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Tick-borne diseases in the United States: Rocky Mountain spotted fever and Colorado tick fever

A review

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Summary

The historical, clinical, ecological, and epidemiological features of Rocky Mountain spotted fever and Colorado tick fever, the two important tick-borne diseases in the United States, are reviewed. Rocky Mountain spotted fever, once considered a disease of the past, has again become a measurable public health problem. Its nationwide incidence has steadily increased since 1960 and has reached record proportions in 1976. The various factors responsible for this trend as well as for the mortality rates, which in spite of availability of effective antibiotics ranges from 5 to 10 per cent, are discussed.

Education of the public about ticks and their potential role as vectors of *Rickettsia rickettsii* and/or Colorado tick fever virus, and about the clinical manifestations of Rocky Mountain spotted fever, is considered the best means for preventing high incidence and mortality from these diseases.

Introduction

Of the diseases caused by tick-borne pathogens occurring in the United States, Rocky Mountain spotted fever and Colorado tick fever are of greatest significance to public health. During recent years, the incidence of both diseases has increased, and Rocky Mountain spotted fever, once considered a "disease of the past", has again become a measurable public health concern. At the same time, research interest, in spotted fever particularly, has been restored and has provided not only more sensitive diagnostic tools but also procedures necessary for a better understanding of the dynamics of infection in nature.

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It is not the purpose of this article to present a complete review of the voluminous literature on these important tick-borne disease agents in the United States, but rather to discuss their present status in the light of the most salient historical, clinical, ecological, and epidemiological features. In the chapters that follow, the two diseases are treated separately with a final chapter devoted to prevention and control of both diseases. For additional information handbooks, monographs, and reviews should be consulted [5, 16, 17, 34, 36, 37, 41, 50, 56, 76, 85, 110, 118].

Rocky Mountain spotted fever

Definition: Rocky Mountain spotted fever is a relatively severe, self-limited disease caused by *Rickettsia rickettsii* transmitted to man by various species of ixodid ticks. It is characterized by fever, headache, bone and muscle pains, and a generalized rash that appears first on the wrists and ankles and frequently becomes hemorrhagic [5].

Before 1930, the disease was thought to occur only in the Rocky Mountain regions. However, a survey of typhus-like diseases in the eastern part of the country revealed the presence of spotted fever in the Atlantic seaboard states [94]. Since then, it has been reported from all the states except Maine, Vermont, Alaska, and Hawaii. Thus, the name "Rocky Mountain spotted fever" has

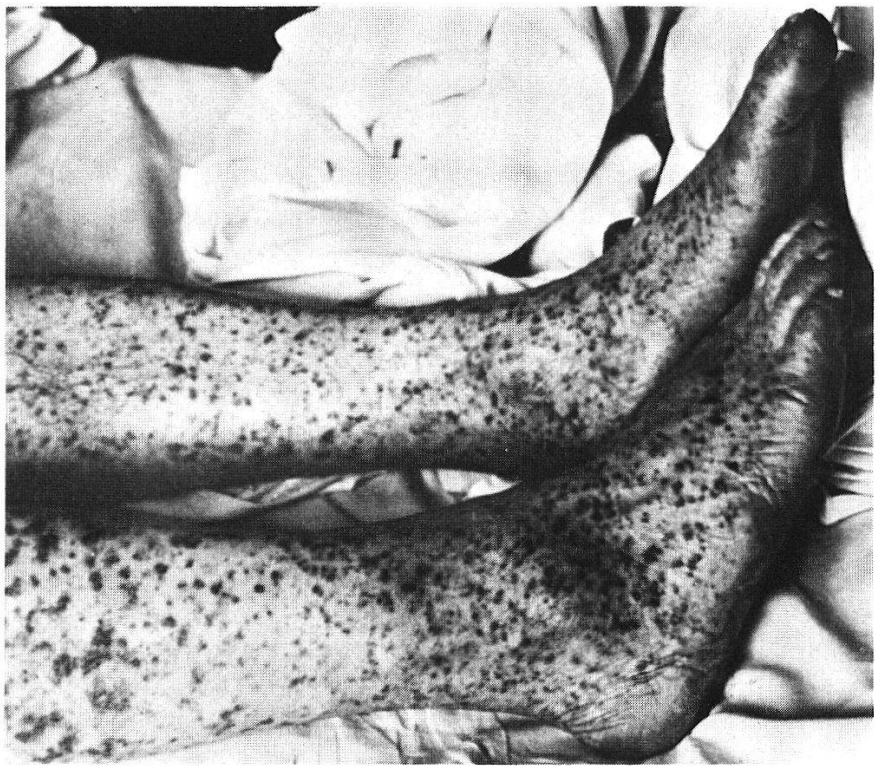

Fig. 1. Typical rash on feet of patient suffering from Rocky Mountain spotted fever (photograph from files of Rocky Mountain Laboratory).

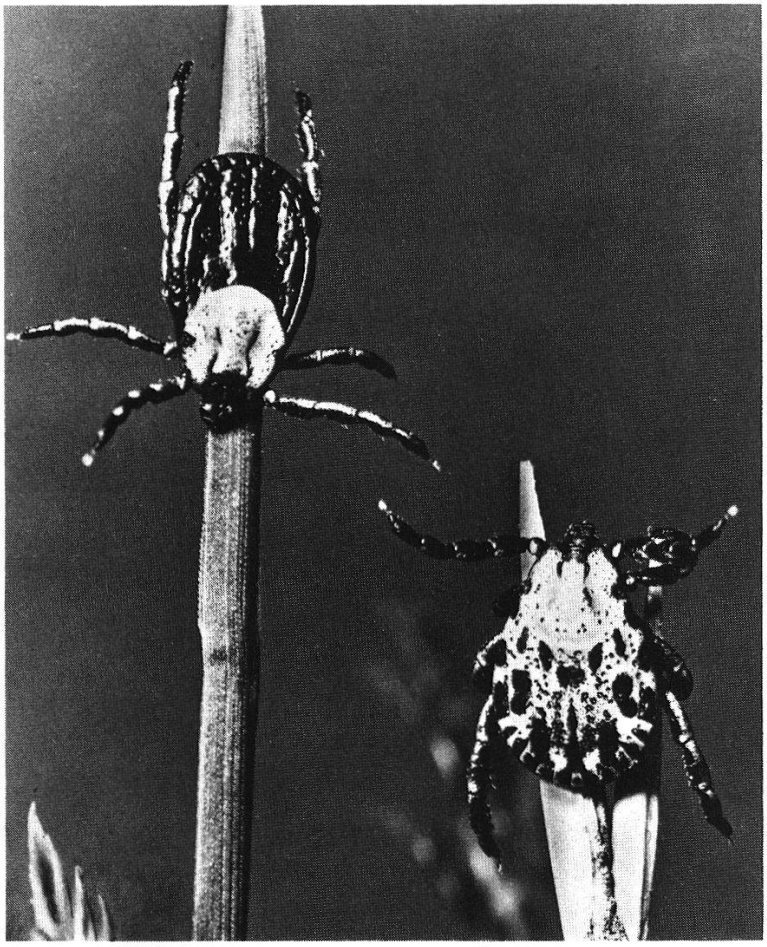

Fig. 2. Female and male of the Rocky Mountain wood tick, *Dermacentor andersoni.*

become a misnomer. To avoid the misleading geographic reference, some investigators refer to it as "tick-borne typhus" [77].

