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ECOLOGICAL  
RELATIONSHIPS  
*and*  
EVOLUTION  
*of the*  
RICKETTSIAE

Volume I  
Nyven J. Marchette

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# Ecological Relationships and Evolution of the Rickettsiae

## Volume I

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## PREFACE

“What song the Syrens sang, or what name Achilles assumed when he hid himself among women, although puzzling questions, are not beyond all conjecture.” In these words Sir Thomas Browne sets no limit to speculation, but it is generally admitted that speculation is idle if it is useless. The present review of rickettsial ecology and evolution assumes that speculation should be carried as far as is necessary to form a working hypothesis, upon the framework of which both the investigator and the student may hang their ideas. Moreover, a detailed examination of the evolution and possible relationships of the pathogenic rickettsiae may provide the fundamental basis for a natural classification of the family Rickettsiaceae and perhaps even the order Rickettsiales.

The ecological relationships of the rickettsiae for the most part are well known or at least amenable to investigation, but many details relating directly to rickettsial evolution are missing or incompletely known and cannot be subjected to rigorous scientific analysis. Fortunately, however, rickettsiae are obligate parasites with complex life cycles dependent upon certain mammals and arthropods about which a great deal is known. Our knowledge of the present geographical distribution of vertebrates, acarines, and pathogenic rickettsiae is especially good, and immunological and biochemical techniques enable us to establish degrees of relationship between microorganisms with some confidence. Many aspects of the relationships of rickettsiae to their hosts are also well known. The paleontological evidence for the evolution of the mammalian hosts of ticks and their rickettsiae, though far from complete, is sufficient to satisfy most critics. The geological record of changes of the Earth over the past 100 million years or so is likewise well documented, if not complete in every detail. Ticks and mites are almost completely absent from the fossil record, but studies of the systematics and distribution of living forms provide valuable, if incomplete, information on acarine phylogeny. Judicious use of the considerable amount of material that is available relative to rickettsiae should enable one to speculate from a firm base as to the probable course of rickettsial evolution.

An axiom of science is that, in the study of natural phenomena, the simplest explanation that logically fits all the data available is likely to be closest to the truth. This assumes, of course, that all or most of the relevant information concerning the phenomenon under investigation is known, but this is not always the case, and seldom is it so in the study of evolution. Thus, it is essential not to construct too rigid a framework for the rickettsial evolutionary tree. The accumulation of new data may require its periodic pruning, with prudent cutting and grafting of branches here and there, to maintain its viability and preserve its natural symmetry.

In the present study, many fields and disciplines are explored for evidence pertinent to an evolutionary history of the rickettsiae. From these data may emerge a logical sequence of events occurring through geological and historical time, culminating in the rickettsial species living today. As you will see, in certain areas so little is known that the conclusions are scarcely more than educated guesses. Perhaps the most valuable contribution of this study will be in pointing out what is not known rather than in reviewing what is known of rickettsial evolution. If even a few students are stimulated to explore some of the many unsolved problems, this work will have served a useful purpose.

Nyven Marchette



## THE AUTHOR

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He received a Bachelor of Science degree in general zoology from the University of California, Berkeley in 1950 and a Master of Science degree in Invertebrate Zoology from the same institution in 1953. The next two years were spent in the U.S. Army as an enlisted man assigned to the Biological Warfare testing facility at Dugway, Utah where he participated in ecological research in collaboration with a group from the University of Utah. Following discharge from the army, he stayed with the university group and received the Ph.D. degree in bacteriology from the University of Utah, Salt Lake City in 1960.

In 1960–1961 Dr. Marchette was appointed Research Bacteriologist at the University of Utah Ecological Research facility at Dugway Proving Ground, Utah. Between 1961 and 1964 he was a post doctoral fellow and then Assistant Research Microbiologist in the International Centers for Medical Research and Training Program at the University of California, San Francisco and the Institute for Medical Research in Kuala Lumpur, Malaysia. From 1965 to 1967, he moved to the Department of Microbiology in the new University of Malaya Medical School and established the University of California ICMRT Arbovirus Research Laboratory. He remained with the University of California until 1970 running the arbovirus research laboratory in San Francisco at the Hooper Foundation (still associated with the ICMRT).

