

In the Shadow of Tuberculosis

At the **Max Planck Institute for Infection Biology** in Berlin, the focus is on such unpleasant companions as chlamydia, HIV and tubercle bacilli. **Stefan H. E. Kaufmann**, as Founding Director, helped establish it 20 years ago. Since then, the scientist has been researching the strengths and weaknesses of the tubercle bacillus. Modern tuberculosis research would be inconceivable without him – and he without it.

TEXT CATARINA PIETSCHMANN


Two billion people are infected worldwide, and one in ten will develop the disease – an old specter has reappeared: tuberculosis. But how can that be? Wasn't this lung disease a scourge of the 19th and early 20th centuries? "That's true, but tuberculosis was never really gone, it just went off our radar screen," says Stefan Kaufmann, Director of the Department of Immunology at the Max Planck Institute for Infection Biology in Berlin. Now tuberculosis, to which Thomas Mann erected a literary monument in his novel "The Magic Mountain," has returned – and with it, images of emaciated people who are literally coughing their lungs out.

And the much-vaunted modern medicine? It stands there nearly empty-handed. "We have an almost one-hundred-year-old vaccine that is bare-

ly effective, and antibiotics that are increasingly powerless against resistant bacterial strains. And there are no tests to distinguish between infected people who won't become ill and those who will develop the disease."

HISTORICAL LOCATION

Kaufmann is one of the world's leading infection biologists. There is hardly any other who has such an extensive knowledge of tuberculosis as the 65-year-old scientist. The fact that his office is located on Berlin's Charité campus just a few steps away from Luisenstraße, where Robert Koch discovered the tuberculosis pathogen *Mycobacterium tuberculosis* in 1882, is no coincidence. "That's one of the advantages of being a Founding Director," says Kaufmann, smiling. "You already have a finished institute lined up." Kaufmann pleaded the case



Tuberculosis is a disease of poverty. That is why Stefan Kaufmann is fighting it at the scientific and political level.



Photo: Jonas Steengard

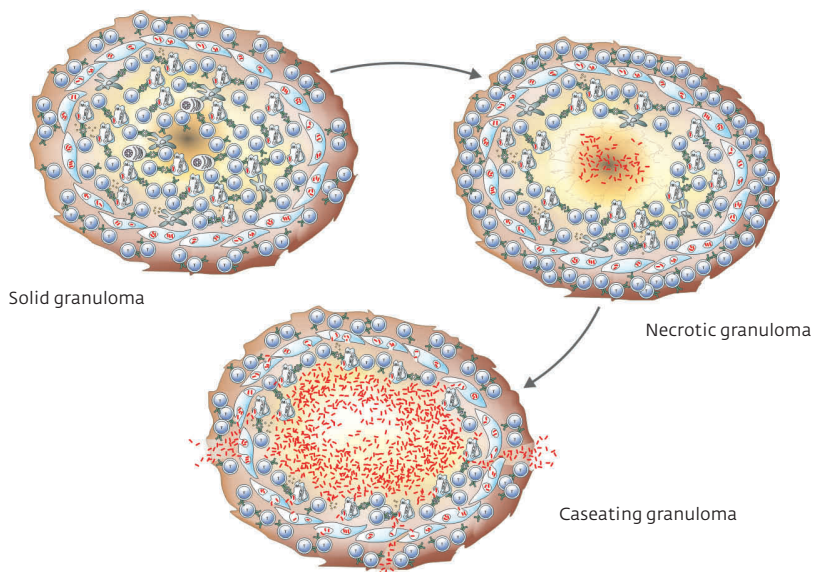


for a big city – due to the proximity to major clinics. So why not go straight to the stronghold of the early infection researchers?

Time and time again, toward the end of the 19th century, Robert Koch studied tissue from infected guinea pigs. Only after numerous attempts did he

succeed in staining the rod-shaped tuberculosis bacteria and making them visible. At that time, one in every three people in Berlin, Paris and London died of consumption. Since 1950, the numbers in Germany have continuously declined, but there are still more than 4,000 cases reported every year. “Tuberculosis is a disease of poverty that has much to do with public health. That is also why it made a comeback after both world wars. Unfortunately, when it disappeared here in Europe, we lost sight of the rest of the world,” says Kaufmann.

