NONVIRAL VECTOR-BORNE ZOONOSES ASSOCIATED WITH MAMMALS IN THE UNITED STATES

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Interest in vector-borne zoonoses has increased during the past few years as new disease agents have been identified and old ones have re-emerged due to important changes in their ecology or epidemiology. This article reviews nonviral vector-borne zoonoses that occur in the United States and are associated with mammals and their ectoparasites. The zoonoses discussed in this review include plague, tularemia, Lyme disease, tick-borne relapsing fevers, Rocky Mountain spotted fever, rickettsialpox, louse-borne typhus, flea-borne typhus, Q fever, and human ehrlichiosis.

Key words: nonviral zoonoses, vector-borne zoonoses, mammals, ectoparasites

A wide variety of nonviral vector-borne zoonoses exist in the United States. Many of these zoonoses are associated with mammals and their tick, mite, flea, or louse ectoparasites. This review discusses the etiologic agents, signs and symptoms, natural history, epidemiology, and prevention and control of these nonviral mammal-associated zoonoses. Significant research topics also are identified. The zoonoses reviewed include plague, tularemia, Lyme disease, tick-borne relapsing fevers, Rocky Mountain spotted fever, rickettsialpox, louse-borne typhus, flea-borne typhus, Q fever, and human ehrlichiosis.

PLAGUE

Plague is a flea-borne zoonosis caused by infection with a bacterium, *Yersinia pestis.* Rodents are the primary vertebrate hosts of *Y. pestis,* but other mammals, including humans, can be infected. The plague bacterium probably evolved in native populations of rodents and fleas in the steppes of central Asia and then spread to other regions by the transport of infected commensal rats (primarily *Rattus rattus*) and fleas along international trade routes. The range of *Y. pestis* expanded most widely during three great pandemics that caused millions of human deaths and changed the course of history (Pollitzer, 1954). Although, in many instances, these range extensions were only temporary, others resulted in the establishment of new foci of *Y. pestis* infection among local species of rodents and fleas in the affected areas. Many of these sylvatic or "wild" rodent foci still persist in certain areas of Asia, Africa, the Americas, and the extreme eastern edge of Europe near the Caspian Sea.

This brief review concentrates primarily on the ecology and epidemiology of plague in western North America. More comprehensive discussions of plague can be found elsewhere (Poland and Barnes, 1979; Po-

land et al., 1994; Pollitzer, 1954; Pollitzer and Meyer, 1961).

Description of disease agent.—*Yersinia pestis* is a gram-negative coccobacillus (Enterobacteriaceae) that is aerobic or facultatively anaerobic, nonfastidious, and grows slowly on a wide variety of commercially available media (Quan et al., 1981). It can be identified by biochemical tests and lysis with specific bacteriophage. Pathogenicity is associated with a number of chromosomal and plasmid-associated virulence factors that often are important for the survival of *Y. pestis* in its mammalian hosts and flea vectors (Brubaker, 1991).

Description of disease.—Plague can cause severe and often fatal illness in rodents and other mammals, including humans. *Y. pestis* is transmitted to mammals by bites of infected fleas, direct contact with infected animals, or rarely by inhalation of infectious respiratory droplets from another animal. The three most common forms of plague are bubonic, septicemic, and pneumonic. Characteristic symptoms in humans include fever, headache, chills, myalgia, malaise, prostration, gastrointestinal symptoms, and, in bubonic cases, extremely painful and swollen lymph nodes (buboes) near the site where *Y. pestis* first entered the body. Buboes usually appear in inguinal, axillary, or cervical lymph nodes, but predators, including domestic cats and bobcats, often develop submandibular buboes after ingesting infected prey (Eidson et al., 1988; Gasper et al., 1993; Poland and Barnes, 1979). Septicemic plague occurs when *Y. pestis* invades the bloodstream and causes a steady bacteremia. It can appear secondarily to bubonic plague or can develop without prior lymphadenopathy (primary septicemic plague). Invasion of the lungs by *Y. pestis* results in pneumonic plague, which is characterized by pneumonia with high fever, difficulties in breathing, and blood-tinged sputum. Pneumonic plague can occur as a secondary complication of septicemic plague or as a result of inhalation of infectious respiratory droplets or other materials (primary pneumonic plague). Case fatality rates for untreated human plague range from 50–60% for untreated bubonic cases to 100% for untreated pneumonic cases (Poland and Barnes, 1979).

Natural history and epizootiology.—Naturally-occurring *Y. pestis* infections have been identified in at least 76 species of mammals in the United States (Barnes, 1982). Despite the diversity of potential hosts, plague is maintained almost exclusively in complex epizootic (amplification) and enzootic (maintenance) transmission cycles involving certain species of rodents and their fleas. The most important flea vectors are those found on ground squirrels, prairie dogs, woodrats, mice, and voles (Table 1). Other mammalian species, especially rodent-consuming carnivores, can play ecologically important roles by transporting infected fleas from one area to another (Gage et al., 1994). Rabbits and hares often are found dead during epizootics, but probably are of little importance for maintaining *Y. pestis* in nature (von Reyn et al., 1976).

Plague epizootics in the western United States cause high mortality (80–>99%) among many populations of rodents, especially prairie dogs, ground squirrels, chipmunks, and woodrats (Barnes, 1982). In the United States, a number of these highly susceptible rodents and their associated vector fleas form regional epizootic host-flea complexes that are important for amplifying *Y. pestis* infections among their own populations and spreading the bacteria to other rodents in nearby areas and to less common or accidental hosts of infection, such as humans, carnivores, and lagomorphs (Table 1).

Some rodents suffer relatively little mortality during epizootics. For example, kangaroo rats (*Dipodomys*) seroconvert after being infected with *Y. pestis,* but probably rarely suffer morbidity or mortality during epizootics (Poland and Barnes, 1979). Other species of rodents, including deer mice (*Peromyscus maniculatus*), California voles

TABLE 1.—*Important plague hosts in the United States and their associated fleas*[a]

Hosts	Commonly associated fleas
Epizootic	
Spermophilus variegatus	*Oropsylla montana, Hoplopsyllus anomalus*
Spermophilus beecheyi	*Oropsylla montana, Hoplopsyllus anomalus*
Spermophilus elegans	*Oropsylla labis, Oropsylla idahoensis, Oropsylla tuberculata tuberculata, Thrassis bacchi*
Spermophilus beldingi	*Thrassis francisi, Thrassis pandorae, Thrassis petiolatus, Oropsylla tuberculatus tuberculatus*
Spermophilus townsendi	*Thrassis francisi*
Spermophilus armatus	*Thrassis pandorae, Thrassis francisi*
Spermophilus lateralis	*Oropsylla idahoensis, Oropsylla montana* (Pacific focus), *Oropsylla labis*
Tamias	*Eumolpianus eumolpi* (widespread), *Eumolpianus fornacis* (Pacific focus), *Eumolpianus* (Pacific focus), *Ceratophyllus ciliatus* (Pacific focus)
Cynomys gunnisoni	*Oropsylla hirsuta, Oropsylla tuberculata cynomuris*
Cynomys ludovicianus	*Oropsylla hirsuta, Oropsylla tuberculata cynomuris*
Cynomys leucurus	*Oropsylla hirsuta, Oropsylla tuberculata cynomuris*
Neotoma	*Orchopeas sexdentatus, Orchopeas neotomae, Anomiopsyllus, Stenistomera alpina, Megarthroglossus*
Enzootic	
Peromyscus maniculatus	*Aetheca wagneri, Atylphloceras, Catallagia, Epitedia, Hystrichopsylla, Megabothris abantis, Malaraeus, Opisodasys keeni, Orchopeas, Peromyscopsylla, Plusaetis sibynus*
Microtus californicus	*Atyphloceras multidentatus, Catallagia wymani, Hystichopsylla, Malaraeus telchinum, Opisodasys keeni*

[a] From Hubbard (1948), Miles et al. (1957), and Barnes (1982). Listings include only those species most commonly found on these hosts.

