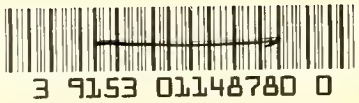

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TICKS
An Ever Increasing Public Health Menace

By Willy Burgdorfer

American Dog Tick
Dermacentor variabilis

Deer Tick
Ixodes dammini

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TICKS
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By Willy Burgdorfer

It is indeed a great honor to stand before this gathering to help celebrate this year's Plant Science Day commemorating Professor Dr. Samuel W. Johnson whose work and strife led to the founding of this Agricultural Experiment Station in 1875, the first institution of its kind in the United States.

I must admit, however, that it was not easy for me to accept your invitation, at least not without reservation. After all, I am not an agricultural scientist, and my achievements and contributions to science fall far short of those attributed to the man in whose memory and honor Plant Science Day is being celebrated.

In familiarizing myself with your founder's biography, however, I came across one characteristic that may in some way reflect on my own career. Like Professor Johnson who set himself to work and succeeded in developing a popular interest in scientific agriculture, I too believe in bringing the subject of my own research, i.e., tickborne diseases, to the general public. I think education of the public about ticks and the disease agents they may transmit, is the best way to prevent the diseases.

According to tick taxonomists, about 800 species of ticks have been identified. All are obligatory ectoparasites. Most require at least three hosts to complete their life cycle consisting of four distinct developmental stages: egg, larva, nymph, and adult. Some ticks parasitize only one or two hosts.

Ticks are not only annoying pests, but in temperate and tropical countries they also surpass all other hematophagous arthropods in the number and variety of disease agents they transmit to man and his livestock.

References to man's struggle with ticks date back to as early as 200 B.C. when M. Procius Cato referred to treatments whereby:

> there will be no sores and the wool will be plentiful and in better condition, and the ticks (*ricini*) will not be troublesome.

Advice was also given by Columella (ca. 60 *B.C.*) that when cattle were purchased

> to pass the hand under the belly . . . that ticks which principally attack cows may be removed.

A later account by Pliny (77 *A.D.*) reads as follows:

> there is an animal occurring at the same season living on blood with its head always fixed and swelling. Being of the animals which has no exit for its food, it bursts with over-repletion and dies from actual nourishment. This animal never occurs on mules, it is frequent on cattle, it occurs sometimes on dogs, on which all kinds of lice are found . . .

Practically no information is available on the role ticks may have played during the Middle Ages; man undoubtedly was exposed to them but did not recognize them as sources of various diseases.

This was soon to change with man's becoming an agriculturist. As he invaded vast areas and developed them into pasture for his domestic livestock, he not only became exposed to hitherto unknown tick habitats, but also through introduction of large numbers of cattle, horses, sheep, etc., provided the conditions necessary for increased tick populations. In addition, intercontinental shipping of stock for breeding purposes, etc., led to the establishment of ticks in areas

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previously tick-free. By the beginning of the 19th century, ticks were suspected as the cause of tick paralysis of calves in Australia, and *Amblyomma hebraeum* was believed to be associated with heartwater in South Africa.

In the summer of 1868, a disastrous epizootic occurred in Illinois and Indiana, following the importation of apparently healthy cattle from Texas and other southern states. Many herds were wiped out, and at least 15,000 native cattle died. The most conspicuous features of the disease, which ran an acute course, were high fever and hemoglobinuria. Death occurred within one week after onset, and the overall fatality rate was about 90 percent. The disease had probably been introduced into the more southerly American colonies in the 17th century by cattle imported from the Spanish West Indies and Mexico. The infection had spread until a high degree of herd immunity prevailed over a wide area of the South, although cattle to the north and east of this region remained susceptible.

The devastating epizootic of *Texas fever* — as the disease was called — began in June near Cairo, Illinois; it was soon reported from various parts of Illinois and Indiana. Early in August, dead or dying animals were discovered in shipments destined for New York. The problem then assumed a new significance, for the issue was no longer confined to economics. The possibility of a public health hazard from human consumption of the butchered cattle had to be considered. Over the next quarter-century, a group of veterinary and medical scientists working under governmental auspices struggled with the mysteries of Texas fever. There was general agreement on certain characteristics of the disease: (1) infection was carried only during warmer weather, (2) the infection did not pass directly from southern to northern cattle but via ground infected by migrants over which susceptible natives later passed (3) at least 30 days elapsed before exposed cattle became sick, and (4) northern cattle sick with Texas fever did not transmit the disease to other cattle.

