary mechanisms by genetic engineering methods. French researcher Felix d'Hérelle discovered bacteriophages when he found a "substance" that kills dysentery bacteria in 1917. A virus by nature, it was called a "bacteria devourer" (bacteriophage). Long before the discovery of antibiotics, d'Hérelle found that bacteriophages were a universal specific antibacterial agent that was safe for humans. In Russia, interest in the study of bacteriophages arose in the early 1920s. In 1939, the renowned Soviet microbiologist Z.V. Ermolieva created a cholera bacteriophage preparation. During World War II in besieged Stalingrad, she produced the cholera bacteriophage in huge volumes and prevented an epidemic of cholera in the Red Army – an important factor in the victory in the Battle of Stalingrad. New molecular biology and genetics technologies have made it possible to reveal the underlying interaction processes of a bacteriophage with a bacterial cell: lysogeny (inclusion of a moderate bacteriophage into the genome of a bacterial cell) and the phenomenon of lysogenic conversion (Eugene and Elizabeth Wollman, 1936), genetic recombination – the mutual exchange of genes between two different lines of bacteriophages (M. Delbruck, S. Luria, A. Hershey, 1946, 1952), integrated with the cell's DNA, the asymptomatic presence of the virus (pro-bacteriophage), and its activation by the inductive effect of ultraviolet radiation, radiation and a number of chemical factors (A. Lwoff, 1965). Nowadays, the study of molecular genetic mechanisms of embedding, regulation, repression, and induction of bacteriophage activity within a bacterium is important for understanding the mechanisms of heredity, tissue growth and development mechanisms of some forms of tumors.

Keywords: *viruses, bacteriophages, infectious diseases, lysogeny, prophage, genetics, Felix d'Hérelle, Zinaida Ermolieva, André Lwoff*

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Bacteriophages are bacterial viruses that were discovered in 1917. Today, bacteriophages are commonly used not only as an effective treatment and preventative in controlling infectious bacterial diseases but also as a tool to investigate underlying processes (at the genetic and molecular biology level) which enables the study of horizontal gene transfer in the microscopic world. These studies pulled back the curtain on global evolutionary mechanisms and provided modern-day biology with genetic engineering technologies.

This article is devoted to analysing the significance of the discovery of bacteriophages

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and the role played by the eminent scientists who made the greatest contribution to the study of these viruses.

Born in 1873 in Montreal to a family of French immigrants, *Felix d'Hérelle* (1873–1949) was a pioneer of these studies. With neither biological nor medical education, but having an inquisitive mind, an extraordinary zest for life and a passion for science, he travelled extensively and by the age of twenty-five, in spite of financial difficulties, he had visited many countries in Europe and South America, educating himself all the while. The turning point in his career and interests came in 1911 when he found himself at the famous Pasteur Institute in Paris as a volunteer. Here the focus of his scientific interests turned to microbiology – to the study of infectious diseases and pest control. On a trip to Mexico, he isolated the *Coccobacillus acridiorum* bacteria which affect locusts and attempted to use them in controlling these pests [1].

The work of our compatriot Ivanovich Ivanovsky (1864–1920), who discovered viruses, was already well known at the turn of the 20th century. While filtering juice from diseased tobacco plants in 1892, he noticed that minute particles were passing through bacterial filters and that these particles could have a specific effect on healthy plants. In 1898, Dutch microbiologist *Martin Beyijrinck* (1851–1931) repeated D.I. Ivanovsky's experiments and called the causative agent of tobacco mosaic a *liquid virus* (Latin, *virus* – "poison"), after which these microorganisms became known as viruses. In the scientific fields, interest in viruses grew steadily and soon many viruses affecting plants, animals and humans were discovered.

Unlike bacteria, viruses have no cell structure and primarily consist of *nucleic acid*, surrounded by a protein coat (capsid); they propagate only inside a living host cell, i.e., they obligate parasites.

The danger posed by viruses (similar to that posed by bacteria) in causing deadly diseases and millions of fatalities came to be understood in the thick of World War I. Soldiers in the trenches died not only from enemy fire but also from microorganisms that found their way into their wounds, food and water. It was at this time that Felix d'Herelle's star rose, when he made a discovery on par with the works of *Robert Koch (*1843–1910), *Louis Pasteur* (1822–1895), *Emil Adolf von Behring* (1854–1917) and other trailblazers who had defined new areas in medicine and laid the foundation for modern-day microbiology [1].