(*Microtus californicus*), and northern grasshopper mice (*Onychomys leucogaster*), vary in their susceptibility to plague-related mortality (Hubbert and Goldenberg, 1970; Quan, 1956; Thomas et al., 1988). Deer mice and California voles are considered by some to act as enzootic hosts for maintaining *Y. pestis* during interepizootic periods (Poland and Barnes, 1979). It is believed that resistant populations of these animals rarely die of plague, but do become bacteremic and, therefore, can serve as sources of infectious bloodmeals for feeding fleas. Deer mice and voles also have relatively high reproductive rates with multiestrous breeding cycles, which allow nonimmune individuals to be introduced frequently into populations.

Plague epizootics in commensal rats (*R. rattus* and *Rattus norvegicus*) and their fleas, especially *Xenopsylla cheopis,* have great epidemiologic significance, but are of little importance for maintaining plague in nature. Although such epizootics occasionally occur in other parts of the world, they have not been reported in the United States since 1924. Occasionally, individual rats infected with *Y. pestis* have been identified in or near certain cities in plague-enzootic areas of the western United States, but widespread epizootics have not occurred in these animals (Centers for Disease Control and Prevention, 1994; Schwan et al., 1985). This probably is due, at least in part, to the low infestations of *X. cheopis* found on rats in some of these areas (Schwan et al., 1985).

Rodent-consuming carnivores in plague-enzootic areas often become infected with *Y. pestis* after ingesting infected prey or being bitten by infected fleas, but many of these animals appear to be relatively resistant to plague. For example, extensive serosurveillance data and limited experimental studies in the United States suggest that dogs, coyotes (*Canis latrans*), and foxes

(*Vulpes* and *Urocyon cinereoargenteus*) typically seroconvert, but rarely die following infection (Barnes, 1982; Centers for Disease Control and Prevention, pers. comm.). Seropositive mustelids (*Taxidea taxus, Mephitis mephitis, Spilogale gracilis, Mustela frenata,* and *Martes americana*), ursids (*Ursus americanus*), and procyonids (*Bassariscus astutus* and *Procyon lotor*) also have been identified (Barnes, 1982), but reports of plague-related deaths among North American members of these families are almost nonexistent. Morbidity and mortality among felids, however, are apparently much higher as indicated by numerous reports of plague-related deaths in domestic cats and bobcats (Centers for Disease Control and Prevention, pers. comm.; Eidson et al., 1988; Gasper et al., 1993; Tabor and Thomas, 1986).

Factors that govern the occurrence of widespread epizootics are poorly understood, but probably include environmental variables, such as rainfall and temperature, that influence food supplies of rodents and, thus, the population dynamics of plague hosts and their flea vectors. The diversity of local habitats and plague hosts also is likely to be important. In general, epizootics occur most frequently in those areas where there are multiple populations and species of epizootic hosts living at relatively high densities in diverse and highly patchy habitats. Such conditions can be found in some mountainous and plateau regions of the southwestern states of New Mexico, Colorado, and Arizona as well as other mountainous habitats in California and immediately adjacent areas in southern Oregon and extreme western Nevada.

Epidemiology.—On a global basis, the greatest risks of plague transmission to humans occur during plague epizootics involving commensal rats and their fleas. However, such outbreaks are not important in the epidemiology of plague in the United States, and the sporadic human cases that occur in this country are due to exposure to infected fleas parasitizing native species of rodents, direct contact with infected animals, or, rarely, inhalation of respiratory secretions of wild animals or domestic cats (Craven et al., 1994; Gage et al., 1994).

In the United States, 334 cases of human plague were reported from 13 western states from 1970 through 1994. More than 80% of these cases occurred in northern New Mexico, northern Arizona, southern Colorado, and extreme southeastern Utah. Another 10% were reported from portions of California, southern Oregon, and extreme western Nevada.

Most persons are exposed to plague when rodent epizootics occur near their homes. Risks of peridomestic exposure are especially high in New Mexico, Arizona, and Colorado, where ongoing suburbanization has resulted in large numbers of humans living within active plague foci (Barnes, 1982; Centers for Disease Control and Prevention, 1994; Craven et al., 1994). Many homesites in the Southwest also provide food and shelter for plague-susceptible rodents, especially rock squirrels (Barnes, 1982; Gage et al., 1992; Mann et al., 1979). Bites of infected fleas on rock squirrels (primarily *Oropsylla montana*) are the sources of infection for almost one-third of the human cases reported in the United States since 1970 (Gage et al., 1992). Smaller percentages of persons are exposed while visiting recreational areas where plague epizootics have occurred or while handling infected animals (Barnes, 1982; Gage et al., 1992, 1994); the likelihood of exposures in recreational sites are higher in the Pacific Coast focus than elsewhere (Nelson, 1980). Work-related exposures are relatively rare.

Of the 382 (29%) human cases reported in the United States between 1947–1994, 109 occurred in Native Americans, particularly Navajos (23% of total cases in the United States). This disproportionately high number of cases among Native Americans is not related to increased susceptibility, but rather due to increased exposure risks (Barnes et al., 1988).

Exposure to infected domestic cats has

been responsible for 16 human cases since 1977, including five cases among veterinarians or their staff (Centers for Disease Control and Prevention, pers. comm.). Five of these 16 cases occurred after persons inhaled infectious materials from cats with plague pneumonia or oral lesions. Fortunately, none of these five cat-associated primary pneumonic cases resulted in secondary human-to-human transmission.

Mammalogists who handle potentially plague-infected animals or animals infested with plague-infected fleas should assume that they are at risk of exposure to *Y. pestis* infection. Despite this apparent risk there has been no case of plague among mammalogists working in the United States. However, at least one American mammalogist acquired plague while performing research in Bolivia. It is possible that she was exposed to infected rice rats (*Oryzomys*) or their fleas (Centers for Disease Control and Prevention, 1990).

Prevention and treatment.—Human-plague risks can be reduced by rodent-proofing homes, removing structures that provide shelter for rodents, limiting rodent access to water and food sources near homes, avoiding sick or dead animals and rodent nests or burrows, exercising caution when handling sick cats in plague-enzootic areas (such cats should be examined by a veterinarian), treating dogs and cats with insecticidal flea powders to prevent transport of infected fleas into homes, applying appropriate insecticides to rodent burrows, nests, and runways to reduce risks of infectious flea bites, and using rodenticides to reduce the populations of plague-susceptible hosts in areas of high human risk. It must be emphasized, however, that killing rodents without first eliminating their flea ectoparasites can actually increase, rather than lower, human plague risks. Therefore, rodenticides should not be used until flea control measures have been implemented and demonstrated to be effective.