Of course, there was a tick theory that is related to us from an 1871 Commissioner's (Dr. John Gamgee) Report. It noted:

> Texas cattle are covered with ticks

and

> the tick theory has acquired quite a renown during the past summer.

It added:

> a little thought should have satisfied anyone of the absurdity of this idea. Southern cattle are affected with a malady that is not inoculable, that is not propagated by the bites of insects.

Even Dr. Daniel E. Salmon, the Director of the Bureau of Animal Industry, in charge of the investigations, wrote in 1881:

> One of the most widely spread opinions in regard to the causation of Southern fever is the pathogenic influence of the ticks with which Southern cattle are generally covered. The acceptance of this view is simply an evidence of the desire of human mind to explain the origin of mysterious phenomena.

Later, he continues:

> The tick theory scarcely explains a single one of the many peculiar phenomena of the disease . . . the post-mortem examination plainly indicates the cause of the disease to be an agent taken into the circulation, and causing the most important changes in the composition of the blood.

Well, in the summer of 1886, Dr. Theobold Smith discovered the infectious agent, now known as *Babesia bigemina*, in the form of small, round bodies, perhaps 1 micron in diameter, in the red blood corpuscles of affected cattle. Shortly thereafter, in 1889 and 1890, he and his associate Dr. F. L. Kilborne solved the complex riddle of the transmission of this agent by the cattle tick, *Boophilus annulatus*. Their discovery was the first instance in history in which the transmission of a protozoan parasite by an arthropod vector was observed.

These findings led to intensive tick eradication campaigns, and by 1960, the United States was declared virtually free of *Boophilus*.

At about the same time the riddle of Texas fever was solved, another disease in humans — often fatal — was encountered by the pioneers as they were pushing their way westward through the Rocky Mountain range. Known since 1873, the disease was referred to as "Mountain fever," "Black Fever," "Black Measles," and "Blue Disease." It was especially feared in the Bitter Root Valley of western Montana where between 1873 and 1910, 295 cases with 190 deaths were recorded. Because of its early detection in the Rocky Mountain region and because of a rash in the form of red-purple, black blotches, the disease was named Rocky Mountain spotted fever.

An old Indian legend has it that a chief of the Nez Perce tribe periodically warned his people of the evil spirits that seemed to visit the west side canyons of the Bitter Root Valley, especially in spring.

As early as 1902, the hypothesis was developed that Rocky Mountain spotted fever was caused by an agent similar to the protozoan causing Texas cattle fever. This agent was said to be present in the blood of ground squirrels from where it was transmitted to man by the bite of the wood tick, *Dermacentor andersoni*.

Let us now briefly pause and listen to the clinical record of Mrs. Frank Doolittle, age 18, who lived up Lolo Creek — one of the Bitter Root's west side canyons. The year is 1903.

> On April 12, Mrs. Doolittle was with husband with team of horses in a small grove of poplars 300 yards north of her residence. On the evening of April 13, a large red tick was found fast under her arm and removed with some difficulty. On the following day, April 14, the wound was sore and swollen, as were also the glands in the axillary space. On April 19, the soreness became much worse, and shooting pains began radiating from

> the axilla through the shoulder, down the arm and side of the body. Patient had severe chills, followed by high temperature and aching pains in back. On the evening of April 22, spots began to appear first on the wrist and ankles. On the morning of April 24, spots were well developed all over her body, being of the small petechial type and quite rosy in appearance. The patient was examined again April 26 by Dr. Wilson. The conditions were the same, except the patient was more restless. Mrs. Doolittle died at 10 o'clock in the morning of April 27.