History: The disease was known to occur among settlers of the Northwestern United States and towards the latter part of the last century was recognized as a distinct clinical entity [69]. Because of its early detection in the Rocky Mountain regions, and because of the rash in the form of red-purple, black blotches (Fig. 1) it was named "Rocky Mountain spotted fever". As early as 1902, the hypothesis was advanced [115, 116] that the disease was caused by a piroplasma-like agent (*Piroplasma hominis*) present in Columbian ground squirrels and transmitted to man by the wood tick, *Dermacentor andersoni.* In 1906 Ricketts initiated investigations to confirm or disprove this hypothesis, but he failed to demonstrate or isolate a protozoan agent in blood smears or from blood samples of patients. However, he infected guinea pigs and monkeys by infecting them with patients' blood [87], and, independently from King [62], proved that the wood tick, *D. andersoni,* was the vector [88] (Fig. 2). Ricketts not only found infected ticks in nature, but also demonstrated that the infectious agent, unknown to him, was maintained transstadially and transovarially in ticks [89]. These observations suggested that the etiologic agent of spotted fever

was maintained in a cycle between the tick and one or more of its host animals. In limited experiments, Ricketts proved the susceptibility of several rodents to the spotted fever agent and showed that ticks feeding on them may become infected and in turn may transmit the infectious agent to normal guinea pigs [90]. 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 [91]. Ricketts was unable to complete his studies; while investigating typhus in Mexico in 1910, he contracted the disease and died. Nevertheless, his contributions were fundamental to our present knowledge of the causative agent, the tick vector, the mode of infection, and the immunologic features of the disease. He also provided a broad outline of how to attack and control the spotted fever problem. Wolbach in 1919 described [117] the etiologic agent, and in recognition of Ricketts' contributions named it *Dermacentroxenus rickettsi,* now known as *Rickettsia rickettsii* [71].

Clinical description of the disease: Rocky Mountain spotted fever in man [5, 56, 95] has an incubation period that varies from 2 to 14 days. Onset usually is sudden with severe headache, chills, general aching, nausea, and fever. The rash that appears between the second and sixth day of fever characteristically begins on wrists, ankles, palms, soles, and forearms, and later extends to the buttocks, trunk, neck, and face. Initially macular, it becomes maculopapular (Fig. 1) and petechial. Thrombocytopenia and coagulation disorders occur in almost 50 percent of patients. Agitation, insomnia, delirium or coma may occur at the end of the first week of fever. Bronchopneumonia, otitis media, and parotitis caused by bacterial infections are the most common complications. Occasionally hemiplegia and peripheral neuritis occur. Thromboses of major blood vessels which may lead to gangrene of the limbs occur in untreated patients. Fever begins to decrease by the end of the second week but complete recovery requires weeks or months, especially in untreated patients. When the disease is fatal, death occurs near the end of the second week as a result of toxemia, vasomotor weakness, shock, or renal failure.

Diagnosis and treatment: Early diagnosis of spotted fever based on clinical grounds alone is difficult. In its initial phases, the disorder resembles other febrile illnesses, such as measles, acute bacterial and viral meningoencephalitis and Colorado tick fever. However, the diagnosis of spotted fever should be considered if fever, chills, headache, and myalgia are seen in a person from an area where the disease is endemic, especially if a history of tick exposure or tick bite is obtained. Development of the petechial rash, especially if it appears first on the palms and soles, is virtually diagnostic and if present, immediate treatment with broadspectrum antibiotics should be started. Any delay could lead to serious complications, and even death. Occasionally, the maculopapular rash is indistinct or absent, especially in severely affected persons who may die as early as 7 days after onset of illness [96].

A clinical diagnosis can be confirmed either by isolation and identification of the causative agent, or by serologic procedures [41]. *Rickettsia rickettsii* may be recovered from a febrile patient's blood by injecting blood suspensions into 5 to 7-day-old embryonated hen's eggs [41, 112], guinea pigs, meadow voles, or into a variety of primary and established cell cultures [51]. Death of chick embryos 4 to 10 days after inoculation suggests rickettsial growth which varies in density from one isolate to another. Guinea pigs respond to intraperitoneal inoculation of infectious blood with fever and scrotal reactions characterized by swelling and reddening. Virulent strains of *R. rickettsii* produce in this animal severe, often fatal infections associated with hemorrhagic and necrotic lesions involving the scrotum and sometimes the footpads and ears. Meadow voles (*Microtus pennsylvanicus*) also are extremely susceptible to *R. rickettsii*; 4 to 6 days after intraperitoneal inoculation massive growth of rickettsiae is seen in the tunica vaginalis [22].

Many serologic procedures have been described [41] for demonstrating specific antibodies in the blood sera of persons sick or convalescing from Rocky Mountain spotted fever. The Weil-Felix reaction and the complement-fixation (CF) test are most commonly used because the diagnostic reagents required are commercially available. *R. rickettsii* elicits antibodies that may agglutinate OX-19 and OX-2 strains of *Proteus vulgaris* in the Weil-Felix reaction. A four-fold increase in titer in a convalescent serum as compared to serum taken during illness is considered positive. However, the Weil-Felix reaction is nonspecific and provides only presumptive evidence of a rickettsial infection. A negative test, on the other hand, does not exclude rickettsial infection.

The CF test with soluble antigen is far more reliable, although CF antibodies to *R. rickettsii* appear slowly and are usually not demonstrable until the end of the second week of illness [96].

