



History of Pathology Society 2009-2010 Officers

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History of Pathology Society Meeting
Sunday, March 21, 2010, 3:30 p.m., Thurgood South
Marriott Wardman Park Hotel, Washington, D.C.
United States and Canadian Academy of Pathology Meeting

The Making of History

Moderator: Robert D. Collins,
Vanderbilt University Medical Center, Nashville, TN

3:30	Introduction – Robert D. Collins, Vanderbilt University Medical Center, Nashville, TN
3:35	History of Typhus – David H. Walker, University of Texas Medical Branch, Galveston, TX
4:05	Fritdjof Nansen: From Neuron to North Polar Sea to Humanitarian Work – Carl Kjeldsberg, ARUP Laboratories, Salt Lake City, UT
4:35	Ernest Goodpasture: “I Was Not Aware of a Connection Between Lung and Kidney Disease” – Robert D. Collins, Vanderbilt University Medical Center, Nashville, TN

The objectives are to describe little-known events behind: the discovery of typhus; the discovery of synapses by Nansen shortly to be confirmed by Cajal; and the attachment of the eponym *Goodpasture's syndrome* to one of the pulmonary-renal disorders.

History of Renal Typhus

David H. Walker

University of Texas Medical Branch, Galveston, Texas

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.



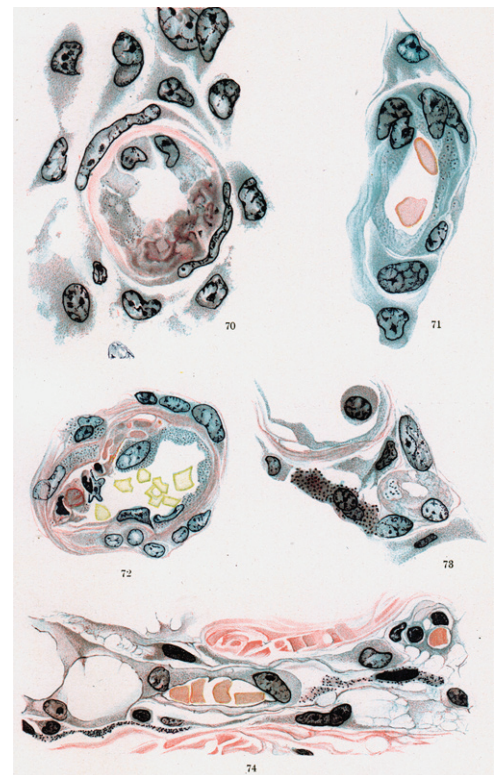
Charles Nicolle proved that typhus was an infectious disease transmitted experimentally to a chimpanzee by human body lice in his laboratory in Tunis.

kii 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.



Howard Ricketts with a monkey used in his research on louse-borne typhus in 1910 in Mexico City where he died of a laboratory-acquired infection.



Pathologist, **Burg Wolbach**, using a staining method that he developed, visualized *Rickettsia prowazekii* in tissues of fatal typhus cases in Poland following World War I and prepared these camera lucida drawings of endothelial cells containing rickettsiae.

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 illness 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.

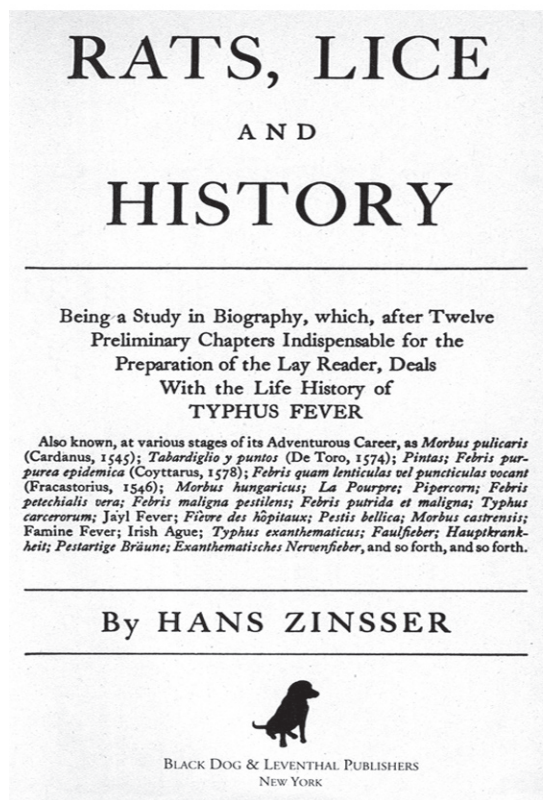
In addition to its own history, typhus altered human history, particularly by altering the outcome of military campaigns, in Granada (1489-1492), Naples (1528), Hungary (1542 and 1566), Metz (1552), the Thirty Years War (1618-1648), Oxford (1643), Prague (1741), and Napoleon's 1812 invasion of Russia 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

