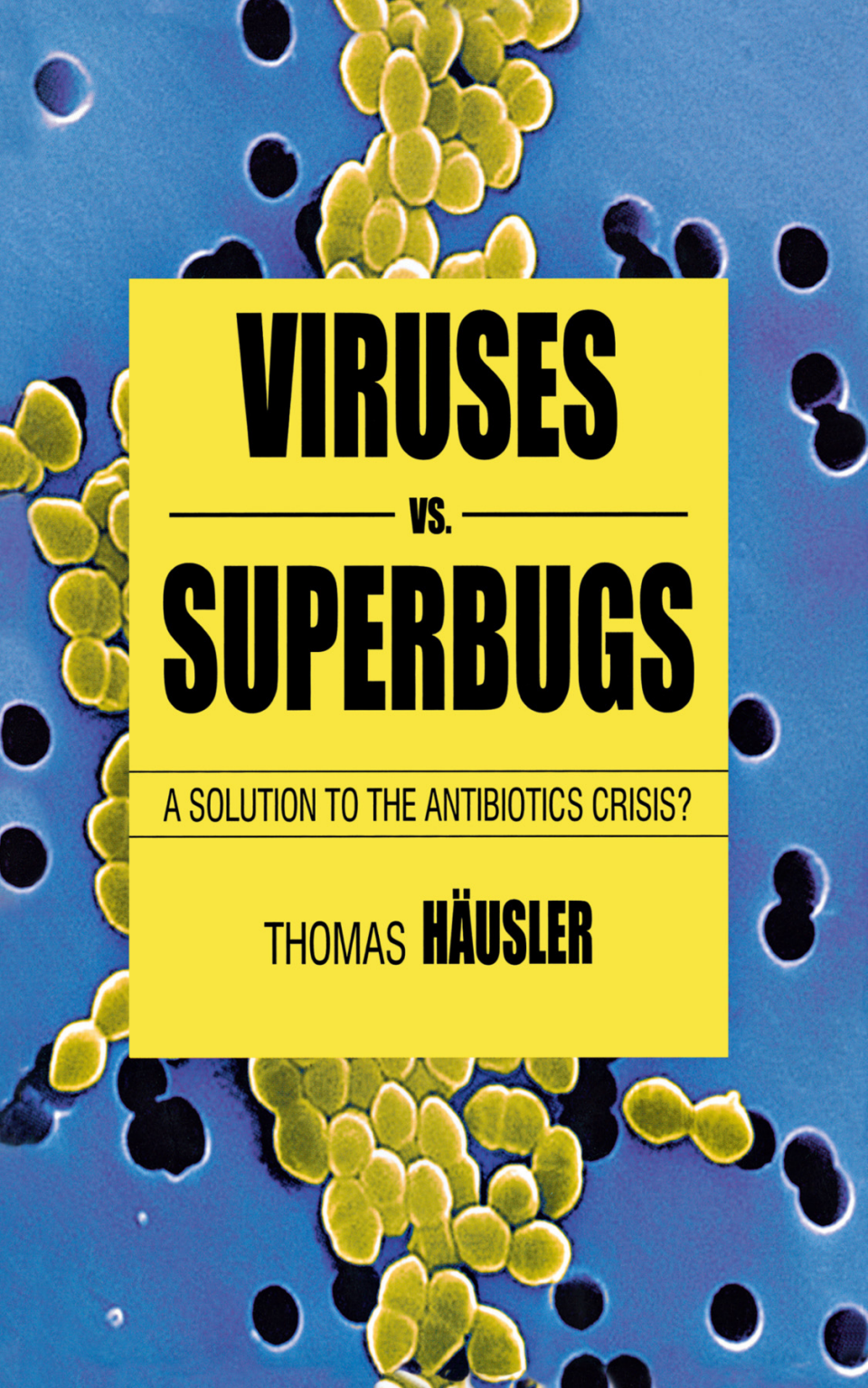

VIRUSES VS. SUPERBUGS

A SOLUTION TO THE ANTIBIOTICS CRISIS?

THOMAS HÄUSLER

Viruses vs. Superbugs

A solution to the antibiotics crisis?

Thomas Häusler

Translated by Karen Leube

Palgrave Macmillan

Softcover reprint of the hardcover 1st edition 2006 978-1-4039-8764-8

First published 2006 by
Macmillan
Houndmills, Basingstoke, Hampshire RG21 6XS and
175 Fifth Avenue, New York, N.Y. 10010
Companies and representatives throughout the world

ISBN 978-0-230-55193-0 ISBN 978-0-230-55228-9 (eBook)
DOI 10.1007/978-0-230-55228-9

A catalogue record for this book is available from the British Library.