In 1917, while searching for a drug that could help French soldiers suffering from dysentery, d'Herelle discovered a "substance" that killed the bacteria causing this disease [2]. At one stage during his research, he passed the gut contents of a sick soldier through a bacterial filter (as D.I. Ivanovsky had done with a tobacco mosaic virus solution). The pores of the ceramic filter were so small that dysentery bacteria (*Shigella)* would not pass through the filter. After obtaining a pure solution and adding it to a Petri dish with bacteria, he discovered areas without growth (lysis zones), which meant the death of Shigella bacteria. After collecting material from the lysis zone and filtering it once more, he mixed the filtrate with new samples of Shigella bacteria (within the *Shigella* genus, four species cause dysentery). Again he noticed the same lysis zones in the Petri dish, and the amount of the lysing agent itself had actually increased (i.e., the agent had multiplied) [3]. D'Herelle brilliantly concluded that the *viruses* had killed the bacteria and he gave them a name – *bacteriophages* (derived from the ancient Greek *bacterion* [staff] and *phagos* [to devour]), which means "bacteria devourers", or simply *phages*. D'Herelle not only isolated the virus which causes lysis of the causative agent of dysentery, but also relatively quickly established its production and began to successfully use it to treat bacterial diseases [4].

D'Herelle's discovery was so unexpected and unusual that many renowned microbiologists doubted the existence of bacteriophages and their effectiveness in treating bacterial infections. One of the sceptics was *Jules Bordet* (1870–1961), Nobel laureate in 1919 and discoverer of the causative agent of whooping cough.

It took many years of scientific debate for d'Herelle's discovery to be validated. At last he was granted well-deserved recognition: he was elected honorary doctor at Leiden University (1925) and professor at Yale University (1928). The debate over the existence of bacteriophages was only settled in the 1940s after the invention of electronic microscopes, which enabled one to see these viruses with one's own eyes.

So how does the bacteriophage, this little killer of bacteria, dispatch its victim? Upon encountering a target cell, the bacteriophage recognises it by way of the specific receptors on its capsid, adsorbs onto it and injects its nucleic acid into the bacteria. The empty capsid remains outside the cell, just like a used syringe. Inside the cell, the viral genome takes over the life of the cell and through cellular biosynthesis mechanisms reproduces itself a multitude of times, killing the host cell in the process. This is the so-called productive or virulent stage of the growth of bacteriophages, which is well-known today. The mechanisms of interaction between phage and bacterium were studied much later, between the 1960s and the 1980s, but a hundred years ago, through his scientific genius and experience, d'Herelle recognised that bacteriophages could be used as a universal and very effective antibacterial factor. Continuing his work with bacteriophages, he successfully used them to treat not only dysentery but also plague in Egypt and Indochina, and later cholera in India.

By that time there were already enough experimental materials to demonstrate that nearly all bacteria have their own bacteriophages, meaning that 1) the existence of bacterial viruses is universal in the microscopic world, 2) bacteriophages possess the highest degree of specificity to the host (i.e., bacteria) and 3) bacteriophages are not pathogenic to humans and do not cause disease. Bacteriophages were therefore deemed a reliable, specific and safe medicinal agent and, in some cases, a preventive agent against infectious diseases of various aetiologies.

Antibiotics had not yet been invented at this time. The era of antibiotics began after the discovery of the antimicrobial effect of penicillin by *Alexander Fleming* (1881–1955) in 1929 and the mass use of antibiotics from the late 1930s to the early 1940s. Interest in bacteriophages cooled and doctors increasingly began prescribing antibiotics in place of phages. Pharmaceutical companies that had been manufacturing bacteriophages switched to the new highly effective drug – antibiotics.

