ifrik

Bacteriophages: An alternative to antibiotics?

[img_assist|nid=87|title=|desc=|link=none|align=right|width=100|height=43]Bacterial resistance to antibiotics has become a serious medical problem. Treatment with bacteriophages might pose an effective alternative that has long been known but has been ignored outside the former Soviet Union. The development of phage therapies exemplifies positive as well as negative implications for scientific development that is restricted in its access to the mainstream, English-language dominated scientific community.

All over the world, the resistance of bacteria to antibiotics is becoming a grave medical problem. Independent of the resources of the medical system, whenever antibiotics are used the development of resistance is a logical consequence; like all other living organisms, bacteria adapt to changing environmental conditions in a continuous process of evolution. The question is not whether but when antibiotic resistance will occur. Ironically, resistance is promoted by both the overuse of antibiotics as well as insufficiency of dose. In industrialized countries, bacteria are developing multiple resistance to a range of antibiotics, which threatens to make the achievements of modern medicine futile. Without the protection against bacterial infections, for instance, large-scale operations and treatments that weaken the patients' immune system, such as chemotherapy or organ transplantation, would not be possible. In developing countries basic medical care is already endangered by single resistance to inexpensive common generic antibiotics. According to the World Health Organization (WHO), a great number of the population of developing countries will not be able to afford the replacements. In these countries, dosage often appears to be too low or treatment is not carried out over the whole course; resistance is encouraged because even if the patient is cured, those bacteria that are best adapted to low doses of these antibiotics survive. Cases of reported antibiotic resistance comprise tuberculosis, pneumonia and dysentery.
Although the spread of antibiotic resistance has long been known as a worldwide phenomenon, research seems to have reached a dead end. During the last 30 years, no new classes of antibiotics have been found, even with the help of modern biotechnology such as genetic engineering. Pharmaceutical companies have mainly focused on the development of new products derived from the known classes of antibiotics.

Bacteriophages: The road not taken

A possible alternative for the treatment of bacterial infections could be the use of bacteriophages, which are viruses that live on bacteria (see box). Each kind of bacterium hosts its own, specific phages, which can be found wherever that particular bacterium grows. Thus, phages can be selected

and isolated as an antidote from sewage, faeces, soil, or springs. Further processing of bacteriophages depends on the intended treatment. For external use, such as for wound healing, the process is simple, whereas for internal treatment the sample has to be cleaned from bacterial debris that might be toxic. Compared with chemical antibiotics, bacteriophages offer several advantages.

- **Limited impact.** Unlike antibiotics, bacteriophages are self-replicating as well as self-limiting. Bacteriophages replicate exponentially as long as the specific bacteria are available in abundance. With a decreasing amount of bacteria, the number of phages declines too and they are gradually eliminated from the patient and from the environment. Depending on the form of application, a single dose may be sufficient.
- **Limited resistance development.** Bacteria will certainly develop resistance to phages too. However, since phages have a higher mutation and replication rate, they can outcompete the adaptation of the bacteria, and development of resistance is therefore limited.
- **Specific targets.** Treatment with chemical antibiotics often causes bacterial imbalance and can lead to secondary bacterial infections with *Pseudomonas sp.* or *Clostridium difficile*, which cause severe diarrhoea and infections of the colon. Bacteriophages, on the other hand, target a particular kind of bacteria far more specifically than chemical antibiotics, and therefore cause much less damage to the human intestinal flora. A complication, however, is that this specificity requires a precise knowledge of the infection. Therefore ready-made phage preparations cannot be used for unspecified infections, which is often the case with antibiotics.
  Few side effects have been reported; nevertheless, phages can cause adverse immune reactions, particularly after internal use. However, this problem could be alleviated by treating patients that show adverse effects with a different, unrelated phage the next time they have a bacterial infection.
  Especially in hospitals, phages can be used prophylactically against nosocomial (hospital-acquired) infections as well as for the disinfection of problem areas. Phages can be used either independently or in combination with antibiotics.

Historical context

Bacteriophages are not a new field of scientific interest. As much as a hundred years ago, it was reported that the waters of the rivers Ganges and Junna in India possessed astonishing antibacterial properties. Edward Twort (1915) and Felix d'Herelle independently described filterable entities that could destroy cultures of bacteria. D'Herelle called them 'bacteriophages'; not so much 'bacteria eaters', but in the sense of 'developing at the expense of bacteria'. Over the following years, research on bacteriophages took off worldwide. In 1921, it was reported for the first time that skin infections caused by Staphylococcus had been successfully treated with bacteriophages. In 1922, d'Herelle published a standard volume 'The Bacteriophage' with classical descriptions of different aspects of phages and their life cycles. By the end of the 1920s, companies in France and the USA commercially produced phage preparations for a wide market.