Plague is treatable with appropriate antibiotics, including streptomycin, gentamicin, tetracyclines, and a combination of trimethroprim and sulfamethoxazole (Dennis, in press). A currently-available, formalin-inactivated plague vaccine might be useful for preventing flea-borne *Y. pestis* infections (Cavanaugh et al., 1974), but has not been determined to be effective for preventing airborne transmission by infectious respiratory droplets. Prophylactic antibiotics are recommended when the risk of exposure is high (Dennis, in press).

Opportunities for research.—Although there has been considerable research on the molecular biology of *Y. pestis* in recent years, relatively few investigators have focused on the ecology, epidemiology, and control of plague in the United States. Among the most interesting topics for ecologic research are mechanisms of interepizootic maintenance of plague, investigations of the environmental factors that influence the occurrence of epizootics, and clarification of the relative ecologic importance of different species of fleas found on various enzootic and epizootic hosts.

Tularemia

Description of disease agent.—Tularemia is broadly distributed over the northern hemisphere where it affects a variety of arthropods and vertebrates, including mammals (Hopla, 1974, Jellison, 1974). *Francisella tularensis,* the etiologic agent of tularemia, is a gram-negative pleomorphic, aerobic bacteria. Two biovars (types A and B) have been described. Type-A strains are considered more virulent than Type-B strains and usually are vector-borne. Type-B strains cause less severe disease and often are water-borne. Both biovars occur in the United States.

Description of disease.—Symptoms of tularemia often resemble those of plague and typically include fever, chills, malaise, fatigue, and lymphadenopathy. Respiratory symptoms also are common (Hopla and Hopla, 1994). Humans can be infected by direct contact with infected animals, bites of infected arthropods (especially ticks), or

contact with water contaminated with urine from bacteriuric rodents, such as *Microtus*. Five distinct syndromes have been described. The most common (75–85% of cases) of these is ulceroglandular plague, which is characterized by an ulcerated skin lesion at the site of initial infection and painful lymphadenopathy. Other forms of disease include glandular, typhoidal, oculoglandular, and oropharyngeal tularemia. The fatality rate in untreated cases is 5–7%.

Natural history and epizootiology.—*Francisella tularensis* has been identified in >100 species of mammals (Hopla and Hopla, 1994). Tick-vertebrate cycles involving lagomorphs are considered to be especially important for maintaining tularemia in North America (Hopla, 1974). The most commonly infected lagomorphs are *Lepus americanus, Lepus californicus, Sylvilagus floridanus,* and *Sylvilagus auduboni.* The most important vectors in these tick-lagomorph cycles are certain species of *Amblyomma, Dermacentor, Haemaphysalis,* and *Ixodes* (Hopla, 1974). These ticks also are important for transmitting *F. tularensis* to other mammals. Biting flies may be vectors in some areas, especially the intermountain West. *F. tularensis* also is frequently identified in rodents. Among the most important rodent hosts in the United States are species of *Microtus* and *Clethrionomys* as well as *Ondatra zibethicus* and *Castor canadensis* (Hopla, 1974). Although these rodents may be involved in tick-vertebrate cycles, they also are capable of excreting viable *F. tularensis* in their urine, which can result in water-borne transmission between susceptible hosts.

Epidemiology.—In 1981–1991, ca. 200 human cases of tularemia/year were reported to health authorities, but underreporting probably is common. Most human cases occur in the southcentral United States where tick-borne transmission, largely by *Amblyomma americanum,* accounts for ca. 60% of cases (Hopla and Hopla, 1994). Biting flies (tabanids), ticks, and direct contact with infected animals are responsible for about equal numbers of cases in the western states. Transmission via contact with infected animals is especially important in the midwestern states. *F. tularensis*-infected rabbits are the most important sources of direct-contact infections in the United States (Jellison, 1974). Water-borne tularemia infections in humans are relatively uncommon in this country, but occur frequently in the Palaearctic region (Hopla and Hopla, 1994). It should be noted, however, that water-borne tularemia epizootics in muskrats have resulted in outbreaks of the disease among muskrat trappers in the northeastern United States (Hopla, 1974). These trappers probably were infected by direct contact with infected muskrats rather than exposure to *F. tularensis*-contaminated water.

Prevention and treatment.—Measures to prevent tularemia include using insecticides and repellents to reduce risks of arthropod bites and wearing gloves while handling potentially infected animals. Although an experimental vaccine exists, it is not likely to be widely available in the near future. *F. tularensis* is susceptible to a variety of antibiotics, but streptomycin remains the drug of choice (Hopla and Hopla, 1994).

Opportunities for future research.—Recent molecular studies are resulting in a reevaluation of certain aspects of the biology of *F. tularensis.* These studies are likely to suggest ecologic and epidemiologic studies of interest to mammalogists (Hopla and Hopla, 1994).

Tick-borne Spirochetal Diseases

In 1975, health specialists documented an unusual cluster of cases of childhood arthritis in Lyme, Connecticut (Steere et al., 1976). Many of these cases of arthritis were associated with prior cases of a skin rash (erythema migrans) known to be linked in Europe to bites from the tick *Ixodes ricinus* (Steere et al., 1977). Later investigations revealed abundant populations of the tick *Ixodes scapularis* (synonymous with *Ixodes dammini*) in the vicinity of Lyme, Con-

necticut, and it was concluded that bites from these two species of ticks were directly linked to similar clinical syndromes observed in Europe and the United States (Steere et al., 1983). Further studies revealed that both species of ticks were host to a previously undescribed spirochete bacterium, *Borrelia burgdorferi,* which is the etiologic agent of the disease (Barbour et al., 1983; Burgdorfer et al., 1982; Steere et al., 1983).

In addition to Lyme disease, there are isolated cases and occasional outbreaks of tick-borne relapsing fever in the western United States. These cases are due to infection with either *Borrelia hermsii* or *Borrelia turicatae* (Burgdorfer and Schwan, 1991). Many other species of *Borrelia* cause tick-borne or louse-borne relapsing fevers in other regions of the world.

Description of disease agent.—Borrelia burgdorferi (Spirochaetaceae) is a helical bacterium 10–30 μm long and 0.2–0.3 μm in diameter, with three to 10 loose coils (Sonenshine, 1993). It can be cultured in BSK-II media, but multiple passages typically result in loss of virulence (Schwan et al., 1988). Genetic differentiation within the nominal species *B. burgdorferi* has been well documented, and further systematic studies are likely to reveal a complex of related species that differ in their clinical manifestations (Barbour and Fish, 1993). For example, strains from northern and eastern Europe and Asia do not commonly cause arthritic symptoms. Even within localized areas, several distinct strains of *B. burgdorferi* may coexist (Brown and Lane, 1992; B. Luft, pers. comm.).

Other species of *Borrelia* are similar in appearance and cause various types of relapsing fevers in Africa, Asia, and North America (Burgdorfer and Schwan, 1991). All, except the etiologic agent of louse-borne relapsing fever (*Borrelia recurrentis*), are involved in enzootic cycles between ticks and vertebrate hosts.