A catalog record for this book is available from the Library of Congress.

10 9 8 7 6 5 4 3 2 1
15 14 13 12 11 10 09 08 07 06

Transferred to Digital Printing 2014

For Susanne and Julia

contents

list of figures

foreword

Just imagine life without antibiotics. It would be like it was 100 years ago, when pneumonia and tuberculosis were the most frequent causes of death, and the risk of infection turned a simple appendectomy into a dangerous operation.

Luckily we do have antibiotics. However, they are becoming increasingly ineffective. Doctors are more and more frequently confronted with infections they can't do anything about because the bacteria have become resistant. This has dire consequences for patients. Many end up living with a chronic infection for years on end, some are forced to become amputees and yet others succumb to the infections.

The crisis affects people in both industrialized and developing countries. In the US and the UK, the bug *Staphylococcus aureus* is wreaking havoc. Forty to fifty per cent of infections that people contract in hospitals are resistant to more than one antibiotic. The developing countries are groaning under the burden of tuberculosis, which claims the lives of 2 million victims throughout the world every year. The increase in multi-resistant TB is especially alarming. Treating it costs 100 times more than treating the regular form, making a cure unaffordable for many people in impoverished countries. And these are only two examples.

Despite this, many pharmaceutical companies have stopped developing antibiotics. They see the financial risk as too big and potential profits too skimpy. This has led to very few new drugs for fighting bacterial infections being launched in recent

years. A survey of 11 large pharmaceutical companies revealed that of 400 substances they were developing, only 5 were antibacterial drugs.

What can be done about the resistance crisis? One thing is needed for sure: new drugs. One of them could be bacteriophages, viruses that attack bacteria without harming people. So-called bacteriophage therapy had its heyday from 1920 to 1940, before it was pushed aside by penicillin. The former Soviet Union is the only place it continues to be used today. Most Western doctors do not even know that this method exists.

However, there are some scientists who have resumed research on bacteriophage therapy, and that's a good thing. We need to pursue any and every approach that can contribute to solving the resistance crisis. Bacteriophage therapy may prove to be a particularly worthwhile area of research. Its long history provides a large stock of knowledge that is freely accessible. Determined researchers now need to use this as a starting point and work out how to turn bacteriophages into drugs that meet today's standards. This would be best carried out in cooperation with science departments at universities, along with private companies and non-profit foundations that support the projects. This is exactly the goal of the Foundation for Fatal Rare Diseases. The foundation supports the development of drugs for neglected infectious and pulmonary diseases and is especially committed to helping affected patients who have not been in the public eye, particularly those in Africa and India.

Thomas Häusler's remarkable book plays a central part in this scheme, because it acquaints the public, researchers and decision makers with a therapy that has the potential to someday heal many patients who cannot be helped at the moment. This is why the Foundation for Fatal Rare Diseases is supporting

the realization of this English edition. The fact that the author writes about bacteriophage therapy in the form of such a gripping story makes reading it all the more exciting.

Vaduz, October 2005
Vera Cavalli, Dorian Bevec and Fabio Cavalli
Founders of the Foundation for Fatal Rare Diseases

preface

Why should anyone be interested in an old cure that hasn't been used in the West for 50 years? It's a method that many doctors aren't even aware of today. The most telling answer to this question came when I received a call in my office from a man one Friday morning in January 2001. It was the day after my article on the Eliava Institute in Georgia had appeared in the German weekly newspaper *Die Zeit*. In the article I had described how this old remedy – phage therapy – had survived in the impoverished country.

Phages are viruses that attack and kill bacteria but not people. Since Stalin's days, doctors in Russia and Georgia have been using phages to cure bacterial infections. In the West this method was also once popular but, in contrast to the Soviet Union, the triumph of penicillin pushed phage therapy aside here after 1940. The Eliava Institute in Tbilisi, Georgia is a place where phage therapy survived even after the collapse of the Soviet Union. It looks back on a glorious 80-year history. However, because of Georgia's economically and politically precarious situation, it is experiencing a gloomy present. From the point of view of today's science, it is unclear how effective phages are in fighting infection. This is because the studies carried out by early pioneers and Soviet researchers do not meet today's standards. All this was in my article in *Die Zeit*.