Between 1917 and 1956, some 800 publications dealt with a range of medical applications of bacteriophages. Phage therapy was used to cure dysentery, typhus, paratyphus, cholera and infections of the urinal tract, but it was also used against diseases such as gall stones or eczema, which are not caused by bacterial infections. The results remained inconsistent and many trials were based more on euphoria than on scientific knowledge of bacteriophages or microbiology. Uncharacterized phages in unknown concentrations were given to patients with unspecified bacterial infections, without follow-ups, without control groups, without placebos.

In 1931, the Council on Pharmacy and Chemistry of the America Medical Association came to the conclusion that "the use of bacteriophages in the treatment of infections…is for the most part contradictory." This assessment seriously influenced the willingness of the medical research community in the USA to invest in further exploration of phage therapy. With the advent of new chemical antibiotics like

penicillin, which became widely available in the 1940s, research on the potent but unpredictable phage therapy was abandoned in the western world.

Research in the Soviet Union and Eastern Europe

Meanwhile in the Soviet Union, the research on phage therapy flourished ever since in 1923 the Institute of Bacteriophage, Microbiology and Virology was founded in Tblisi, Georgia. From the 1950s, antibiotic resistance was a known problem also in the Soviet Union. By decree from Moscow, specimens of all antibiotic-resistant bacteria from all over the Soviet Union were sent to Tblisi to set up what became the world largest collection of antibiotic resistant bacteria and corresponding phages. Here, the replication, biochemical properties and the phage sensitivity of several thousands different pathogenic strains of bacteria, such as *Staphylococcus, Streptococcus, Proteus, Pseudomonas aeruginosa* and *Clostrium* were studied.

Next to the Institute of Bacteriophage, Microbiology and Virology in Tblisi, already since the 1920s industrial manufacturing sites were set up for the large-scale production of phage preparations on a self-supporting basis, with Russian production facilities in Ufa, Kharbarowska, Nijnyi Novgorod and Sratov. Based on the research of the institute, phage preparations have been continuously improving. One of the latest developments is called 'IntestiPhage', containing 17 different phages against different intestinal bacteria. According to Georgian physicians, phage therapy is part of common medical care, especially in paediatric, surgical and burns hospital settings. They are used independently or in combination with chemical antibiotics against primary as well as hospital-acquired infections, as prophylactics, for treating the incision area before surgery, and for disinfecting operating theatres.

Most of the scientific research carried out in Tblisi was confined to Eastern Europe. During the Cold War, an iron curtain also came down between scientists. On the one side, a western scientific community contributed to a seemingly worldwide exchange of scientific results with English-language multinational conferences and the validation of research results by peer review in international, English-language journals. Scientists of the Soviet Union and of other countries of the Warsaw Pact were on the other side, not part of this community.

Research on bacteriophages was not limited to the Soviet Union. For instance, one well-documented clinical phage therapy was carried out at the Institute for Immunology and Experimental Medicine at the Polish Academy of Science in Wroclaw. Between 1981 and 1986, 550 patients in different clinics were treated with bacteriophages after having previously been treated unsuccessfully with antibiotics. These results were published between 1982 and 1987 in English, thus also becoming accessible to the non-Russian speaking world.

In general, however, further scientific exchange was prevented by both Eastern and Western governments, and conference visits were possible only in exceptional cases. Even today, the greater part of the research of the Tblisi institute remains inaccessible to most English-speaking scientists, because the results are published in Russian or Georgian. Nowadays scientific exchange is generally not prohibited by government decree, and the internet, especially, suggests an increasing exchange of information worldwide. Along with language barriers, there are still political, financial, and cultural conditions, as well as gender relations, which set up boundaries against the free flow of scientific knowledge. On the other hand, the example of phage therapy shows that being cut off from the scientific mainstream might also give rise to alternative approaches.

The second advent of bacteriophages

In the 1980s, interest in phage therapy had slowly resurfaced in the West, just as it was about to be lost again in the East. With the breakdown of the Soviet Union at the beginning of the 1990s, financial support from Moscow was stopped for the Institute of Bacteriophage Research in Tblisi, Georgia. The newly-founded Georgian state faced financial restrictions and internal warfare caused a breakdown in infrastructure. Parts of the phage collection had been lost as a result of power cuts affecting the electric storage units. Furthermore, the production of phage preparations on an industrial scale could not be continued, because the technical devices needed to check for purity were no longer available.