Description of disease.—Early symptoms of Lyme disease include low-grade fever, muscle aches, and lethargy, accompanied in ca. 90% of cases by erythema migrans in the vicinity of the tick bite (Barbour and Fish, 1993). Later manifestations of Lyme disease include arthritis, carditis, and various neurologic symptoms.

Relapsing fever is characterized by 3–7 days of fever followed by a non-febrile period and then multiple relapses (usually three to five). Spirochetes are easily visualized in the patient's blood during the initial phase of each febrile attack and then disappear as they are destroyed by specific antibody (Felsenfeld, 1979). Relapses are related to the ability of these spirochetes to express antigenically distinct surface proteins during each successive relapse and, thus, temporarily evade the host's immune system (Schwan et al., 1995). Each succeeding relapse is generally milder than the previous one and mortality for tick-borne relapsing fevers generally is considered to be low (<5%) (Felsenfeld, 1979).

Natural history and epizootiology.—The primary vectors of the Lyme disease bacterium are *I. scapularis* and *Ixodes pacificus* in eastern and western North America, respectively, *I. ricinus* in Europe, and *Ixodes persulcatus* in northern Asia (Lane et al., 1991; Sonenshine, 1993). Transmission of Lyme disease is intimately connected with the life cycle of the tick vector. The generalized life cycle of *I. scapularis* is typical of the genus and is subsequently described. Note, however, that considerable variation exists among species and geographic regions.

The life cycle of *Ixodes* is typical for hard ticks (Ixodidae) and includes four stages: egg; larva; nymph; adult. Egg masses consisting of ≤3,000 eggs are laid on the ground or in leaf litter in spring or early summer and hatch into tiny (0.5 mm wide) larvae in mid- to late summer. Larval *I. scapularis* begin seeking a host shortly after hatching and will feed on a variety of vertebrates, including small mammals, birds, and lizards. In the northeastern and north-central United States, where the majority of

Lyme-disease cases occur, the white-footed mouse (*Peromyscus leucopus*) is the most commonly parasitized host (Anderson and Magnarelli, 1993). Larvae feed until becoming fully engorged with blood in 3–5 days, after which they drop to the ground and molt into nymphs, which are ca. 1 mm wide. Nymphs overwinter in a quiescent state and begin seeking hosts the following spring or early summer. Similar to the larval stage, nymphal *I. scapularis* will attach to a wide variety of vertebrate hosts and feed to engorgement, which usually takes 4–5 days. Engorged nymphs then drop off and molt into adults (2.0–2.5 mm wide), which commence activity in early to mid-autumn. Adult *I. scapularis* are more host-specific than the two juvenile stages and feed predominantly on white-tailed deer (*Odocoileus virginianus*).

Larval *I. scapularis* are almost never infected with Lyme disease spirochetes when they hatch (Piesman, 1991). However, feeding ticks may acquire *B. burgdorferi* from their host during bloodmeals. Host species that effectively transfer the spirochete to feeding ticks are considered competent reservoirs. In eastern and central North America, the most competent reservoir for Lyme disease is *P. leucopus* (Mather, 1993). However, less competent reservoirs, e.g., eastern chipmunks (*Tamias striatus*), gray squirrels (*Sciurus carolinensis*), short-tailed shrews (*Blarina brevicauda*), and raccoons (*Procyon lotor*) may contribute significantly to the infection of tick populations (Fish and Daniels, 1990; Fish and Dowler, 1989). In the western United States, the dusky-footed woodrat (*Neotoma fuscipes*) is the principal reservoir; whereas, in Europe and Asia, competent reservoirs include the bank vole (*Clethrionomys glareolus*) and several species of *Apodemus* (Anderson and Magnarelli, 1993; Lane et al., 1991). Other enzootic rodent hosts have been identified in areas where few human cases are reported (Maupin et al., 1994). In a few unusual cases, the enzootic cycle of *B. burgdorferi* may be maintained by lagomorphs (Tallelint and Jaenson, 1993), or seabirds (Olsen et al., 1993) in the absence of rodents.

The phenology of the 2-year life cycle of *I. scapularis* is crucial to the epizootiology of Lyme disease. In the northeastern and northcentral United States, larval ticks from one generation are active later in the season than nymphs from the prior generation. Thus, larvae typically acquire *Borrelia* from mouse hosts in August–September after the mice themselves became infected in June–July by feeding nymphs. In parts of Eurasia and the southern and western United States, lower *Borrelia*-infection rates of ticks could be related to the more rapid completion of the tick life cycle, such that nymphs feed later in the season than do larvae or simultaneously with larvae.

Borrelia burgdorferi typically occurs in the midgut of its tick hosts, adhering to the digestive epithelium (Zung et al., 1989). Once an infected tick attaches to a host and begins its blood meal, the spirochetes are activated and travel to the tick's salivary glands within 24–48 h (Zung et al., 1989). The most likely route of transmission from tick to human is through the tick's saliva, although transmission through regurgitation of midgut contents has not been ruled out (Burgdorfer et al., 1989). Feeding ticks typically do not transmit spirochetes until $\geq$24 h after attachment (Piesman et al., 1991).

Although some have suggested that *B. burgdorferi* infection results in systemic disease in *P. leucopus* (Burgess et al., 1990), it is unlikely that survival or reproductive rates in populations of white-footed mice are affected strongly by the spirochetes. Eighty to 100% of mice in some foci are infected with *B. burgdorferi* (Anderson et al., 1987; D. Fish, pers. comm.); yet, these populations of mice behave quite similarly to those outside the range where Lyme disease is endemic (R. S. Ostfeld, pers. observ.; J. Wolff, pers. comm.). In addition, infestation of *P. leucopus* by ticks does not reduce longevity of mice (R. S. Ostfeld, pers. observ.).

Three species of tick-borne relapsing-fe-

ver borreliae occur in the United States (*Borrelia hermsii, Borrelia turicatae,* and *Borrelia parkeri*). Each is transmitted by a different species of argasid tick in the genus *Ornithodoros* (*O. hermsi, O. turicata,* and *O. parkeri,* respectively). All three species infest primarily rodents and usually feed for only short periods (<1 h) when their hosts return to their burrows or nests. These ticks have multiple nymphal stages, and adults feed more than once, usually laying small batches of eggs (<200 eggs) after each successful feeding. Transmission of spirochetes occurs via infectious tick saliva or contamination of the bite wound with infectious body fluids secreted by the tick's coxal glands (excretory organs).

The most epidemiologically important relapsing fever spirochete in North America is *B. hermsii,* which is found in the Rocky Mountains and certain mountain ranges in the Pacific states. *O. hermsi* is a vector and reservoir of infection. Chipmunks (*Tamias amoenus*) and red squirrels (*Tamiasciurus hudsonicus*) are likely mammalian reservoirs (Burgdorfer, 1976; Burgdorfer and Mavros, 1970). Laboratory studies indicate that these two species and meadow voles (*Microtus pennsylvanicus*) become spirochetemic, but northern flying squirrels (*Glaucomys sabrinus*), Columbian ground squirrels (*Spermophilus columbianus*), bushy-tailed woodrats (*Neotoma cinerea*), and deer mice (*P. maniculatus*) do not develop detectable spirochetemias following inoculation of *B. hermsii* (Burgdorfer and Mavros, 1970).