More sensitive than both the Weil-Felix and the CF test are the recently developed microagglutination (MA) [45] and micro-immunofluorescence tests [81]. Because both procedures require reagents available only to research laboratories, their general use is limited. Comparable sensitivity has been reported with an indirect hemagglutination test [98]; its epidemiological usefulness remains to be demonstrated because of its inability to consistently detect antibodies in animal sera. Most persons affected with spotted fever, especially early in the disease, respond well to the broad-spectrum antibiotics tetracycline, oxytetracycline, and chlortetracycline [64]. These antibiotics suppress the development of the rickettsiae while the patient overcomes the disease. For a 70 kg adult, an initial dose of 2 g is followed by an oral dose of 250 mg every 6 h until fever subsides. Usually headache and other toxic signs abate within 24 to 48 h, the rash fades in 2 to 3 days, and the body temperature returns to normal in 3 to 4 days. Chloramphenicol is also very effective but is usually not recommended because of possible dangerous side effects, such as blood dyscrasias. In addition

to antibiotic treatment, symptomatic treatment including administration of oral analgesics and intravenous infusions of saline, glucose, plasma, or whole blood may be required.

Ecology of Rickettsia rickettsii: As suggested by Ricketts, the natural history of the spotted fever agent is closely associated with ticks and their host animals. The wood tick, *Dermacentor andersoni,* and the American dog tick, *D. variabilis,* are the important vectors of *R. rickettsii* to man. The lone star tick, *Amblyomma americanum,* also has been incriminated as a vector. Its distribution, however, lies within that of *D. variabilis,* and there are only few reports with direct evidence for regarding this tick as a vector [75]. A short description of the biology of each of these ticks follows. For more detailed information, the reader is referred to general articles about ticks [7, 14, 84], and to publications dealing specifically with *D. andersoni* [33], *D. variabilis* [99–102, 104–106], and *A. americanum* [55, 103].

The distribution of the wood tick, *D. andersoni,* is limited to the mountainous regions of the western United States and to the southern parts of British Columbia, Alberta, and Saskatchewan in Canada. This tick is not host specific and practically any mammal may be attacked. The larvae and nymphs feed on a large variety of rodents and other small mammals, such as rabbits and hares. Nymphs feed occasionally also on man. The adults feed on large domestic and wild animals such as cattle, horses, goats, sheep, elk and deer, as well as on man. Several animals of intermediate size, such as lagomorphs, porcupines, badgers, etc. serve as hosts for all three developmental stages.

D. andersoni has a two-year cycle that may be described as follows: with the disappearance of the snow in spring, the adult ticks leave their hibernation places and climb to the tips of low vegetation where they wait for an opportunity to attach to a host (Fig. 2). Spring and early summer are the feeding periods of adult ticks. Once the relative humidity decreases with the advent of warmer weather, as in June and July, the activity of adults ceases and those that have not found a host disappear under ground cover to pass the late summer, fall, and winter. Ticks that attach to a host feed for 5 to 9 days and mating takes place during the last days of feeding. Replete female ticks drop to the ground, and, about 7 days later, begin to oviposit 5,000 to 7,000 eggs. These hatch after an incubation period of about 40 days, and the larvae disperse to attach a few weeks later to small animals.

After 2 to 6 days of feeding, the engorged larvae drop, become inactive and molt into nymphs. These usually do not feed during the hot summer; they hide until the following spring when they attach to small rodents for a blood meal. After feeding for about 7 days, they drop and molt into adults. The majority of newly-emerged adult ticks do not seek a blood meal during the same year; they hide under waste or near the soil surface where they remain through summer, fall, and winter until the next spring when they reappear and search for a blood meal. Under laboratory conditions, the life cycle of *D. andersoni* is completed

within a single year, and there is evidence that this may occasionally occur also in nature.

The American dog tick, *D. variabilis*, occurs in the Great Plains regions and east to the Atlantic coast, in California, and in several other western states [113]. The host range of its immature stages is much narrower than that of the wood tick. Larvae and nymphs feed primarily on voles and mice, particularly meadow voles (*Microtus* spp.) and white-footed mice (*Peromyscus* spp.) and to lesser extent on squirrels and lagomorphs. The dog is the principal host of adult ticks, although cattle, horses, hogs, sheep, coyotes, raccoons, wildcats, badgers, foxes, skunks, and occasionally also rabbits serve as hosts.

Larval activity of *D. variabilis* has two seasonal peaks, one in April or May and another in August or September. The first peak represents overwintered larvae that hatched the previous year. The second peak is caused by larvae that hatched in early or late summer. Nymphal activity begins in March or April, increases during July and August, and decreases in September or October. Again it appears that activity before June is by nymphs from the previous year, whereas that after June is by ticks derived from larvae of the same season. Activity of adults begins in March and April, reaches a peak in June or July, and declines until it ceases in August or September.

The lone star tick, *A. americanum*, is primarily a woodland species and is distributed from central Texas, north to Missouri, and east in a broad belt to the Atlantic coast, including northern Virginia. All of its developmental stages feed on man and attack deer, cattle, horses, and dogs. The immature stages feed also on rabbits, squirrels, foxes, raccoons, skunks, and a variety of birds, particularly quail, turkeys, and other poultry. The tick is active from early spring until fall. Unfed adults appear in February or March, and are most abundant in April through June. Activity ceases by the end of July. Nymphal activity, noted as early as March, results from overwintered nymphs and from ticks that overwintered as engorged larvae. Nymphal activity in August results from ticks that molted from larvae engorged in June or July. Larvae become active during June and July and reach their peak abundance in August and September. Those that engorge during the fall overwinter in the engorged state, those that fail to find a host, die.

Several other species of ixodid ticks including *Haemaphysalis leporispalustris* [73], *Dermacentor parumapertus* [79], *Ixodes dentatus* [74], *I. brunneus* [9], and *I. texanus* [9] have been found naturally infected with *R. rickettsii* or closely related spotted fever group rickettsiae, but because they rarely attack man they are of little significance in the epidemiology of spotted fever. Nevertheless, these ticks are important in maintaining and distributing rickettsiae in nature. In recent years, rickettsiae, closely related to or identical with *R. rickettsii*, have been recovered also from *Amblyomma maculatum* [21], *Dermacentor occidentalis* [6], *Ixodes scapularis* [28], *I. pacificus* [58], and *I. cookei* [9]. These ticks do attack man and therefore must be considered as potential vectors of *R. rickettsii*.

As yet, however, no *bona fide* spotted fever cases have been reported as a result of bites from these tick species.

The main mechanisms by which ticks become infected with *R. rickettsii* consist of a) simultaneous feeding of normal and infected immature ticks on susceptible host animals, particularly young rodents, and b) transovarial infection, i.e. the passage of rickettsiae through the eggs of infected female ticks to their progeny.