However, in our country the study and use of bacteriophages to combat infectious diseases continued. In 1923, d'Herelle visited the Soviet Union, giving a boost to scientific and practical interest in the study of bacteriophages among local scientists. The *Eliava Institute of Bacteriophage, Microbiology, and Virology* was established in Tbilisi. During World War II, this institute played a key role in manufacturing bacteriophages to treat pyoinflammatory diseases (staphylococcal bacteriophage), as well as intestinal infections (salmonella polyvalent and coli-protein bacteriophages).

One of the crucial areas of Soviet bacteriology in the 1920s was the fight against such a widespread intestinal toxicoinfection as *cholera*. The epidemiology of this deadly infection was the work of renowned Soviet bacteriologist Zinaida Vissarionovna Ermolieva (1898–1974), who continued on the path set by d'Herelle.

During a cholera outbreak in Afghanistan in 1939, Z.V. Ermolieva travelled to Central Asia. To prevent the infection from spreading across the border (for emergency prophylaxis), her cholera bacteriophage preparation – the most effective means of combating what was then a mortal disease – was used for the first time [5]. It is worth noting the undoubtedly urgent need to create such a preparation, given that cholera was considered inevitable during the war. During the Crimean War in 1854–1855, for example, Anglo-French forces lost thousands of soldiers to cholera. Isolated cholera cases were also reported in the Russian army that defended Sevastopol.

In the early 1940s, while working at the Tashkent Institute of Vaccines and Serums, Z.V. Ermolieva created a compound bacteriophage preparation which was capable of combating causative agents of not only cholera, but other dangerous infectious diseases (such as typhoid fever) as well. The results of her studies played a critical role during World War II in besieged Stalingrad, where in 1942 her cholera bacteriophage prevented an epidemic of cholera in the Red Army after the disease was brought into the city by Fascist troops [5]. Unable to bring bacteriophage preparations from unoccupied parts of the country, Ermolieva established the production of the cholera bacteriophage in besieged Stalingrad in a basement laboratory she had set up. With her colleagues, she cultivated a cholera bacteriophage population in large bottles filled with a culture medium and Vibrio cholerae growing in the medium. The so-called culture filtrate was then transported to the Red Army at the front line, where each soldier was administe-

red per os a spoonful of the bacteriophage solution. Tens of thousands of people were served a day. At the same time, the preparation was also being used to prevent cholera among the civilian population in the city. In the end, a cholera outbreak in the Red Army was prevented, while the disease continued to wreak havoc among German soldiers. For the successful control of infections and phagoprophylaxis of cholera at the Stalingrad Front, in late 1942 Z.V. Ermolieva was awarded the Order of Lenin, and in 1943 she was awarded the State (Stalin) Prize of the 1st degree. The achievements of renowned bacteriologist Zinaida Vissarionovna Ermolieva and her contribution to victory in one of the greatest battles of World War II were thus recognised.

The mass use of antibiotics to treat infectious diseases began after World War II. This was largely made possible by the isolation of penicillin in crystal form in 1940 by *Ernest Chain* (1906–1979) and *Hovard Flory* (1898–1968; Nobel Prize winner of 1945, along with A. Fleming), as well as the discovery of streptomicin – the first effective anti-tuberculosis antibiotic, which was isolated in pure form in 1944 by *Selman Waksman* (1888–1973; Nobel Prize winner of 1952). It was Waksman who introduced the term "antibiotic" into scientific vernacular (Latin, *anti* – "against" and *bios* – "life").

H. Flory and E. Chain established mass production of penicillin in 1943. In our country, Z.V. Ermolieva, while working at the All-Union Institute of Experimental Medicine, set the goal in 1942 of producing penicillin from *Penicillium* fungus strains locally. Her greatest achievement was that she not only was the first in our country to produce penicillin (*benzylpenicillin*), but also during the most difficult years of World War II was actively involved in organising and establishing mass production of this first locally produced antibiotic. In the autumn of 1944, a team of researchers and doctors (the group of microbiologists was led by Z.V. Ermolieva) tested this preparation in the field. The preparation passed the test on the front line and demonstrated high effectiveness, on par with its American counterparts [5].

Many of the antibiotics (such as chloramphenicol, polymyxin and erythromycin) that are well known and widely used in medicine today were discovered in the twenty-year period from 1940 to 1960.

What about bacteriophages? Was there any remaining scientific interest in the phenomenon of bacterial viruses?

