

## Perspective

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# How Charles Nicolle of the Pasteur Institute discovered that epidemic typhus is transmitted by lice: Reminiscences from my years at the Pasteur Institute in Paris

Ludwik Gross

Veterans Affairs Medical Center, Bronx, NY 10468

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Until the first decade of this century, our information about epidemic, i.e., exanthematic typhus was rather scarce. We knew only that there existed a very dangerous, easily communicable disease, which decimated populations during wars, hunger, or flood, spreading with great speed and affecting large numbers of people. After World War I, 20–30 million people died in Eastern Europe from this disease, and an additional several million died during and after World War II. Crowding, the scarcity of clean clothes, and dirt were the principal factors enabling the spread of typhus. The disease causes high fever and maculo-papular eruptions of the skin. Typhus is similar to a disease that occurs in the Rocky Mountains in the United States and is transmitted by ticks.

The fact that epidemic typhus is transmitted by lice was discovered by Dr. Charles Nicolle; a discovery for which he received the Nobel Prize in 1928 (1). I met Dr. Nicolle in 1934 at the Pasteur Institute in Paris during my years as a guest investigator. I spoke to him several times in the corridor adjoining my laboratory. At my invitation he came to visit. He was a tall man, distinguished looking, impeccably dressed, lean, and slightly stooped, with dry skin and sparkling eyes. He was 68 years old at that time. It was difficult to talk with him because he was hard of hearing. In spite of his listening device, with its batteries and wires, which he was carrying, one had to almost shout to be understood. He was, like many Frenchmen, very polite and attentive. He agreed, at my request, to spend some time in my laboratory at the Pasteur Institute, and talk about his discovery.

Before long, still a few years before World War II, he came to my laboratory. He arrived wearing a shirt with a starched collar and starched cuffs, and sat himself comfortably in a large chair. He told the following story.

“I was delegated, some 30 years ago, recalled Dr. Nicolle, to become director of the Pasteur Institute in Tunis, and decided to do something about typhus, which was decimating the local population. The first step was to try to transmit the disease to experimental animals. I injected guinea pigs with blood from patients with typhus and observed that, at least in some of these animals, the injection produced only high temperature. I realized, nevertheless, that even though some of them did not develop fever, they still carried the causative agent. This way we learned that typhus could exist, at least in some species, without any symptoms, except now and then, only fever. The most important point, however, was to discover how it was transmitted from man to man under natural life conditions. I learned this by accident. Tunis was full of typhus patients; the hospital was full and the number of new patients increased every day. Not only was every bed occupied and waiting rooms filled, but patients were waiting in front of the hospital, on the streets, to be admitted. At that point I made the crucial observation, said Dr. Nicolle, that patients infected others out on the street, and also that their clothing was infectious; service personnel at the hospital and also in the laundry room became

infected. The moment the patients were admitted to the hospital, however, after they had a hot bath and were dressed in hospital clothing, *they ceased to be infectious*. There was no longer fear of disease transmission in a hospital room full of patients. This observation was so simple and uncomplicated that it could have been made not necessarily by a physician, but by an administrator without professional medical training. I determined that there must therefore exist a transmitting vector, in the clothing and underwear of the patients. I anticipated, said Dr. Nicolle, that most probably lice could be responsible for the transmission of typhus from man to man.” Dr. Nicolle continued his story. “At the end of June, 1909, I asked Dr. Emile Roux, who was at that time Director of the Pasteur Institute in Paris, for a few chimpanzees. My request was granted, and the chimpanzees arrived promptly. I injected one chimpanzee with blood from a patient suffering from typhus. After several days, I collected from the injected chimpanzee a few lice, and transferred them to another chimpanzee; before long, after about 10 days, this animal developed typhus. I repeated this experiment, with similar results. It was now obvious that typhus was transmitted by lice. That was in September, 1909. The first step in the search for typhus control was accomplished. Lice were demonstrated to be the transmitting vectors. The Tunisian government now began intensive measures to limit the typhus epidemic with attempts to combat infestation by lice.

The initial step had been accomplished, but great difficulties were ahead. Typhus is very infectious and many laboratory workers engaged in research on the typhus epidemic became infected accidentally, in the course of their laboratory work, and some of them died of the disease.

To become infected, a bite by a louse is not necessary. Lice infected with typhus become sick, change their color to red, and excrete millions of live infectious typhus microbes in their feces, which look like powder. A minimal amount of their excreta, rubbed or scratched into the skin, will cause the deadly disease. The infectious agent can also be absorbed through the eye; it is sufficient for a few fecal powder particles from an infected louse to find their way accidentally, carried perhaps unexpectedly on the tip of the finger of an investigator, into the eye, and a slight rubbing can then induce infection. A person infected with typhus and carrying lice may also carry louse droppings on the skin and clothes, and this becomes highly infectious at contact. The infected individual ceases to be infectious, however, after a hot bath with soap and sterilization of clothing and underwear.

