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Bacteriophages – Alternatives to Antibiotics and Beyond

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ABSTRACT

Bacteriophages are viruses that infect bacterial host and are estimated to be the most numerous biological entities in the biosphere. Phages exist wherever bacteria occur, and share a common ecology with their respective bacterial hosts. They are the most abundant living entities on Earth - the estimates range from 10^{30} to 10^{32} in total - and play key roles in regulating the microbial balance in every ecosystem where this has been explored. Medical science has begun to acknowledge the emergency of drug resistant bacteria a fact made more amimous when one realizes that no fundamentally new antibiotic has been discovered for more than 30 years. Are we losing the battle? The emergence of pathogenic bacteria resistant to most, if not all, currently available antimicrobial agents has become a serious and critical problem in modern medicine. The use of host specific bacteriophages has been promoted as an important and cost effective adaptable approach to control zoonotic bacteria.

INTRODUCTION

A virus is a very small, non-cellular parasite of cells. Its genome, which is composed of either DNA or RNA, is enclosed in a protein coat. Viruses infect all cellular life forms: eukaryotes (vertebrate animals, invertebrate animals, plants, fungi) and prokaryotes (Bacteria and Archaea). The viruses that infect prokaryotes are often referred to as bacteriophages, or phages for short. The presence of viruses is obvious in host organisms showing signs of disease. Many healthy organisms, however, are hosts of non-pathogenic virus infections, some of which are active, while some are quiescent. Furthermore, the genomes of many organisms contain remnants of ancient virus genomes that integrated into their host genomes long ago. As well being present within their hosts, viruses are also found in soil, air and water. Many aqueous environments contain very high concentrations of viruses that infect the organisms that live in those environments. There is a strong correlation between how intensively a species is studied and the number of viruses found in that species. Our own species is the subject of most attention as we have a vested interest in learning about agents and processes that affect our health. It is not surprising that there are more viruses known that infect mankind than any other species, and new human viruses continue to be found. The intestinal bacterium Escherichia coli have also been the subject of much study and many viruses have been found in this species. If other species received the same amount of attention it is likely that many would be found to be hosts to similar numbers of viruses. It is undoubtedly the case that the viruses that have been discovered represent only a tiny fraction of the viruses on the Earth. Most of the known plants, animals, fungi, bacteria and archaea have yet to be investigated for the presence of viruses, and new potential hosts for viruses continue to be discovered. Furthermore, the analysis of DNA from natural environments points to the existence of many bacterial species that have not yet been isolated in the laboratory; it is likely that these 'non-cultivable bacteria' are also hosts to viruses. The distribution, prevalence, and dramatic manifestations of bacteriophages make it surprising that they were not recognized for almost 40 years after the beginning of serious bacteriological work in the laboratories of Europe and America in about 1880. In retrospect, there are a few reports in the literature that hint at the presence of bacteriophages, but the interpretations in these papers did not suggest useful pathways for further research. Hankin (1896) reported that the waters of the Jumna and Ganges Rivers in India had antiseptic activity against many kinds of bacteria and against the cholera vibrio in particular. This activity was filterable and destroyed by boiling. He concluded that the antiseptic principle was some volatile chemical substance. Emmerich and Löw (1901) reported in that some substance in autolyzed cultures was capable of causing the lysis of diverse cultures, of curing experimental infections, and of providing prophylactic immunity to subsequent inoculations. In addition, there is substantial literature on bacterial autolysis by Gamalieya, Malfitano, Kruse, and Pansini, which was reviewed by Otto and Munter (1923). At this point, however, it is difficult to provide unambiguous interpretations of these early studies. Although some of these observations are compatible with the action of bacteriophages, These reports all describe experiments on liquid cultures, and in this period of bacteriology, a culture was conceptualized not in terms of the population dynamics of individual cells, but as an organism in itself. It was not until the 1920s that a significant shift in thinking took place that allowed a reconceptualization of the bacterial cell as the organism rather than the entire culture (summers, 1991). The first dramatic and clear experiments on bacteriophages employed cultures on solid medium, and they were based on the observation of localized bacteriolysis (i.e., plaques).