Many people in a very cramped space plus catastrophic hygiene conditions – that’s a perfect environment for tubercle bacilli. With the start of urbanization in poorer countries, the pathogen spread like wildfire in slums and townships, for instance in southern Africa. Like the coal mines in Great Britain and Germany at one time, there, gold and gemstone mines became an eldorado not only for those seeking their fortune, but also for agents of disease. “People come together there from throughout Sub-Saharan Africa to work. Lonely men who seek out prostitutes and additionally con-



The different stages of a tuberculosis granuloma: Solid granulomas can successfully keep the tuberculosis pathogen in check. Necrotic granulomas form a core of decayed cells in which the pathogen multiplies. Caseating granulomas lose all structures; decayed host cells and dead germs form an exceptional breeding ground for *Mycobacterium tuberculosis*. The pathogens that are released get into the lungs and can easily be transmitted by droplet infection.

- left page | Ward in a municipal hospital in Durban. The doctors are very dedicated in caring for their patients. However, long waiting times reduce the chances of recovery.
- below left | The Global Clinical & Viral Laboratory in Durban has ultramodern equipment for studying infectious diseases. Here, Stefan Kaufmann tests his biomarker candidates.
- below right | A young patient in a private hospital in Durban. At this extremely well-managed hospital, patients with HIV and tuberculosis receive medical and psychological care around the clock. Patients must contribute to the expenses to ensure that they take the treatment very seriously.



tract HIV,” says Kaufmann. HIV and tuberculosis make an infernal duo. HIV weakens the immune system, allowing the tuberculosis to truly blossom. Then a latent infection can turn into an active illness. HIV literally dragged tuberculosis in tow.

THE DISEASE IS ADVANCING

India and China likewise have a huge tuberculosis problem, and Eastern Europe joined the ranks in the 1990s. The collapse of the Soviet Union also led to the collapse of its previously quite functional health system, and the pathogen was able to spread throughout all of Eastern Europe. Breeding grounds include Russia’s crowded prisons: one in every ten inmates suffers from a highly contagious active tuberculosis.

Mycobacterium tuberculosis is clever. “It’s quite a lazy character, dividing only once every 16 hours, but it chose the most effective means of transmission: droplet and smear infections.” Once inhaled, the pathogens get into the lungs, where they are confronted by the immune system. Phagocytes move in and surround the bacilli, but

don’t kill them. Additional helper cells form a solid wall and encapsulate them in so-called granulomas.

This is no pleasant situation for the microbes, but they make the best of it: they reduce their metabolism almost to zero and wait, slumbering, for better times. This “dormancy,” something like Sleeping Beauty, can last ten years or more, and the infected person has no idea the intruders are there.

“But once in a while, a pathogen awakens – we call it a scout – and checks out the situation.” If the immune defense is still standing with guns at the ready, it dies. But if the immune system is distracted because it is currently battling on other fronts – for instance against HIV or another infection – the scout awakens its cronies. The late risers are hungry. So what they do is first eat, then multiply. “The granuloma gives them all the nutrients they need. More and more tissue dies until the granuloma finally dissolves,” explains Kaufmann. Every coughing fit now catapults the active pathogens into the environment, to new hosts – an active tuberculosis has emerged.

Kaufmann’s team is researching the metabolism processes of sleepers and

scouts, their communications and the signals between the scout and the host. Born the son of a chemist in Ludwigshafen, Kaufmann made his acquaintance with the microbe during his biology studies in Mainz. Classical biology topics didn’t interest him much, but then he attended a medical microbiology lecture by Paul Klein, a renowned immunologist and microbiologist. “Klein was a charismatic, eloquent teacher and mentor. He taught me just how exciting science can be.”

CAREER IN GERMANY

Kaufmann had found his topic. He completed his doctorate at the University of Mainz in 1977, qualified as a professor four years later at Freie Universität Berlin with a thesis on the characterization of T cells in bacterial infections, and was authorized to teach immunology and microbiology.

