EXTENDING THE CURE

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BACTERIOPHAGES: A New Old Biomedical Technology

Antibiotic resistance is a challenge that calls for good science as well as ingenuity. Although we will always need new antibiotics, there are alternative therapeutic approaches worth considering. One example is *bacteriophage therapy*. Bacteriophages—or "phages"—exist in abundance in nature, including in and on the human body. Phages are viruses that infect bacteria and use the bacterial cell's genetic apparatus to produce more phages. In the process, they kill their host. By harnessing phages' natural ability to destroy bacteria, infections can be cleared.

After Felix d'Herelle's discovery and isolation of the first bacteriophage in 1917, the long-sought cure for bacterial infections seemed to be at hand. But with the dawn of the antibiotic era in 1941, when penicillin was discovered, the western medical establishment lost interest in phages. Meanwhile, phage therapy was alive and well in the Soviet Union, isolated from the West by the Cold War. Widespread claims of success in curing disease—accurate or not—lacked the support of controlled experiments and were largely ignored by the rest of the world.

Modern Phage Successes

Recent studies have been conducted under rigorous scientific control. Phage therapy has cured or controlled *Pseudomonas aeruginosa* infections in mice; *Escherichia coli* diarrhea in calves, piglets, and lambs; *E. coli* septicemia and meningitis in chickens and calves; multidrug resistant *Klebsiella pneumoniae* in mice; methicillin-resistant *Staphylococcus aureus* in mice; and vancomycin-resistant enterococci bacteraemia in mice.

A few trials in humans have been reported recently. Biocontrol, in the United Kingdom, completed a small, double-blind placebo-controlled clinical trial of chronic ear infections caused by *P. aeruginosa* (Biocontrol Limited 2009). Bacterial counts and symptoms were reduced. Encouraged, the company is moving on to a larger trial. In the United States, Intralytix successfully concluded a preliminary safety trial of bacteriophage therapy of venous leg ulcers (Wolcott et al. 2009). Other clinical trials (*P. aeruginosa* and *S. aureus* in burns and genetically engineered bacteriophages) are under way in the United Kingdom.

Bacteriophages have shown promise as tools for infection control as well. Scientists from the University of Strathclyde have chemically bonded phages to nylon products such as strips, sutures and implantable beads (The Medical News 2005), which they use during surgery. This preparation is effective against most major epidemic methicillin-resistant *Staphylococcus aureus* (MRSA) strains. Bacteriophages on sutures can prevent wounds from becoming infected (The Medical News 2005). When tagged with "luciferase cassettes," phages light up once they successfully infect bacteria. This makes them useful not only for diagnosing bacterial infections but for quickly determining antibiotic susceptibility (Kropinski 2006). Still experimental today, we should not be surprised if one day these applications are routine.

Phages in Food Safety

Work on therapeutic phages will undoubtedly continue, but phages and their proteins may also find a place in diagnostics, infection control, veterinary treatments, and agriculture. In the United States, phages are already in use in food safety. One approved product, Intralytix's LMP-102, targets *Listeria monocytogenes* with a six-phage cocktail that is sprayed on meat, seafood, and poultry products before packaging. Intralytix, and other companies, are developing similar treatments for *Salmonella* and a particularly virulent type of *E. coli*.

Potential Advantages and Disadvantages of Phage Therapy

Cost and Sustainability

Phages are inexpensive and quick to produce (Inal 2003). New phages can sometimes be selected in days or weeks. In contrast, the process of discovering and testing a new antibiotic can take decades. Like with antibiotics, bacteria can also develop resistance to phages. But unlike antibiotics, phages are dynamic and can evolve alongside bacteria in a mutually escalating arms race (Donlan 2009). Because of concerns about resistance, phages are usually used in tandem, with multiple phages directed against a specific pathogen. Even if the bacteria being targeted have evolved resistance to one phage, there remains a high likelihood that they will be killed by the other phage, minimizing both the risk of treatment failure and the possibility that resistance will be passed on to new generations of bacteria. As antibiotic resistance mechanisms do not affect phages, phage therapy provides an ideal way to treat highly antibiotic resistant microorganisms, such as the *Acinetobacter* species found to infect soldiers returning from Iraq.