The caller explained that he had read the article. He was calling directly from the hospital and appeared to be under a great deal of pressure. Not mincing words, he explained that he had been suffering from an infection in his foot for two

years. Doctors couldn't get it under control because the bacteria were resistant to all antibiotics. He was scheduled to have his foot operated on a fourth time the next day. Could I put him in touch with someone in Georgia? He was afraid that before long he would lose his foot.

More than any research I have done, his call hit me between the eyes. Never before had I been so aware of the power that bacteria continue to wield over us. We have grown up with the certainty that every bacterial infection can be cured by antibiotics. Most of us have no idea of the destruction that bacteria are capable of rendering, because our doctors prescribe drugs at the slightest symptom.

One year after I received this call, I accompanied an expedition of botanists and fragrance researchers to a rain forest in Madagascar. One night, as I slept in my hammock, I woke up, and my right foot was hot, red and swollen. The next morning I could hardly walk. Bacteria must have entered places where my sandals had rubbed against my skin while we were hiking. The doctor accompanying the expedition gave me some antibiotics that he found in his first-aid kit. The effect was hit or miss – more miss than hit, in fact. Four days later, I arrived home – with my foot still swollen. My GP prescribed some other antibiotics and luckily they worked. He cut to the chase: 'That could have been the end of you.'

At that point, however, I no longer needed that kind of graphic demonstration of the power of bacteria, since I had already started doing research for this book. The 80-year-old history of the tiny phages and their potential role in reining in the antibiotic resistance crisis were constantly on my mind.

The fascination produced by phage therapy is particularly striking as I write these lines. In Southeast Asia, veterinarians and doctors are combating bird flu. A pandemic is in the making. This was only just averted in the case of SARS, a new

atypical kind of pneumonia. These health crises show viruses in their familiar role – as lethal villains. Phage therapy takes this image and turns it upside down, turning the bad guys into unexpected allies.

This book is not a health manual whose purpose is to testify to the efficacy of phages. First, it's too early to reach a clear conclusion about their effectiveness. Researchers are still working on this. Second, I found the detective work on the origins of the captivating idea that bacteria can be fought with their natural enemies at least as interesting as the analysis of phages' curative powers. I hope that this has led to a book that sheds some light on the sometimes winding paths of medical research and in turn provides some insight into an area of our society that is becoming increasingly significant. Never has so much medical research been undertaken as at the present time, nor has so much money ever been spent to cure us of diseases.

This English edition came about some three years after the German edition was published. I have taken great pains to update the material in the book. As I did so, I saw that some companies had been confronted with scientific or financial obstacles, leading them to abandon their projects altogether. On the other hand, other companies and university researchers have joined the ranks of phage therapy research, contributing good ideas. What they require is support from public and private sponsors in order to produce drugs from phages. They are desperately needed.

I could not have written this book without the help of many researchers, doctors, patients, librarians and helpers. They provided me with information, books and photos, gave me accommodation, told me about their lives, interpreted or handed out advice. I extend my gratitude to all of them.

I would specifically like to thank Elizabeth Kutter, Hans-Wolfgang Ackermann and Harald Brüssow for sharing their

expertise. Zemphira Alavidze, Nino Chanishvili, Liana Gachechiladze, David Gamrekeli and Mzia Kutateladze not only provided me with exhaustive information, but made my research in Georgia possible in the first place. I will never forget their hospitality.

Reto Schneider, Elizabeth Kutter and my wife Susanne read the entire manuscript. I thank them for their countless suggestions for improvement in style and content. I also express my thanks to my translator Karen Leube, my editors Sara Abdulla (Macmillan) and Wolfgang Gartmann (Piper), and the team at Aardvark Editorial. Without the support of Tamedia AG, the publisher of *Facts* news magazine, this book would not have been possible. *Facts*, my employer, continued my salary while I worked on this book, and Tamedia's media forum paid for the research expenses. I would like to thank my colleagues at *Facts*, Odette Frey, Beate Kittl and Rainer Klose, for their willingness to put up with the additional work and reorganization brought about by my absence. The English translation was generously funded by the Foundation for Fatal Rare Diseases. Thomas Fritschi and Rich Weber drew the graphics for Figures 3.4 and 3.5. I thank Susanne and Julia for putting up with a husband and father who was more of a phantom for a year and, at times, an overworked, nervous one at that.