Other North American relapsing-fever spirochetes include *B. turicatae* and *B. parkeri. B. turicatae* occurs in the southwestern United States from Kansas into northern Mexico and is maintained in enzootic cycles involving the tick *O. turicata* and its rodent hosts. *O. turicata* inhabits rodent burrows and nests where it feeds on ground squirrels (*Spermophilus*), prairie dogs (*Cynomys*), kangaroo rats (*Dipodomys*), woodrats (*Neotoma*), and a variety of other vertebrate hosts (Cooley and Kohls, 1944). *B. parkeri* is found primarily in the Great Basin and adjacent regions where it presumably exists in enzootic cycles involving *O. parkeri* and their burrow-dwelling hosts, including *Spermophilus* and, perhaps, *Cynomys.*

Epidemiology.—The number of cases of Lyme disease grew steadily throughout the 1980s; in the early 1990s, ca. 10,000 cases/year were reported (Barbour and Fish, 1993; Dennis and Lance, 1994). As of 1991, all states except Montana and Alaska had reported cases. The majority of cases occurred in the northeastern seaboard states, upper Midwest, and California (Barbour and Fish, 1993; Sonenshine, 1993). Reports of cases in states in which infected ticks are rare or nonexistent are likely due to misdiagnosis. Accurate and reliable diagnosis is complicated by the lack of a standardized serological assay and nonspecific symptoms (Barbour and Fish, 1993).

Most cases of Lyme disease probably are transmitted during the early summer, when peaks in activity of nymphal ticks and humans in natural areas coincide. Although adult *I. scapularis* are about twice as likely to be infected with *B. burgdorferi* as are nymphs, contact with adult ticks appears less likely to lead to transmission of Lyme disease for two primary reasons. First, adult ticks are substantially larger than nymphs and feed for longer periods; therefore, detecting them before they have attached and transferred spirochetes to a human host is more probable. Second, people engage in more outdoor activities in summer, when nymphs are most active, than in autumn and spring, when adults seek hosts.

The primary risk factor for Lyme disease is abundance of *Borrelia*-infected, nymphal ticks (Falco and Fish, 1989; Lane et al., 1991). In the eastern United States, populations of *I. scapularis* appear to have increased in abundance and distribution following regional abandonment of agriculture in the past century and consequent regeneration of good habitat for white-tailed deer (Barbour and Fish, 1993; Ginsberg, 1993).

However, populations of ticks can vary tremendously within regions that sustain populations of deer and mice (Fish, 1993). Effects of climatic conditions and natural enemies on the geographic distribution and population density of *I. scapularis* are poorly understood (Ginsberg, 1993). Some regions may be suitable for populations of *I. scapularis* but simply have not yet received a sufficient number of tick immigrants to establish a Lyme-disease focus. It appears likely that the geographic distribution of dense populations of ticks and Lyme-disease cases will increase in the United States.

Within areas of established populations of ticks, density of hosts may affect the density of ticks in complex ways. Modeling efforts indicate that the density of ticks is more sensitive to the density of hosts for juveniles (e.g., mice) than to density of hosts for adults (e.g., deer—Van Buskirk and Ostfeld, in press), and this is supported by empirical observations. Wilson et al. (1988) showed that deer must be nearly eliminated to substantially reduce the density of ticks, but that moderate reductions in the density of deer have little or no effect. The effects of variation in density of mice and other juvenile-stage hosts are not as well understood. However, within local landscapes, habitat types supporting dense populations of ticks also support the greatest abundances of white-footed mice (Ostfeld et al., in press). Generally, populations of *I. scapularis* reach high densities in forested habitats and are more sparse in herbaceous and shrubby community types (Adler et al., 1992; Ginsberg and Ewing, 1989; Ostfeld et al., in press; Piesman and Spielman, 1979).

Infection rates of ticks with *B. burgdorferi* are determined by the relative abundance of reservoir-competent hosts (Mather, 1993; Van Buskirk and Ostfeld, in press; Wilson and Deblinger, 1993). For instance, populations of *I. scapularis* in the southeastern United States and of *I. pacificus* in California have low rates of infection, evidently because larvae and nymphs commonly parasitize lizards, which are not competent reservoirs (Apperson et al., 1993; Brown and Lane, 1992; Oliver et al., 1993). Few tick hosts are highly competent reservoirs for *B. burgdorferi*; this high diversity of species in host communities probably reduces infection rates of ticks by dilution, and this diminishes risk of exposure to Lyme disease (Van Buskirk and Ostfeld, in press). Generally, a high risk of Lyme disease exists in forested habitat that supports high densities of ticks and host communities dominated by *P. leucopus* (Mather et al., 1989).

Most persons are exposed to tick-borne relapsing fever when they sleep or rest in cabins or other sites that have rodent nests containing infected ticks. Cabins and similar structures are especially important as exposure sites for cases caused by infection with *B. hermsii,* but do not appear to be significant exposure sites for *B. turicatae*-associated cases. Exposure to the latter spirochete is most likely to occur when persons enter or rest in caves or near rodent burrows or nests in natural habitats. The two best documented outbreaks in the United States involved boy scouts camping in cabins in eastern Washington (11 cases) and tourists staying in cabins on the North Rim of the Grand Canyon (62 cases—Burgdorfer, 1976). Both of these outbreaks involved transmission of *B. hermsii* by *O. hermsi. B. parkeri* has yet to be incriminated as a human pathogen, possibly because the risks of human exposure are low rather than any innate resistance to infection.

Prevention and treatment.—Efforts to prevent Lyme disease have focused largely on means of personal protection against tick bites rather than on vector-control or host-control. People entering tick-infested habitats are encouraged to cover arms and legs, tuck pant legs into socks, apply repellents containing DEET to skin and clothing or pyrethroids to clothing, and wear pale-colored clothing that makes it easier to see and remove ticks before they attach (Mwase et

al., 1990). Careful inspection of the body and removal of ticks during and after potential exposure is advisable because ticks typically do not transfer spirochetes during the first several hours after attachment (White, 1993).

Insecticides have been used successfully to reduce the abundance of ticks and Lyme-disease risk in local areas, such as individual properties (Curran et al., 1993). However, environmental hazards associated with many insecticides and effects on nontarget organisms severely limit the usefulness of areal (area-wide) application of these products. To reduce effects on nontarget organisms, a commercial product was developed in which insecticide-impregnated cotton is presented in small dispensers that are attractive to free-ranging mice. Because mice are likely to retrieve this cotton and use it as nesting material, such a product may eliminate ticks in and around nests of mice. The success of this product in reducing local abundance of ticks has been mixed, and its efficacy is controversial (references in Wilson and Deblinger, 1993). Because the insecticide-impregnated cotton is specifically designed to take advantage of the nesting behavior of *P. leucopus,* it may be ineffective for treating other host species that do not incorporate the treated cotton in their nests.

