"What a Revelation Any Science Is!"

Sensitive to the environment in which diseases occur, Howard T. Ricketts was one of the first great microbial ecologists

Lynn Margulis and Betsy Palmer Eldridge

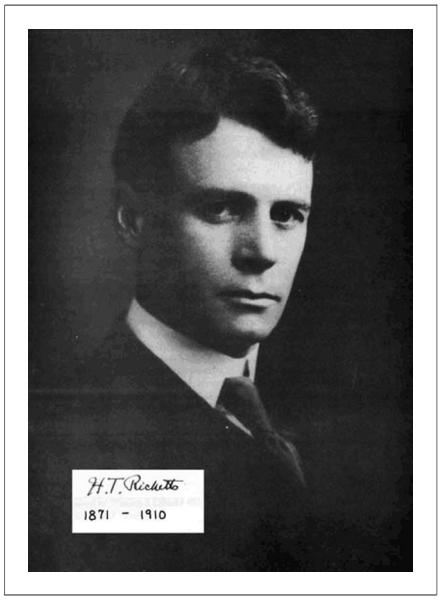
On 3 May 1910, Howard Taylor Ricketts died at the age of 39 while being treated in a tent in the yard of the isolation wing of the American Hospital in Mexico City. In its obituary, the *Chicago Tribune* wrote, "The death of Howard Taylor Ricketts adds another name to the long honor roll of science. The endless warfare that mankind has fought against ignorance, and its child, disease, has claimed another victim, but the fight goes on. . ." He succumbed to illness while searching for pathogens responsible for typhus fever and had earlier discovered the louse-borne bacteria that bear his name: *Rickettsia typhi*.

Years before, while an undergraduate at the University of Nebraska in Lincoln, he wrote to his future wife Myra Tubbs: "am taking a course in Botany this semester to become better acquainted with the plant kingdom. We started with the very lowest single-celled plants and go up the scale examining them microscopically as well as their general structure. What a revelation any science is!"

Education, Courtship, and Early Commitment to Infectious Diseases Research

Howard Taylor Ricketts was born in Findlay, Ohio, in 1871, but spent his boyhood in Illinois. He attended Northwestern Preparatory School in Evanston, where he met Myra Tubbs, a vivacious, auburn-haired romantic. One evening he sent her a note inviting her to go boating, saying, "It is too bad to let this moon go to waste. Best moon I ever saw." They both began college at Northwestern University in the class of 1894, but Howard transferred to Nebraska for his last two years. He then returned to Evanston to attend Northwestern Medical School, graduating in 1897. He obtained a much-coveted Internship at Cook County Hospital, and then accepted a fellowship in "cutaneous pathology" at Rush Medical College, which was then affiliated with the University of Chicago.

Often during their long engagement, Howard told Myra that she could go out with others as long as she remembered that she was going to marry him! A year after they were married in the small town of Kirkwood in western Illinois in April 1900, they left for Europe. There he had arranged to study in Berlin, Vienna, and Paris, the preeminent medical centers of the time. Myra was pregnant and their son, Henry, was born in Berlin in August 1901. After their year abroad, Howard returned as a faculty member



Howard Taylor Ricketts

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H. T. Ricketts, Myra Ricketts, son Henry, and daughter Elisabeth at the Marine Biological Laboratory beach, circa 1906.

at the University of Chicago. Their daughter, Elisabeth, was born in June 1903 in Chicago.

Ricketts' first research project was undertaken while he was at Rush and later published as a monograph while he was abroad: *Oidiomycosis [Blastomycosis] and its Fungi, with special reference to the disease in the skin; Allied Considerations* (Fig. 1). The manuscript had to be severely cut for reasons of cost. After it was published, Ricketts received two congratulatory letters—one from his mentor Ludvig Hektoen at Rush and the other from Elie Metchnikoff, the Russian scientist credited with developing the cell theory of immunity.

Metchnikoff thanked Ricketts for his interesting monograph on the skin and lung disease caused by *Blastomyces dermatitidis*. This fungal pathogen, endemic in the Eastern United States, is associated with the inhalation of plant debris. In infected human tissue the fungus, which can be filamentous, takes on the appearance of yeast. In culture at lower temperatures, the fungus produces *Chrysosporium*-like small conidiospores. Today we recognize *Blastomyces* as an ascomycete. In the sexual stage where the product of mating is an ascus, the fungus is classified as *Ajellomyces dermatitidis*.