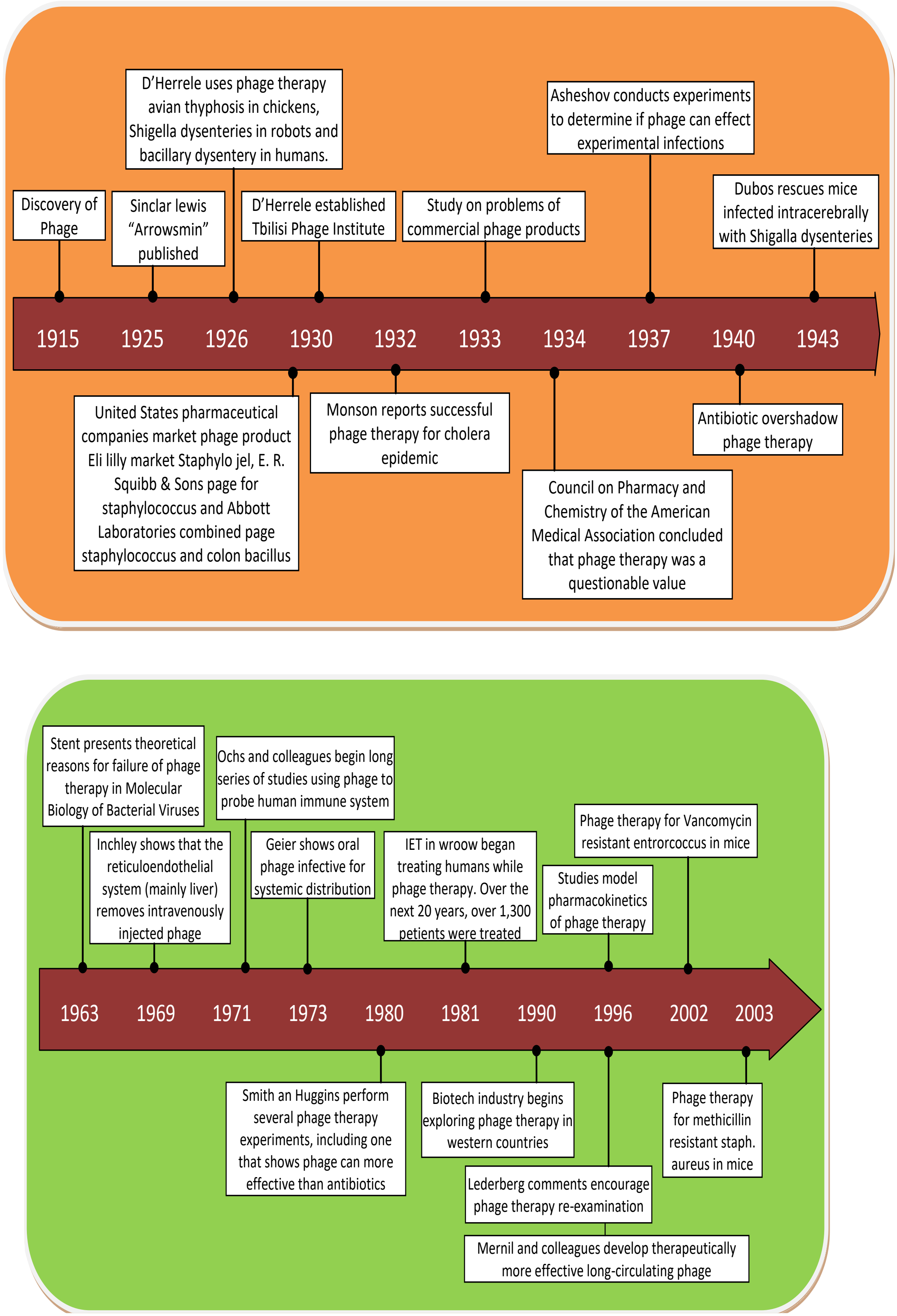

Figure - 1: Highlights in the development of phage as a potential therapeutic agent.

