Georgia: an unlikely stronghold for bacteriophage therapy

The increasing failure of antibiotics to combat infections like multi-drug resistant Staphylococcus aureus has renewed interest in a long-forgotten treatment developed over 60 years ago in ex-Soviet Georgia. Tom Parfitt travelled to Tbilisi to witness the revival of bacteriophage therapy.

It was a fortunate, if curious, discovery—or so it seemed to the three woodsmen as they settled down to another bitterly cold night, deep in the forests of western Georgia.

Wandering through the snow, they stumbled across two metal canisters that were warm to the touch. Intrigued, the men picked up the tubes and took them back to their camp. There, they huddled around the canisters as if they were hot water bottles, hardly believing their luck. It turned out to be a near fatal mistake: the strange metal objects were the highly radioactive strontium-90 core of a long-abandoned radio-thermal generator, once used to power a navigation beacon for Soviet aircraft.

Within days, two of the men had severe radiation burns. They were rushed to hospital in the capital Tbilisi where doctors found the purulent lesions were deeply infected with an antibiotic-resistant strain of Staphylococcus aureus.

Conventional drugs had little effect, but the Georgian specialists had another idea. The wounds were treated with a preparation of bacteriophages (or phages, for short); viruses that are targeted to attack bacterial cells. Within days, two of the men had recovered. "We've known how effective phages are for decades", explains Zemphira Alavidze, head of the phage morphology and biology laboratory at the Eliava Institute in Tbilisi, and one of the team that treated the woodsmen. "But it's only recently that the west has started to sit up and take notice."

Across the world, a growing number of scientists are crowing the advantages of bacteriophages, touting them as the only serious answer to the "superbugs" like multi-drug resistant Staphylococcus aureus (MRSA) that resist antibiotics. Lined against these cheerleaders are the critics who cite a lack of impartial clinical trials to back up the claims.

A phage is a tiny virus that latches its fibres onto a bacteria and impregnates it with DNA, hijacking the machinery of the cell and forcing it to produce countless more phages which eventually burst out, destroying the bacteria.

Billions of phages occur naturally; their weight in the oceans alone is thought to be equal to the weight of human beings on Earth.

The first inkling that phages existed came in 1896 when British chemist Alexander Fleming's discovery of penicillin in 1928, interest rapidly died out. It was not until 1916 that Felix d'Herelle, a Canadian microbiologist working at the Pasteur Institute in Paris, figured out that the microbes were viruses themselves, coining the term bacteriophage ("bacteria eater").

He used his knowledge to develop a phage preparation to treat World War I soldiers with dysentery. D'Herelle struck up a partnership with a Georgian scientist named George Eliava; the pair later worked together in Tbilisi, where the Eliava Institute was founded in 1923.

Early results were promising and western companies soon began to market phage therapies for typhoid and urinary-tract infections. Then, with Alexander Fleming's discovery of penicillin in 1928, interest rapidly died out. It would not revive outside the Soviet bloc for more than half a century.

In Georgia, however, research continued apace. At its height after World War II, the Eliava Institute employed 1300 people. Thousands of remedies were distributed all over the USSR, used in tandem with antibiotics.

The Soviet collapse in 1991 was a disaster for the institute. "It was a very difficult time", remembers Alavidze. "There was often no electricity, no heating. It was as cold in here as it was outside in winter. Our salaries stopped. But we came every day, and somehow we saved our phage bank."

Now, international grants are trickling in and employees at the sprawling institute on the edge of Tbilisi are beginning to strike up partnerships with commercial companies keen to push the potential of phages abroad.

One of those is the Phage Therapy Centre, an American-owned subsidiary which is bringing foreign patients to Tbilisi for phage treatments on diabetic foot, burns, ulcers, osteomyelitis, and drug-resistant infections such as MRSA.

A course of treatment costs between US$8000 and $20 000. So far, only a handful of patients have made the trip but demand seems to be slowly growing and the centre's parent company has opened a new clinic in Mexico. The USA and many European countries have yet to approve commercial sale of phage therapies.