In 1970, Dr. Marchette accepted a position as Associate Professor of Tropical Medicine and Public Health at the Department of Tropical Medicine and the School of Public Health at the University of Hawaii, Honolulu. From 1974 to the present his title has been Professor of Tropical Medicine and Public Health.

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# Ecological Relationships and Evolution of the Rickettsiae

Nyven J. Marchette

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Evolution of the Tick-Rickettsia Relationships

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Chapter 1

INTRODUCTION

N. Marchette

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## I. BACTERIAL CLASSIFICATION

Cowan<sup>1</sup> correctly pointed out that without a fossil record much of bacterial taxonomy is a “. . . mixture of speculation and wishful thinking.” However, I do not agree completely with his claims that “. . . the ‘best’ classifications are those made by artists with the keenest appreciation of what is both useful and intellectually satisfying.” In my opinion the “best” classifications are those which attempt to place organisms in groups on the basis of their phylogenetic relationships (presumed or otherwise). Admittedly this is not an easy task when dealing with the bacteria for which there is essentially no fossil record. It may not be possible to force them into structurally rigid classification systems similar to those of morphologically more complex organisms, but the basic philosophy of classification still applies. As Stanier and Van Niel<sup>2</sup> have pointed out, an imperfect natural system is preferable to a purely empirical one.

An overall view will show that microorganisms do fall into natural units which are recognizable and definable. What is not always appreciated is that these natural units cannot be defined in exactly the same way that species of higher organisms are defined,<sup>3</sup> but they can be described in similar terms. There are natural units (species) that have geographical-distribution area. For example, *Franciscella tularensis* occurs only in the North Temperate Zone, *Rickettsia tsutsugamushi* is restricted to parts of Asia, and *Bartonella bacilliformis* occurs only in Peru, Ecuador, and Colombia. If another dimension of distribution is added, namely, the specific habitat or ecosystem occupied by the organism, other natural units (on the species level as well as on the generic and higher taxonomic levels) can be recognized. The rickettsiae are good examples; certain “natural groups” are parasites or symbiotes of ticks, others of insects, and these may also have restricted geographic distribution coinciding with that of their hosts.

These natural groups are self-perpetuating. The rate of change (evolution) of bacterial “species” may appear to be greater than that of more complex organisms, but this is not necessarily true of “field populations”. In the laboratory, “evolution” can be accelerated, but natural populations tend to change more slowly. *Yersinia pestis*, for example, does not appear to have changed substantially in the last 2000 years, at least with regard to its pathogenicity for man.

Morphologically distinguishable groups of microorganisms obviously exist, but morphological characters per se may not be as important in microbial taxonomy as they are for more complex organisms.<sup>4</sup> The addition of cytological, chemical, physical, and biochemical parameters to structural characteristics, however, does provide sufficient diversity and complexity to serve as useful criteria for group definition.<sup>5</sup> The relative proportion of nucleotide bases in microbial nucleic acid and DNA homology between organisms, as well as polypeptide fingerprinting, are becoming powerful tools for the systematist. Comparisons of macromolecular sequences can reveal evolutionary trends and phylogenetic relationships which may or may not fit with those derived by other methods.<sup>6-9</sup>

Microbial genetics, differing in many respects from that of higher organisms, has been used to some extent in systems of classification. Bacteria are essentially asexual, but gene-flow does occur through nonsexual mechanisms such as transformation, transduction, and perhaps others.<sup>10,11</sup>

A natural system of classification must take into account (as any good system should) all the parameters that can be measured and defined. Most important of all, natural units must be defined on the basis of all the characteristics of *natural populations*, not on those of laboratory stock cultures, which may or may not be representative of the population as a whole. A good deal of logic and reason, and not a little speculation, are also essential ingredients for devising a classification based on phylogenetic rela-

tionships. Excellent discussions of microbial classification and comprehensive bibliographies have been published<sup>1,11-14</sup> and will not be repeated here.

