

Antibiotics failed, then a Minnesota man turned to an old remedy that worked

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John Haverty was ready to have his leg amputated.

Haverty, 62, of Brownsville, had 17 surgeries over a decade to rid his right leg of a stubborn infection that lingered after knee-implant surgery. He had no way of knowing his eventual cure lay in a bacteria-killing virus known as a "phage," found writhing in a sewer treatment plant.

In February, before Haverty knew anything about [phages](#), his doctor at the Mayo Clinic leveled with him: Antibiotics were proving ineffective against the *klebsiella pneumoniae* bugs causing Haverty's infection, and he would probably grow so weary of surgeries that he would eventually opt to have the leg removed at the hip.

"You are going to tell me when you want your leg amputated," Haverty recalled his doctor telling him. "We're not going to tell you."

Haverty and his wife soon went shopping for a post-amputation wheelchair, but he kept looking for answers online.

Many leads went nowhere. Then, one day, a response email arrived from a company called Adaptive Phage Therapeutics in Gaithersburg, Md. The email would trigger a series of events that would prevent Haverty's planned amputation, by getting rid of the infection.

Haverty, it turned out, was just the 14th person worldwide treated with a phage (rhymes with "rage") selected by Adaptive Phage Therapeutics

(APT). He was also the first patient treated in the nascent [phage-therapy](#) program at the Mayo Clinic in Rochester.

The rising incidence of "superbugs," which have evolved to resistant human-made antibiotics, is driving renewed interest in phage therapy. Researchers say phage are the most common organism on the planet. Experimental efforts a century ago to harness phage for infections faded from mainstream science partly because antibiotic drugs worked so well and were relatively cheap.

Modern phage researchers and entrepreneurs now have the tools to rapidly analyze the genomes of bacteria and phages, and machine-learning may aid in finding the perfect match.

Haverty's procedure, approved by the Food and Drug Administration as a compassionate use of an unapproved therapy, was described by APT as "pioneering" because Haverty was one of the first people to have a prosthetic joint infection treated with a phage selected by the company.

"You have to realize that the standard of care when antibiotics have failed, like in the case of John Haverty, often involves amputation and, sometimes, extended time in an intensive care unit. And too often, (it) results in death," APT CEO Greg Merrill said. "We can deliver (phage) therapy extremely fast, and at price points well below the current standard of care for dealing with these infections."

APT is an early-stage operation that is in the business of precisely matching a person's infection with the specific bacteria-killing virus, known as a phage, that will treat it. The for-profit company acquired worldwide exclusive rights to phage technology developed by the U.S. Navy's Biological Defense Research Directorate, and is now developing and refining its systems for identifying, storing and transporting phage therapies.

In Minnesota, Haverty's doctors at the Mayo Clinic worked with APT to do genetic analysis of the infectious bacteria and its potential phage treatment. Infectious-disease physician Dr. Gina Suh, one of the Mayo doctors who has treated Haverty, said she couldn't discuss specifics about Haverty's procedure before publication in a medical journal.

But, in general, she noted the benefits of phage aren't limited to targeting bacteria with genetic resistance to traditional antibiotics. Phage therapy is also believed to be highly effective at penetrating "biofilm" that grows on infected implants. Once biofilm covers a metal implant, it becomes vastly more difficult to treat the infection, even if the bacterium isn't totally resistant to antibiotics.

"Phage can play a role in biofilm infections. Prosthetic joint infection is one. Other examples of this would be, if someone has plates and screws, fracture-fixation devices that become infected, spinal hardware that becomes infected, indwelling brain devices called VP shunts, cardiac devices such as ICDs (implantable cardioverter defibrillators)," Suh said. "The list goes on and on."

A phage is a virus that can only kill a bacterium. It has a head like a 20-sided die from a role-playing game, mounted on a thin body with tiny fibers at the bottom that look like spider legs. An animation from the National Institute of Allergy and Infectious Diseases shows a phage dropping onto a bacterium like a moon lander and injecting its phage DNA into the bacterium to "hijack" the host's genetics. Eventually, umpteen new phage spawn inside and obliterate their bacterial host as they break free, restarting the phage life cycle.

Unlike other early-stage phage companies, APT is not genetically editing the phage it uses in its treatments. "We have evolved on earth in the presence of these phages, so they are regarded as safe for humans. But they are very effective killers of bacteria," said Merrill, the son of widely

known phage expert, Dr. Carl Merrill, who was profiled in an extensive report about phage therapy in the biomedical publication *Stat* last year.

Haverty says the specific bacteria-killing virus used in his case was culled from gunk found in sewage treatment plant. That icky location doesn't surprise him or medical experts, since viruses that kill bacteria tend to live in bacteria-rich environments.

Haverty said the treatment from APT was free to him, since it's not yet approved by the FDA. (He declined another phage therapy, partly because the center wanted to charge him \$10,000.) The FDA is interested in facilitating the "development and rigorous clinical assessment" of phage products, and in 2017 the agency held a two-day meeting to highlight the goal.

Today, numerous phage organizations exist, including 28 private entities like APT and 54 phage labs worldwide listed on the open-source research website *Phage. Directory*.

APT's Greg Merrill said the company plans to recruit patients in up to four different clinical trials at 10 sites in 2020. The company has nearly 1,000 phages meticulously cataloged and stored, and is targeting eight common types of bacterial infections.

"It's like having many arrows in your quiver—we should be able to have an arrow that takes out the target," said APT chief operating officer Subhendu Basu.

For John Haverty, a doctor's stark assessment has given way to a life of renewed vigor. Recent photos show Haverty and his wife taking a walk among the red rocks of Arches National Park on a car trip through Utah.

"I'm like a kid again. I've gone back 10 years in age," he said. "I can see

myself as an old man now walking my dogs down the road again, whereas before, I didn't have much of a life span in mind at all."

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