His next stop was Freiburg, where he spent six years conducting research at the Max Planck Institute of Immunobiology. In 1987, he answered the call to relocate to the University of Ulm, resisted various attempts to lure him away, and was granted a full professor-

- below left | Stefan Kaufmann in the South African province of KwaZulu-Natal. It is particularly badly affected by the HIV/tuberculosis pandemic. Patients must take a regular drug cocktail.
- below right | Work discussion at the Tugela Ferry Hospital, 250 kilometers southeast of Durban. This is where extremely resistant tuberculosis pathogens that no longer respond to any drug were first observed in South Africa.
- right page | Visit to a former mine worker in KwaZulu-Natal who is infected with HIV and multidrug-resistant tuberculosis. Thanks to the drugs, he is in stable condition.



ship in 1991. Kaufmann did all the hard work on his own: “I never had a great mentor in the US – which, looking back, I don’t actually regret. It had its advantages: I had to learn early on how to organize things.” The Max Planck Society got him back in 1993 and asked him to establish an institute for infection biology.

Kaufmann’s research career began with *Listeria*, a simple model pathogen. The infection runs a course that is very similar to that of tuberculosis, but listeriae are faster. At that time, the established dogma was that, in bacterial infections, special immune cells known as CD4 T cells appear, while in the case of viral infections, it is CD8 T cells. Kaufmann discovered that, though the tuberculosis agent is indeed largely controlled by CD4 T cells, CD8 nevertheless become active. This was preliminary work for Kaufmann’s endeavor to create a better vaccine, which he began in the 1990s.

Up until 1970, every infant in West Germany was vaccinated against tuberculosis, while in the East, vaccination continued until German reunification. Does this mean that seniors are safe? Kaufmann shakes his head. “Then, as

now, the only vaccine in existence was *Bacillus Calmette-Guérin*, BCG, an attenuated agent of bovine tuberculosis. Today we know that it protects only infants.” So everyone reading this article could be infected – Stefan Kaufmann himself was, too.

AIM: A NEW VACCINE

A new vaccine is thus at the top of epidemiologists’ wishlists. Kaufmann’s hypothesis is that BCG stimulates primarily CD4 T cells. That’s enough to hold the bacteria in check. Then, however, a broad immunological arsenal is needed to kill the pathogens. “Upon learning that, we inserted a listeria gene into the genome of the vaccine,” says Kaufman. “In this way, the formerly weak vaccine also became a stimulator of CD8 T cells, which generates a strong defense.”

The candidate vaccine is currently in clinical phase II and is being tested in South Africa – even on newborns, the primary target group. “We have to conduct such studies in areas with large numbers of tuberculosis cases, because ultimately that’s the only way we can determine whether the vaccination truly provides protection against the disease.”

One of the partners in the vaccine study is Vakzine Projekt Management GmbH, a company initiated by the German Federal Ministry of Education and Research. Now, one of the world’s largest vaccine manufacturers, Serum Institute of India, is also on board. “One thing I learned in the past few years is that the exciting new things we learn about infectious diseases don’t come from basic research, but from clinical studies. They show us what we have to look for in the lab.”

From their studies on patients, the scientists are currently learning that tuberculosis isn’t a single disease. Rather, the many granulomas in the lungs are individual units. In addition to active lesions, there are also solid ones in which the germs still lie dormant. Treated in this phase, the active lesions recede, since the active pathogens are vulnerable. That is why active tuberculosis must be treated for six months in order to also kill all the pathogens that are gradually awakening from their slumber.

A cocktail comprising at least three antibiotics is used for this purpose. But the bacilli have armed themselves. They have since become resistant to many antibiotics. The bill for treating a



patient infected with multidrug-resistant germs can quickly run up to 50,000 euros. So it's clear that such patients can be treated only in rich countries.

There are already 50 million people infected with multidrug-resistant strains.