As suggested by Ricketts, one or more of the tick's host animals may serve as a source of the causative agent. During studies to identify reservoirs, strains of *R. rickettsii* were isolated from the following animals: meadow voles (*Microtus pennsylvanicus*) [8, 53], a pine vole (*Pitymys pinetorum*) [8], a white footed mouse (*Peromyscus leucopus*) [8], a cotton rat (*Sigmodon hispidus*) [8], cottontail rabbits (*Sylvilagus floridanus*) [8, 97], opossum (*Didelphis marsupialis virginiana*) [8], a snowshoe hare (*Lepus americanus*) [29], chipmunks (*Eutamias amoenus*) [29], and golden-mantled ground squirrels (*Spermophilus lateralis tescorum*) [29].

Serologic evidence of exposure to *R. rickettsii* has been recorded for many other mammals and birds that serve as blood donors of tick vectors, and a variety of hosts including rodents [25, 67], lagomorphs [25, 65], and other mammals [8] as well as birds [66] have been shown to experience more or less prolonged rickettsemias following experimental injection of virulent strains of *R. rickettsii.* In susceptible animals, rickettsiae circulate for 5 to 8 days, rarely longer. Rickettsemias of 3 to 4 weeks duration were reported for opossums [8].

In a limited quantitative study [25] in which rodents were exposed to infectious tick bites, the minimal dosage of rickettsiae required to infect 50 percent of larval *D. andersoni* ranged between 10 and 100 guinea pig infectious doses per 0.5 ml of blood. Meadow voles, Columbian ground squirrels (*Spermophilus columbianus columbianus*), golden-mantled ground squirrels, chipmunks, and snowshoe hares responded with rickettsemias of sufficient degrees to infect normal ticks, especially when the ticks were allowed to feed during periods of high rickettsial concentrations in the blood. Dogs, particularly puppies, are susceptible to infection by *R. rickettsii* and respond with rickettsemias of sufficient concentration to infect a low percentage of normal ticks feeding simultaneously [2, 86]. The significance of dogs as reservoirs for infecting *D. variabilis,* however, is minor, for only adults of this tick feed on dogs.

The fact that ticks have to ingest a high concentration of rickettsiae before they become infected, suggests that the rickettsiae in the tick's digestive system face physical or chemical barriers that can be surmounted only when rickettsiae are present in large numbers. The nature of such barriers remains to be investigated, and one can only speculate that digestive enzymes, for instance, may be responsible for inactivation of large numbers of rickettsiae.

As early as 3 to 5 days after ingestion, rickettsiae are found in hemocytes. By the time a fed larval or nymphal tick has molted, i.e. from 10 to 15 days after

repletion, all tissues are infected with rickettsiae which multiply in the cytoplasm and occasionally also in nuclei of infected cells [13, 19, 117]. Rickettsiae in oogonia and oocytes of female ticks may lead to transovarial infection. The extent to which such transmission occurs depends on the degree of rickettsial infection in ovarian tissues. When the infection is heavy, transmission and filial infection rates of 100 percent regularly occur, when it is mild, the rates vary [20].

Because large numbers of tick host animals are susceptible to *R. rickettsii* and transovarial infection occurs, rather high infection rates would be expected in ticks in nature. On the contrary, infection rates are low. In the Bitter Root Valley of western Montana for example, they vary from less than 1 to 5 percent of *D. andersoni;* the highest rate ever recorded was 13.5 percent [78]. Infection rates in *D. variabilis* also vary. In South Carolina, 47 (4.6%) of 1,024 specimens were positive for rickettsiae [18], and in Jefferson County, Alabama, where 12 cases of spotted fever had occurred, 11 (10.4%) of 106 *D. variabilis* removed from dogs were positive [26].

Although hundreds of *A. americanum* from endemic spotted fever areas have been examined by the reviewer, no *bona fide* strains of *R. rickettsii* have been found in these ticks. However, 194 (41.9%) of 482 ticks of this species from Arkansas [28], 64 (11.7%) of 545 from Tennessee [22], and 15 (17%) of 88 from South Carolina [18], contained a rickettsia similar to but distinct from *R. rickettsii.*

Transmission of *R. rickettsii* to man, in most instances, is through the bite of an infected tick acquired either during activities in tick-infested areas, or brought into homes by household pets, particularly dogs. The bite of an infected tick usually is not infective unless the attached tick has been feeding for at least 10 h. In starving ticks, the rickettsiae appear to be in an avirulent phase; they become virulent by the tick's prolonged attachment or ingestion of blood [107]. This phenomenon known as "reactivation" is said to be related to the metabolic state of *R. rickettsii* [52]. Infection may also occur through abraded or even intact skin after contamination by fresh tick feces, crushing infected ticks between fingers while removing them from man and animals, or handling infected or tick-infested wild animals. Aerosol infection from dried tick feces is unlikely because *R. rickettsii* rapidly loses its infectiousness in such material. However, infections via the respiratory tract have been reported, especially among laboratory personnel [59, 83].

Incidence and epidemiology of Rocky Mountain spotted fever: Information about the incidence of Rocky Mountain spotted fever among settlers in the Rocky Mountain regions is incomplete. According to records available at the Rocky Mountain Laboratory, 295 cases including 190 deaths occurred between 1873 and 1910 in the Bitter Root Valley of western Montana alone. During 1910 to 1930, a total of 5217 cases were recorded in the western United States. The annual incidence during that period ranged from 108 to 596 cases and averaged 248 cases. Fatality rates varied with localities. In Idaho, for instance, not more