Thomas Häusler

1
at the limits of medicine

At some point during those fateful days, microbes barged their way into Alfred Gertler's life. They lodged themselves there, spread all over and took control. They devoured his bones.

Gertler, who was 41 at the time, had signed up for a gig on the cruise ship MS *Maasdam* for a few months. His lopsided house in Toronto was 'full of my two sons' diapers, but we were pretty short on money', as he put it. He hoped to remedy the situation by working as a musician on the ship. In March 1996, the *Maasdam* was cruising in the Pacific along the shores of Central America. Gertler left the luxury liner during a stop in Caldera, Costa Rica to rest from his hard work as a bass player. It was intended to be a break from the gruelling daily concerts, which ended with the players up to their ankles in music because there wasn't even enough time to turn pages. Yes, a hike in the hills at the end of the Pacific Ocean would do him good. That's not quite how it turned out. On the way back he lost sight of the footpath. Since the 4 o'clock rehearsal would begin shortly, Gertler decided to climb down the steep slope below the path down to the road. This decision would change his life forever.

It was a short fall, less than 15 ft. The root Gertler grabbed onto on his way down broke off. Suddenly he was lying on his back, completely unable to move. 'My foot was folded like a sock', he recalls. 'My bones were sticking out. They looked

white and soft', he told me when I visited him in Toronto six years later. Some local souvenir vendors strapped him to a board and carried him down to the city, where his foot was bandaged and put in makeshift splints and his wounds rinsed out. And all this without any anaesthesia. Gertler was afraid that if he had an injection, his foot might become infected. He was transported over a bumpy road to the hospital in San José, the capital. Six days later, he flew back to Toronto. His GP inspected his cast and decided to leave it at that.

At this point, the bacteria must have already sneaked into the wounds. The germs would cripple his foot, confine him to bed for years and expose the limits of medicine. Perhaps the microbes were lurking in the soil where he tumbled down the slope. Or maybe they were hiding in the mildewed bathroom in the San José hospital, which had filled Gertler with such utter panic that he had scrubbed the shower for two hours before setting foot in it. There's no way to say for sure, since the bacteria silently ran rampant under the cast until the pain in Gertler's swelling foot drove him to the hospital. Too late.

The orthopaedist at Sunnybrook Hospital made a shattering diagnosis: 'If you don't die, then your foot will.' Gertler was given an ultimatum: have his foot amputated or the bacteria would continue to eat their way up the bones, damaging first the foot, then the lower leg and then the thigh. Gertler panicked. He didn't want to lose his foot. Desperate, he dragged himself to another hospital. The doctors there agreed that his foot should be amputated. Gertler again refused to have the operation. That was the beginning of a battle between the doctors and the staphylococci – the germs commonly known as 'staph' – in his ankle. They used the strongest medicine available. For more than two years, Gertler continuously received antibiotics. For a year, they were injected directly into his bloodstream via an electric pump.

These miracle drugs, which many people consider to be the greatest medical achievement of the 20th century, were a complete flop. The sustained attack of cloxacillin and ciprofloxacin, the drug made famous by the anthrax attacks in the US in autumn 2001, barely dented the microbes in Gertler's foot. They hunkered down in the bone, gnawed away at it, kept the joint swollen for years and held open two gaping, weeping wounds. Gertler spent most of the time in bed: 'Even going to the pharmacy around the corner on my crutches and hobbling back was enough to make all hell break loose.' The movement in the broken joint ejected the microbes from their hiding places in the bone and the neighbouring tissue and sent them to the bloodstream, where they multiplied like crazy. The ensuing blood poisoning and the overreaction of the immune system connected with it – doctors refer to this life-threatening combination as 'sepsis' – confined Gertler to bed for weeks with fever, chills and continuous fatigue. 'The worst thing was when the wounds healed up again', he told me, 'because then the hope returned that it was all over. I finally got out of bed, played music and, whoosh, it broke out again.' He experienced this so often that you could hardly hear the bitter disappointment in his voice any more.

The strange thing was that, in a test, the microbes didn't even show a particularly raised resistance to antibiotics. Antibiotic resistance is a nightmare for infectious disease specialists, who increasingly have to stand by and watch helplessly as bacteria dupe the drugs aimed at them and people die because no drugs work. Ironically, an estimated 10 per cent of all patients in hospitals are infected by bacteria. In the US alone that makes 2 million patients per year, and 90,000 of them die, 70 per cent from highly resistant bacteria.[1]

In Gertler's case, the antibiotics simply couldn't reach the colonies of staphylococci in the bones: 'I couldn't believe it. I

had an infection with staph – one of the most common complications of surgery – and not a thing could be done about it.' Gertler was just one of many patients who suffer the same fate. Just because an antibiotic destroys the germs in a test tube doesn't guarantee that it will pack the same punch in a patient's body. The drugs are especially ineffective in places with a poor blood supply, like bones. Victims are constantly subjected to new operations to cut out affected tissue which disfigures them more and more.