"We've had a lot of experience, a lot of success with Georgian patients", says director, Vakhtang Beridze. "Now we need to go to the mass market and show the world this is a reality."

Among the latest products available in Georgia is a kind of biodegradable artificial skin made from a polymer impregnated with phages that attack the most common bacterial infections. Laid over a wound, it slowly releases the preparation. Lesions can also be treated with a powdered form of the mixture or local injections.

Despite such modern methods of administration, the experts' sources of phages have changed little since the times of d'Herelle.
Many are extracted from sewage, where they live alongside the bacteria on which they are parasitic. "We get ours from the river Mtkvari that runs through the city", Beridze enthuses. "It’s like liquid gold; only nobody except us realises how precious it is!"

The resulting phages—extracted, filtered, and purified—are “natural born killers” designed to infect a specific bacteria, he says.

Trust in the treatment remains strong in Georgia, and it is routinely used. In the early 1990s soldiers engaged in combat in breakaway Abkhazia were supplied with aerosols of phages for treating five common infections in wounds. Even president Mikhail Saakashvili has claimed the therapy was successful in curing a relative with gangrene.

Phages’ supporters say they have distinct advantages: they only attack specific bacteria and cannot harm human cells or the “good” bacteria that live in places like the gut; they can penetrate deep into wounds; they increase with increasing infection; and if resistance develops against a bacteriophage, a new one can be found from a parent strain within days whereas a new antibiotic takes years and millions of pounds to develop.

At least ten biotech companies worldwide—including Intralytix in the USA, Novolytics in the UK, and GangaGen in India—are seeking funding for commercial development of phage therapy. Yet the enthusiasm of people like Beridze is tempered by widespread scepticism and, in the west, regulatory hurdles.

Potential foreign patients are often deterred by talk of sewage and viruses, and public awareness of the therapy remains low. With only a trickle of patients so far, the Phage Therapy Centre is obliged to use wards in two decaying Tbilisi hospitals.

"There are too many evangelists and too little data and it’s still being hyped”, says Ian Molineux, a microbiologist at the University of Texas who specialises in bacteriophages and host–parasite interactions. “There have never really been any proper controlled experiments.” Much of the positive spin on phage therapy is little more than hyperbole, he says.

Molineux is collaborating with a team of Georgian experts who are testing the efficacy of phages to treat cows with mastitis. An initial experiment showed phages extracted from the cows’ teats were just as efficient as antibiotics in eliminating Staphylococcus aureus, Escherichia coli, Streptococcus pyogenes, and other Streptococci. But Molineux says it is not yet conclusive. “A lot of the available studies show positive results—but would they have been published if they didn’t? We’re going to publish our findings whatever happens.”

One doubt about phages is the fear that some types do not kill bacterial cells but integrate into the bacterial genome and carry bacterial genes with them when they multiply. These lysogenic phages are thus responsible for the “horizontal” spread of antibiotic resistance genes among related bacteria.

But Mike Mattey of Strathclyde University says such lysogenic phages are unlikely to ever get regulatory approval and should not detract from the positive effect of lytic phages that kill (lyse) bacterial cells. “It must be stressed that lytic phages cannot spread either resistance or virulence”, he says.

Nick Mann, a phages expert at the University of Warwick and a founder of Novolytics, says that strict regulation in the USA and Europe is likely to prevent the widespread use of phage therapy for many years to come.

“One of the main reasons that phages are not being used is that big pharma can’t see how to get intellectual property protection because people have been using phages for years”, he adds. “And they also wouldn’t make a significant profit out of them.”

Phage therapies have yet to pass even the first phase of clinical trials demanded by regulatory bodies in the USA or the EU, he pointed out.

“The big companies are more interested in developing a drug for a chronic, western ailment like irritable bowel syndrome or depression than an efficient, one-off treatment for a bacterial infection”, says Mann.

Tom Parfitt