The Truth about Phage Therapy
or a Memo to Physicians and Patients

The first clinical experiments with bacteriophages began a century ago. It seemed that the new method was bound to be a success: the approach looked faultless from a scientific standpoint and the results of its application were most promising. Then why did the interest in the therapeutic use of bacteriophages disappear in the subsequent decades? Why did this interest emerge once again, and why has this idea not been implemented to the fullest so far? Both medical practitioners and their patients should understand well not only the essence of this promising therapy, but also its merits and flaws.

Bacteriophages are not just common drugs. They are neither simple chemicals, like antibiotics and most other medicines, nor true living organisms since they, like all the other viruses, are able to reproduce only in the cell of their host. Actually, bacteriophages are nano-automatons with their own genetic program, which can penetrate into a bacterial cell and reproduce there causing its destruction. Therefore, standard pharmacological approaches to bacteriophages are not always satisfactory. Although phage preparations are now produced and applied in medicine, our knowledge about the diversity of these viruses, about mechanisms of their interaction with bacteria, and about competition with their cognates is still insufficient to use their full therapeutic potential.

Phage therapy emerged almost immediately after bacteriophages were discovered, however, expanded trials of these antibacterial tools were launched in the Soviet Union only in the late 1930s. The trials proved the efficiency of bacteriophages as preventive measures against dysentery and cholera epidemics, and using them for healing wounds and curing pyoinflammatory diseases demonstrated their potential as an alternative to antibiotics. However, the results achieved at that time were often contradictory: in some cases the phages immediately inhibited the progression of infection but sometimes they were of no use. The specialists grasped the reason right away: the treatment was successful only when they used phages that were able to infect the particular bacterial strain that had caused the target infection. Thus, it was necessary to isolate the pathogen that caused the epidemic, assay the available phages for their ability to inhibit this agent, and produce the most efficient bacteriophage as a drug.

Unfortunately, the results of the studies performed in the Soviet Union were not properly documented and described in scientific literature; moreover, they were conducted not in compliance with the currently recognized protocols for clinical trials. Nonetheless, the major results of that work were undoubted: phages demonstrated their safety and high efficiency in real situations. Since then they have been widely used as a treatment for various infections, including those caused by antibiotic-resistant bacteria.
Diabetic foot, a severe complication of diabetes with potential development of gangrene, foot loss, and disablement, is experimentally treated in a Novosibirsk clinic. Bacterial infection is one of the factors underlying this pathology. Phage therapy comprises the following stages: swabbing the affected tissues to isolate the pathogenic bacterium; selecting the bacteriophage that can lyse the target bacterium from a phage collection; and applying the bacteriophage preparation (on a sterile pad) to the wound. The treatment takes about a week.

ANTIBIOTICS

ADVANTAGES:
- Broad spectrum;
- Simple patenting

DISADVANTAGES:
- Destroy the microflora of the body, creating a threat of secondary infections;
- Are unable to accumulate at the infectious lesion;
- Cause side effects, such as allergies and gastrointestinal disorders;
- Cause emergence of drug-resistant bacterial strains; and
- Require much time and money for developing new antibiotics

BACTERIOPHAGES

ADVANTAGES:
- High specificity, which makes it possible to find an individual bacteriophage killer for any bacterium;
- Search for a new target phage takes only several days or weeks;
- Inexpensive and ecologically friendly production;
- Never cause dysbacteriosis;
- Nontoxic and have no side effects; and
- Are eliminated from the body after destroying the target pathogen

COMING TO KNOW—FEAL MICROBIOTA TRANSPLANTATION

A common aftereffect of antibiotic therapy is rapid propagation of an aggressive bacterium, Clostridium difficile, which causes severe diarrhea and resistance to drugs. This is a very serious problem: not long ago it caused about a thousand lethal outcomes in the United States annually. A very simple means of curing diarrhea was found quite recently: the fecal microflora of a healthy donor is administered to the patient’s intestine. The recovery is almost immediate, literally on the following day. Evidently, the “transplantation” of feces gives the patient a complete set of “proper” microorganisms that had been killed by antibiotics and bacteriophages that control the abundance of pathogenic strains.

Initially, the FDA restrained the spread of this approach, trying to apply the regulatory rules approved for ordinary drugs. However, the protests of both therapists and patients came into play, and the method was approved with common precautions, i.e. selection of healthy donors and performance of the procedure by specialists and in healthcare facilities. The method has recently become widespread in the United States and shows good results. It is likely that only the prejudice of physicians still hinders the use of fecal microbiota transplantation in several European countries; in Russia, this treatment is available only at the Center for New Medical Technologies in Novosibirsk Akademgorodok used in clinical practice in this country along with common therapeutic tools.

With the advent of antibiotics, western countries lost interest in phages; however, the emergence of antibiotic-resistant bacterial strains made several countries begin to elaborate phage preparations and conduct clinical trials, which in fact were the same as the ones that had been performed in the Soviet Union. The new results confirmed the safety of bacteriophage preparations, which was confirmed by the Food and Drug Administration (FDA).

