History of Typhus

By David H. Walker

The first definite description of epidemic typhus based on its appearance in Italy in 1505 and 1528 was published in *De Contagione* by Fracastorius in 1546. The first appearance of an epidemic likely to have been typhus was at the siege of Granada in 1489-1492. Typhus was differentiated from typhoid fever on the basis of the rash by Huxham in 1739 and named exanthematic typhus by Boissier de Sauvages in 1760. The ultimate differentiation from typhoid fever was made by Gerhard during an epidemic in Philadelphia in 1836 based on the absence of ulcers in Peyer’s patches. Charles Nicolle, at the Institut Pasteur d’Tunis in 1909, was the first to prove that typhus is an infection by transmitting the disease to a chimpanzee and, more importantly, he demonstrated transmission experimentally from monkeys to *Pediculus humanus corporis* to monkeys that lice are the vectors of typhus. Howard Ricketts, a pathologist who died of the disease during research in Mexico in 1910, was the first to visualize the small coccobacilli in patients’ blood and louse intestine and to demonstrate that it was non-filtrable, i.e., not what we now know as viruses. In 1916 da Roche-Lima observed intracellular rickettsiae in gut epithelium of lice from typhus patients but not from healthy persons. Wolbach, another pathologist, led a Red Cross-sponsored research team in Poland after World War I, and using uninfected body lice fed on typhus patients demonstrated the xenodiagnosis of typhus by development of the bacteria-infected louse gut epithelium. He also devised a stain that identified the intracellular bacteria in endothelial cells of the typhus lesions. In 1934, Hans Zinsser determined that the mild typhus-like illnesses occurring in louse-free eastern European immigrants living in New York and Boston were recrudescence of latent *Rickettsia prowazekii* infection. Thus, the mystery of where the rickettsiae reside between epidemics was solved.

Typhus has retreated to impoverished louse-infected populations afflicted by poor nutrition, alcoholism, cold weather, and stressful lives where outbreaks and epidemics occur in association with wars, famines, and natural disasters when bathing and washing clothes are difficult or impossible. Outbreaks have yielded to control of lice by insecticides and antimicrobial treatment of patients. An epidemic involving as many as 100,000 persons in Burundi in 1995-1997 might never have been identified if a Swiss nurse working in a jail with an undiagnosed illnesses having a 15% case fatality rate had not been med-evacuated, died, undergone autopsy, and been investigated by CDC pathologists.

The first widely used typhus vaccine was produced by Rudolf Weigl by propagating *R. prowazekii* in the intestines of intrarectally inoculated lice that were maintained by twice daily feeding on immune humans for a week or more. As much as 100 formalin inactivated rickettsiae infected louse intestines were required for one vaccine dose. Other killed-*R. prowazekii* vaccines were prepared from infected mouse lungs or yolk sacs of embryonated eggs. The latter protected US soldiers during World War II when illness, but no deaths, occurred even where there were civilian epidemics. A
spontaneous mutant (Madrid E) strain resulted after numerous laboratory passages during World War II in Spain. It was very effective in field trials in South America and Africa, but was determined to undergo spontaneous reversion to virulence and to cause mild typhus in 14% of vaccinees. Recent identification of the frame shift mutated gene and successful attenuating homologous recombinant knockout of another virulence gene of *R. prowazekii* provide hope that a permanently attenuated E strain-like, or other engineered vaccine, may be developed.

In addition to its own history, typhus altered human history, particularly by altering the outcome of military campaigns, in Granada (1489-1492), Naples (1528), Hungary (1542 and 1566), Metz (1552), the Thirty Years War (1618-1648), Oxford (1643), Prague (1741), and Napoleon’s 1812 invasion of Russia in which only 3000 of 700,000 troops returned alive with as many as half having died of typhus. Epidemic typhus was an enormous scourge on the Eastern Front during World War I. In Russia alone in the aftermath of the war and the Bolshevik revolution, there were 30 million cases of typhus with 3 million deaths.

The origin of typhus is controversial. The imperfect evolutionary fitness of *R. prowazekii* in the human (15% fatal)-louse (100% fatal) cycle contrasts with the highly adapted zoonotic cycle in which 40% of Eastern flying squirrels are infected asymptotically and transmission involves its species-specific flea and louse in which infection is not deleterious. In addition, *Hyalomma* ticks in Ethiopia and *Amblyomma* ticks in Mexico carry *R. prowazekii*. There is evidence of lice in pre-Colombian mummies and historic descriptions prior to Cortez’s arrival of *cocolixtle* and *matlazahuatl* that have features of typhus. That typhus did not spread unidirectionally from America to Europe is excluded by its distribution throughout Spain before Cortez landed in Mexico. The possibility of an origin in Africa and spread to the eastern Mediterranean are modestly supported by attribution of the 1489 Granada epidemic to soldiers from Cyprus where it was said that the disease was known and apparent immunity in Turks during military epidemics in Hungary. Genetic analysis of geographically dispersed collections of strains of *R. prowazekii* show minimal divergence or an ancestral strain by phylogeny. Detection of *R. prowazekii* DNA in remnants of lice in clothing of mass graves of Napoleon’s retreating soldiers in Vilnius, Lithuania suggest that the future may hold more answers of the history and origins of typhus.
Figure 1: Wolbach SB, Todd JL, Palfrey FW. The Etiology of Pathology of Typhus. The League of Red Cross Societies at the Harvard University Press: Cambridge, MA, 1922.
Figure 2: Scrapbook prepared by Mrs. Howard Taylor Ricketts. 1965.
RATS, LICE
AND
HISTORY

Being a Study in Biography, which, after Twelve Preliminary Chapters Indispensable for the Preparation of the Lay Reader, Deals With the Life History of TYPHUS FEVER

Also known, at various stages of its Adventurous Career, as Morbus pulicaris (Cardanus, 1545); Tubardigio y puntos (De Toro, 1574); Pintas; Fever purpura epidemica (Coyttarus, 1578); Febris quam lenticulas vel punctualas vacant (Fraconarius, 1546); Morbus hungaricus; La Pourpre; Pipercorn; Febris petechialis vera; Febris maligna pestilens; Febris purpura et maligna; Typhus carcerorum; Jyl Fever; Fièvre des hôpitaux; Pestis hellica; Morbus castrensis; Famine Fever; Irish Aague; Typhus exanthematicus; Faulscheer; Hauptbrankheit; Pestartige Bräune; Exanthematisches Nervenfeber, and so forth, and so forth.

By HANS ZINSSER

Figure 3: Zinsser H. Rats, Lice and History: A Chronicle of Pestilence and Plagues. Little and Brown, Boston, 1934.
Fig. 6  Nicolle before the Door of his Institute, ca. 1909.