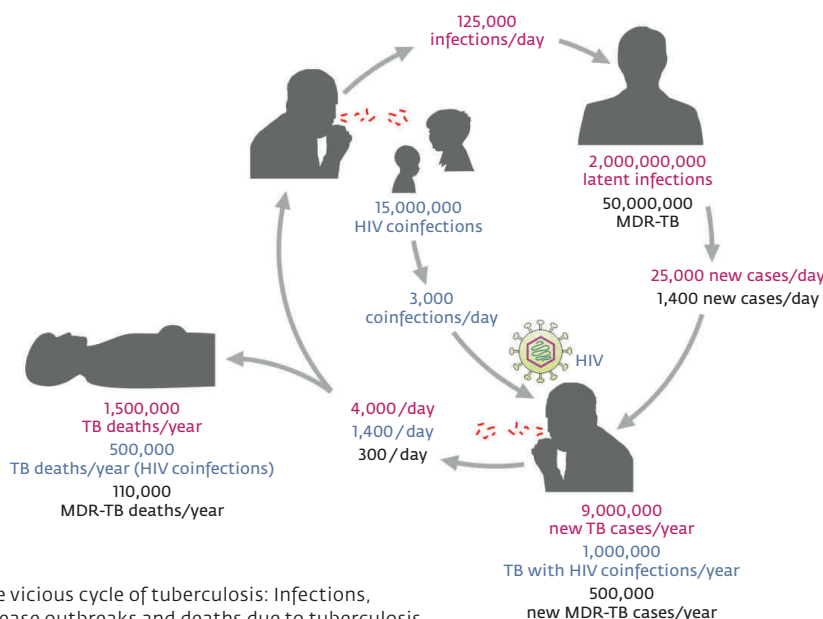
Extensively resistant strains have already been discovered in 85 countries, and completely resistant pathogens have even emerged in India, Italy, Iran and South Africa. Not a single antibiotic can fight these strains.

Besides his research into a new vaccine, Kaufmann is also searching, with support from the Bill & Melinda Gates Foundation, for biomarkers that will allow doctors to tell who is going to come down with tuberculosis and why some people – like himself – are able to shake off the pathogens. After all, only one in ten people actually develop the disease. Several thousand test subjects from families with a tuberculosis patient are being monitored over two years in seven African study centers, and their blood regularly analyzed.

BIOMARKERS FOR DIAGNOSIS

According to this study, those who have a latent or an active tuberculosis differ in the expression of nearly 2,000 genes. Kaufmann plans to select four to six such unusually strongly regulated genes to define a distinct signature that shows, as early as a few months following infection, who will get sick and should therefore be given prophylactic treatment.

Stefan Kaufmann could have become Director of the Robert Koch Institute in 2010, but he turned down the offer. Not just because he greatly values the independent research at the Max



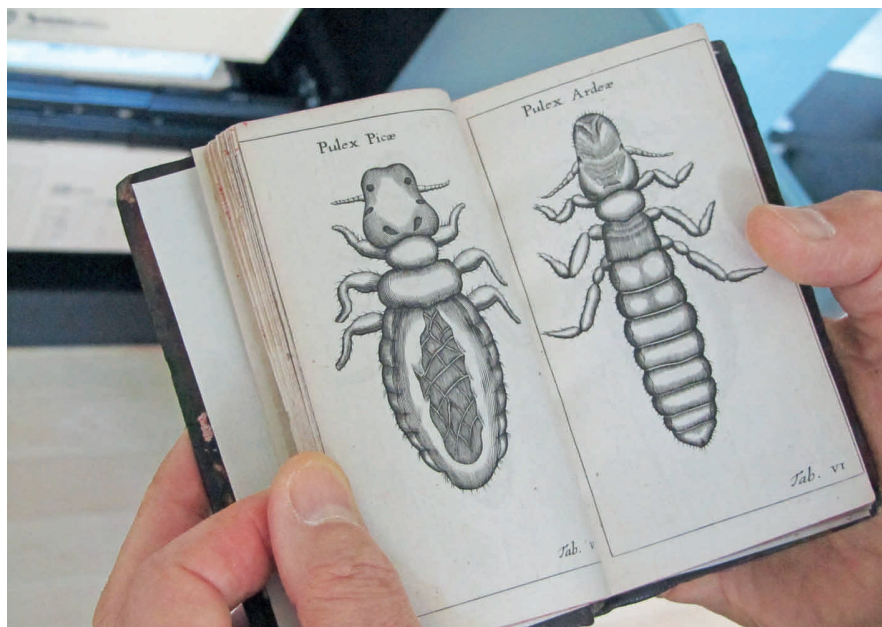
The vicious cycle of tuberculosis: Infections, disease outbreaks and deaths due to tuberculosis (red); of those, coinfection with HIV (blue) and multidrug-resistant tuberculosis (MDR-TB, black).

