

A Foul Enemy in Fowl

Flu viruses are highly mutable – and thus able to swap hosts. **Werner Schäfer** at the **Max Planck Institute for Virus Research** in Tübingen suspected as early as the mid-1950s that bird flu can also pose a threat to humans. Decades later, his suspicions were confirmed.

TEXT **ELKE MAIER**

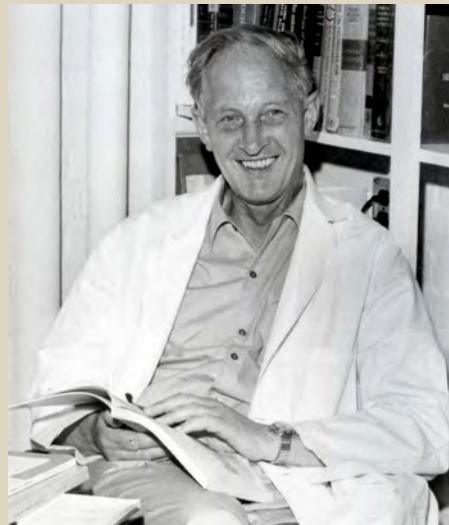
The birds began to die in the spring of 1997. Within the span of a few days, 7,000 chickens on three poultry farms in Hong Kong perished. A short while later, a three-year-old boy who had been admitted to the hospital with flu symptoms died. Tests revealed that the same pathogen was the cause of death in both cases: a bird flu virus of the H5N1 type. After 18 more people were infected, six of whom died, experts became alarmed. Was a new flu pandemic imminent?

The incident brought to mind images from 1918/1919, when the Spanish flu claimed an estimated 50 million lives. To ward off the danger, more than 1.2 million chickens and hundreds of thousands of other birds were slaughtered in Hong Kong's poultry markets and on the surrounding farms. In time, the scare passed – but the concerns remained.

The Hong Kong outbreak is the first documented case in which a bird flu virus not only infected humans, but also killed them. However, fears had been circulating for quite a while that this could happen one day. Virologist Werner Schäfer at the Max Planck Institute for Virus Research in Tübingen had already speculated about it in the 1950s.

Schäfer was born in Wanne, Germany on March 9, 1912. He originally wanted to become an architect and, after completing his secondary education, did an apprenticeship in carpentry. He later changed his mind and studied veterinary medicine in Gießen. After earning his doctorate, he joined the Veterinary Hygiene and Animal Infection Institute under Erich Traub, an expert in foot and mouth disease.

He then yielded to his thirst for adventure. In the summer of 1939 – shortly after marrying – he headed for East Africa on a grant from the German Research Council. In Tanzania, he set up a simple laboratory in a building on a German farm, where he began to carry out research into animal diseases such as anthrax, blackleg, brucellosis and pseudorabies, which were threatening the country's livestock.



Bird flu as a research field: Werner Schäfer dedicated much of his scientific career to studying avian influenza.

Schäfer could well imagine a future as a researcher in Africa, but his plans were thwarted by the war. He was incarcerated and deported to Germany in 1940, where he was drafted into the army as a veterinary officer. For a while he was based on the island of Riems, near Greifswald, to work at the Reich Research Institute there in a program aimed at developing vaccines against influenza, rinderpest and bird flu.

After the war, there were no immediate prospects for a post as a virologist. Without further ado, Werner Schäfer opened a veterinary practice in Usseln, Hesse. Business flourished, and he had no concerns about his family's subsistence. Nevertheless, he didn't hesitate for a moment when Nobel laureate Adolf Butenandt, then Director of the Kaiser Wilhelm Institute for Biochemistry in Tübingen, looked him up in the spring of 1948 and offered him a research post. After three

years as a rural veterinarian, the 36-year-old moved to Tübingen to head the Animal Virology Department.

The research team was initially housed in a ramshackle outbuilding of the Pharmacology Department. The annual budget for equipment was a mere 10,000 marks. Despite this, Werner Schäfer was inordinately productive; he had learned how to improvise in Africa. His career soon took off. In 1954 he was elected a Scientific Member of the Max Planck Society. Two years later, he was appointed Director of the Biological and Medical Department of the newly created Max Planck Institute for Virus Research in Tübingen.

