

## ***Nobel Prize in Medicines 1928***



**Charles Jules Henri Nicolle**

**The Nobel Prize in Physiology or Medicine 1928 was awarded to Charles Nicolle "for his work on typhus".**

In awarding the 1928 Nobel Prize for Medicine to Dr. Charles Nicolle, Director of the Pasteur Institute at Tunis, the Caroline Institute wished to pay tribute to a man who has realized one of the greatest conquests in the field of prophylactic medicine, i.e. the vanquishing of typhus.

Typhus is an acute infectious disease which, by its clinical evolution, its contagiousness and the conditions under which immunity is conferred shows considerable resemblance to ordinary measles. In severe cases, a state of stupor or even deep coma may occur. On account of the rash it causes the disease has been called exanthematous typhus; it has nothing in common, however, with what is properly called typhoid, i.e. enteric fever. In certain epidemics, particularly where children are concerned, epidemic typhus takes a relatively benign form; in adults, however, and if conditions are unfavourable, the mortality rate can reach the frightening proportion of between 50 and 60%.

The epidemiology of typhus presents a number of characteristics which, understandably, appeared most mysterious to physicians of past ages. It seemed, in fact, impossible to protect oneself against this disease which claimed many victims, even in the medical profession itself.

The general opinion used to be that typhus was transmitted more or less in the same way as measles or influenza, i.e. by direct contact, by dust, or by what is known as «droplet» infection. Around 1880 and 1890 when the part played by insects as carriers of infection was established, various people began to suspect that typhus could well be transmitted in the same way, in particular by parasites affecting man. This hypothesis, however, excited no special interest. The way in which the disease was actually disseminated was unknown and remained so, and there were, therefore, no effective measures available to combat the disease.

One of the peculiarities of typhus is the way in which it tends to cause serious epidemics, flaring up suddenly and coinciding with the previous occurrence of some serious public calamity. Populations in the throes of war or famine fell victim to the disease, which caused numerous deaths, sometimes as many as hundreds of thousands. Thus originated certain expressive synonyms, such as «camp typhus», «famine typhus», «jail typhus» by which the disease has sometimes been known. As one author so truly says, the history of typhus is the history of human misfortune.

The disease has been known since the beginning of all time. The plague which devastated Attica, especially Athens in the year 430 B.C., and which Thucydides describes in his work on the Peloponnesian War, was most likely an epidemic of typhus. The picture that the great historian draws of the disease agrees in certain respects, down to the smallest details, with the clinical picture we were able to observe during the Great War. Epidemics followed one another without respite during the great wars of the sixteenth and seventeenth centuries. At the end of the Thirty Years' War, typhus raged over the whole of Central Europe. The Napoleonic Wars caused the disease to flare up again. In the general disorganization which followed the Grand Army's retreat from Russia, typhus claimed

innumerable victims amongst the troops and amongst the civilian population. Further epidemics broke out during the Crimean War and the Russo-Turkish War, affecting both sides.

With the progress of civilization and during the period of peace and prosperity which, in all, lasted from the end of the nineteenth century until 1914, typhus seemed of its own accord to have become restricted to certain remote regions of Europe and to certain extra-European countries where, from time immemorial, the disease had existed endemically.

At the beginning of this North Africa was among these non-European countries where the disease had been a veritable national scourge for several centuries. As soon as he took up his appointment as Director of the Pasteur Institute at Tunis, young Dr. Charles Nicolle was immediately brought into contact with the scientific and practical problems that typhus had created in this country. As soon as he took up his post, Nicolle immediately with extraordinary energy attacked these problems. He visited patients in their own homes, examining their beds and their sordid rags, whilst undertaking at the same time a strict enquiry within the hospitals. This work was to cost the life of two of his collaborators. He was led to an observation which could hardly have escaped the attention of earlier workers, i.e. that whilst typhus patients continued to spread infection up to the point when they entered the hospital waiting-room and amongst those who took charge of their clothing, they became completely inoffensive as soon as they had been bathed and dressed in the hospital uniform. At this point they could be admitted to the general wards without the slightest risk. Nicolle concluded that the pathogenic agent must necessarily be related to one factor, carried by the patient himself and transmissible to others, a factor which no longer acted once the patient had bathed and changed his clothing; this factor, therefore, could only be a parasite, the body louse, which lives on the patient's body and in his clothing. This simple observation contains in essence Nicolle's discovery.