Few Side Effects

One particular advantage of phage therapy is the apparent lack of serious side effects (Sulakvelidze and Kutter 2005). So far, phages have been well tolerated, while antibiotics have a range of side effects. There are concerns about possibly harmful molecules released when bacterial cells burst because of phage activity—specifically, endotoxins released from the cell walls of bacteria killed by phages into a patient's bloodstream. The same side effects may occur after antibiotic therapy, and various approaches (corticosteroid therapy, for example) used to reduce the problem during antibiotic therapy may also be used during phage therapy (Donlan 2009; Sulakvelidze and Kutter 2005). These issues remained unresolved, however, because there has been little experience with them.

Immune Responses

Sustaining the presence of phages in the human body long enough to treat infection is a one of the main challenges of phage therapy. A patient's immune system will inactivate phages in the body with regular use; they can be quickly excreted and the immune system develops antibodies against the phage. So, treatment with the same phages may not work a second time. It may be that phages can be genetically modified to evade the immune system but this is still unknown (Donlan 2009).

Other Applications

Besides direct treatment of infected patients, creative scientists may find a host of uses for phages, including reducing bacterial levels in places such as hospitals and food processing plants. The U.S. Environmental Protection Agency recently registered Intralytix's LMP-102 phage preparation for various environmental applications targeted at eradicating or reducing contamination with *L. monocytogenes* (as in food processing plants) (Intralytix, 2009).

Regulatory Obstacles

Although phage therapy seems to be a viable alternative or complement to antibiotic therapy, the market for phages is not yet completely defined. The U.S. Food and Drug Administration (FDA) has not yet issued guidelines for regulating phages for human therapeutic use, in part because the laws and regulations governing approval of medical therapies is based on our understanding of conventional drugs (or vaccines, for preventive interventions). Phages are unlike drugs in some important ways, and so they challenge the FDA's methods. It would be impractical to test every phage in large-scale randomized trials—potentially thousands of phages may be used. That's not to say that the method of selecting and preparing the phages could not be tested. It would, however, be a deviation from current practice.

Phage cocktails could be deployed against bacteria while the disease-causing bacteria are still being fully identified, but that creates another stumbling block for the FDA. Current rules require that every component of a combination treatment be first tested individually.

Incentives

Companies may be discouraged from entering the market because of uncertainty over intellectual property rights. Phages are, after all, naturally occurring living organisms. While individual phages seem to be patentable, there are plenty of other phages in the environment that may be isolated and used to formulate a competing phage preparation.

In addition, public acceptance of phage therapy is not yet fully tested, and regulatory strategies and obstacles are still not fully defined for various applications. Still, with the ever-increasing problem of drug resistance, and the current positive momentum toward development of new, natural ("green"), and safe alternatives to antibiotics and chemical disinfectants, phage-based products seem poised for increased recognition and growth in the years ahead.

The Road Ahead for Phage Therapy

Some companies have invested in early stage clinical trials, but following up with subsequent trials is very costly—too costly for start-up companies, particularly when even successes may not be rewarded because of regulatory hurdles. A small investment by the National Institutes of Health in clinical trials of promising phages, could make a big difference in getting these therapies to market.

Then there's FDA approval. Intralytix spent four years getting approval for their phage food additive for *Listeria*. What it would take to get approval of a drug for use in humans is simply unknown. A more clear and appropriate pathway for approving phages for clinical use is needed.

Work with phages dates back well before the identification of the first antibiotics, but we are only now beginning to appreciate the ways in which they may be used—in a time of increasing levels of bacterial resistance to antibiotics and uncertainty about the potential environmental impact of widespread use of disinfectants and antibiotics. The success achieved so far and the immensity of the problems we face suggest that we should not, once again, turn our backs on phages.

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CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

JANE ZHAO
Princeton University
ALEXANDER SULAKVELIDZE
Emerging Pathogens Institute, University of Florida