Mysterious hope

For Gertler, doing gigs as a bass player was now out of the question. Money became tight. And being deprived of music – his passion – was just as bad. In his old house on Kensington Market in Toronto, whose esoteric shops, jazz cafés and vegetarian restaurants are reminiscent of hippy capital Haight-Ashbury in San Francisco, there are always lots of different radios in the different rooms all tuned to the same jazz station, even at night. 'The infection was like a wish from hell. Hey – you want to sit in bed all day and listen to music? Okay, here it is.'

It got even worse. His wife moved out and took the two children with her. 'I don't blame her. It's pretty hard to stand it with a guy who lies in bed all day, is tired all the time and constantly complains that he's in pain', he told me as we sat sipping tea in his kitchen. The corners and walls of Gertler's house are full of pictures of his sons. On the doorframe you can still see the marks he used to record the boys' heights as they grew. The last is at 89 cm. When Gertler sees it, he always thinks of what the doctor told him: 'When your foot gets bigger than your life, get rid of it.'

Gertler's foot is still attached. He started fighting, looking for ways to conquer the bugs and liberate his foot from the

destructive staph. Since Gertler wasn't internet savvy, his brothers and his parents helped him to search for information. As it turned out, it wasn't the Web that helped the desperate musician. It was pure coincidence. In early 2000, nearly four years after his fateful accident, a friend of Gertler's collapsed while riding his bike. The emergency doctors' diagnosis was acute blood poisoning – caused by staph.

Gertler paid his friend a visit in the hospital. The 6 February 2000 issue of the *New York Times Magazine* was lying on his tray table. In it was an article about an amazing treatment from the Republic of Georgia.[2] Gertler devoured the article, learning that in this distant land in the Caucasus, microbes were being used to fight microbes. The physicians there let special viruses loose on the bacteria. For each type of bacteria, nature provides a matching virus that decimates the pack with chilling efficiency, leaving humans unharmed.

The treatment operates on the principle: 'My enemy's enemy is my friend.' It was also used in the Western world well into the 1940s. Yet the success of the treatment varied widely and, with the discovery of penicillin, it was abandoned. In contrast, in the Soviet Union, therapy involving bacteriophages, as the tiny bacteria-exterminators are called, continued over the years – almost unnoticed by Western medicine. In Gertler, the seeds of hope began to germinate. Especially intriguing was a bit in the feature describing how, in Georgia, the method was used to target cases in which antibiotics didn't work. 'That same evening I limped off and made ten copies of the article.'

At the very end of the text, it was reported that a bacteriophage conference was about to be held in Montreal, only 530 km from his home. Gertler contacted the organizer, Michael DuBow, a researcher at McGill University in Montreal. 'DuBow told me that it was a scientific conference, but I could

attend if I paid the registration fee.' The conference was primarily dedicated to basic research on phages, which had also been carried out in the West. However, the growing crisis regarding resistance to antibiotics had sparked the interest of several biotech companies and scientists in phage therapy, so some lectures on this topic were scheduled too.

So here was Alfred Gertler, a jazz bassist, at his first scientific conference. Even among the crowd of scientists, who were otherwise oblivious to the outside world, he stuck out, with his crutches and his inevitable Greek fisherman's cap. 'In the breaks he hung around the smokers who would stand around outside on the steps', recalls Elizabeth Kutter, a phage researcher who later ended up helping Gertler. It didn't take long for him to get to know several scientists who were exploring phage therapy. Treating him, however, was something altogether different, too much of a risk for them. As a treatment that had not been sufficiently tested or approved, no one in Canada or the US was allowed to use it without risking serious consequences from the health authorities. 'Despite this, though, there were a few scientists who offered to help me right away', Gertler said. "Bring us a bacteria sample from your wound", they said, "and we'll pick out the phages that will work in our lab."'