In 1906, Dr. Howard Taylor Ricketts of the University of Chicago came to Montana and initiated studies to confirm or disprove the hypothesis that a protozoan agent — similar to that of Texas fever — caused the disease. Ricketts could not demonstrate a protozoan agent. Instead he succeeded in infecting guinea pigs and monkeys by inoculating them with patients' blood. He also proved that the wood tick, *Dermacentor andersoni*, was the vector. He not only found infected ticks in nature, but also demonstrated that the infectious agent — unknown to him — was maintained transstadially and transovarially in ticks. In 1909, Ricketts referred to the agent as

> "an organism which appears typically as a bipolar staining bacillus of minute size in tick tissues and tick eggs."

Ricketts was unable to complete his work on spotted fever. While investigating typhus in Mexico, he concontracted the disease and died in 1910. In 1919, the causative agent of spotted fever was named *Rickettsia rickettsii* in recognition of Ricketts' contributions.

The severity of Rocky Mountain spotted fever, and the research activities initiated by Dr. Ricketts, (who also provided a broad outline of how to attack and control the spotted fever problem) led to the establishment of the Montana Research Laboratory in Hamilton to develop tick control and a vaccine for the protection of people exposed to ticks. Eventually, in 1931, the laboratory was purchased by the Federal Government for research on spotted fever and increased vaccine production, which had been underway since 1925. During 1910 through 1930, an average of 248 cases of spotted fever were reported annually (ranging from 108 to 596). The fatality rates varied according to localities. In Idaho, the rate was as low as 5 percent, whereas in western Montana as many as 90 percent of the patients died. The yearly incidence did not change significantly until 1944 when the number suddenly dropped to 65; it has been below 50 ever since.

In 1938, it became apparent that many more cases of spotted fever occur in the eastern and southeastern regions than in the Rocky Mountain region. In fact for the past 20 years, more than 95 percent of all cases occurred in the East.

With the advent of effective broad spectrum antibiotics (chloramphenicol and tetracyclines in 1948), the number of recognized cases of spotted fever decreased to a low of 199 with 10 deaths in 1959. Spotted fever was no longer regarded as a disease of public health significance, and there was little interest in continuing research into the many unsolved ecologic, epidemiologic, and diagnostic problems of the once feared illness.

In 1960, however, the morbidity began to increase and has been doing so ever since. It reached a record high in 1981, with 1,175 cases reported to the Center for Disease Control (CDC) in Atlanta. A sharp drop to 979 cases with 35 deaths occurred in 1982.

Spotted fever is still a measurable public health problem and there are still many questions unanswered, particularly those related to the survival and distribution of the causative agent *R. rickettsii*, in nature.

I will mention only a few studies under way. Tick rickettsial surveys in many regions of this country have revealed at least four rickettsial agents closely related to, yet distinctly different from, the spotted fever agent, *R. rickettsii;* as far as we know, they are nonpathogenic for man (*R. montana*, *R. rhipicephali*, *R. bellii*, and WB-8-2) from whom the only strains isolated so far have been *R. rickettsii*.

Is it not puzzling that in areas with a high incidence of spotted fever, such as North Carolina, Long Island, and even in western Montana, the prevalence of ticks infected with *R. rickettsii* may be nil or far below 1 percent, whereas the percentage of ticks carrying the closely related, nonpathogenic rickettsiae may be as high as 15 percent?

On Long Island, for instance, a total of 3,872 American dog ticks, *Dermacentor variabilis*, were collected from vegetation where spotted fever had been contracted. We found 221 (5.6%) to harbor rickettsiae — none of these proved to be *R. rickettsii*. In North Carolina, which had the highest incidence of spotted fever for many years, we examined 2,123 ticks. Only one was infected with *R. rickettsii*, whereas 71 carried the nonpathogenic strains.

Similar results were obtained in Connecticut, where since 1965, 25 cases of spotted fever have occurred and where my colleagues Dr. John F. Anderson and Dr. Louis A. Magnarelli of The Connecticut Agricultural Experiment Station are doing an excellent job in identifying the foci of spotted fever and of other tick-borne diseases.

What is the relationship of these nonpathogenic rickettsiae to the agent of Rocky Mountain spotted fever? Is it possible that such strains upon entry into man's body change their antigenic makeup and convert to pathogenic organisms? In other words, are rickettsiae subject to antigenic shift for which we have no evidence in experimental animals?