- **Reasons for studying viruses**
- **Some viruses cause disease**

Viruses are important agents of many human diseases, ranging from the trivial (e.g. common colds) to the lethal (e.g. rabies), and viruses also play roles in the development of several types of cancer. As well as causing individuals to suffer, virus diseases can also affect the well-being of societies. Smallpox had a great impact in the past and AIDS is having a great impact today. There is therefore a requirement to understand the nature of viruses, how they replicate and how they cause disease. This knowledge permits the development of effective means for prevention, diagnosis and treatment of virus diseases through the production of vaccines, diagnostic reagents and techniques, and antiviral drugs. These medical applications therefore constitute major aspects of the science of virology. Veterinary virology and plant virology are also important because of the economic impact of the many viruses that cause disease in domestic animals and crop plants: foot and mouth disease virus and rice yellow mottle virus are just two examples. Another area where viruses can cause economic damage is in the dairy industry, where phages can infect the lactic acid bacteria that are responsible for the fermentations that produce cheese, yogurt and other milk products.

❖ **Some viruses are useful**

Some viruses are studied because they have useful current or potential applications.

• Phage typing of bacteria. Some groups of bacteria, such as some Salmonella species, are classified into strains on the basis of the spectrum of phages to which they are susceptible. Identification of the phage types of bacterial isolates can provide useful epidemiological information during outbreaks of disease caused by these bacteria.

• Sources of enzymes. A number of enzymes used in molecular biology are virus enzymes. Examples include reverse transcriptases from retroviruses and RNA polymerases from phages.

• Pesticides. Some insect pests are controlled with baculoviruses and myxoma virus has been used to control rabbits.

• Anti-bacterial agents. In the mid-20th century phages were used to treat some bacterial infections of humans. Interest waned with the discovery of antibiotics, but has been renewed with the emergence of antibiotic-resistant strains of bacteria.

• Anti-cancer agents. Genetically modified strains of viruses, such as herpes simplex virus and vaccinia virus, are being investigated for treatment of cancers. These strains have been modified so that they are able to infect and destroy specific tumour cells, but are unable to infect normal cells.

• Gene vectors for protein production. Viruses such as certain baculoviruses and adenoviruses are used as vectors to take genes into animal cells growing in culture. This technology can be used to insert into cells genes encoding useful proteins, such as vaccine components, and the cells can then be used for mass production of the proteins.

• Gene vectors for treatment of genetic diseases. Children with severe combined immunodeficiency (baby in the bubble syndrome) have been successfully treated using retroviruses as vectors to introduce into their stem cells a non-mutated copy of the mutated gene responsible for the disease.

❖ **Why Alternative of Antibiotics?**

For more than half a century, the human society has been relying primarily on antibiotics to treat infectious diseases caused by pathogenic bacteria. However, the emergence of bacterial resistance to antibiotics following widespread clinical, veterinary, and animal agricultural usage has made antibiotics less and less effective (Teuber, 2001; Heuer et al., 2006). We are now facing the threat of superbugs, i.e. pathogenic bacteria resistant to most or all available antibiotics. It was warned by the World Health Organization that those multiple antibiotic-resistant pathogens would very likely bring the world back to the preantibiotic era.