A new partner emerged from an unexpected quarter. In 1997, a North American stockbroker founded a company called Georgia Research Institute Inc. (GRI) in the USA, with a small laboratory located at the institute in Tblisi. While the company received samples from the Tblisi institute, disputes over future intellectual property and production rights prevented a longstanding cooperation. However, GRI took up commercial manufacturing activity under the name Phage Therapeutics International Inc. in a plant in Seattle, USA.

The institute in Tblisi is now working most closely with the US company Intralytix, which was started by a group of researchers of the University of Maryland Hospital, USA. One of the outcomes of these joint activities is the development of an artificial skin called 'PhageBioderm', which is impregnated with phage for wound and burn healing. A similar product has already been used successfully for the treatment of soldiers during the war in Georgia.

Next to the treatment of burns and wounds the Institute of Bacteriophage, Microbiology and Virology in Tblisi cooperates with a local hospital to use phages to combat nosocomial infections. A spin-off of one of the industrial production sites, Biopharm Ltd., produces three different commercial phage preparations – one a cocktail of five phages, another of seventeen, both against enteric bacteria, and one anti-Staphylococcus preparation with a single phage. These products are produced in volumes that satisfy the Georgian market. However, production standards and protocols for testing would not meet the requirements of drug approval authorities in many industrialized countries.

Companies in the USA therefore pursue their own approaches towards testified phage therapies, but are still going through trials with their products. For instance, Exponential Biotherapies Inc. (USA) tries to improve the efficiency of phage therapy by preventing phages from being cleared out through the human body's filtering system against foreign material. In 1997, a patent was issued to the company both for a process of purifying phages that can circulate for a long time in the blood, and for their use to treat infections in animals and humans.

Alternative and future applications

Approximately half of the world's antibiotic production is not used as human medicine but for animals. Some antibiotics for industrialized husbandry are sold freely over the counter as growth promoters. Several of these antibiotics are known for cross-resistance to those used in human medicine. It has been shown that antibiotic resistant bacteria are present in meat products and can also be found in humans who have not received these substances in the course of a medical treatment. Although so far there is no evidence for a causal relationship, this potential spread of resistance adds to the problems with antibiotics for future medical applications. Phage therapy will not prevent the use of antibiotics as growth promoters, and could only substitute those antibiotics used for animal health purposes. As such, phage therapy would also be useful in uncoupling medical care and growth promoting.

In principle, the application of bacteriophages is not limited to medical uses for humans or animals. It might be used in agriculture to deal

with bacterial infestations like citrus canker (Xanthomonas citri), which are treated with antibiotics. This application also affects the soil microbiology. Replacing antibiotics with bacteriophages might be one step towards a sustainable agriculture.
Phage therapy is especially interesting for medical care in developing countries. According to the WHO, in developing countries infections and parasitic diseases are responsible for the death of twenty million people per year. Every year about eight million children under five die of acute respiratory tract infections of bacteria such as Streptococcus pneumonia,Haemophilus influenza type B or of diarrhoea related diseases caused by bacteria such as Shigella sp., Vibrio cholera and several types of E.coli. Especially in Africa, dysentery caused by Shigella dysenteria is common. Since the late 1970s, drug-resistant strains of S. dysenteria have caused epidemics in various parts of Central and Southern Africa. By 1990, several of these epidemics were caused by strains resistant to all antibiotics used in those countries. The availability of advanced antibiotics is often limited by their higher costs. On the other hand, phage therapy has proved to be effective against dysentery since the first days of phage therapy research.
In the case of serious burns, the biggest cause of death within the first two days is an infection of Pseudomonas aerginosa (Bunting 1997), and bacteriophages might combat this. Especially for such external applications, bacteriophages might become an inexpensively and locally produced remedy, making them ideal candidates for basic medical care.
Phages will not be the panacea of medicine, but phage therapy research will gain momentum because traditional antibiotic research has come to a stop. Appropriately selected phages can easily be used to help prevent bacterial diseases in humans or animals, with potential for alternative applications and special interest for developing countries.

September 1999

- bacteriophages - antibiotics

A. Lorch, < a href="http://www.biotech-monitor.nl/3905.htm">Biotechnology and Development Monitor September 1999