One may also postulate that these rickettsiae represent derivates of the spotted fever agent, *R. rickettsii*, that have lost their ability to cause disease because of certain as yet undetermined interactions with the tick vector or animal host. They are maintained in the tick population by transovarial transmission only, i.e. the passage of rickettsiae via eggs to the progeny of in-

fected female ticks. A change from virulent to nonvirulent rickettsiae would indeed explain why certain areas once known as dangerous foci of spotted fever, no longer report the disease.

Another interesting and exciting observation made in my laboratory is the phenomenon of *interference* between rickettsiae. Because ticks carrying the nonpathogenic rickettsial organisms cannot be infected with the disease-producing *R. rickettsii*, a tick population harboring the nonpathogenic rickettsiae will never play a role as vectors of spotted fever. *Interference* explains the absence of *R. rickettsii* from many areas that otherwise contain all factors necessary for disease transmission. In the Bitter Root Valley of western Montana, for instance, practically all spotted fever cases occurred among residents on the west side or among persons exposed to ticks and bitten by ticks from the west side of the valley (remember the legend of the Indian chief!). On the other hand, many persons have been bitten by east side ticks, but none has contracted spotted fever. Similarly, *R. rickettsii*, with one exception, has never been recovered from ticks collected on the east side of the Bitter Root Valley.

This phenomenon of disease focality has been the subject of numerous speculations and investigations, none of which led to a reasonable explanation until we found that up to 80 percent of ticks on the east side harbor a rickettsial organism that interferes with and inhibits the development of the pathogenic *R. rickettsii*. The mechanism of this interference is still under investigation.

Of the 250 species of ticks belonging to the genus *Ixodes*, 35 are known to occur in the United States. Although some have been considered potential vectors of human and animal pathogens, until recently, none has been associated with a specific illness. In 1969 and for several years thereafter, human babesiosis — a rare disease of man — was recognized on Nantucket Island, Martha's Vineyard, and on Shelter Island. The causative agent, the protozoan *Babesia microti*, was readily identified as the causative agent and was thought to be transmitted to man by the nymphal stages of the deer tick, *Ixodes dammini*. This assumption was supported by Dr. Andrew Spielman from the Harvard School of Public Health who showed that *I. dammini* can be infected readily with *B. microti* and is capable of transmitting it to experimental animals. He and his associates also identified the white-footed deer mouse, *Peromyscus leucopus*, as the natural source of infection for ticks on Nantucket. Indeed, *B. microti* had been found there as early as 1937 and quite likely had occurred there long before, maintained in a rodent-tick cycle. Why then the sudden spillover into humans? It is said that *I. dammini* had been introduced into Nantucket along with deer imported from Michigan in the mid-1930s to increase the local deer population. As a result, a large deer herd did develop and along with it a tick population that attacks man residing or vacationing on the island.

Babesiosis in man is a flulike disease characterized by weakness, fever, chills, earaches, and pain in muscles and joints — manifestations that develop 7 to 10 days after an infectious tick bite. The disease usually is nonfatal unless it is contracted by persons who have had their spleens removed. The full spectrum of human babesiosis in this country is not known. About 150 cases have been reported since 1969. However, *B. microti*, the causative agent, has been identified not only in Massachusetts but also in widely separated areas such as California, Utah, and New York. Similarly, the tick vector, *I. dammini*, is widespread throughout the East and Midwest. Other man-attacking ixodid species closely related to *I. dammini* are the Western deer tick, *I. pacificus*, in the West and the black-legged tick, *I. scapularis*, in the South and Southeast. Although these species have not as yet been shown to play a role in the distribution and maintenance of *B. microti*, the possibility of additional foci of human babesiosis exists and should not be overlooked.

The remaining portion of this Bulletin will be devoted to still another tickborne affliction of man — a disease known in Europe since the beginning of this century but not recognized in this country before 1969. The Europeans call it *Erythema chronicum migrans* — or ECM — a disease contracted by the bite of the ixodid tick, *Ixodes ricinus*, the most common tick in many parts of Europe.

ECM is characterized by a ringlike skin lesion with advancing indurated borders and central clearing radiating from the site of the tick bite. It is associated with fever, general malaise, swelling of the regional lymph nodes, varying degrees of headache, and occasionally meningitis and facial paralysis. Untreated, the disease may last for months or years. Penicillin and tetracyclines are effective antibiotics that treat ECM within days.