On the final day of the conference, on a boat ride on the St Lawrence River, Gertler struck up a new acquaintance during a smoking break. 'I asked the guy if I could have a puff. I don't really smoke, but it restricts the circulation in my foot and helps me to get home without it hurting so much. And we got to talking.' The chain-smoking researcher was from Georgia, the country featured in the *New York Times Magazine* article.

> He asked me for a bacteria sample. I hobbled to the restroom. A storm was in progress and rocked the boat like crazy. I had to be

really careful not to fall over as I was taking off my shoe and sock. I took one of the cotton swabs that I'd been carrying around with me the whole time during the conference, scraped off some secretion from the wound and put my sock and shoe back on again. Then I limped back on deck.

The researcher gave Gertler his business card. It said: Revaz Adamia, Chairman of the Defence and Security Committee of the Georgian Parliament. 'I thought he was from the KGB, and I'd never hear back from him again.' Yet soon after the encounter, Adamia, who worked full time as the head of a lab at the Eliava Institute for Bacteriophages, Microbiology and Virology, sent Gertler an email from the Georgian capital of Tbilisi: 'We have the right phages. Treatment at the local hospital is no problem.'

So close and yet so far away

But Gertler decided he would rather have his foot treated in Canada or the US. He was too uncertain about what to expect in Georgia, where a civil war had been raging only a short time before. That's the way he saw it back then, anyway. Gertler preferred to accept the offer of an Israeli researcher he had also met at the conference. The Israeli cultivated phages for diagnostic purposes and had found a virus in his inventory that, in a test tube, had wiped out the staph from Gertler's foot. The researcher planned to send him these phages; all Gertler had to do was to find a doctor who would treat him with them. He put together a file of articles and printouts from the internet with information about phage therapy and set out to find a Canadian doctor who would be willing to risk an attempt at the exotic method. 'I felt like a nut, the way I limped from practice to practice with my bundle of paper all marked up

with yellow highlighter.' His limping only landed him in a blind alley. There wasn't a single doctor willing to put his or her head on the block.

Finally, Gertler happened upon some exciting news on the internet. In 1999, doctors at a hospital in Toronto – his own city! – had used phages to snatch a dying woman from the jaws of death. The woman had Marfan syndrome, a serious genetic disorder, and was also suffering from an acute staph infection, this time of the heart. The microbes were resistant to everything the doctors had pumped into her. Organ after organ had failed.

By chance, the woman's son had heard about a company called Phage Therapeutics in Seattle, Washington, which had just developed a bacteriophage drug used to treat highly resistant staphylococci. After my visit to Gertler, I talked to Richard Honour, then the head of the tiny start-up. Honour vividly recalled how a man had called him, desperate for help. 'Mom is dying!', he yelled into the telephone. Honour immediately agreed to provide the drug for emergency treatment, despite the fact that it had only been tested in animal trials up to that point, meaning that to all intents and purposes he was circumventing the law. The two swore each other to confidentiality. The doctors quickly had a bacteria sample flown to Phage Therapeutics.

Honour's researchers put the deadly staphylococci in a test tube and set their phages on them. 'And zoom, the phage killed the bacteria', Honour told me. He sent a few vials to the Canadian border, where they were received by a hospital worker. Following the instructions of Phage Therapeutics, the doctors sprayed the phage solution on the dying woman's heart, which had been exposed in the chest cavity. The next day, they injected a gigantic dose – 100 billion viruses – into her. Within 20 hours, the patient had recovered, and the

bacteria had completely disappeared from her heart and her blood. According to Honour, she died of the heart problem caused by the genetic disorder several months later, but at the time of death, she was still free of the staph.

The pact of confidentiality that Honour and the hospital had agreed to was short-lived. The identity of the person responsible for leaking the information to the press remains unknown, but the news that a dreaded 'superbug' infection had been instantaneously cured made the headlines. The Canadian health authority threatened to have Honour arrested. The patient's family and her physicians went underground. For six months, Gertler tried to find out the names of the hospital or the doctors. Although various sources gave him tips, including email addresses, 'they refused to communicate, and I finally figured out that the doctors didn't want to be reached. I don't blame them. After all, they had already put their careers on the line once before.'

Rusty surgical instruments and vodka as a disinfectant

Just then, Gertler got a call from Elizabeth Kutter, the phage researcher he had met at the conference who was in close contact with the scientists from Georgia. Kutter was planning another trip to Tbilisi and asked him if he'd like to join her. 'From the outset I had told him to get treatment in Tbilisi, because the doctors there had years of experience with phage therapy', Kutter says. Her call couldn't have come at a better moment. Gertler was ready to go to Georgia this time. In the three weeks leading up to the trip, his family arranged the flight, visa and money for Gertler, whose illness had taken a huge financial and physical toll.