In order to further his research Nicolle now made experiments on animals. Previously, some research workers had succeeded in inoculating healthy individuals with

typhus by injecting blood from a patient, but all attempts to inoculate animals had failed up till then. After several unsuccessful attempts, Nicolle succeeded at the beginning of 1909 in inoculating chimpanzees with typhus and, from the chimpanzee, he was able to inoculate monkeys of a lower order by injection of blood. As early as September of the same year Nicolle and his collaborators were able to demonstrate that lice which had previously bitten contaminated monkeys transmitted the infection to healthy animals simply by biting them. The part played by the body louse as a transmission agent had thus been proven experimentally.

The secrets of this terrible disease were then laid bare one after another. The first problem was to define the conditions under which infection by the body louse took place. It was possible to establish that the blood of a typhus patient could transmit infection from some hours before the appearance of fever until the first days of recovery. The insect could therefore absorb the pathogenic agent during the whole course of the disease, even before the disease became apparent and after the fever had disappeared.

The parasite's bite is not however immediately dangerous; it only becomes virulent after about a week when the pathogenic agent has had time to multiply in the parasite's digestive tube. Contagion is also possible by means other than the parasite's bite: it is sufficient that the skin and clothing be soiled by the excreta of an infected parasite and that the patient infect himself by scratching, for the disease to develop. This form of transmission most probably plays at least as important a role as the direct bite.

Nicolle was not long in making another important discovery: he established that the germ of typhus is not transmitted to new generations of parasites. The epidemic dies out of its own accord when the contaminated adult insects die. All these observations are obviously of the greatest importance from the point of view of combating the disease.

Nicolle and his collaborators had established at an early stage of their researches that monkeys who had recovered from a first attack of the disease became resistant to further contamination. This observation led them to a series of important discoveries concerning the conditions necessary for immunization against typhus, and led to a series of

successful attempts to exert preventive and attenuating effects on the disease with serum taken from convalescents and by vaccination.

Nicolle's discovery that it is possible to inoculate the guinea pig with typhus was an important step forward in the study of this disease. By successive inoculations from one animal to another, it became possible to preserve the agent of typhus in the laboratory for an unlimited period; it has not yet been possible to cultivate the virus on artificial substrates, and our knowledge of its morphology and biology is still extremely limited.

The study of typhus in the guinea pig led Nicolle to another very important discovery: certain infected animals may be germ carriers even though they present no apparent symptoms. Not even a slight fever indicates that they are contagious. This form of the disease had been hitherto unknown. Nicolle calls this form of typhus «inapparent» typhus and considers it to be the prototype of a group of latent infectious diseases of the same type. Nicolle's discovery of the inapparent infection orientated the work of scientists towards a hitherto unexplored field of research. These new concepts are highly significant, even as regards direct action against infectious diseases.

It soon became apparent that the discovery of the part played by the body louse in the transmission of typhus was of the greatest practical importance: it now became possible to combat the terrible disease by rational methods. In fact, within two years Nicolle and his collaborators succeeded in ridding Tunis entirely of a disease which had raged there each winter from time immemorial.

But in 1910 who would have guessed that the results of Nicolle's research were about to be put to practical use on a vast scale?

When the Great War broke out and many Russian and Serbian prisoners were interned in German and Austrian prison camps, typhus, which until then had hardly attracted the attention of European doctors at all, was not long in making an appearance. In spite of the precautions ordinarily taken against epidemics, it was quickly transmitted from one man to another, from home to home, regardless of age and in defiance of all the laws of epidemiology. The armies were threatened with a veritable catastrophe. The epidemic

broke out in the same way amongst the civilian population in regions of the eastern front devastated by war. The Balkan Peninsula was affected badly, but the disease spared no part along the whole front, from Finland to Mesopotamia. The value of Nicolle's discovery was once again made apparent. The Great War provided the opportunity for a clinico-experimental application of Nicolle's work on a large scale. As a French doctor said, one had to see the deserted Serbian towns to realize the desolation that can be caused by typhus, the satellite of war; one had to see for oneself the resurrection of whole areas, entirely due to the hygienic measures developed from Nicolle's discoveries, to appreciate fully the significance of these discoveries. Remembering the great losses incurred through another wartime epidemic, Spanish influenza, a far less serious disease in itself, one shudders to think of what might have happened in the Great War if we had been unable to combat typhus successfully.

Indubitably, the nature has not changed and we still know of no effective therapeutic action against this disease. Nevertheless, this terrible plague has become a mere contagious disease and is no longer considered in terms of devastating epidemics. Thanks mainly to the work of Charles Nicolle, we have now completely mastered the disease. The man who has vanquished typhus deserves the gratitude of the whole human race.

In the absence of Mr. Nicolle, the honour of whose presence is denied us today, I ask your Excellence, in your quality of Minister representing the French Republic, to accept on his behalf and to convey to him the prize and diploma. May I also ask you to convey to your illustrious compatriot the tribute and sincere congratulations of the Caroline Institute.

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