Ricketts' Attention to Details in the Investigation of a Spotted Fever Case

Ricketts, who became a superb microscopist, was steadfastly concerned with the details of pathogenic microbes in relation to the appearance of disease symptoms. He followed Metchnikoff's work with great interest. In an editorial published in the *Journal of the American Medical Association* (JAMA) in 1903, Ricketts' handwritten draft states:

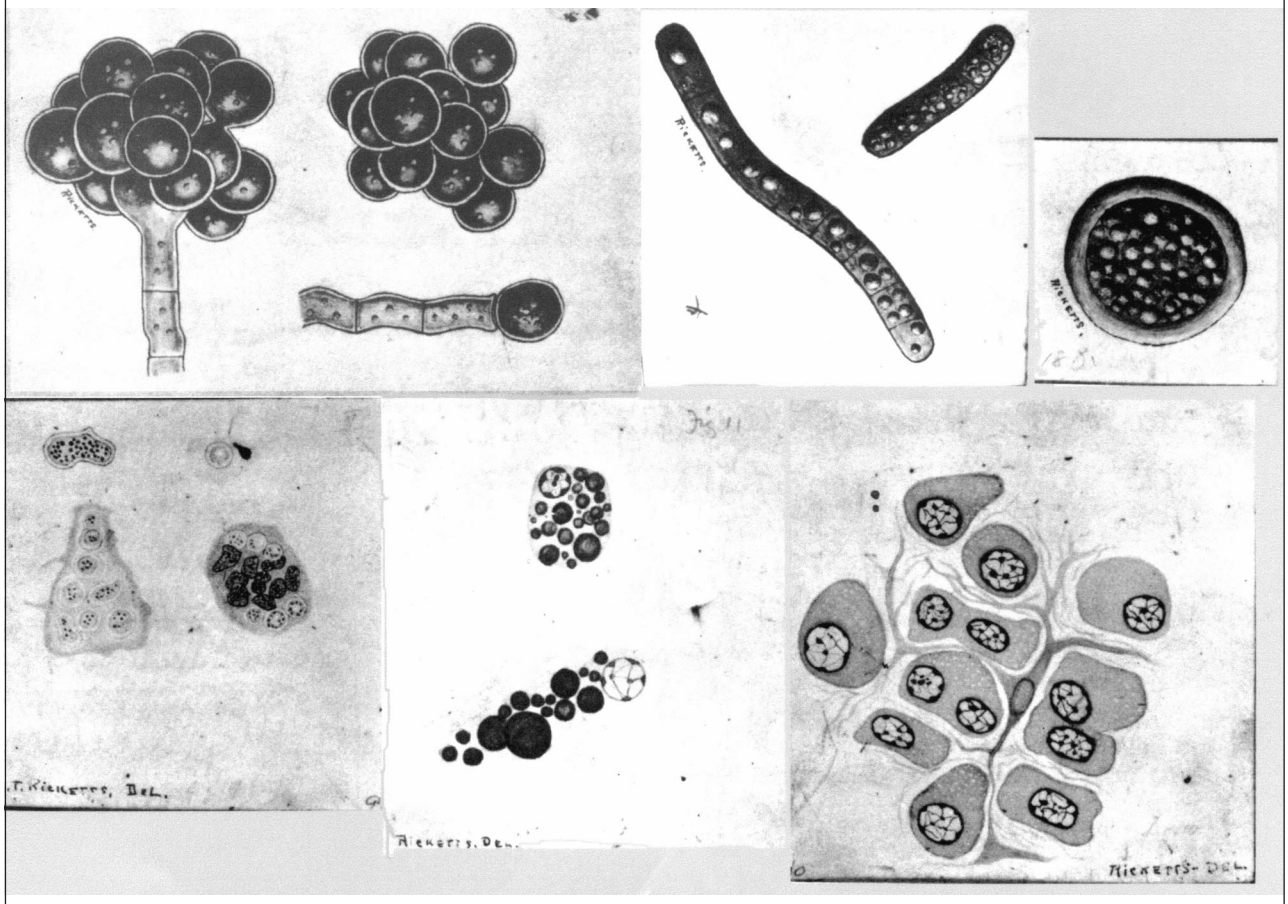
> Recently Metchnikoff and Roux have given a concise statement of their observations which are most interesting and which may be of great importance to furthering the study of syphilis. The first chimpanzee was infected with "syphilitic virus." After 25 days a hard sore developed which Fournier and others were willing to consider of syphilitic nature. About a month later about 15 papules [appeared] on various parts of the body and remained until the death of the animal, 14 weeks after the inoculation was made.