Management of host populations will likely prove an inefficient means of preventing Lyme disease, in part because diversity of hosts is high in most Lyme-disease foci. Moderate reduction of density of deer has little effect on the density of ticks, and even near elimination of deer does not abolish risk of Lyme disease (Duffy et al., 1994; Wilson and Deblinger, 1993). In some cases, exclusion of deer by fences has substantially reduced, but not eradicated, juvenile ticks (Daniels et al., 1993; Stafford, 1993). Control of the small and medium-sized vertebrates that are hosts for juvenile ticks is neither practical nor desirable in many cases. However, management of individual properties to discourage use by deer and small mammals may reduce the abundance of ticks at small spatial scales. Habitat management to reduce Lyme-disease risk, for instance by burning, may be effective, but also may have unpredictable results (Mather et al., 1993).

Currently, field trials of a human vaccine for Lyme disease are underway (G. Wormser, pers. comm.). The vaccine consists of an antigen that occurs on the outer surface of *B. burgdorferi* (the OspA lipoprotein), which is genetically engineered using recombinant-DNA techniques. Recombinant OspA induces an effective immune response in several mammals (Barbour and Fish, 1993; Fikrig et al., 1992), and its effectiveness in immunizing humans is under evaluation.

During early stages of Lyme disease, when patients exhibit erythema migrans, low-grade fever, and myalgia, oral administration of antibiotics, such as amoxicillin or doxycycline, usually cures the disease (Barbour and Fish, 1993). If Lyme disease is untreated during its early manifestations, it may lead to more serious and persistent health problems, including arthritis, carditis, and neurologic symptoms. These symptoms occasionally do not improve readily under antibiotic therapy. In some cases, the lack of response to antibiotics probably is due to the misdiagnosis of Lyme disease (Barbour and Fish, 1993).

Prevention of tick-borne relapsing fevers involves avoiding rodent-infested cabins, caves, or other sites that are infested with rodents and likely to harbor infected ticks. The efficacy of such personal protective measures as repellents and insecticide-impregnated clothing have not been evaluated. Rodent-proofing cabins and insecticidal treatment of cabins known to be rodent-infested should be effective. Relapsing fever can be treated with tetracyclines and penicillin (Burgdorfer and Schwan, 1991).

Opportunities for research.—Description of Lyme disease and discovery of its causative agent are recent, and much research remains to be done to reduce or control its

effects. For mammalogists, abundant opportunities for research exist concerning the interactions among mammalian hosts, their tick parasites, and the transmission of *B. burgdorferi*. The following are examples of unanswered questions amenable for study by mammalogists. What physiological processes determine the relative competence of hosts as reservoirs for *B. burgdorferi*? What determines the probability of a tick finding and feeding on a mammalian host? What are the effects of ticks and spirochetes on the longevity and reproductive success of hosts? What is the relationship between abundance of host and community composition and the abundance of infected ticks? How effective and feasible is control of host for reducing abundance of infected ticks? What is the role of grooming behavior in reducing feeding success of ticks on hosts? How are the population dynamics and spatial distribution of mammals linked with those of ticks and spirochetes? The ecology of tick-borne relapsing fever in the United States is poorly understood, especially the diversity of mammalian hosts involved in enzootic cycles in different regions.

Rickettsial Diseases

Members of the order Rickettsiales are represented by a diverse group of gram-negative bacteria that are largely intracellular parasites. Although many species are adapted to existence within arthropods, frequently they also are capable of infecting vertebrates, including humans. At least 13 species in five genera are pathogenic for humans. Rickettsial diseases, especially louse-borne typhus, have had significant roles in the history of civilization, but recently these diseases have been overshadowed by others that have greater epidemic potential and lack effective interventions. Because of space limitations, this review will concentrate primarily on those vector-borne zoonoses that are caused by infection with members of the genera *Rickettsia, Coxiella,* and *Ehrlichia.*

Description of disease agents.—Traditional classification of the Rickettsiales has been based on a variety of direct phenotypic features, such as morphology and antigenic properties, as well as indirect properties, including geographic distribution, host cell type, animal reservoir, and disease characteristics. However, recent molecular-genetic characterizations using DNA:DNA hybridization, PCR/RFLP, and 16S-rRNA sequencing are causing reevaluation of phylogenetic relationships within this order. Currently, the Rickettsiales is composed of three families: Rickettsiaceae; Bartonellaceae; Anaplasmataceae. The latter family is primarily of veterinary importance and is not discussed in this review. The Rickettsiaceae currently contains eight genera (*Rickettsia, Rochalimaea, Coxiella, Ehrlichia, Cowdria, Neorickettsia, Wolbachia,* and *Rickettsiella*—Weiss and Moulder, 1984). The latter two genera are found in invertebrates and will not be discussed further. *Cowdria* and *Neorickettsia* are primarily of veterinary importance and also will not be discussed in this review. A recently proposed taxonomic change would include species of the genus *Rochalimaea* in the genus *Bartonella* and move the family Bartonellaceae to another order (Brenner et al., 1993). Although *Bartonella quintana* (*Rochalimaea quintana*) and *Bartonella bacilliformis* are vector-borne, these agents are not considered zoonoses and will not be discussed in this review. Another member of this genus, *B. henselae,* is the etiologic agent of cat-scratch disease, a zoonosis that results in >22,000 cases each year in the United States (Jackson et al., 1993). *B. henselae* is transmitted primarily by scratches, bites, or other contacts with cats (Koehler et al., 1994; Tappero et al., 1993). It is not considered to be vector-borne and will not be discussed in this review. However, it should be noted that contact with kittens infested with fleas has been suggested to increase risk of cat-scratch disease (Zangwill et al., 1993), and *B. henselae* has been identified in cat fleas (*Ctenocaphalides felis*).

TABLE 2.—*Vector-borne rickettsial diseases in the United States.*

Rickettsial species	Disease in humans	Distribution	Mode(s) of transmission
Rickettsia rickettsia	Rocky Mountain spotted fever	Western Hemisphere	Tick bite
Rickettsia akari	Rickettsialpox	United States, former USSR, and probably elsewhere	Mite bite
Rickettsia prowazekii	Epidemic typhus	Primarily highland areas of South America and Africa	Infected louse feces
	Recrudescent typhus (Brill-Zinsser disease)	Worldwide; follows distribution of persons with primary infections	Reactivation of latent infection
Rickettsia typhi	Murine typhus	Worldwide	Infected flea feces
Coxiella burnetii	Q fever	Worldwide	Infectious aerosols
Ehrlichia chaffeensis	Monocytic ehrlichiosis	United States, possibly Africa and Europe	Tick bite

Description of disease.—Most of the illnesses caused by rickettsial agents are characterized by sudden onset of fever and other, often nonspecific, signs and symptoms. In many rickettsial diseases, a characteristic rash follows the systemic symptoms and may be pathognomonic. Table 2 provides a list of the etiologic agents discussed in this review, along with their associated diseases, geographic distributions, and modes of transmissions.

Rocky Mountain spotted fever (RMSF), caused by infection with *Rickettsia rickettsii,* is an acute, potentially fatal tick-borne disease characterized by fever, headache and rash, and frequently myalgia and anorexia. Complications include vascular damage, edema, hemorrhage, disseminated intravascular coagulation, interstitial pneumonitis, central-nervous-system (CNS) involvement, myocarditis, and renal failure (Clements, 1992).

Louse-borne (epidemic) typhus, caused by infection with *Rickettsia prowazekii,* is an acute febrile disease accompanied by headache, myalgia, and rash. Complications include interstitial pneumonitis, CNS involvement, myocarditis, and acute renal failure. A recrudescent form of the disease (Brill-Zinsser disease) generally is milder than the initial episode. Recrudescent typhus may occur years to decades after initial infection as a result of diminished immunity due to age, illness, or other causes (Foster, 1981).