This classic book by the scientist who elucidated recrudescence typhus, Brill-Zinsser disease, reflects the confusion generated by the discovery of what we now know as *Rickettsia typhi* in rats.

asymptomatically 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.

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Fridtjof Nansen: From Neuron to North Polar Sea to Humanitarian Work

Carl Kjeldsberg

ARUP Laboratories, Salt Lake City, Utah

“Fridtjof Nansen (1861-1930) was as comfortable with the microscope as he was with his ice ax.” This Norwegian explorer, oceanographer, statesman, and Nobel Peace Prize winner is best known for his arctic explorations. However, he started his career as an invertebrate zoologist with a special interest in the histology of the nervous system. At the age of 24, he was one of the first to express doubts about the “reticular” nature of the nervous system. He learned from Camillo Golgi the new method of staining nerve cells.

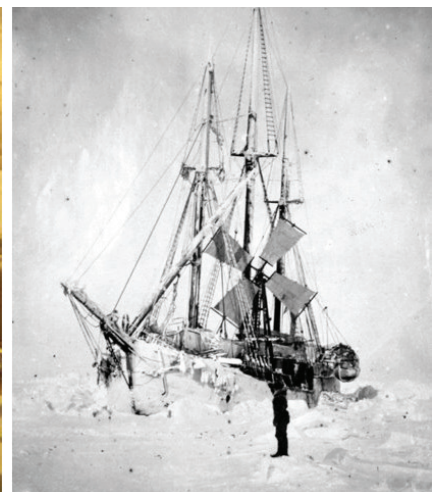
Nansen was particularly interested in how nerves communicate with each other, and he was a pioneer advocate for what later became the so called neuron doctrine. He was adamant that nerve units were not fused, but only touched each other. His conclusions were as daring as his subsequent geographic exploration.

Nansen, His and Forel, working from different points, in different countries, became the cofounders of the modern view of the nervous system. Nansen also offered an explanation of the reflex arc; he discovered that spinal ganglia bifurcate into ascending and

descending processes and was the first to postulate the ectodermal origin of Schwann cells. Two weeks following a controversial PhD dissertation at the University of Kristiana, he was on his way to be the first person to cross Greenland on skis. Two years later, 1893, he set sails for the North Pole, a trip which lasted three years. By 1906 Raymon y Cajal and Golgi shared the Nobel Prize in medicine for their contributions to the “neuron doctrine.” At that time Nansen was Norwegian ambassador in London having played a key role in the dissolution of the union between Norway and Sweden, ensuring a peaceful collaboration.

Nansen also made major contributions to the foundation of the science of physical oceanography. He was made professor of oceanography in 1908. After the First World War he was in 1920 asked by the League of Nations to assist with the repatriation of thousands of prisoners of wars and refugees in Russia. He played a key role with the famine relief in Russia. In 1922 he was awarded the Nobel Peace Prize for his humanitarian efforts. He continued to be involved with humanitarian work until his death at the age of 69.

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Dr. Goodpasture: “I was not aware of such a connection between lung and kidney disease.”

Robert D. Collins

Vanderbilt University Medical Center, Nashville, Tennessee

Ernest William Goodpasture, a native Tennessean, received his undergraduate degree from Vanderbilt in 1907 and his M.D. from Johns Hopkins in 1912. After training in pathology at Hopkins and Harvard, his first major contribution in the field of virology was the result of an autopsy study of patients dying in the great influenza pandemic of 1918-1921. At that time, influenza was thought to be a bacterial infection. However, in a meticulous study of more than fifty autopsies, Dr. Goodpasture found two cases in which there were no bacteria. On this evidence and morphologic changes, he predicted in 1919 that influenza was a viral rather than bacterial disease. It was another fourteen years before the influenza virus was actually isolated.