In 1906 he began a four-year study of the cause of a "spotted fever" that was prevalent in the Rocky Mountains but was limited to the western slopes. The next year, Ricketts set up a 14-by-14-foot tent in the hospital yard in which he slept (under army blankets, since it was cold) and which he also used as a laboratory (Fig. 2). In the course of these studies in Montana, Ricketts made extensive collections of local ticks in the Bitteroot Valley and designed tick cages to better observe the "bipolar bacilli." He aligned the caged and labeled ticks in rows. Working mostly alone and separated from his young family, he oversaw every aspect of the field and laboratory project.

Ricketts was careful and observant. His notes indicate attentiveness for any clues to the behavior of the pathogens he sought. Shortly after his arrival in Montana in 1906, Ricketts had recorded observations related to the clinical case of William Robert Landon, a 10-year-old boy, his farmer father, and other family members. Ricketts noted that members of Landon's family drank unboiled water from Mill Creek and irrigation water from a nearby ditch, for instance. He also observed that tick populations increase in spring, and that this rise seems to follow the melting of the snow. He wrote of the Landons and their exposure to insects:

> Ticks are around the house, on trees, on ground, everywhere. Every body bitten innumerable times.. . .Mosquitoes most numerous in July. Has seen a few this spring. Has not been bitten, nor has boy. Boy has been bitten many times by ticks.

FIGURE 1



Some original drawings made by Ricketts for his monograph on blastomycosis.

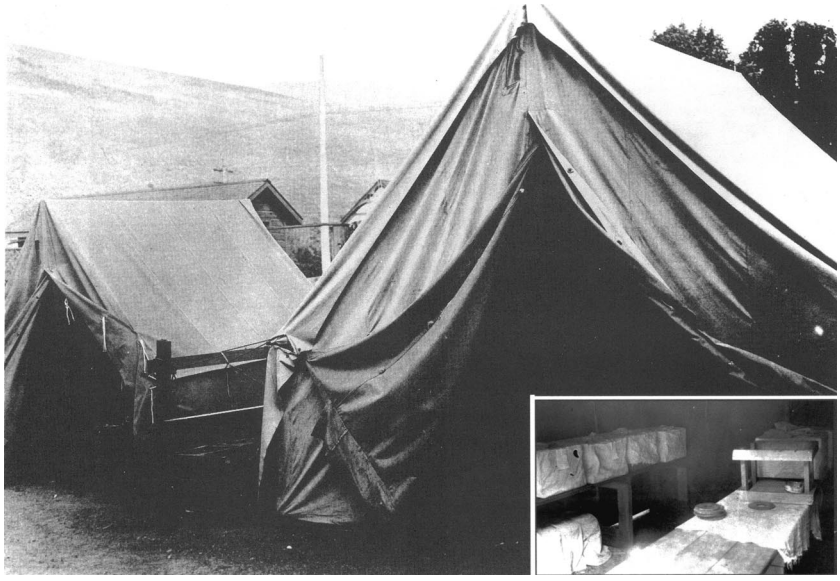
Ricketts took a blood sample from this boy, stained it with eosin, and observed a "bacillus-like body to the left of erythrocyte. Apparently it takes up the same color as the erythrocyte." This entry in his notebook is the first mention of the gram-negative bacterium that today is placed in the alpha subdivision of the *Proteobacteria*. Ricketts himself "described no formal name for the organism" but suggested it be referred to as "the bacillus of Rocky Mountain Spotted Fever." The bacterium, found in "astonishing numbers" in tick eggs, was subsequently named *Rickettsia rickettsii* and proved to be the cause of spotted fever.

Early Analysis of Rocky Mountain Spotted Fever

Later that spring, Ricketts studied guinea pigs, some of which were inoculated with the blood of a patient stricken with the disease while others were exposed to ticks. When he autopsied a guinea pig whose fever spiked to 104.8°F and died, severely emaciated, a week later, he became convinced of the similarities between the tickborne guinea pig fever and the typhus symptoms in his human patients. Ricketts became increasingly certain that the bacteria were injected via tick bites into mammals.

After many attempts to culture microorganisms from the blood of infected ticks, guinea pigs, and people, Ricketts wrote in 1907: "Although infected ticks had been examined previously in a more or less cursory manner, their systematic study was not undertaken until recently. In pursuit of this work, advantage was taken of the fact that the disease is transmitted by the infected female to her young through the egg. . ."

FIGURE 2



Tents erected in the hospital yard in Montana, used as both laboratory space and sleeping quarters for Ricketts and his assistant, J. J. Moore. Inset: Ricketts's tick cages inside the tent.

