

Charles Nicolle (1866–1936): Bacteriologist and conqueror of typhus

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The history of typhus," wrote the German physician August Hirsch, "is written in those dark pages of the world's history which tell of the grievous visitations of mankind by war, famine, and misery of every kind."

The high fever, headache and delirium that are the characteristic manifestations of typhus, and that distinguish it from typhoid fever, are now so rarely encountered that many physicians would have trouble recognising the syndrome. This blissful ignorance is due in large part to the efforts of Charles Nicolle, a man interested in history, whose immense contribution to the conquest of typhus in the 20th century would make a fitting epilogue for Hirsch's work.

BACKGROUND Born in Rouen, France, Nicolle grew up in a well-educated family in which the expectation of success was high. His father was a physician and his elder brother was a prominent microbiologist. Although he studied medicine and completed an internship in Paris in 1893, the young Charles Nicolle was equally interested in literature, history and architecture. Perhaps because of early hearing loss that made clinical work difficult, he opted for a research career and studied at the Pasteur Institute in Paris, later accepting the directorship of its satellite institute in Tunis in 1902. The town, built alongside the ruins of Carthage on the southern shore of the Mediterranean, may have seemed a colonial backwater to his Parisian colleagues, but for Nicolle the scene was charged with vivid historical memory. The following lines, pinched by Nicolle's biographer Kim Pelis from *Le Naissance des Muses*, capture the spirit of Nicolle's oriental adventure:

The heaviness of the warm air hung over the sea. The fishermen's lanterns made furrows in the gulf's steamy haze, like living reflections of the fires lit in the sky... And I dreamed of Apuleius, before the sleeping sea of Carthage, by the light of a lamp made of clay.

A CRUEL HISTORY Unfortunately for North Africa's inhabitants, the ghost of Apuleius was not the only thing haunting the ruins at Carthage. A host of plagues, of which typhus was most

ancient and terrible, ravaged the population without mercy. Sensing an opportunity to distinguish the Pasteur Institute in Tunis from its parent organisation, Nicolle steered the research activities of his team toward the diseases most prevalent in the Mediterranean basin. In choosing this course, the student of ancient texts and decaying ruins could not have imagined the contribution he would make to the halting of one of history's cruelest recurring epidemics.

The story of typhus predates modern medicine. Spreading outwards from its endemic area of origin in the Southern Mediterranean, the first true epidemic occurred in Europe in 1489, when it ravaged Castilian troops during the siege of Granada. It



emptied swaths of Europe during the religious wars of the 17th century, as well as the imperial struggles of the 18th, and continuing its pitiless progression alongside social upheaval, blossomed anew during the French Revolution. The disease again surfaced during the 19th century in the Crimean War, the Balkan Wars, and in Ireland during the great periods of famine. Typhus epidemics decimated Native American populations in both North and South America, and epidemics following immigration were common in America's port cities throughout the colonial period and early decades of independence.

The disease carried not just death, but stigmatisation, due to its association with immigrants and refugees. In its epidemic form, cases of typhus, growing exponentially amongst masses of desperate and displaced people, respected neither borders nor political authority. Instead, the disease bloomed under conditions of lawlessness, and wherever it spread lawlessness followed. This has led to the observation that typhus is the friend and ally of xenophobes. Some decades after Nicolle's work it was a simple step, conceptually, for the Nazis to cease distinguishing between the Jews, gypsies and other migrant populations on the one hand, and the vectors of disease that these miserable and displaced people carried with them on the other. The SS leader Heinrich Himmler stated that "[a]nti-semitism is exactly the same as delousing," an assertion that went unchallenged by cowed German science. It was insecticide, after all, that Hitler used in his gas chambers.

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HALTING THE PLAGUE Writing in a time before public intellectuals could imagine horror on such a scale, Nicolle made the observation about typhus in North Africa:

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 that patients infected each other on the street, and also that their clothing was infectious... 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.

The observation could have been made by a layperson, but in 1909 Nicolle took the next step and began looking for a vector that could transmit typhus in the clothing and undergarments of the patients. Receiving a chimpanzee from the Pasteur Institute in Paris, he injected the animal with blood from a typhus patient. In a few days, he collected lice from the animal and placed the lice on another chimpanzee. The second animal became symptomatic of typhus.