Planck Society, but also because he believes that he can accomplish far more, scientifically and socially, by being active in international organizations. In the GAVI Alliance, for instance – a public-private partnership that advocates the use of existing vaccines for the benefit of poor countries, not just the rich. Or as a member of a Bill & Melinda Gates Foundation committee of experts that assesses the feasibility of ideas of scientists from poorer countries.

Furthermore, he has his sights set on collaboration with doctors and scientists on the ground. This requires good partners. “That is why I am also proud that, on my initiative, two Max Planck research groups with a focus on tuberculosis and HIV were set up in Durban, South Africa.” Beyond this, as President of the International Union of Immunological Societies (IUIS), he aims to close some gaps: communication gaps between young and more experienced scientists, between basic and applied research, and between scientists from different cultures.

On the conference table, two small Buddha figures that Kaufmann brought back from China and Cambodia urge tranquility. No, he isn’t particularly patient. Not even with himself, he admits. Fruitless meetings are anathema to him. “As short as possible and as long as necessary,” is his motto. But impatience also has its advantages. “Everyone is usually satisfied when I’m appointed to chair a committee. Because they get to leave with an outcome after one or two hours,” he says grinning. “But I’m still something of a long distance runner, otherwise tuberculosis wouldn’t have been the right subject for me.”

Kaufmann has seen and experienced a lot in his travels, which have taken him to every continent, but especially frequently to Africa and India. The interwovenness of poverty and disease and the disinterest of the pharmaceutical industry in developing drugs “that don’t generate much profit” disgust him and spur him on. The biologist, who is father to two grown sons and recently became a grandfather, is far from entertaining any thoughts of quitting.



In his book *Experimenta circa generationem insectorum*, published in 1671, Francesco Redi describes different disease vectors, such as the flea species *Pulex picae* and *Pulex ardeae*. We have him to thank for the insight that life can emerge only from life and not from dead matter, as had generally been assumed in his day.

On the seat next to Kaufmann lies a well-stuffed backpack. It contains a fat binder for working at home, a laptop and workout gear for the evening. For the short route between the institute and his home, he jumps on his bike, as usual. Kaufmann has consciously chosen not to own a car for some time now.

A LIBRARY IN THE OFFICE

His fascination for microbes has also become a personal hobby. Kaufmann stands and opens the large library cabinet next to the desk that has nearly disappeared under neat stacks of paper. Behind tinted panes and between well-thumbed leather-bound volumes stands a treasure trove: bound original works of famous researchers. Among them are the complete *BERLINER KLINISCHE WOCHENSCHRIFT* with all of Robert Koch’s important articles, and the 16th century work of Girolamo Fracastoro, who first described infections with syphilis and tuberculosis. Some of the images are not for the faint of heart.

One of his favorite books is by Antoni van Leeuwenhoek, published in

1685. The cloth merchant was the first person to behold bacteria, under a microscope he built himself. “He had scraped them from his teeth. From then on, he supposedly drank only very hot tea,” says Stefan Kaufmann with a laugh, “because he believed he could kill the germs that way.”

So much for the history. What does the future of infection biology look like? Since 1980, more than 30 potentially dangerous new pathogens have been discovered, and others will surely follow. Due to globalization, infectious diseases can quickly turn into pandemics that can reach anywhere on Earth. “Vaccinations are the key – prevention is always better than cure. The pathogens are largely powerless against vaccines, because there are always only a few of them in the early stages.”

Kaufmann publishes books and articles in which he urges society, politics and industry to act in unison – particularly against the main risk factor for disease: poverty. In that regard, Stefan Kaufmann likes to cite Voltaire. “We are responsible for what we do, but also for what we do not do.”

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