He repeated these experiments in 1907–1908 with the help of Maria B. Maver, and found that allowing the larvae to feed on both normal and infected guinea pigs led to transmission in 50% of the cases in which ticks were used. In his reports, he noted:

> . . .[one tick] had produced fatal infections of spotted fever in guinea-pigs 1740 and 1764. A number of eggs from the first days laying were crushed individually on coverglasses, fixed in absolute alcohol and stained with Giemsa's stain. Each egg was found to be laden with astonishing numbers of an organism which appears, typically, as a bipolar staining bacillus of minute size approximating that of the influenza bacillus, although definite measurements have not been made. . .
> . . .the salivary glands, alimentary sac and ovaries of infected [tick] females are literally swarming with exactly similar microorganisms. ...[However,] they appear to be entirely absent from the viscera of the uninfected tick, both male and female.
> . . .Morphologically the organism is a bacillus and somewhat pleomorphic as described. Its resemblance to the [agent responsible for] hemorrhagic septicemia is striking, and in this connection it is important to note that spotted fever is a hemorrhagic septicemia. It has not been cultivated although work with this end in view is in progress. That a bacillus may be the causative agent of a disease in which an insect carrier plays an obligate role under natural conditions may be looked at with suspicion in some quarters. Yet even without the evidence in this case, it would seem to be unscientific to be tied to the more or less prevailing belief that all such diseases must, on the basis of several analogies, be caused by parasites which are protozoon in character...

Ricketts Fateful Visit to Mexico to Study Typhus Fever

In the autumn of 1909, the Mexican government offered funds for work on rampant typhus fever in Mexico City. F. McCampbell of the Ohio State University, who had also worked on Rocky Mountain spotted fever, was appointed to head a medical expedition. McCampbell invited Ricketts to join that expedition, writing in a 26 November 1909 letter:

> It has occurred to me, and it is possible from my control of the situation here, that perhaps we might combine forces to attack this problem if you would care to do it. . .I hope that I may have the pleasure of hearing from you as soon as possible in regard to this proposition. . . . . .I am getting some interesting results on Rocky Mt Spotted fever in regard to the micro-organism which I recently isolated. I hope you may be able to send the immune serum soon. . ..

After Ricketts learned that two researchers employed by the Mexican government had successfully transferred the typhus disease to monkeys by inoculating them with blood from a feverish patient, he agreed to go to Mexico.

Rufus Cole in New York City invited Ricketts to consider moving to the Rockefeller Institute, where his work would be better funded. Ricketts turned down that invitation, explaining:

> There are some features regarding the bacillus I have found in spotted fever which will

> have to be worked out before I would want to leave the subject. Particularly there is the possibility of avirulent strains existing in ticks naturally, which has been suggested by some observations, and which would need to be determined before the bacillus could feel perfectly sure of its ground. I am still inclined to think that typhus should come next after spotted fever, and that was incorporated in the plan which I presented to the University [of Chicago]. . .It is my plan to go to Mexico City as soon as things can be arranged after I return from the West. . .

On 11 September 1909, Ricketts wrote to N. Charles Rothschild in England: "I have become interested in the transmission of infections by mosquitos, fleas &c. and contemplate taking up the study of typhus fever on the basis of insect transmission." By 23 December, Ricketts was hard at work in Mexico, again separated from his family. He explained to his professional mentor and closest confidant Ludwig Hektoen, who was still in Chicago:

> Of course I am rushing into this heels over head because of the manifest success of the transfer of the disease to monkeys by the direct innoculation [sic] of human blood on the part of the government men. As to whether the susceptibility of the monkey is high enough or of the right quality to permit of insect transfer is of course not definitely known and of course we take chances on this to a certain extent. Shall deal with lice (vestamentorum), fleas and bedbugs and shall try to carry all three along at the same time; incidentally shall try ticks. . .

Handwritten at the bottom of this letter is Ricketts' first suspicion in writing of the filterable infectious culprit: "It may be that I have found a faintly staining bipolar bacillus [in the louse] (p. 92), but it is too uncertain to justify much excitement."

On 25 January 1910, Hektoen sent a telegram to Ricketts at the American Club in Mexico City: "McCampbells assistant dead. Typhus. No insect bite. Be careful."

Ricketts answered:

> We were shocked to hear of the death from typhus of McCampbell's friend. It is impossible to be certain that one is not bitten by a louse, and this does not shake our faith in insect transmission. We shall, of course, be as careful as possible, the chief element of care being in spending as little time as possible in the typhus ward, where the conditions are most excellent for the acquisition of lice. . .