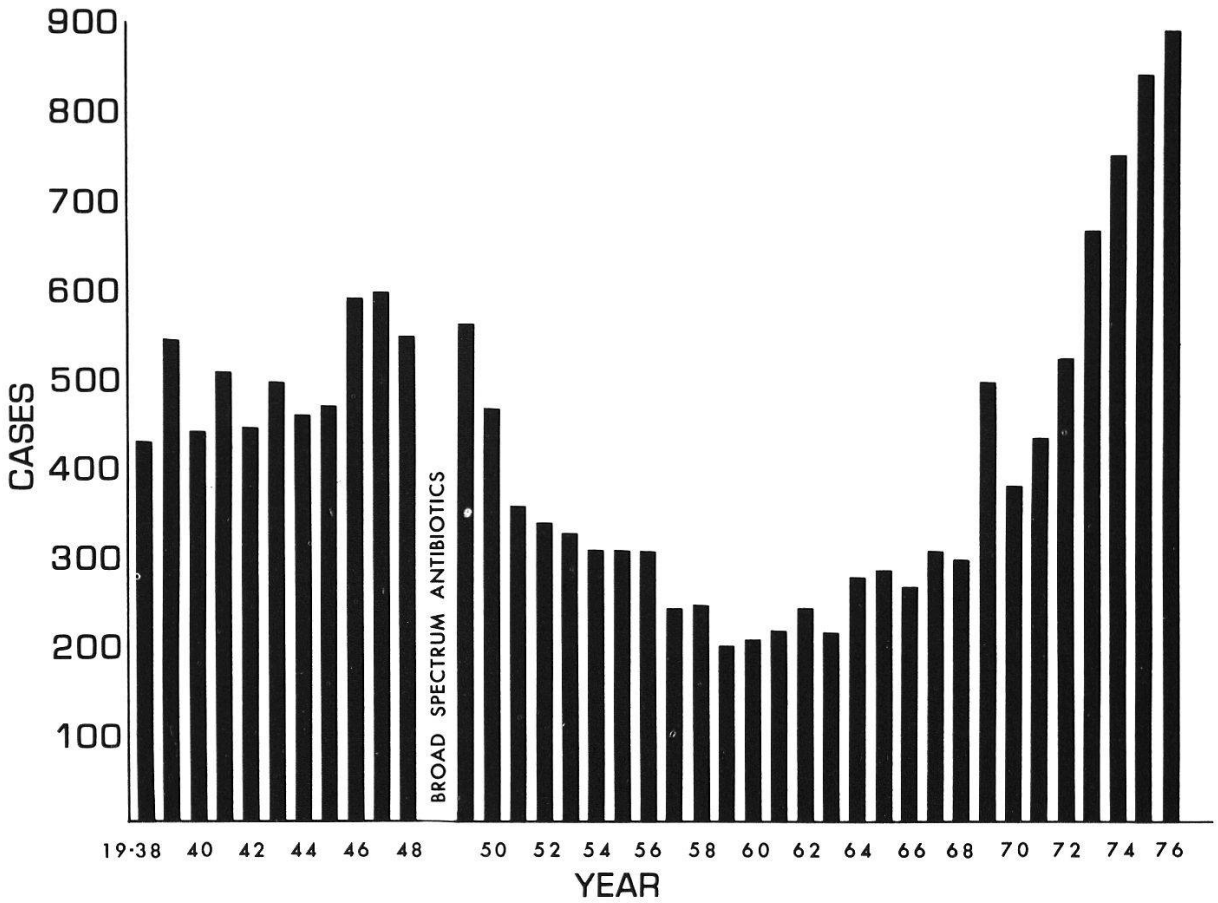

Fig. 3. Rocky Mountain spotted fever (tick-borne typhus) in the United States, 1938–1976 (data for 1975 and 1976 are provisional).

than 5 percent of cases were fatal, whereas in the Bitter Root Valley as many as 90 percent were fatal. From 1931 through 1944, the mortality rates varied from 11.8 to 22.3 percent and averaged 17.6 percent. The incidence did not change significantly in the West until 1944, when the number of annually reported cases decreased sharply to 65; it has been well under 100 ever since.

In 1938, it became apparent that many more cases of spotted fever occurred in the eastern and southeastern United States than in the Rocky Mountain regions. This trend has continued ever since, and in the past 5 years more than 97 percent of all cases came from the eastern parts of the country [70]. In 1948, the broad-spectrum antibiotics, chloramphenicol and tetracyclines, were first used clinically. As a result of their widespread use, the number of recognized cases of spotted fever, including fatal ones, decreased sharply (Fig. 3). A low was reached in 1959, when only 199 cases with 10 deaths were reported. Indeed, spotted fever was no longer considered an important infectious disease, and there was little interest in continuing research into the many still unsolved ecologic and diagnostic problems of this once greatly feared illness.

In 1960, however, the morbidity rates began to increase again and have been doing so ever since, especially in the eastern and southeastern states (Fig.

Table 1. Annual incidence and fatality rates of Rocky Mountain spotted fever in western and eastern Unites States, 1960–1976. Source CDC Morbidity and Mortality Reports (data for 1975 and 1976 are provisional)

Year	U.S. total	Western states[1]	Eastern states[2]	Case fatality rate (nationwide)
1960	204	23 (11.2%)	181 (88.8%)	5.4%
1961	219	24 (10.9%)	195 (89.1%)	5.0%
1962	240	28 (11.6%)	212 (88.4%)	5.0%
1963	216	20 (9.2%)	196 (91.8%)	7.4%
1964	277	24 (8.6%)	253 (91.4%)	6.1%
1965	281	26 (9.3%)	255 (90.7%)	5.6%
1966	268	12 (4.4%)	256 (95.6%)	7.8%
1967	305	20 (6.5%)	285 (93.5%)	9.2%
1968	288	11 (3.8%)	277 (96.2%)	7.3%
1969	498	24 (4.8%)	474 (95.2%)	7.2%
1970	380	12 (3.1%)	368 (96.9%)	7.6%
1971	432	13 (3.0%)	419 (97.0%)	8.3%
1972	523	13 (2.4%)	510 (97.6%)	9.6%
1973	668	20 (2.9%)	648 (97.1%)	5.7%
1974	754	8 (1.1%)	746 (98.9%)	6.5%
1975	844	13 (1.5%)	831 (98.5%)	?
1976	892	10 (1.1%)	882 (98.9%)	?

[1] States west of the 100th meridian
[2] States included by and east of the 100th meridian

3, Table 1). The 668 cases reported in 1973 represented the highest number recorded in a single year up to that time. Since then, the incidence has continued to rise and in 1974, 1975, and 1976 reached 754, 844, and 892 cases, respectively. These data from the Center for Disease Control do not represent the true incidence of spotted fever in the United States. Although spotted fever is a reportable disease, not all cases come to the attention of the Center.

Even though effective antibiotics are available, fatality rates since 1960 have ranged from 5 to 9.6 percent [56, 70] (Table 1). Most of these deaths occur because patients do not seek medical care, the disease is not recognized and treated properly, or specific treatment is delayed.

The decline of spotted fever in the Rocky Mountain regions since 1944, and the alarming increase in the eastern parts of the United States have been subjects of much speculation. Some epidemiologists attribute these changes to a gradual invasion of the eastern United States by *R. rickettsii* from the Rocky Mountain regions, while others postulate that in the West, for unknown ecologic reasons, the causative rickettsia has become avirulent for man. In my opinion, neither argument has any scientific merit. The reasons for the changing status of spotted fever in the United States are closely related to the epidemiology of the disease. In the Rocky Mountain regions, spotted fever was initially an occupa-

tional disease among people settling in enzootic areas. Settlers were continuously exposed to ticks and lived and worked in close association with the animals that are part of the natural cycle of *R. rickettsii.* Once the land was cleared, cultivated, and freed of rodents, tick infestations decreased and concurrently, so did the incidence of the disease. In the Bitter Root Valley, annual rodent extermination campaigns were and still are responsible for the absence of ticks from the cultivated portions of the valley. However, the uncultivated territories bordering this valley remain heavily populated with tick-infested rodents. It is in such areas where even today spotted fever is contracted by persons who, for a short period, become part of the ecologic cycle of *R. rickettsii.*

In contrast, spotted fever in the eastern parts of the country is characterized by high incidence among children and women – a phenomenon related to infestations of household pets, particularly dogs, with the vector tick. Indeed, dogs and cats play an important role in the epidemiology of spotted fever; they are the means by which ticks are brought into homes and human surroundings.