The causative agent of this illness has remained unknown, although tick-transmitted toxins, and various bacterial agents, including spirochetes and rickettsiae, have been considered.

The first case of ECM in the United States was in a physician who had been bitten by a tick while hunting grouse in north central Wisconsin. Four additional cases occurred between mid-July and mid-August 1975 in southeastern Connecticut. None of these four patients recalled specific insect or tick bites.

The same year, the Connecticut State Department of Health Services received a call from a mother concerned about an outbreak among 12 children in the town of Old Lyme of a disease diagnosed as juvenile rheumatoid arthritis. Her call and that of another woman who contacted the Yale Rheumatology Clinic about an "epidemic" of arthritis in her family, led to clinical and epidemiological investigations headed by Dr. Allen Steere from the Yale Medical School, and subsequently to the description of Lyme arthritis and Lyme disease. Although first described to be different from and far more severe than the Euro-

pean ECM, recent comparative clinical and serological investigations suggest Lyme disease is similar, if not identical to ECM.

Epidemiological evidence supported by ecological investigations by my colleagues from the Department of Epidemiology and Public Health of the Yale University School of Medicine incriminated the ixodid tick, *Ixodes dammini,* as the vector. The causative agent, as in Europe, remained unknown until September 1981, when I discovered it to be a spirochete.

Since this discovery represents one of the highlights of my professional career, I have no reservations in sharing it.

For several years, I have been collaborating with Dr. Jorge Benach from the State of New York Department of Health in studies related to spotted fever on Long Island. One of the questions under investigation concerned the potential role of the deer tick, *I. dammini,* as a vector of the spotted fever agent, *R. rickettsii.* Although we had already tested several hundred ticks without finding evidence of rickettsial infection, one additional shipment was received in September 1981. While examining the tick blood (hemolymph) for rickettsiae, I twice encountered the advanced stages of a microfilaria. Eager to find the younger developmental stages of this nematode, I dissected both ticks and prepared smears. I did not find what I was looking for, instead I detected poorly-stained spirochetes associated with the gut lining. Dissection of additional ticks revealed similar spirochetes in 77 of 126 specimens. These were subsequently isolated in cultures and serologically shown to react with antibodies of former Lyme disease patients. Independently with Dr. Steere and Dr. Benach and their respective associates, we recently confirmed the spirochetal etiology of Lyme disease by isolating from patients spirochetes indistinguishable from those recovered from the ticks.

In addition, we also have isolated spirochetes identical to those recovered in this country, from the European tick, *I. ricinus.*

At present, several studies including those by Drs. Anderson and Magnarelli of The Connecticut Agricultural Experiment Station are clarifying the natural history of this interesting agent by determining (1) the sources for infecting ticks in nature; (2) the development or behavior of the spirochete in the tick, and (3) the mode of transmission by its tick vectors. From 1975 through 1979, 512 cases of Lyme disease were recorded. Most were contracted within the range of the deer tick, *I. dammini.* This area extends from the southernmost tip of Delaware northward, primarily in coastal areas, through Pennsylvania, New Jersey, New York, Connecticut, Rhode Island, and Massachusetts. The tick is also found in southern Ontario and in the North Central states of Wisconsin and Minnesota.

Lyme disease also occurs in the west where in 1978 the first case was seen in Sonoma County, California. There, and in Oregon, we recently isolated from the Western deer tick, *I. pacificus* — a vicious biter of man — spirochetes identical to those detected in *I. dammini.*

According to Dr. George P. Schmid from the CDC in Atlanta, cases of Lyme disease have been reported also from Texas, Arkansas, and Georgia. In these states neither *I. dammini* nor *I. pacificus* occurs, but the closely related *I. scapularis* may well become an efficient vector to man once the causative agent has been introduced.

Lyme disease or tickborne ECM — whatever you may want to call it — is spreading rapidly. In 1980, 216 cases came to the attention of CDC; in 1982 the number recorded was more than 400. This number undoubtedly will increase as practicing physicians become more aware of the clinical manifestations of this disease. Indeed, Lyme disease may well become the number one tickborne disease in the United States.

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