Flea-borne (murine) typhus, caused by *Rickettsia typhi* infection, is an acute febrile illness. It typically is associated with headache, myalgia, anorexia, and rash (Miller and Beeson, 1946).

Rickettsialpox is caused by infection with *Rickettsia akari* (Brettman et al., 1984; Lackman, 1963) and is an uncommon febrile illness characterized by sparse, discreet, maculopapular lesions on the face, trunk, and extremities that become vesicular. Eschars occur in most (90%) patients and begin as red papules and develop into shallow, punched-out ulcers.

Q fever is a febrile disease caused by infection with *Coxiella burnetii* (Sawyer et al., 1987). Commonly, patients have sudden onset of headache, chills, myalgia, arthralgia, photophobia, lymphadenopathy, conjunctivitis, nausea or vomiting, diarrhea, and pharyngitis. Pulmonary involvement also is reported frequently. Unlike many other rickettsial diseases, rash is rare. Most cases resolve without serious complications, but endocarditis does occur in a small proportion of chronic cases.

Human ehrlichiosis in the United States,

caused by infection with *Ehrlichia chaffeensis,* is an acute febrile disease characterized by headache, arthralgia, myalgia, anorexia, nausea or vomiting, chills, pneumonia, and, infrequently, rash. Laboratory findings include leukopenia, thrombocytopenia, and elevated liver enzymes (Fishbein et al., 1994).

A new granulocytic form of ehrlichiosis has been reported from Minnesota and Wisconsin. This disease is caused by infection with an ehrlichia closely related to *Ehrlichia phagocytophila* and probably is transmitted by tick bite (Bakken et al., 1994; Chen et al., 1994). Symptoms include fever, headache, myalgia, leukopenia, thrombocytopenia, and pulmonary interstitial infiltrates. Three of the 41 patients confirmed by laboratory testing have died (J. S. Dumler, pers. comm.).

Natural history and epizootiology.—The natural cycle of tick-borne, spotted-fever-group rickettsiae involves both transovarial and transstadial transmission among vector ticks, which are the primary reservoirs, and transmission to mammalian hosts that may serve as amplifying hosts for infecting other ticks. *R. rickettsii,* the etiologic agent of RMSF in the United States, is the most studied of the tick-borne spotted fevers. Although transstadial and transovarial transmission of *R. rickettsii* in its tick vectors is extremely efficient, this rickettsiae probably would not be sustained in nature without mammalian amplifying hosts. Experimental studies have shown that *R. rickettsii* infection has a deleterious effect on survival and fecundity of infected female ticks (McDade and Newhouse, 1986). The eventual loss of these infected lines of ticks presumably is compensated by female ticks feeding on rickettsemic mammalian hosts and then passing their newly acquired infections to their offspring by transovarial transmission.

Several species of small mammals are important as hosts for ticks and sources of infectious blood meals for feeding ticks. In the United States, *R. rickettsii* has been isolated from *Microtus pennsylvanicus, Microtus pinetorum, P. leucopus, Sigmodon hispidus, Sylvilagus floridanus, Didelphis virginiana, Tamias amoenus, Lepus americanus,* and *Spermophilus lateralis.* Serologic evidence of *R. rickettsii* infection has been found in numerous other species including many rodents, carnivores, and deer (McDade and Newhouse, 1986).

The only significant reservoir for louse-borne typhus is man. The disease is maintained endemically in a few areas where transmission occurs almost continuously among humans infested with human body lice (*Pediculus humanus humanus*). These endemic foci can serve as sources of epidemics when normal sanitary practices are interrupted. Persons with recrudescent typhus can serve as sources of infection for lice many years after they were initially infected with *R. prowazekii* and are, thus, the main reservoirs of infection. Occasionally, these recrudescent-typhus cases are responsible for sporadic epidemics of louse-borne-typhus. One documented exception to the generalization that louse-borne-typhus rickettsiae lack a nonhuman reservoir is the identification of an agent that is indistinguishable from *R. prowazekii* in flying squirrels and their ectoparasites (McDade, 1987) in the southern United States. This natural cycle, however, does not contribute to the maintenance of the louse-borne disease of humans.

Rickettsia typhi is naturally maintained in *Rattus rattus, Rattus norvegicus,* and a few other species of rodents and their fleas. Several species of fleas (especially the rat flea, *Xenopsylla cheopis*) are capable of transmitting the agent to susceptible hosts (Fahrang-Azad and Traub, 1985; Traub et al., 1978). There is evidence of transovarial transmission of *R. typhi* in *X. cheopis* (Farhang-Azad et al., 1985). A natural cycle of *R. typhi* also is maintained by opossums and cat-fleas (*Ctenocephalides felis*) in California (Williams et al., 1992).

The natural history of *R. akari* is poorly understood. *Rickettsia akari* naturally infects *M. musculus* and its mite (*Liponysso-*

ides sanguineus—Brettman et al., 1984; Lackman, 1963). There is a single report of *R. akari* isolated from the Korean vole, *Microtus fortis pelliceus,* suggesting that extramurine cycles may exist (Jackson et al., 1957).

The natural cycles of *Ehrlichia* pathogenic for humans are less well known than those for *Rickettsia.* Emerging evidence suggests that *Amblyomma americanum* may be the primary vector of *E. chaffeensis* and that *Ixodes scapularis* may be the vector of the *Ehrlichia* that causes human granulocytic ehrlichiosis (Chen et al., 1994). Transovarial transmission of *Ehrlichia* has not been shown, although transstadial transmission of *E. chaffeensis* in *A. americanum* recently has been demonstrated (C. P. Ewing, pers. comm.).

Ehrlichia has not been recovered from naturally-infected ticks or vertebrates; however, serologic evidence suggests that *O. virginianus* and *P. lotor* have high prevalences of antibody to *E. chaffeensis.* Small mammals, including many species of rodents, do not appear to be involved in an endemic maintenance cycle of *E. chaffeensis.* Laboratory experiments have shown that *E. chaffeensis* is capable of infecting *O. virginianus* and causing a long-lasting rickettsemia (Dawson et al., 1994). These experiments also indicate that *A. americanum* may acquire the infection from rickettsemic deer (C. P. Ewing, pers. comm.). Epidemiologic evidence suggests that domestic dogs may have a role in the maintenance of the agent in nature (Chen et al., 1994).

Coxiella burnetii is maintained in several species of ticks in the United States, including *Haemaphysalis leporis-palustris, Amblyomma americanum, Amblyomma cajennense, Ixodes dentatus, Dermacentor andersoni, Dermacentor occidentalis,* and *Rhipicephalus sanguineus.* These ticks probably transmit *C. burnetii* among animals, but such transmission is not essential to maintain the organism in nature (Aitken et al., 1987; Lang, 1990). A variety of wild and domestic animals, including rodents, lagomorphs, carnivores, and artiodactyls, become infected with *C. burnetii* (Stoenner, 1980). Cattle, sheep, and goats also are common hosts for the Q-fever agent.