The factors responsible for increased disease incidence are probably associated with the changes in land use that have been occurring during the past 20 years, particularly in the eastern and southeastern parts of the country. Populations have shifted from cities to suburbia (suburbanization), and in many places cultivated land has been allowed to revert to forest for recreational purposes. These changes have again brought people into close contact with the natural foci of disease and have created new tick habitats. In addition, renewed awareness of spotted fever by physicians and the public in general, either as the result of increased incidence or of recent research and educational programs [18], have led to improved surveillance and better reporting [56].

Colorado tick fever

Definition: Colorado tick fever (CTF) is usually a benign disease caused by a virus transmitted to man by the bite of the wood tick, *Dermacentor andersoni.*

History: During early investigations of Rocky Mountain spotted fever, sporadic cases were recognized that differed from spotted fever by the absence of the characteristic skin rash after tick bite [3,116]. Because CTF was thought to occur predominantly in Colorado, it was named "Colorado tick fever " [4], to distinguish it from the more severe Rocky Mountain spotted fever. The etiologic agent was recognized as a virus in 1946, when an isolate was shown to be infectious after it had been passed through a gradacol membrane of 181 nm average/pore diameter [48].

Description of the disease: From 3 to 5 days after tick bite, patients suddenly become ill with chills, headache, severe general muscle aching and fever (up to 40° C). A 2 to 3-day febrile period is usually followed by a remission of similar duration. This in turn is followed by a second 2 to 3-day febrile period. Leukopenia usually occurs during the second febrile period, when the leukocyte

count may fall to 2,000 to 3,000 cells per mm^3. A few patients may develop a faint and transient rash, and involvement of the central nervous system (encephalitis, meningitis) may supervene, especially in children [39, 111].

Diagnosis and treatment: CTF virus has been shown to persist in erythrocytes of patients for as long as 120 days [57] – a phenomenon that facilitates the diagnosis during illness or convalescence. Direct immunofluorescent staining of thick drops of a patient's blood permits reliable and rapid diagnosis [44].

For the isolation of CTF virus from a patient's blood or from ticks, 3 to 4-day old Swiss mice are the animals of choice [72]. Five to 8 days after intraperitoneal inoculation with infectious tissue suspensions, these animals show definite signs of excitability, hyperirritability, and muscular incoordination. Death usually occurs within 48 h after the first appearance of such clinical signs. The virus is identified either by neutralization test in suckling mice, or, more economically, by direct fluorescence microscopy [27, 44]. In addition to suckling mice, various types of primary and established cell cultures have been recommended for the isolation of the virus [82, 119, 120]. For the demonstration of antibodies, a variety of serologic procedures such as neutralization tests in suckling and weanling mice, tissue culture neutralization, plaque-reduction methods, complement fixation, and direct immunofluorescence have been used [43,63]. The indirect immunofluorescence test [43] detects antibodies as early as 10 days after onset of the disease, and is the most sensitive and most economical procedure.

Colorado tick fever usually runs a benign course, and most patients recover within a few days after they become afebrile. Treatment is symptomatic with analgesic drugs given to control myalgia and headache.

Ecology of Colorado tick fever virus: Most cases of Colorado tick fever result from the bite of an infected adult wood tick [37], *Dermacentor andersoni.* No other tick species has been incriminated as a vector to man, although sporadic isolations of CTF virus have been reported from *D. albipictus* [37], *D. parumapertus* [37], *D. occidentalis* [37], *Otobius lagophilus* [37], and *Haemaphysalis leporispalustris* [32]. Adults of *D. occidentalis* only feed accidentally on man. A report of virus isolation from the American dog tick, *D. variabilis,* on Long Island, suggested the presence of CTF virus also in the eastern United States [47]. However, extensive efforts to obtain additional isolates from ticks in that area as well as from *D. variabilis* collected from different regions failed [37].

CTF virus is maintained in nature in a cycle between the immature stages of its tick vector, *D. andersoni,* and some of their host animals. Nymphal ticks carry the virus through the winter and in spring infect small mammals, particularly young rodents that have inapparent infections with prolonged viremias. Larval ticks feeding on such animals become infected, molt to nymphs and maintain the virus through the following winter season. Transovarial passage of CTF virus to progeny of infected female ticks has been claimed [46] but could not be confirmed [40].

Of the large variety of animals that serve as hosts for immature *D. andersoni*, the following have been found naturally infected with CTF virus: porcupine (*Erethizon dorsatum epixanthum*) [38], wood rat (*Neotoma cinerea cinerea*) [60], golden-mantled ground squirrel (*Spermophilus lateralis tescorum*) [23, 24, 31, 38], Columbian ground squirrel (*S. c. columbianus*) [23, 24], pine squirrel (*Tamiasciurus hudsonicus richardsoni*) [23], chipmunk (*Eutamias* spp.) [23, 24, 60], meadow vole (*Microtus* spp.) [23], red-backed mouse (*Clethrionomys* spp.) [60], and deer mouse (*Peromyscus maniculatus*) [23, 31]. The parasite-vector-host relationships of CTF have been the subject of several investigations. On the southeast slopes of the Bitter Root Mountains in western Montana, sharply localized areas of infection were found [23, 24] which appeared to be correlated with the presence of golden-mantled ground squirrels. In areas populated by this rodent, the incidence of infected adult *D. andersoni* collected from vegetation ranged from 8.1 to 40.0 percent, and of 115 golden-mantled ground squirrels, 54 (46.9%) yielded virus. In the same areas, virus isolations were also made from other tick hosts including 24 (18.3%) of 131 Columbian ground squirrels, 15 (20%) of 75 chipmunks, 1 of 6 deer mice, and 1 of 4 pine squirrels. In areas not populated by golden-mantled ground squirrels, infection rates in ticks ranged from 0 to 3.3 percent, and virus was isolated only from 11 (7%) of 157 Columbian ground squirrels. These results along with the fact that golden-mantled ground squirrels were more heavily infested with immature ticks than any of the other rodents present, suggested that the golden-mantled ground squirrel, in these well defined study areas, was the preferred host of *D. andersoni* and the main virus source for tick infection.