In the United Kingdom, experiments on treating chronic otitis caused by have proved to be successful. Under the Phagoburn project, seven medical centers in France, Belgium, and Switzerland are involved in the clinical trials of a phage cocktail for preventing infections in burn injuries. Several United States companies (Intralytix, Enbiotix, and AmpliPhi) report testing their original phage cocktails for a wide range of diseases, though none of these large-scale clinical trials has been completed yet.

What is a “medicinal bacteriophage?”

In Russia, bacteriophage preparations are available in pharmacies, but unlike other drugs with their precise chemical formula and concentration of the components, a bacteriophage preparation is a nonstandard solution containing live virus particles. Preparations that have the same name but were manufactured at different facilities or at different times may differ in their composition and/or ratio of phages.
All the differences are determined by the specificity of the phage selection procedure and their production. Bacteriophages are selected according to their ability to lyse an individual bacterial isolate; then a mixture of phages is grown on a specified bacterial culture, and goes into production, i.e. bacteriophages are grown in voluminous reactors (fermenters) with the help of bacterial strains. As a result, a drug that can kill the necessary bacterial strain is created. For example, the Pseudomonas aeruginosa bacteriophage contains the phages that kill P. aeruginosa, but the physician does not know either the number of phages in the preparation or what phages it contains, what P. aeruginosa strains it can kill, and whether it is appropriate for a particular patient. The preparation will have an excellent effect if the patient is infected with the same bacterial strain as was used for phage production; otherwise, the only hope is that since the phage cocktail contains many components, one of the bacteriophages may be specific to the target pathogen. Thus, it does not pay to buy a bacteriophage in a drugstore for self-treatment. It is up to the doctor to prescribe the treatment and drugs. The range of diseases susceptible to bacteriophage therapy is wide, including trophic ulcers, burn and wound infections, as well as various infections of respiratory, urogenital, gastrointestinal organs, and bones. In these cases, the causative agents are non-penicillin-resistant bacteria, such as Staphylococcus aureus, Pseudomonas aeruginosa, pathogenic Escherichia coli strains, salmonellas, Pneumococcus, and Staphylococcus, including their drug-resistant variants. In fact, it is possible to find naturally occurring bacteriophages against any bacteria, including those that cause plague and anthrax. Bacteriophages can also be used to prevent communicable bacterial diseases; for example, they were successfully used in kindergartens to prevent a dysentery epidemic.

Bacteriophage preparations are administered either locally, to the lesion, or orally. Advertisements allege that phages can spread within the human body and pass from the stomach to bloodstream; however, there is no clear and unambiguous scientific proof yet. Note that a bacteriophage preparation may contain most different phages, the cases, the causative agents are non-penicillin-resistant bacteria, such as Staphylococcus aureus, Pseudomonas aeruginosa, pathogenic Escherichia coli strains, salmonellas, Pneumococcus, and Staphylococcus, including their drug-resistant variants. In fact, it is possible to find naturally occurring bacteriophages against any bacteria, including those that cause plague and anthrax. Bacteriophages can also be used to prevent communicable bacterial diseases; for example, they were successfully used in kindergartens to prevent a dysentery epidemic.

Bacteriophage therapy should follow the pattern of personalized medicine. First, it is necessary to isolate the culture of the pathogen and test it for sensitivity to different phages, i.e. bacteriophage therapy requires not only a clinical facility, but also a laboratory production site with a collection of phages and the staff skilled in identifying bacteria as well as in selecting and isolating bacteriophages for individual patients. The question here is whether large-scale production of bacteriophage preparations not only a clinical facility, but also a laboratory production site with a collection of phages and the staff skilled in identifying bacteria as well as in selecting and isolating bacteriophages for individual patients.
necessary phage cocktail for an individual rather than to test many individual phages from a large collection.

For all that, bacteriophages are not likely to replace antibiotics completely: these preparations are complementary and applicable to different situations. When a patient is severely ill, with a good reason to suspect a bacterial infection, there is time for experiments in selecting the proper phage preparation. The only satisfactory solution then is a broad-spectrum antibiotic.

However, bacteriophage therapy is preferable when you deal with a chronic infection or with a disease caused by multidrug resistant bacteria. In the case of chronic illnesses, such as cystitis, the physician has enough time to administer a phage cocktail or to select a specific phage. Another example is a post-surgery infection with an antibiotic-resistant bacterial strain, which causes rapid deterioration of the patient’s state; here phage therapy can be the only option.

Wide experience in the clinical use of bacteriophages acquired over the last 100 years demonstrates the promising future of phage medical technologies. Further efforts of the experts working in this area, in combination with synthetic biology tools, will certainly create preparations with incomparably higher efficiency than that of the currently available phage cocktails.

However, several factors unrelated to science hinder the advances in designing and producing “medicinal” bacteriophages. The fact is that bacterial viruses are very easily reproduced, which offers exciting possibilities for their counterfeiting, thereby infringing on the rights of bona fide manufacturers. The requirements for phages as therapeutics have not been established yet either. It is only clear that they should be different from the requirements for synthetic drugs. Bacteriophage genomes are diverse; so, if a personalized approach is used, they should be selected individually.

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