One of Schäfer's main research interests was the virus responsible for avian influenza, now commonly known as bird flu. The highly infectious pathogen affects birds in the wild as well as poultry of all kinds. Infection leads to dyspnea, apathy, high fever and motor disorders. Infected animals usually die within a few days.

The dreaded virus offered a number of advantages as a study object: It proved to be an excellent model for studying enveloped viruses. Moreover, public health policy forbade US competitors



Epidemic source: Close contact between birds and humans favors the emergence of new influenza pathogens.

from working with the pathogen. The virus is easy to handle in the laboratory and multiplies vigorously in incubated chicken eggs. Heinz Schwarz, an electron microscopist who worked closely with Werner Schäfer at the Institute, recalls: "Some of our colleagues periodically drove in the Institute's car, an Opel P4 dubbed Friedolin, to a chicken farm in Tuttlingen to pick up pallets of eggs."

Soon they were cultivating viruses at full speed. Schäfer's aim was to find out the functions of the various viral components and to determine the role they play in infections. To this end, he combined electron microscopic structural analyses with physicochemical and immunological investigations and observed the course of the disease in experimental animals.

"Schäfer was a true pioneer, since there was no DNA sequencing at the time," says Volker Moennig, veterinary professor at the University of Veterinary Medicine Hannover, Foundation who had

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It was Schäfer who surmised – correctly – that certain bird viruses could act as an inexhaustible reservoir for the emergence of new influenza variants.

earlier worked at the Institute in Tübingen. "The times were also different with regard to handling the virus. Today, a laboratory safety rating of 3 would be mandatory."

Despite the limited resources, Schäfer managed to characterize the bird flu virus in detail. He noted an astonishing similarity to another pathogen – the causative agent of influenza A in humans. Under the electron microscope, both appeared to be studied with fine spikes, which Schäfer compared to the "detonators of a naval mine." The viruses also shared many physicochemical and immunological properties. For example, both pathogens were able to infect mice, causing a pneumonia that proved fatal after a few days. The pathological changes in lung tissue caused by both forms looked identical. Schäfer even managed to immunize mice against influenza A with the bird flu virus and vice versa.

The striking similarity of the two pathogens led Werner Schäfer to a troubling conclusion: "It is conceivable that representatives of this group occasionally change their host specificity so that a new type of influenza virus [...] emerges," he wrote in a seminal work in 1955. He was to be proven right.

Today we know that avian viruses do, in fact, act as a natural gene pool from which new flu viruses can emerge that can potentially infect humans. A tiny change to a protein building block is enough to enable the virus to evade the immune system and change its host. The danger is especially acute in places where people and poultry live in close proximity, as in many Asian countries.

Experts particularly fear the emergence of hybrid viruses: when a bird virus and a human virus come together in an infected cell, they are able to exchange DNA segments to form a new virus that spreads from human to human – a recipe for a pandemic. The Spanish flu may have been the result of such dangerous liaisons. In the 1997 Hong Kong flu epidemic, the viruses made the leap from bird to human, but fortunately not from human to human.

Werner Schäfer presented his findings on viral kinship at a symposium in London in 1956. Luminaries including James Watson and Francis Crick, who had discovered the structure of DNA three years earlier, were in the audience. It proved to be an international breakthrough for Schäfer. There followed invitations from all over the world, and the "Tübingen Group" ranked among the most pre-eminent virus researchers in the world.

Werner Schäfer devoted 16 years of research to the avian flu virus. Thanks to his work, the pathogens have long ranked among the best characterized of all animal viruses. Schäfer also laid the groundwork for the development of vaccines when he discovered that a component of the viral envelope is sufficient to confer immunity in a host. This led to the development of split-virus vaccines, which are still used today in some flu and hepatitis B vaccines.

Schäfer finally closed the bird flu chapter of his career in the early 1960s. At over 50, he switched to an entirely new research field: retroviruses, which were thought to play a role in the development of cancer. In fact, oncogenes, which promote unbridled cell growth, were discovered for the first time in the genomes of retroviruses. Schäfer and his team investigated the role of the viruses in the development of leukemia and carried out successful immunization experiments.

In the 1980s, retroviruses made headlines when it was discovered that they cause AIDS. By that time, Schäfer had already retired. The winner of many awards, he died in Tübingen on April 25, 2000 at the age of 88.