In nearby Mill Canyon, a different biocenosis was encountered [31] because the study areas were located in the bottom and on the northern and precipitous slopes. Here, the dominant rodent species, in addition to golden-mantled ground squirrels, were deer mice, wood rats, red-backed mice, and long-tailed voles (*Microtus longicaudus*). Golden-mantled ground squirrels and wood rats were shown to be the dominant tick hosts. Virus isolations were made from 15 of 383 blood samples from deer mice, and from the blood of two young golden-mantled ground squirrels.

Ecologic conditions different from those in either of the above cited areas existed in Spearfish Canyon, South Dakota [60]. There, in the absence of golden-mantled ground squirrels, the immature stages of *D. andersoni* were found to feed on wood rats, chipmunks, deer mice, and voles. The infection rate in adult ticks was 3.5 percent, and virus was isolated from the blood of chipmunks, deer mice, a wood rat, a red-backed vole, and a red squirrel.

Of the host animals found naturally infected with CTF virus, several species have been shown to experience viremias that last from 16 to 50 days, either when inoculated by syringe or when fed on by infected ticks [11, 12]. Of the animals examined to date, chipmunks and golden-mantled ground squirrels

appear to be most susceptible. In chipmunks, virus concentrations as high as $10^{6.2}$ mouse LD_{50} per ml of blood were recorded [12].

The minimum dosage requirement for infecting larval and nymphal ticks has not been established. Preliminary observations suggest that virus concentrations of $\leqq 10^{2.1}$ LD_{50} are not sufficient to infect ticks permanently [12]. On the other hand, feeding of ticks on chipmunks and golden-mantled ground squirrels during peak viremias regularly resulted in high percentages of infected ticks [12].

The growth of CTF virus in *D. andersoni* has been studied quantitatively [93]. Viral concentrations ingested by larval and nymphal ticks remained rather constant through quiescence of ticks but increased significantly during metamorphosis to the subsequent stages, or shortly thereafter. In some experiments, in which nymphs fed on viremic hamsters, there was a decrease in viral concentrations during the quiescent period followed by an increase from 1.5 to 3.7 logs in freshly molted adults. Larval ticks that fed on viremic hamsters ($10^{5.9}$ to $10^{6.3}$ LD_{50} per ml of blood) maintained the virus through the adult stage. The type of tick tissue that supports survival and/or development of CTF virus is not known. The fact that a tick's piercing of the host skin results in virus transmission, suggests the presence of high concentrations of virus in the salivary gland tissues. On the other hand, lack of transovarial passage of CTF virus to progeny of infected female ticks [40], may reflect a lack of virus in germinal cells of the ovary.

Epidemiology of Colorado tick fever: Colorado tick fever affects young and old persons who through occupational or recreational activities come into contact with *D. andersoni.* The seasonal incidence is a reflection of the tick's activity that lasts from early March through July, although sporadic cases have been reported as late as October [36]. Because the disease is relatively benign, the true incidence cannot be assessed. Many cases never come to the attention of a physician and, if they do, may not be recognized as CTF. In Colorado, where physicians are obligated to report cases to the state health authorities, the yearly incidence for the past five years has been 115, 244, 192, 261, and 220 cases, respectively [42]. In western Montana's Ravalli County, a 2,380 square mile area with a population of about 20,000 persons, 9, 11, 26, 24, and 19 cases were reported for the years 1972 through 1976, respectively [80].

Prevention and control of Rocky Mountain spotted fever and Colorado tick fever

Following early investigations of Rocky Mountain spotted fever in the Bitter Root Valley, one of the most intensive tick eradication programs ever recorded was initiated to suppress and prevent the disease [49, 68]. This program was based on the facts that domestic animals serve as hosts of the adult *D.*

andersoni and small wild rodents serve as hosts of the immature ticks. Measures, therefore, included dipping of cattle, horses, and dogs in a solution of arsenite, destroying wild rodents by poisoning, shooting, and trapping, handpicking of ticks from domestic animals, restricting cattle grazing on infested pastures during the period of adult tick activity, and burning, clearing, and developing land.

Extermination of wild rodents, particularly the Columbian ground squirrel, which was considered the host animal responsible for supporting about 95 percent of ticks in the valley, proved to be the most successful tick control measure. As a result of these efforts, the cultivated farmland in the valley was made tick-free.

In the eastern and southeastern parts of the United States, where *D. variabilis* infests homes and immediate surroundings, tick control is effectively carried out by application of acaricides, in the form of dusts, emulsions, and aqueous suspensions, to land, animals, and dwellings [54]. Because of national restrictions on the application of such insecticides, local pesticide authorities and agricultural extension offices should be consulted for information on products currently recommended before such control programs are undertaken.

Tick collars, such as VET-KEM containing o-Isopropoxyphenyl methylcarbamate, have been shown effective in controlling ticks on dogs and cats.

In areas of the wood tick, *D. andersoni*, application of acaricides is often impractical. Here, area control and rodent extermination campaigns are far more effective. After the ground cover of heavily tick-infested forest and sage brush areas is altered by lumbering, land clearing, irrigation and cultivation, and after periodically conducted poisoning programs, tick infestations rapidly decrease. However, there are vast areas of uncultivated land, especially in mountainous regions, where a large variety of rodents and other wild animals provides optimal conditions for tick development. Persons entering such areas should wear proper clothing to reduce the chances of tick bite. Trouser legs should be covered by high socks, and shirt tails should be tucked inside trousers. Because ticks seldom attach at once, it is necessary to repeatedly search the body and inside clothing for loose ticks. Effective tick repellents, such as diethyltoluamide and dimethylphthalate, applied to clothing and exposed parts of the body are recommended, but are seldom used. Attached ticks should be removed immediately after they are found by pulling them off gently with the fingers or with broad-tongued forceps, being careful not to crush the ticks. The bite wound should be treated with an antiseptic, and the hands, which may be contaminated with tick fluids, should be washed thoroughly.