A new surge of interest in bacteriophages emerged following advances in molecular biology and genetics. The study of the physiology of phages had started in the early 1930s, although new experiments using more refined techniques were aimed at revealing underlying processes of the interaction between phages and bacterial cells – processes often investigated at the molecular genetic level [6]. First Australian *Frank Burnet* (1899–1985) – and later *Max Delbrück* (1906–1981), a German American physicist who had emigrated to the USA in 1937 for political reasons; *Salvador Luria* (1912–1991), an Italian doctor who had also emigrated to the USA when Italy joined the war on the side of Germany; and American chemist and microbiologist *Alfred Hershey* (1908–1997), along with colleagues working at different universities, and often on different continents – discovered genetic variations of bacteriophages (phage mutants) and investigated their development cycle [7–10]. Their studies confirmed the similarity between molecular genetic mechanisms of the functioning of viral and cellular genomes, and also created a foundation for understanding the antigenic diversity of viruses.

The interaction of such bacteriophages with bacteria did not always lead to the death of the bacteria, but more surprising was that the replication of bacterial DNA during propagation was accompanied by the replication of phage DNA. Such bacteriophages were called temperate phages. Luria described these phenomena in the 1980s thus: "The coexistence of bacteriophage and bacteria may continue throughout many cell division cycles. Such a latent genome of a phage is called a prophage and bacteria containing such phages are called lysogens. The following two conditions must be met during formation of such an established cell line. First, during each cell division the daughter cell must contain at least one copy of the prophage. Secondly, there has to be repression of viral genes capable of violating the integrity of bacteria" [11, p. 259]. However, the most remarkable discovery was made during further analyses: under the influence of some factors (repressors) lysogens are resistant (immune) to superinfection by a phage of the

same type. However, under certain internal and external effects, this immunity vanishes and new-generation bacteriophages, after killing and exiting the previous host, integrate into their genome part of the information inherited from the lysed bacterium.

These conclusions, which are promising for modern-day genetic engineering, were first reached in 1936 by a Russian immigrant couple – Eugéne and Elisabeth Wollman (née Elisabeth Michelis) – working at the Pasteur Institute in Paris [12]. Based on years of meticulous experiments, the Wollmans arrived at a revolutionary idea for molecular biology – the link between phage and cell heredity, i.e., the integration of viruses into the genetic material of the cell. They demonstrated that if a bacterium is infected with a lysogeny-inducing phage, all bacteria derived from it will contain the same phage [13, p. 357]. Unfortunately these conclusions, which were then ahead of their time, failed to garner support, but they antedated many crucial hypotheses that would later seem obvious to molecular biologists, in the field of decoding the genetic code, gene structures, horizontal gene transfer mechanisms and much more, which forms the foundation of modern-day genetics. However, in their own time these ideas never received their proper recognition, and the Wollmans' discovery had to wait [14]. Much later it became clear that lysogeny is widespread in nature as a universal mechanism of the associative existence of a parasite and a host and is an evolutionally balanced system with the least harmful effect of the virus on the bacterium.

After the tragic death of the Wollmans at the Auschwitz concentration camp in 1943, M. Delbrück and A. Hershey continued the Wollmans' work. Simultaneously but independently, they discovered that genetic information (genes) can be exchanged between two different lines of bacteriophages if the same bacterial cell is infected by multiple bacteoriphages at the same time (1946). This phenomenon, which they called *genetic recombination*, was the first experimental proof of DNA recombination in viruses.

The footprint of the discoveries made by Delbrück, Hershey and Luria can be found in any genetic study conducted in subsequent years. However, as often happens, their recognition came much later than that of scientists who had been inspired by their work – the Nobel Prize in Physiology or Medicine "for their discoveries concerning the replication mechanism and the genetic structure of viruses" was only awarded in 1969 [15]. When presenting this award, Sven Gard from the Karolinska Institute (Stockholm, Sweden) noted that in this discovery "most of the credit belongs to M. Delbrück, who moved the study of bacteriophages from the realm of wandering empiricism to exact science" [16, p. 1124].