The revelation that lice were the vector of typhus opened a floodgate of additional research, some of it carried out by Nicolle, into the pathogenesis of the disease. Within a few years, additional papers proved that the disease could be transmitted by patients scratching their skin during lice infestation – a behaviour that inoculated small scrapes and cuts with highly infectious lice faeces. A year after Nicolle's discovery, Howard Ricketts identified tiny bacteria in the blood of patients suffering from typhus in Mexico. The Polish researcher Rudolf Weigl produced the first effective vaccine for typhus, but it was not until Harvey Cox of the United States discovered a safe and large-scale culture method in fertilised hens' eggs that a vaccine became widely available.

In the meantime, Nicolle's discovery influenced the way that health authorities responded to typhus outbreaks. In World War I, typhus again flickered to life first in the chaotic eastern theatre of the war where health authorities intervened and focused on the decolonisation of lice. On the western front, all sides employed similar methods to control a variant of typhus known as trench fever, caused by a different species of Rickettsia, but also spread by lice. The disease recurred with devastating impact in Russia after the war, however, when public health efforts became impossible amidst the fighting between Bolshevik and anti-Bolshevik forces. This epidemic, arising from the perfect storm of world war, revolution, and anarchy, may have been the largest in history, infecting tens of millions of Russians. In World War II, the arsenal against lice was more formidable. An outbreak

in Naples in 1943 at the time of the Allied advance into the city was quickly brought under control with the use of DDT, a powerful new insecticide.

LEGACY If Charles Nicolle had done nothing but describe the mechanism of typhus transmission, it may have been enough to justify the Nobel Prize for medicine that he received in 1928. As it stands, he did much more, producing an anthology of original research that defies simple categorisation. He had a particular genius for culture and biochemical analysis, which allowed him to grow and identify pathogens that others were unable to investigate. He cultured *Leishmania tropica*, the causative agent of Oriental sore, another common affliction in North Africa. He developed chemical tests using benzene that aided in the differentiation of various species of Trypanosome. He identified, for the first time, the parasite later named *Toxoplasmosis gondii*, now a known pathogen in patients with AIDS. He conducted animal experiments with trachoma, the blinding disease caused by chlamydia infection of the eye, demonstrating key aspects of disease transmission.

In focusing on diseases of the Mediterranean and Africa, Nicolle showed by example that quality research could be used to benefit the world's humblest citizens. At the time of his death in 1936, Nicolle was admired as a hero both in France and in Tunis. The legacy he left was as moral as it was impressive, and it was as attuned to the needs of history and geography as it was to science.

BIBLIOGRAPHY

- Castellani A, Chalmers AJ. Manual of Tropical Medicine. New York: William Wood & Company, 1910: 136-7, 256, 280.
- Gross L. 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. Proc Natl Acad Sci USA 1996; 93:10539-40.
- Harrison M. Disease and the Modern World: 1500 to the Present Day. Cambridge: Polity Press, 2004: 138-42, 153-6.
- Hurst AF. Medical Diseases of War. Baltimore: Williams & Wilkins Company, 1941: 162-5.
- Manson P, Manson-Bahr PH, eds. Manson's Tropical Diseases. 10th ed. London: 1935: 217-20.
- McGrew RE. Encyclopedia of Medical History. New York: McGraw-Hill, 1985: 350-5.
- Pelis K. Charles Nicolle, Pasteur's imperial missionary: typhus and Tunisia. Rochester: University of Rochester Press, 2006.
- Raju TN. The Nobel chronicles. 1928: Charles Jules Henry Nicolle (1866-1936). Lancet 1998; 352:1791.
- Strong RP. Typhus fever with particular reference to the Serbian epidemic. Cambridge: Harvard University Press, 1920.
- Talbot J. A Biographical History of Medicine. New York: Grune & Stratton, 1970: 794-6.
- West SK. Trachoma: new assault on an ancient disease. Prog Retin Eye Res 2004; 23:381-401.
- Nicolle C. Nobel Lectures, Physiology or Medicine 1922-1941. Amsterdam: Elsevier Publishing Company, 1965.