Anna Kuchment

THE FORGOTTEN CURE

The Past and Future of Phage Therapy

Springer

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For Mark, Eliza and my parents.

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Prologue

In April 2002, Fred Bledsoe was doing construction work on his parents' lake house near Fort Wayne, Indiana, when he stepped on a rusty nail. As sharp as it was strong, the nail bore through Bledsoe's shoe and lodged in the sole of his foot. He cleaned up the wound and drove to a nearby hospital where doctors gave him a tetanus shot. "Case closed", he thought.

One week later, his foot swelled up, and the wound began oozing pus. Bledsoe, who has diabetes, went to see his brother, Larry, an internist, who prescribed a 10-day course of antibiotics. That seemed to do the trick; Bledsoe felt much better. But in August, the infection came back again with a vengeance. He grew feverish, his foot tripled in size – "it looked like a football," said his sister, Saharra – and a new infection site appeared at the base of his big toe. He could barely get out of bed. Dr. Bledsoe had his brother hospitalized, and physicians started him on a heavy course of IV antibiotics. But diabetes had damaged the circulation in Fred's foot, making it more difficult for the antibiotics to penetrate deeply enough and for his body's own white blood cells to help beat back the invading organisms. Nine weeks later, Bledsoe's physicians gave up. "My doctor told me I'd have a good quality of life without my toes," Fred says.

In desperation he called Saharra, his closest confidant in a six-sibling family. Growing up in Fort Wayne's impoverished, predominantly black South Side, Saharra, now 50, took on the role of keeping her younger brother out of trouble. Now, 35 years later, she saw this as another chance to come to his aide. She was convinced that doctors weren't doing enough to save Fred's foot. "There had to be something, somewhere, that could be done," she thought.

The answer arrived a short time later via an episode of the CBS news program "48 Hours." Saharra was on her way out of the house, when the show came on and caught her attention. The segment was called "Silent Killers" and discussed the growing problem of antibiotic-resistant infections. After reporting on two scary incidents: a woman whose paper cut turned into a blood infection; an 18-month old girl who nearly died from an ear infection, the story turned to a case that was eerily similar to Fred's. Alfred Gertler, a jazz musician from Toronto, Canada, had

developed an infection in his ankle after fracturing it while hiking in Costa Rica. As with Fred, doctors had advised him to have his foot amputated.

But Gertler refused to listen to his physicians. Desperate for an alternative, he had scoured the medical literature until he came upon a magazine article describing a treatment called "bacteriophage therapy." Practiced in the United States until the 1940s and still used in parts of Eastern Europe, it pits tiny viruses – bacteriophages, or phages for short – against disease-causing bacteria. These viruses, the most ubiquitous organisms on earth, are bacterial parasites: they reproduce by attacking and destroying deadly germs.

The world's oldest institute dedicated to the study and practice of phage therapy is in Tbilisi, the capital of the former Soviet Republic of Georgia. Unable to find a cure in the state-of-the-art hospitals of Canada, Gertler bought himself a plane ticket to the Third World. There, doctors infused his wound with an amber-colored broth teeming with the invisible creatures. After 3 days of treatment, he reported, his infection was gone. Though it recurred later, after he returned to Canada, it was in a mild enough form that doctors could finally fuse together his anklebones.

Saharra, whose father is a Baptist minister, saw the program as a sign from God. She called Fred and Larry and then spent the night surfing the Web, reading everything she could find on phage therapy. She contacted Betty Kutter, a phage biologist at Seattle's Evergreen University who maintains close ties with Tbilisi. Kutter warned Saharra that the process of treatment was lengthy and that it did not work for everyone. When Saharra insisted, she put her in touch with the microbiologists who had prepared Gertler's phages. They were from Tbilisi's G. Eliava Institute of Bacteriophages, Microbiology and Virology, established in the 1930s by the French-Canadian discoverer of bacteriophages, Felix d'Herelle and his close friend, the Georgian bacteriologist Georgi Eliava. The treatment, Saharra was told, could take as long as 30 days and would cost $2,000.

At first, Larry Bledsoe resisted the idea. "You know your sister, she'll try anything," he grumbled to Fred. But, prodded by Saharra, he did some of his own research. He learned that bacteriophages exist naturally in the soil, in tap water, in lakes and rivers, even in people's guts and nasal passages. After speaking with Kutter, Larry determined that the treatment, even if it didn't cure his brother, most likely would not hurt him. He gave his consent.

The last step was raising the money. The family, which lives in one of the poorest areas of Fort Wayne, pooled its resources to buy the plane tickets, and the Eliava Institute agreed to let them pay for the treatment in installments. Fred and Saharra packed their bags.