I was trying to find a vaccine against typhus, said Dr. Nicolle, and I mixed typhus bacilli with blood serum from those patients that had recovered. I injected myself with the mixture and remained in good health. I then injected a few children, because they are more resistant than adults, and you can imagine how frightened I was when they developed typhus; fortunately, they recovered.

Epidemic, or exanthematic typhus is caused by a small rod-shaped microbe called *Rickettsia prowazeki* in honor of its discoverers, a young American pathologist from Chicago, Dr. H. T. Ricketts (2), who in 1910 contracted typhus and died in the course of his research studies and that of another worker, Stan J. M. Prowazek, who also developed typhus, and died.

This disease is closely related to Rocky Mountain spotted fever, which is caused by a related species of Rickettsias, and transmitted by ticks. It is also related to the endemic, or murine typhus, which is caused by different Rickettsias carried by rats, and transmitted to man by rat lice, as well as by rat fleas.

In 1925, Drs. R. R. Spencer and R. R. Parker of the United States developed a vaccine against Rocky Mountain spotted fever (3). The intestines of ticks infected with the Rickettsias are full of these microorganisms. These investigators prepared a vaccine from such infected intestines by adding a small amount of an antimicrobial chemical. Based on this idea, Dr. Rudolph Weigl (4) of Poland developed, in 1930, a similar vaccine against epidemic typhus, by grinding up intestines of lice infected with typhus Rickettsias.

In 1936, I visited the laboratory of Dr. Weigl in Lwów, Poland (Weigl's laboratory was transferred, after World War II, to Kraków). Dr. Weigl had a very modest laboratory in which he worked with his wife and a few assistants. Here are the results of his studies. A normal, healthy louse is relatively free from microbes. When the louse ingests a drop of blood from a patient suffering from typhus, it becomes red and dies after a few weeks. In the meantime, the Rickettsias multiply by the millions in the intestinal tracts of the infected lice. Millions of live Rickettsias are then excreted in the feces of such lice, in the form of a dark powder, which is highly infectious. Dr. Weigl transmitted the Rickettsias from louse to louse by making a watery suspension from their infected intestines and infecting healthy lice through miniature enemas. In the course of these experiments, several members of his staff became infected with typhus and died. Dr. Weigl himself became infected with typhus, but recovered. The lice had to be fed daily with human blood. Dr. Weigl and his wife fed healthy lice kept in small boxes, similar to match boxes, except that one side of these boxes consisted of a very dense screen, through which the lice could pick the skin and ingest blood. Dr. Weigl developed typhus a second time while trying to feed infected lice located on his skin, and he learned from this that one can develop typhus twice, although this was probably an exceptional occurrence. Over 100 infected lice were needed to produce a single dose of vaccine. Subsequently, this number was reduced

to 30. Nevertheless, production of very large doses of vaccine by this method, which was very complicated and dangerous for laboratory technicians, presented tremendous difficulties (5).

The problem was finally solved by Dr. H. R. Cox of the United States in 1938 (6), who found that typhus Rickettsias will grow without difficulty in embryonated chicken eggs. This method made it possible to produce very large quantities of live Rickettsias. They can be then killed by the addition of a one-half percent solution of phenol, to produce an efficient vaccine against typhus. Large quantities of vaccine could thus be prepared and used. An attenuated, live *Rickettsia prowazeki* vaccine against epidemic typhus is now also available, although only infrequently used.

At the same time, the introduction of chemicals, such as DDT which destroy lice and various insects, helped tremendously in the control of typhus. DDT is a poisonous powder, which was discovered in the last century. Only relatively recently, however, was it determined that this powder is particularly poisonous for insects, and that a minimal amount would kill disease-transmitting flies, mosquitoes, lice, and fleas. In larger quantities, DDT is also toxic for small animals and humans.

At present there exist antibiotic and chemotherapeutic medications, such as doxycycline, tetracycline, chloramphenicol, and other varieties, which can treat typhus very efficiently. These medications can also prevent infection.

In one of my conversations with Charles Nicolle, we also briefly discussed the general problems exerted not only by microbes, but also, and perhaps particularly, by viruses, which are invisible in the optical microscope, on human populations. "These micro-organisms, said Dr. Nicolle, do not have any brain, not even a miniscule fraction of it. If they would have any understanding, or a minimal intelligence, they would be able to promptly destroy and annihilate human populations on this planet; they are invisible and are transmitted in manners either not known, or not fully understood and not anticipated by human beings."

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6. Cox, H. R. (1938) *Public Health Rep.* **53**, 2241-2247.