## II. EVOLUTION OF RICKETTSIAL CLASSIFICATION

### A. Arthropod Association and Pathogenicity

Wolbach,<sup>15</sup> recognizing the similarity of various rickettsia-like microorganisms that occur in insects and acarines, proposed that they be separated into three groups on the basis of their mode of life and pathogenicity for man. Thus, he placed all the non-pathogenic symbiotes of insects in one group, the obligate intracellular organisms pathogenic for man in another, and those that grow extracellularly in the gut lumen of lice or sheep keds (*Rickettsia* [= *Rochalimaea*] *quintana* and *Wolbachia melophagi*) in a third group. He also recognized that the extracellular rickettsiae closely resemble ordinary bacteria, the intracellular parasites differing from them in degree as a result of their specialization to an intracellular environment. These remarkably astute observations made over half a century ago are now generally accepted.

Wolbach was interested more in the organisms themselves than in the diseases they produced. About the same time, others were concerned with the diseases caused by these organisms in man. Megaw<sup>16,17</sup> was the first to bring a semblance of order to the perplexing array of exanthematous fevers recognized at the time. In this early stage, he grouped typhus, Rocky Mountain spotted fever, tsutsugamushi fever, and related diseases of uncertain origin into a single typhus group of fevers caused by rickettsiae and transmitted by arthropods. A short time later he also classified these typhus fevers according to vectors,<sup>18</sup> that is, louseborne, tickborne, and miteborne diseases; fleas were soon added to the list as vectors of fleaborne (endemic or murine) typhus.

Meanwhile Fletcher and Lesslar<sup>19</sup> were trying to unravel the puzzling array of typhus-like fevers occurring in Malaya. They made the extremely important observation that the sera of patients who recovered from some, but not all, types of typhus-like fevers in Malaya agglutinated certain strains of *proteus* bacilli. Audy and Savor,<sup>20</sup> in the excellent history of the Institute for Medical Research in Kuala Lumpur, give a detailed account of this fascinating story which resulted in a classification of rickettsial diseases on the basis of the Weil-Felix reaction.

The Weil-Felix reaction is so intimately associated with the early typhus fever studies in Malaya that the story is worth repeating here. Professor W. J. Wilson was the first to discover that an organism isolated from the urine of a typhus patient was agglutinated by serum from other typhus patients. His observations were made in 1909. It wasn't until 1915 that Weil and Felix isolated *Bacillus proteus* (*Proteus vulgaris*) from the urine of a typhus patient and found that it was agglutinated by the patient's serum and that of other typhus patients. A year later Felix isolated another *proteus* bacillus, which he called the "X 19" strain, and it became the basis of the Weil-Felix reaction, which, to be fair, should be called the Wilson-Weil-Felix reaction.

In 1924, a sample of *B. proteus* X 19 was obtained from the Bland-Sutton Institute by A. N. Kingsbury and brought to the Institute for Medical Research in Kuala Lumpur, Malaya. This strain had been sent from the National Collection of Type Cultures to the Bland-Sutton Institute in 1921. Fletcher and Lesslar began to use the strain on so-called tropical typhus cases and found that serum from these patients agglutinated the organism. This linked the Malayan cases to the louseborne typhus fevers of Europe (fleaborne typhus had not yet been discovered), but the epidemiology of Malayan typhus was so different that suspicions were aroused. A detailed comparison of nine different *B. proteus* strains was then made.<sup>21</sup> Eight were similar to each other, the ninth was different. It was the "Kingsbury" strain. It was agglutinated by the serum of "typhus" cases

**Table 1**  
**CLASSIFICATION OF THE TYPHUS GROUP BASED ON THE *PROTEUS***  
**OX AGGLUTINATION TEST**

	Group 1	Group 2	Group 3
Proteus agglutinin	(OX 19)	(OX K)	(OX 19, OX K, OX 2—slight agglutination)
Human disease	Epidemic typhus, tabardillo, Brill's disease, endemic typhus	Tsutsugamushi fever, scrub typhus	Rocky Mountain spotted fever, Sao Paulo fever, <i>Fievre boutonneuse</i> , South African, Indian, Kenyan tick bite fever
Rickettsia	<i>Rickettsia prowazekii</i> <i>R. typhi</i>	<i>R. tsutsugamushi</i>	<i>R. rickettsii</i> <i>R. conorii</i>

which did not agglutinate any of the other strains and vice versa. It also did not produce indole by fermentation as did the other strains. Several strains that were unable to produce indole were compared to the Kingsbury strain, but they were not the same. The Kingsbury or "K" strain was unique. Subsequent use of these two strains of *Proteus vulgaris* resulted in the identification of two forms of typhus, one of which, scrub typhus or tsutsugamushi disease (chiggerborne rickettsiosis), was unique to Asia.<sup>22</sup> The other form was fleaborne typhus, which resembles louseborne typhus in possession of antigens similar to those of *proteus* OX 19, as it is generally referred to today.