A few days later, he wrote to Myra: ". . .I think we undoubtedly have transmission by lice. . . Obtained it by the bite of the lice, and also by rubbing into incisions contents of the alimentary canal, or rather of the whole body cavity. . ."

Despite the care taken, Ricketts, in his tent in the hospital yard, was close enough to lice to be bitten and on 18 April, only a few days before he was scheduled to return home, he fell ill. On 19 April, in shaky handwriting that revealed his illness, he wrote to Myra, trying not to alarm her, "I have decided to stay here two or three (or a few) days more, to help Russell [Wilder] in getting the balance of the work started." When Myra was notified that his condition was worsening, she left Chicago to join him.

In the American Hospital in Mexico City, Ricketts had been sleeping in a tent erected at his suggestion near the isolation wing. Always the acute observer, he took notes on his progress and thought he had survived the crisis. At the end he succumbed to heart failure, perhaps aggravated by the altitude. When Myra arrived, he told her that he was so glad that she could take charge. He also said that there was something that he had been longing to tell her. . .but she interrupted him and insisted that he rest. A few minutes later, his heart failed. Myra wondered for the rest of her life—another 40 years—what it was that he wanted to tell her. And she and others often wondered what he would have accomplished if he had lived.

The Legacy of Ricketts

The importance of his work on the "bipolar bacilli" puts Ricketts among microbiology's immortals. *Rickettsia*, named after his death, later proved to be obligate intracellular symbionts found in a wide range of insects. Several distinguishable morphological and serological types of *Rickettsia* may coexist within the same animal cell.

Today *Rickettsia* are known to be close free-living relatives of the mitochondria. These nearly ubiquitous organelles, present in all oxygen-respiring nucleated organisms, including fungi, animals, plants, and most protoctists, resemble avirulent and pathogenic *Rickettsia* in many

The authors of this article, Lynn Alexander Margulis and Betsy Palmer Eldridge, who is a granddaughter of Howard Taylor Ricketts, became good friends in the late 1940s and remained so during their school days at the University of Chicago Laboratory School, when they often spent afternoons together sharing their thoughts and dreams. This homage to Betsy's grandfather was first suggested during the Lab School reunion in 1994 and then again at the 50th reunion in the summer of 2004.

Much of the information in this article comes from a family scrapbook about Howard Taylor Ricketts that was assembled under the guidance of Myra by Elisabeth Ricketts Palmer, their daughter, for an exhibition at the Academy of Medicine in Rochester, N.Y., in 1941. The material on which this scrapbook was based, along with his notebooks, manuscripts, and correspondence, resides permanently in the Special Collections of the University of Chicago Library.

Palmer assembled an expanded version of that document in 1965, and gave photocopies to Ricketts' 7 grandchildren and 14 great-grandchildren as well as a number of libraries. Copies of this scrapbook are also regularly presented to recipients of the annual University of Chicago's Howard T. Ricketts Award, which recognizes outstanding accomplishments in the medical sciences. The first such awards were presented to Ludvig Hektoen and Russel Wilder in 1949. In Myra's words, she hoped the Award "would seem to bring him back to the work once a year and what he did would seem to be living on." Nearly a century after his ultimate contribution to science, we celebrate Myra's generosity and affirm that what he did for microbial ecology and medical symbiotics certainly lives on.

ways. Christopher Bazinet of St. John's University, Jamaica, N.Y., has argued that the mitochondria of fruit fly (*Drosophila melanogaster)* sperm, like *Rickettsia*, induce actin fibers that look like "comet tails." These long, fibrous, proteinaceous structures ensure the transmission of the organelles—or bacteria—from one cell to another in the animal body. The behavior of mitochondria reveals their ancient origin as bacteria.

Ricketts' only full-length book, *Infection, Immunity and Serum Therapy*, written in 1906 and published in 1908, was widely used in medical school classes as a text. Yet, the genius of Ricketts transcended his curiosity, persistence, imagination, and dedication in search of pathogens. True, his talent as a microscopist, writer, and teacher, and his cooperative spirit and willingness to work under conditions of deprivation, were remarkable. Beyond this, however, and unlike so many of today's investigators, Ricketts was always acutely sensitive to all aspects of the environment in which the disease was detected. Although he would not recognize current terminology and would be baffled by the large number of scientists required to investigate arthropod-bacterial symbionts compared to what he did virtually alone, we conclude that he was one of the first, and one of the world's greatest microbial ecologists.

SUGGESTED READING

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