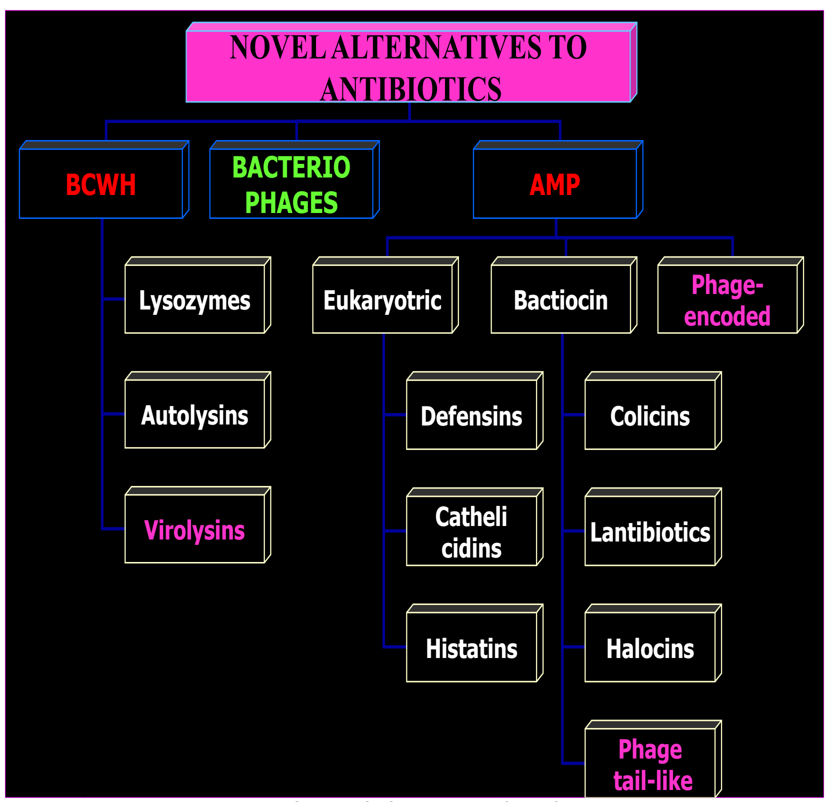

Figure – 2: Novel alternative of Antibiotics

❖ **Bacteriophages (Phage Therapy) Selected Best Alternative to Antibiotic**

Bacteriophage therapy was largely abandoned in the West in favour of the newly emerging antibiotics. Now as the problem of antibiotic resistance become ever more acute a number of Scientists and clinician are looking again at bacteriophages as a therapeutic option in the treatment of bacterial infection. As interest in bacteriophages increase, a number of companies throughout the world have begun investing in phage technology and this has led to novel approach to therapy.

TABLE – 1: Comparison of the prophylactic and /or therapeutic uses of phages and antibiotics

Bacteriophages	Antibiotics	Comments
Very specific (i.e. Usually affected only the targeted bacterial spices); therefore, dysbiosis and chances of	Antibiotics targeted both pathogenic micro organism and normal micro flora. This affects the microbial balance in	High specificity may be considered to be a disadvantage of phage because the disease causing bacterium must be identified before phage therapy can be successfully

developing secondary infections are avoided (15).	the patient. This may lead to serious secondary infections.	initiated. Antibiotics have a higher probability of being effective than phage when the identity of the etiologic agent has not been determined
Replicate at the site of infection and are thus available where they are most needed (59).	They are metabolised and eliminated from the body and do not necessarily concentrate at the site of infection.	The " Exponential growth " of phages at the site of infection may require less frequent phage administration in order to achieve the optimal therapeutic effect.
No serious side effects have been descried.	Multiple side effects, including intestinal disorder, allergies and secondary infections (e.g. Yeast infection) have been reported (76).	A few minor side effects reported (17 , 58) for the therapeutic phages may have been due to the liberation of endotoxin from bacterial lysed in vivo by the phages, such effects also may be observed when antibiotics are used (42).
Phage resistant bacteria remain susceptible to other phages having similar target range.	Resistant to antibiotics is not limited to targeted bacteria.	Because of their more broad spectrum activity, antibiotic select for many resistant bacterial species, not just for resistant mutants of the targeted bacteria (47).
Selecting new phage (e.g. against phage resistant bacteria) is a relatively rapid process that can frequently be accomplished in days or weeks.	Developing a new antibiotics (e.g. against antibiotic resistant bacteria) is a time consuming process and may takes several years (16, 51).	Evolutionary argument support the idea that active phage can be select against every antibiotic resistant or phage resistant bacterium by the ever on-going process of natural selection.

❖ **Application of Phage Therapy**

- Biofilm infection control
- Treatment of mycobacterial infections
- Alteration of host binding profile
- Use of bacteriophage in SASP technology
- Epidemiological fingerprinting of bacteria isolates (Phage typing)
- Use of phages as tools in molecular biology
- Use of bacteriophage to express peptides and proteins (Phage display)
- New phage diagnostic tools
- Important ecological role in recycling or organic matter including cells
- Use of bacteriophage in the preparation of Engineered prophages

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