*André Lwo*ff (1902–1994), the son of Russian immigrants, a staff member and later department head at the Pasteur Institute in Paris (1938) and professor of microbiology in the faculty of sciences at the University of Paris (1959), was concurrently working with bacteriophages in the 1950s [17].

A. Lwoff generalised and organised all of the knowledge accumulated by his predecessors and concluded that a bacteriophage exists in a bacterium not as an abstract non-infectious form (*prophage*), but in a state integrated with the cell genome, which state he named *probacteriophage*. Lwoff in particular investigated the molecular genetic mechanism of embedding, regulation, repression and induction of phage activity inside bacteria and demonstrated that after entering a bacterial cell, the genetic material of the virus (bacteriophage) can be incorporated into the DNA of the cell in the form of an inactive prophage and becomes part of the genetic apparatus of the cell, which can later be activated by external effects. The portion of the bacteriophage which is homologous to the portion of the bacterial chromosome, Lwoff noted, integrates with it, thus becoming an integral part of the chromosome, and behaves as if it were its own bacterial gene [18, p. 6].

A bacteriophage often imparts pathogenic properties to a bacterium. For instance, a non-pathogenic *Coryne-bacterium* turns into a highly toxicogenic variant of the diphtheria microbe once a specific phage brings the diphtheria histotoxin synthesis gene into the bacterium. A similar process transforms a non-pathogenic vibrion into an agent that causes cholera. Many other phages spread antibiotic multiple resistance genes or bacteriocin synthesis genes among bacterial populations. Data on additional (extrachromosomal) molecules of bacterial

DNA (for the first time for the *Shigella flexneri* bacterium), transferred from population to population and also bearing antibiotic-resistant genes, began to emerge in 1952. These molecules would later be known as *plasmids* – autonomous small hereditary units revealing another secret of the bacterial genome.

Observation of lysogenic bacteria led A. Lwoff to his conclusion on the inductive effect of ultraviolet radiation, radiation and a number of chemical substances on bacteriophage activation – its transformation from an integrative state to a lytic (or productive, i.e., leading to cell lysis) pathway. "It thus appeared that the development of the prophage into bacteriophage is a fatal disease. The prophage is a potentially lethal factor. Irradiation forces it to express its potentialities", A. Lwoff said of the results of his experiments [18, p. 5].

In the following years, A. Lwoff studied certain human viral diseases, in particular herpes. For this disease, the natural phase of the existence of the virus is its asymptomatic presence in the host cell, its DNA integrated with the DNA of the host cell (similar to a prophage inside a bacterium). Activation of the virus is caused by a number of external and internal factors.

In his acceptance speech, after he and his colleagues had received the Nobel Prize in Physiology or Medicine in 1965, A. Lwoff cited novel conclusions on the possible application of knowledge about the integrative existence of virus and cell in studying genome transformation during the formation of malignant cells: "A cell becomes cancerous under the action of a virus. The virus has introduced into the normal cell its genetic material, which brings with it new functions, and these functions are the cause of the malignancy. If so, there are two possible ways of combating malignant cells. One of them is to suppress the viral genome in its integrative state and hope some day to convert a malignant cell into a phenotypically normal one. There is also another obvious possibility. Instead of attempting to repress the viral functions, we might attempt to intensify them in such a manner that the virus whose cycle is blocked develops and kills the malignant host cell" [18, p. 10].

A. Lwoff therefore transformed what was supposedly a narrow, specific phenomenon of parasitism into the global understanding of the role of virus-cell genetic integration in the development of malignant transformation of cells and defined possible areas of further research on one of the most serious and, unfortunately still unresolved, problems – the nature of cancerous diseases.

The study of lysogenic conversion itself and the possibility of horizontal gene transfer opened the door for further extensive studies and practical application of genetic engineering technologies in order to obtain recombinant substances and preparations, as well as genetically modified organisms.

The study of bacteriophages enabled a deeper penetration into the nature of viruses and viral diseases; it had a great influence not only on the development of virology but also on the understanding of mechanisms of heredity, tissue growth and the development of certain forms of tumours.

Today bacteriophage preparations are being manufactured and successfully used in therapy and emergency prophylaxis of many bacterial infections, especially in cases when antibiotic treatment is ineffective or contraindicative.

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