At dawn on 29 January 2001, Kutter and Gertler arrived at Tbilisi airport. The long journey had stirred up the germs in

Gertler's foot and acute blood poisoning was imminent. After a brief rest at the flat of Liana Gachechiladze, a phage researcher from the Eliava Institute, his hosts took him to the tiny diagnostic practice, Diagnos 90. Gachechiladze, along with fellow researchers, had founded the practice as a stopgap after the Eliava Institute had been hit hard by the collapse of the Soviet Union. The mighty production units that had once churned out masses of phage drugs had been cannibalized, and the staff had shrunk from more than 1000 to fewer than 100. The employees who had stayed on in the crumbling institute had to supplement their $30-a-month salary that the impoverished government paid (or sometimes didn't) by taking on a second job, like the one Liana had at Diagnos 90.

The practice was situated in a former gatehouse at the entrance to the extensive institute complex. Stray dogs greeted Gertler as he hobbled up, and signs of fire on the walls only added to the desolate conditions of the building. Gertler, completely exhausted, must have felt queasy at the sight of the run-down place. As soon as he entered the practice, a physician's assistant wanted to take a sample in the freezing exam cubicle, and utter fear descended upon him. 'She went straight at my ankle with this rusty coat hanger.' Was everything going to get even worse here? Wouldn't it have been better to have his foot amputated after all?

Two days later, these fears gave way to cautious admiration, as Inga Georgadze, the head of Diagnos 90, presented the results of their analyses. She had tested a long list of antibiotics and phages for their effectiveness on the staph. Gertler, whose odyssey had turned him into an antibiotics specialist, saw many drugs on the list he had never heard of. In the ruins of a battered country, here were scientists and doctors who were doing their best to maintain their skills and their art – and to help him.

Several phages from the institute's collection completely eradicated his staph in the test. The Eliava researchers combined them into a powerful cocktail. An X-ray revealed the extent of the damage to his foot and confronted Gertler with the severity of his injury. 'The doctors squirted a contrast medium with a lot of pressure in the wound on the outer side of my ankle, and it came out through the opening on the inside of my ankle', he recalled, shuddering at the thought. 'Over the years, I had made a point of washing out the wounds every day, but I had no idea that they were so directly connected.'

After the weekend, Elizabeth Kutter and the Eliava researchers brought Gertler to the Tbilisi central hospital, where surgeon Guram Gvasalia, who had years of experience with phage therapy, wanted to perform the treatment. In the tight, windowless foyer of the 12-storey hospital, the only bit of light came from a red Coke machine. The gloomy lift was operated by a toothless elderly man, whose services proved to be necessary, since the tin box could only be opened by fiddling around with the inner workings of the clanking doors. As a special guest, Gertler was allowed to pick out a room, either one that was close to the toilet in the corridor or one with a view of the city. Otherwise, the features were the same as those of the other freezing hospital rooms: bare, peeling plaster, holes in the unfinished parquet and ancient iron pipes. Patients' families crouched outside in the dark corridor. They cooked meals for their sick relatives or went to the chemist to pick up prescriptions. The hospital received practically no money from the city, so the patients had to have their drugs bought for them.

For Gertler, a cook was hired, who 'bought vegetables, cooked like a dream and spoke to me in Georgian as if she were my mother'. One night he was awakened by a fellow

patient's family member looking for a bed to sleep in. Although Gertler had become convinced of the medical skills of his Georgian friends, the strange and shabby surroundings began to take a toll on his mental state. Kutter had to get him several bottles of vodka. 'Alfred kept wiping off everything he saw with it to disinfect it', she recalls.