Ricketts' suggestion [92] to prepare a vaccine for protection against Rocky Mountain spotted fever materialized in 1924, when one was developed from tissues of infected ticks [108]. It successfully protected guinea pigs, rabbits, and monkeys, and the following year it was given for the first time to human volunteers in the Bitter Root Valley [109]. Between 1927 and 1940, 455,000 persons were vaccinated in other parts of the Rocky Mountain region. Only 61 devel-

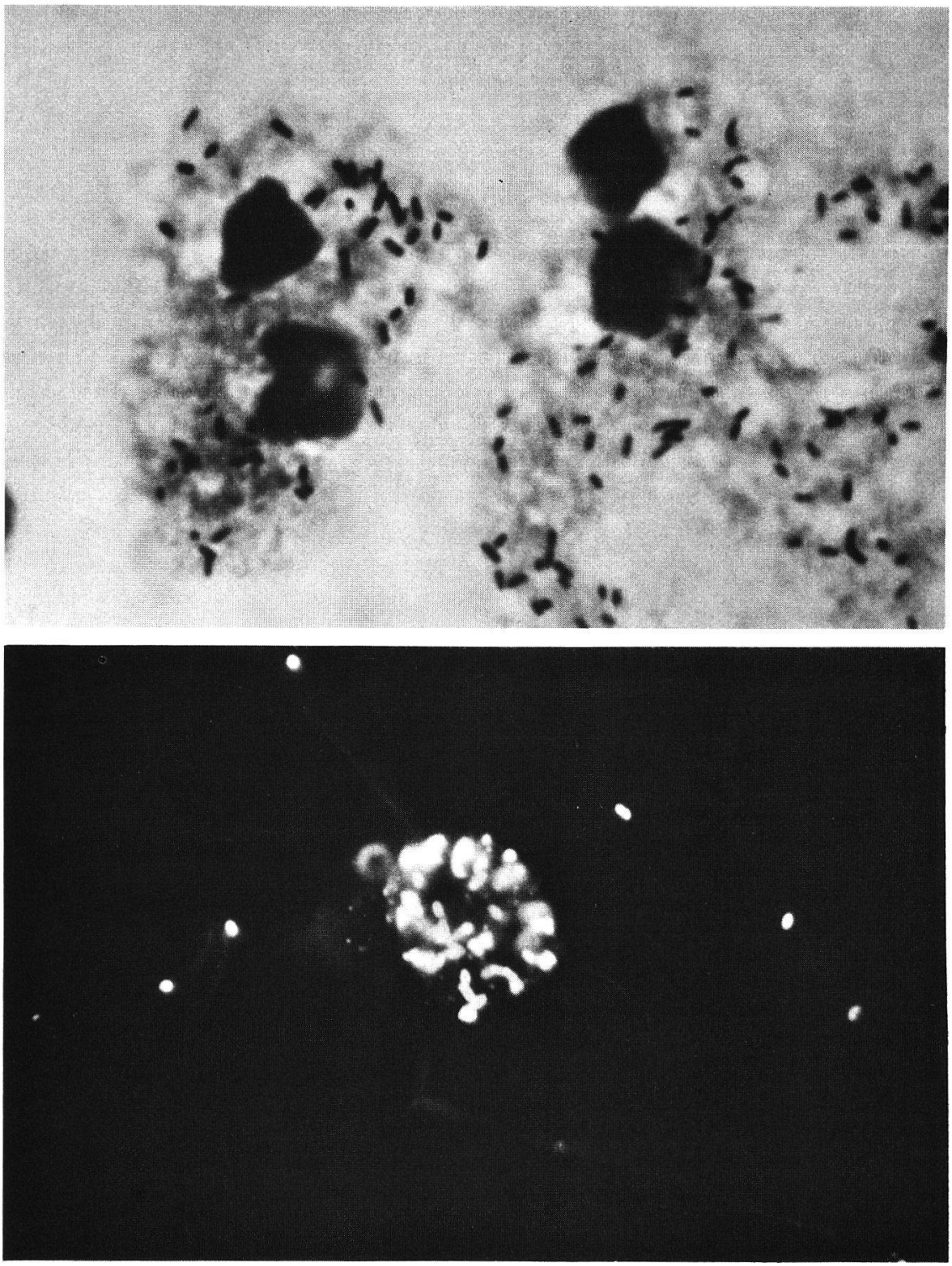

Fig. 4. Rickettsiae in hemocytes of *Dermacentor variabilis.* Above, Giménez stain, X 2,800; below, fluorescent antibody staining with anti-*R. rickettsii* conjugate, X 1,400.

oped the disease, and of these none died. Today's commercial vaccine consists of a formalin-treated ether extracted product derived from *R. rickettsii* grown in yolk sacs of embryonated hen's eggs. Although relatively ineffective in protecting man [35], it is still recommended for persons living in highly endemic areas; it does not prevent infection, but lessens the severity of the disease.

Recent advances in propagation and purification of rickettsiae have led to the development of better vaccines. Thus products prepared from duck or chick embryo cell culture-grown *R. rickettsii* were found [61] far more immunogenic, and those from yolk sac or mouse L cell-grown *R. rickettsii* purified by sucrose density gradient centrifugation in a zonal rotor, were at least 2,000 times as effective as the commercial vaccine [1]. These products, however, have been tested only in laboratory animals; their protective efficacy in man remains to be established. A vaccine against Colorado tick fever has also been developed, but is not available commercially [114].

Fatality rates of 5 to 10 percent, as reported during the past 15 years, are far too high for a disease that can be treated successfully, and may reflect a lack of public awareness of both the presence of spotted fever and the potential danger of ticks. Therefore, in South Carolina, where twice as many cases occurred in 1972 as in the previous year, an education program was initiated to remind the general public and physicians that spotted fever is not a historical curiosity but a serious illness, particularly if not recognized and treated properly. Through pamphlets, newspaper releases, TV shows, etc., information was provided about the clinical aspects of the disease and about the ticks that transmit *R. rickettsii.* Persons bitten by ticks were asked not to discard the ticks but to submit them for examination by the hemolymph test [15]. This test, in conjunction with fluorescent antibody staining, has been shown to be a dependable tool in determining within less than one hour whether a tick is infected with spotted fever group rickettsiae (Fig. 4). It involves microscopic examination of hemolymph obtained by amputating a portion of one or more tick legs, and is an adaptation of a similar procedure developed to detect spirochaetal infections in ticks [10]. The hemolymph test is equally effective for the detection of CTF virus in its tick vector, *D. andersoni* [30]. The South Carolina campaign was enthusiastically received by the public, and hundreds of ticks were submitted for examination. In several instances, the test results led to an early unconfirmed diagnosis of spotted fever.

Conclusions

Rocky Mountain spotted fever and Colorado tick fever are zoonoses that have causal agents maintained in rather complex cycles between tick vectors and their host animals. They cannot be eradicated from the United States and will continue to affect large segments of our population, especially in view of current and future population shifts (suburbanization), and increased recre-

ational activities. Since education is by far the best means of preventing these diseases, campaigns similar to those conducted in South Carolina should be initiated in other areas where the diseases are endemic. The public should periodically be reminded of the clinical features of spotted fever and of Colorado tick fever and the potential danger of the ticks that transmit the causative agents. Once this awareness has been established and/or restored, incidence and mortality rates will decrease.

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