At 5 am, on an early November day, Saharra and Fred touched down at Tbilisi's small international airport, unsure of what to expect. Georgia, which had been independent from the Soviet Union for more than a decade, was at that time one of the poorest and most unstable of the former republics. Rent by a conflict over two breakaway provinces, Abkhazia and Ossetia, it faced a refugee crisis and mounting crime.

Zemphira Alavidze, a dignified woman in her sixties who had treated Gertler and who runs one of the oldest phage therapy labs at the Institute, met them with

her husband and an English-speaking friend. Together they drove from the airport along unlit roads, headlights occasionally illuminating a dead dog or a street vendor sleeping beside his fruit stand. When Saharra spotted a curious looking billboard with the face of a middle-aged man staring out beneath Hebrew-like Georgian lettering, Alavidze explained that it was a missing person's announcement. Not long before the Bledsoes arrived, a British banker had been kidnapped from downtown Tbilisi in broad daylight. Fred turned to Saharra: "What have you gotten me into?"

The next day, Alavidze drove the Bledsoes to Republic Hospital, a large cinderblock structure with knocked-out windows and stray cats meowing in the small weedy yard outside. Inside, Alavidze showed them to an elevator that would take them upstairs. It was operated by an old man who made his living off the 10 tetri (about 2 cents) fee he charged per ride. Because the call buttons were broken, the shaft reverberated with the sound of people banging on the doors and yelling out their floor numbers in Georgian.

Fred was admitted to the hospital, where Saharra was allowed to share his room. Soon, their doctor, Chief of Surgery Gouram Gvasalia, arrived and explained that his hospital would attempt to heal Fred's whole body – not just the infection in his foot. His circulation was poor and his blood sugar was high, so they would put him on a diet and try to wean him off the massive doses of insulin he had been taking. Meanwhile, Alavidze would take a bacterial sample from his foot and test it against the phages in her lab to see which ones would work.

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Under an electron microscope, bacteriophages look like insects from outer space. They have a round, polyhedral head, elongated bodies, a tail, and spindly, spider-like legs. Just one-fortieth the size of a bacterium, they eviscerate their prey in a meticulously choreographed operation: they start by clinging to the wall of a bacterial cell and, like a syringe, injecting their DNA inside. There, the DNA particles operate with stealthy efficiency, shutting down the cell's reproductive machinery and reprogramming it to make phages instead of bacteria. In the span of about 30 min, the phage produces hundreds of offspring inside its unwilling host, creating a brood of new "daughter phages" that burst from the cell, destroying it and scurrying off in search of more prey.

Unlike antibiotics, bacteriophages make more of themselves as they work, eventually outnumbering and eradicating the bacteria they were sent to destroy. But, while antibiotics are effective against a wide variety of bacteria, each phage is specific, meaning that microbiologists must spend days and sometimes weeks in the lab identifying the bacteria in a patient's tissue sample and finding a phage that will eradicate it.

The diagnostic center at the Eliava Institute determined that Fred's infection was caused by two types of bacteria, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and Alavidze and her coworkers set to work. They grew up bacteria from Fred's wound in a series of petrie dishes, each containing two cloudy stripes of a

single germ. Alavidze keeps her pseudomonas phages, of which she has around 20, in small glass bottles capped with eye droppers. A coworker of hers placed one drop of the first phage on the left side of one of the pseudomonas stripes. The next phage she dripped over the opposite end of the stripe, and so on. Each bacterial stripe got two different phages, four per plate. Then, she put the plates in an incubator for 18 h, to allow the phages to reproduce and do their job. The next morning, they read the results.

Some phages did not work at all. In these areas, the stripe was as cloudy and opaque as it had been the day before. Others had left patchy circles – small areas where some of the bacteria had been eaten away. Only one phage had worked perfectly: where the coworker had dripped it, it had eaten away a clear circle where the foggy bacterial growth had been. This is the one they would use for Fred. They performed a similar experiment on Fred's strain of staph bacteria, and then mixed, multiplied, sterilized their phage solution and poured it into a set of small glass vials that were sealed shut over a Bunsen burner. The process took 10 days.

In the meantime, the Bledsoes were getting to know their neighbors at the hospital. Across from them lived a family of refugees from Abkhazia, one of Georgia's two breakaway provinces. The two simmering conflicts had uprooted 10% of the country's population, and there was not enough housing for all of them. The hospital had given the family a room where they installed a makeshift kitchen and made themselves at home. They frequently invited Fred and Saharra across the hall for lunch and dinner. The matriarch of the family had a small loom on which she wove handicrafts to sell on the streets. She made Fred and Saharra each a pair of socks and a small tapestry with an illustration of Georgia woven into it.