Epidemiology.—The case-fatality ratio of RMSF has been reduced to 3–5% since antibiotic therapy became available, but, untreated, the case-fatality ratio ranged from 23 to 70% (Harrell, 1949). Most of the ca. 600 cases reported annually in the United States are located in the southeastern and southcentral states where *Dermacentor variabilis,* the primary vector in the eastern United States, is prevalent. Smaller numbers of cases occur in western states, especially those states in the northern Rocky Mountain region, where the primary vector is *D. andersoni.* The incubation period varies from 4 to 14 days. The highest incidence occurs in children 5–9 years old, and males outnumber females by nearly two to one. Delay in initiating antibiotic therapy and increased age of patients are risk factors that significantly increase complications and death. Humans are at greatest risk of acquiring RMSF when they enter environments that support large numbers of vector ticks (Burgdorfer, 1975).

During epidemics, louse-borne typhus may have case-fatality ratios of 10–66% (Foster, 1981; Megaw, 1942), depending on the health and nutrition of populations afflicted. Outbreaks of louse-borne typhus occur when pediculosis (louse infestation) is widespread as a result of the disruption of regular hygiene and lack of adequate water supplies for bathing. Typical settings where outbreaks of louse-borne typhus occur include refugee camps, prisons, and communities ravaged by war or disaster. An endemic form of the disease occurs in several areas of the world where high altitude and cold weather combine to promote conditions of pediculosis.

In general, humans are the only mammalian host for *R. prowazekii,* although a zoonotic form of *R. prowazekii* has been identified in North America that results in a few human cases. This zoonosis is main-

tained in flying squirrels and their ectoparasites and might be transmitted to humans by aerosols from infected ectoparasites (McDade, 1987).

Flea-borne typhus is mild compared to louse-borne typhus, and fatalities are rare (Miller and Beeson, 1946). The worldwide distribution of the disease is attributed to the distribution of the rat flea (*X. cheopis*) and its hosts, *Rattus rattus* and *Rattus norvegicus*. Flea-borne typhus is a major cause of febrile illness in the tropics and occasionally occurs in the United States, especially along the Gulf Coast and in southern California. Populations that are occupationally exposed to commensal rats and their fleas have increased risks of infection.

Rickettsia akari is transmitted to humans via the bites of infected mites (*Liponyssoides sanguineus*). This typically occurs when humans live in or enter premises infested with house mice (*M. musculus*), which are hosts for the vector mites. Most cases in the United States are from urban environments of low socioeconomic status (Brettman et al., 1984). Rickettsialpox probably occurs throughout much of the world where house mice and their mites are found.

The case-fatality ratio for human ehrlichiosis in the United States is ca. 3%. More than 300 confirmed cases of human ehrlichiosis have been reported from 25 states (Centers for Disease Control and Prevention, pers. comm.). The southern Atlantic and eastern southcentral states account for the majority of cases. More than 90% of cases occur from April to September when vector ticks are actively questing for blood meals (Fishbein et al., 1994). Seventy-five percent of reported cases occur in males. It is not clear whether the difference in incidence between males and females is due to exposure or other factors. Preliminary evidence suggests that *A. americanum* may be a vector (Anderson et al., 1993). The white-tailed deer is a potential reservoir for maintaining *E. chaffeensis* in nature (Dawson et al., 1994). Risk factors for infection include occupational and recreational exposure to tick-infested areas.

Q fever (case-fatality ratio of ca. 1%) is worldwide in distribution and usually is transmitted to humans by inhalation of infectious aerosols from animal tissues or products and occasionally by ingestion of unpasteurized milk. The disease is rarely reported in the United States, and it is possible that many cases go unreported. Ticks often are infected and may play a role in maintenance and transmission of *C. burnetii* among animal hosts, but probably play little or no role in transmission to humans. Occupational exposure to infected livestock is a major risk factor. Abattoir workers, sheep shearers, and wool gatherers have disproportionately high rates of infection (Bernard et al., 1982). Persons who have contact with sheep, particularly fetuses and birth products, are at especially great risk. A rare but frequently fatal chronic form of the disease manifests as endocarditis among patients who have preexisting heart-valve disease (Ellis et al., 1982; Turck et al., 1976).

Treatment and prevention.—Antibiotic therapy is, in general, of great benefit to patients infected with rickettsiae (Harrell, 1949). Although tetracyclines, doxycyclines, and chloramphenicol are the antibiotics of choice for treating most rickettsioses, including RMSF, erythromycin and ciprofloxacin have been used successfully to treat Mediterranean spotted fever (Beltran and Herrero, 1992). Q-fever cases usually can be treated successfully with any of the aforementioned rickettsiostatic antibiotics, but the recommended treatment for chronic Q fever is a combination of doxycycline and ciprofloxacin. These chronic-Q-fever patients may require many years of antibiotic therapy to prevent episodic illness (Levy et al., 1991).

Prevention of the arthropod-borne diseases caused by rickettsia-like agents includes a variety of measures that reduce the likelihood of contact between vectors and susceptible humans. In general, avoiding

exposure to habitats known to be endemic for the diseases or the vectors of these diseases is prudent, but often not practical, advice. Persons who must enter mite-, tick-, or flea-infested areas should take certain personal protective measures to minimize contact with potentially infected vectors. Commonly recommended measures include wearing light-colored trousers and shirts that fit tightly around ankles and wrists, respectively, wearing clothing impregnated or sprayed with permethrin or repellents (DEET), spraying repellents on skin, and promptly removing any ticks from the body to reduce risks of infection. Environmental modifications, including removing vegetation or other materials where ticks quest or their rodent hosts live, may be effective means for reducing risks of tick-borne spotted fevers. Prevention of flea-borne typhus depends on measures similar to those described for plague control. Personal-hygiene measures, such as regular bathing and washing clothes with soap and hot water, are important for preventing louse-borne typhus. Disinsection of human populations infested with body lice also is an effective measure to contain epidemics of louse-borne typhus.

Several vaccines for diseases caused by *Rickettsia* have been produced, but none has been completely effective, including a previously available vaccine for Rocky Mountain spotted fever. The use of a formalin-killed vaccine may have been a factor in limiting the spread of louse-borne typhus during World War II. Prophylactic administration of antibiotics has been shown to be effective for preventing mite-borne (scrub) typhus among populations with occupational exposure risks (Olson et al., 1980), but has not been adequately evaluated as a preventive measure for other rickettsioses.

Q fever can be prevented by avoidance of contact with potentially infectious animal tissues or products. Occupationally-exposed persons may reduce their risk by wearing respirators that prevent aerosol infections. A vaccine in Australia is highly effective in preventing illness among abattoir workers (Marmion et al., 1984).

Opportunities for research.—Recent molecular advances have allowed rickettsiologists to perform many investigations that previously were difficult or impossible because of the obligate intracellular nature of most of these agents. Among the most interesting questions for mammalogists are those related to the identification of the natural hosts and vectors of the newly-discovered ehrlichiae described in this review. Ecological and laboratory investigations also are needed to clarify the interactions between *R. rickettsii* and other antigenically-related rickettsiae that are found in ticks but presumed to be nonpathogenic for humans and most mammals (McDade and Newhouse, 1986). Long-term ecological studies to determine factors affecting the focality of rickettsial and ehrlichial disease agents also are needed.

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