Surprisingly, this remarkable achievement was not the reason Dr. Goodpasture became one of the world's leading virologists. Rather, he attributed his interest in

viral diseases to collaboration from 1922-1923 at Pittsburgh's Singer Research Institute with Dr. Oscar

Teague. Teague also graduated from Vanderbilt before obtaining his M.D. from Berlin in 1902. At Singer, they studied the mechanism by which herpes viruses reach the central nervous system after a superficial infection.

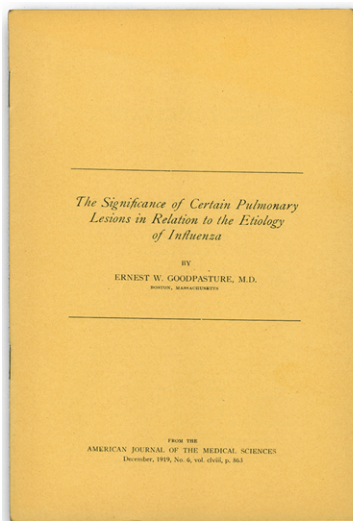


Lieutenant J.G. Ernest Goodpasture in uniform at Chelsea Naval Hospital in 1918-1919. It was in this period that he studied patients dying with influenza.

Goodpasture and Teague were able to write six papers before the latter's untimely death in a car accident in September, 1923. This burst of scientific productivity attracted the interest of Dean G. Canby Robinson, who invited Goodpasture to become Chair of Pathology in Vanderbilt's newly reorganized School of Medicine in 1924.

To return to the 1919 paper, the second of the two cases without bacterial superinfection had a bout of typical influenza before returning to hospital a month later with pulmonary hemorrhage and glomerulonephritis. This case came to the attention of Stanton and Tange at the Melbourne Hospital in Australia in 1958, and for reasons to be discussed, was the basis of their naming their cases

of pulmonary-renal syndrome as “Goodpasture's syndrome.”



Reprint of 1919 American Journal of Medical Sciences article on pathogenesis of influenza. The second of two cases in the report had pulmonary and renal disease and was the basis of Stanton and Tange's naming this syndrome for Dr. Goodpasture.

In 1959, Dr. Goodpasture was in his fourth year as Scientific Director of the Armed Forces Institute of Pathology when he learned that Doctors Stanton and Tange had applied his name to an apparent pulmonary-renal syndrome. There is no correspondence in Dr. Goodpasture's papers between these three, and his reaction in 1959 as quoted in the title of this paper indicated that he was an unwilling participant in this eponymic happening, stating that he did not feel his name should be attached to a disease he had not studied. It is somewhat incongruous that he is best known for something he disclaimed knowing about, while not being generally recognized for his substantial discoveries and contributions to medical science.

Dr. Goodpasture served for thirty years as the first head of the Pathology Department in the newly-reorganized medical school at Vanderbilt. As such, he was directly responsible in a ten-year span for three major discoveries in the

field of virology, thereby firmly establishing the reputation of the medical school and of his own research laboratory. These discoveries were the demonstration that viral inclusions in fowlpox contained active viral particles, that embryonated eggs could be used as a culture medium for viruses as well as to study the

pathogenesis of viral and bacterial diseases, and finally the proof that mumps is a viral infection.



Dr. Goodpasture is shown in his laboratory in 1955, shortly before retirement from Vanderbilt. This photograph is courtesy of Dr. Sam Paplanus.

Dr. Goodpasture thereby contributed enormously to research into the pathogenesis of viral infections; furthermore, the ability to culture viruses (and other infectious agents) in eggs greatly facilitated the development of vaccines that prevented viral and rickettsial diseases during WW II. It is of note that chick embryos are still the favored culture medium for influenza vaccines in 2009. In 2000, these various accomplishments led Dr. John Craighead in his book *Pathology and Pathogenesis of Human Viral Disease* to recognize Dr. Goodpasture as "the father of viral pathology in the United States." - END -