When Fred's phage preparation was ready, doctors doused his foot with it. Three times a day, a nurse would come, take two glass vials of phage out of a cardboard box, cut the tip of the vial off with a razor blade, transfer its contents into a syringe and squeeze it over Fred's toe. Physicians also put him on a low-sugar, low-fat diet and helped improve the circulation in his feet by administering electrical stimulation to the area. After 30 long days, his wound finally healed – and he had lost 19 lb on his diet. What was once a gaping hole that would not crust over had become a large but benign callus. Fred had arrived on crutches but left on his feet.

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Bledsoe's case exposes deadly gaps in one of the world's most advanced medical systems. After penicillin was first mass-produced in the mid-1940s, wealthy nations enjoyed decades of relative peace of mind when it came to infectious diseases. Pharmaceutical companies pumped a steady stream of antibiotics into the marketplace, drugs that tamed once-fatal disease like pneumonia and strep throat. But, as patents expired and germs seemed to have been bowed into submission, that once fertile pipeline has dried up. Major drug companies have turned their attention toward newer, more profitable areas, like the diseases of aging: hypertension, heart disease, and diabetes. Patients take these drugs for life, while a course of antibiotics can last as little as a few days.

As a result, germs have made a comeback. So-called superbugs, bacteria that are resistant to one or more antibiotics, are on the rise across the United States. These bacteria used to be confined to hospital wards, but they are increasingly seeping out into the environment, where they infect otherwise healthy adults and children. From 1999 to 2008, the rate of children admitted to hospitals with methicillin-resistant *Staphylococcus aureus* (MRSA), one of the strains that infected Bledsoe, has grown tenfold[1] At the moment, there are still drugs to fight MRSA, but a growing number of bacteria are impervious to every antibiotic available. In a January, 2009 report, "Bad Bugs, No Drugs," the Infectious Diseases Society of America wrote, "There is an urgent, immediate need for new agents with activity against these panresistant organisms. There is no evidence that this need will be met in the foreseeable future." Just as in the pre-antibiotic era, doctors are battling to save the lives of patients with pneumonia, cuts and sinus infections.

Phage therapy holds potential as an important new weapon in the fight against superbugs. Rediscovered in the West in the mid-1990s, the treatment has brought a steady stream of venture capitalists, entrepreneurs and physicians through the Eliava Institute's halls. Independently, and with the help of specialists there, Western biotechnology companies are exploring ways of using phages to battle these deadly infections.

Once dismissed as a backward treatment, phage therapy has gained important ground in the last several years. In 2009, British company Biocontrol Limited completed the first double-blind clinical trials showing that phage therapy is safe and effective for the treatment of chronic, antibiotic-resistant ear infections. The United States Army is funding research into whether phages can heal some of the hardest to treat wound infections in Iraq war veterans. Meat and seafood companies are spraying the viruses on their equipment to protect consumers from foodborne illness. And researchers are exploring ways that phages can treat illnesses as diverse as lung infections in cystic fibrosis patients, breast infections in nursing mothers, sinusitis and chronic urological infections. In some ways, phages fit perfectly with the conventional wisdom that simple and natural products top artificial and chemically enhanced ones; one company has had its phages certified organic, Kosher and Halal.

But phages are no magic bullet. Critics point out that they can cause disease as well as cure it; by mingling their own genes with those of bacteria, phages have given rise to some of our worst killers, including diphtheria and food poisoning caused by *E. coli* 0.157. And, just like antibiotics, they breed resistance, though phage researchers say isolating a new phage is faster and cheaper than synthesizing a new antibiotic. Rapid genetic sequencing techniques help keep out so-called "lysogenic" phages that can pass dangerous genes to bacterial cells. While some still see phage therapy as a cultish phenomenon backed by weak science, the current crop of biotech startups is beginning to prove them wrong.

[1] Pediatrics "Antibiotic Management of Staphylococcus aureus infections in US Children's Hospitals, 1999 2008. Jason G. Newland et al. 2010; 125; e1294–e1300.

"The Forgotten Cure" weaves together the history of phages with the stories of scientists who've championed them at the risk of their careers and, occasionally, their lives. It will take you from the Pasteur Institute during World War I, through Stalin's Great Purge, to the Nobel podium and the bedsides of patients battling infections that no antibiotic can touch.

In the process, you'll learn that this treatment stands at the crossroads of two vastly different medical cultures. To the East: a country that provided free but substandard medical care. To the West: a country that offers superior medical care that not everyone can afford. Americans are accustomed to high-tech treatments and rapid-fire cures. Pharmaceutical and biotech companies, in order to keep the flow of innovation coming, expect vast profits.

Can the Western phage companies make money off an ancient, ubiquitous virus? Can they adapt this complex treatment to America's quick-fix culture? And, finally, can they solve the long-held medical mystery at the center of the story: are bacteriophages a long-forgotten cure for deadly, reemerging infections or an unreliable folk medicine with the false gleam of fool's gold?