The treatment began. In the operating room, Gvasalia, the surgeon, carefully washed out the pierced foot. Then he flushed its deep caverns with the phage solution before he attached IV tubes to its two open sides. The tubes pumped into the injured joint the staph killers and enzymes to break

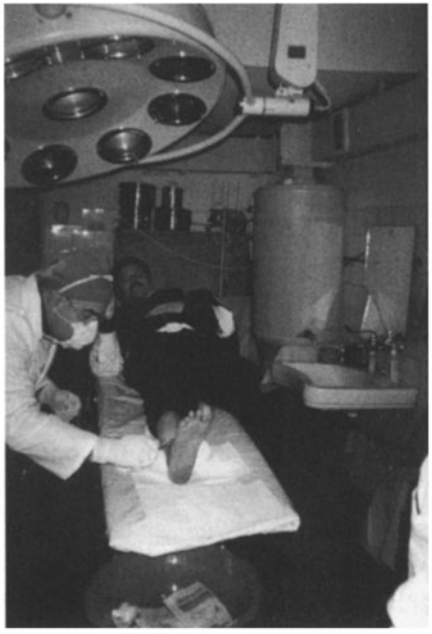

Figure 1.1 Surgeon Guram Gvasalia uses phages to treat Alfred Gertler's foot at the Tbilisi central hospital

down the scarred tissue. The next day, the doctor repeated the procedure. In addition, he placed slivers of a biodegradable membrane – impregnated with phages and selected antibiotics – deep inside Gertler's foot. As the strips slowly disintegrated, new phages and drugs continuously forced their way into the tissue. The cornered microbes experienced sustained bombardment. After three days, the doctors could no longer find the staphylococci, previously teeming in the wound secretion.

Gertler had to hold out in the central hospital for another two weeks. Gvasalia urged him to have surgery to stabilize the joint that had been worn down by infection for so many years. There might still be nests of staphylococci deep inside the bone that would be released by the constant friction of walking.

Now, four-and-a-half years later, Alfred Gertler is doing better than at any time between his fateful fall and his stay in Tbilisi. Since undergoing phage therapy, he no longer takes antibiotics. He walks to concerts from his jazz-filled house, supporting himself on crutches and hobbling, carrying weights that the doctor has outlawed – and not once has he come down with acute blood poisoning. From a strictly scientific point of view, no one can really say how much of a role phage therapy has played in this improvement. In an isolated example like this, it could be a simple case of spontaneous healing, or some other factors may have had an impact. The only way to prove the effect of the bacteria killers is to carry out carefully planned and documented studies with a large number of patients.

Wily enemies call for unorthodox methods

After 50 years in the cold, the massive increase in resistant bacteria has brought phage therapy back to the attention of

researchers in the West. Humans are in a constant struggle against microbes that we will never win. Bacteria have always proved to be tricky. This is why we need new drugs, as well as the rediscovery of old ones, since new antibiotics are extremely slow to enter the market. Therefore, for several years now, a small number of universities and biotech companies have been working on phage drugs again.

Yet many infectious disease specialists continue to be extremely sceptical. They argue that researchers in the controversial early history of phage therapy never managed to produce clear proof of its efficacy. The critics are also suspicious of the work of researchers from the former Eastern bloc because most of their results were reported years ago in Russian or Georgian journals – making them almost impossible to check. Political turbulence and economic decline in the countries of the former Soviet Union only add to the doubts.

To get an idea of the contribution that phage therapy can make to the fight against bacteria, you have to go back to its beginnings around 1920 and comb through the reports that numerous scientists have amassed since. What you find is a rich history, filled with hopes and disappointments, eccentric heroes and tragic fates, gigantic experiments with thousands of subjects and evidence that our grandparents swallowed phage medicine. In France, you can even come across retired researchers who used phages around 1970 to cure patients who had been declared incurable. Now it's time to reactivate all this knowledge after years of fooling ourselves into thinking that modern medicine is the victor.

2
invincible microbes

'It is time to close the book on infectious diseases', US Surgeon General William H. Stewart announced in 1969. 'The war against pestilence is over.'[1] According to America's highest ranking physician, scientists should have been investigating cancer instead of tuberculosis and replacing the study of cholera with research on heart attacks. Stewart wasn't the only one who was so optimistic. The development of penicillin in the early 1940s in particular had brought euphoria. The medical community was sure that it was just a matter of time before bacteria would be conquered. They were wrong.

Reconquest

Infectious diseases had only taken a breather. Take tuberculosis. In several countries of the former Soviet Union, the number of people infected with tuberculosis doubled within just seven years of the collapse of the USSR. Today, in the area around the Aral Sea, 300 out of every 100,000 people suffer from TB. In the prisons, the number of infected people is up to 100 times higher.[2] On a global level, some 2 billion people carry the tuberculosis bacterium, approximately one-third of the world's population. It is estimated that 2 million people die of tuberculosis every year.[3] In England and Wales, the number of infections rose by 20 per cent between 1994 and 2004.[4] In countries of the former Eastern bloc in particular, many tubercu-