When and how the National Collection of Type Cultures strain of *P. vulgaris* OX 19 got replaced by or mutated into *P. vulgaris* OX K will never be known. This fortuitous accident was instrumental in clarifying a very confusing situation in which two clinically similar but epidemiologically distinct diseases were found to be caused by different organisms transmitted by different vectors.

## B. Immunological Characteristics

Classification of parasitic bacteria and viruses at the species level is based largely on antigenic relationships as measured by various serological techniques. Thus, Felix<sup>23,24</sup> distinguished three subgroups among the "typhus group" of fevers on the basis of the *Proteus* agglutination test (Table 1). This classification was for the epidemiologist and fit in well with Megaw's classification of the typhus fevers according to vectors. Those diseases transmitted by lice and fleas are in Group 1, those transmitted by trombiculid mites in Group 2, and those transmitted by ticks in Group 3. All subsequent workers have confirmed the integrity of these groups of rickettsiae, and, by working with the agents themselves, have further characterized the "species" of rickettsiae within each group and added new ones.

The development of immunological and serological techniques and their application to rickettsiae has further defined the species, and the process is still going on. The named *Rickettsia* species grouped according to modern immunological tests are shown on Table 2.

### 1. The Louseborne and Fleaborne (OX 19-Agglutinating) Group

The agents of louseborne typhus (*R. prowazekii*) and fleaborne typhus (*R. typhi*) were long known to be closely related on the basis of many observations, not the least of which was their ability to produce cross-immunity in guinea pigs.<sup>25</sup> Crude antigens also produced cross-reactions in the complement fixation test, but Plotz<sup>26</sup> demonstrated that

**Table 2**  
**IMMUNOLOGICAL GROUPING OF THE NAMED RICKETTSIA SPECIES**

Group 1	Group 2	Group 3
<i>Rickettsia prowazekii</i>	<i>Rickettsia tsutsugamushi</i>	<i>Rickettsia rickettsii</i>
<i>R. typhi</i>		<i>R. sibirica</i>
<i>R. canada</i>		<i>R. conorii</i>
		<i>R. parkeri</i>
		<i>R. akari</i>
		<i>R. australis</i>
		<i>R. montana</i>
		<i>R. rhipicephali</i>
		<i>R. slovaca</i>

purified antigens are highly specific and can distinguish between them. Gildemeister and Haagen<sup>27</sup> added another tool to the serologists' armamentarium by showing that murine typhus rickettsiae produce a toxic factor with immunologic properties, and Hamilton<sup>28</sup> demonstrated that toxins produced by *R. typhi* and *R. prowazekii* are immunologically distinct. The results obtained with the toxin neutralization test, the conclusions drawn from the complement fixation reaction, and many other lines of evidence indicated that *R. prowazekii* and *R. typhi* are closely related but antigenically distinct organisms. Furthermore, immunization and cross-challenge tests showed a weak relationship between this group and the tickborne group. Guinea pigs immunized with typhus rickettsiae are often also protected against challenge with virulent Rocky Mountain spotted fever rickettsiae.<sup>29</sup>

**A Tickborne Member of the Typhus Group**—In 1963 strains of a *R. typhi*-like rickettsia were isolated from the rabbit tick *Haemaphysalis leporispalustris*, taken from a sentinel rabbit and from a wild snowshoe hare in Ontario, Canada.<sup>30</sup> In complement fixation tests with guinea pig sera, this agent was shown to be nearly identical to *R. typhi* rather than to any known tickborne agent. It can be distinguished from *R. typhi* and *R. prowazekii*, however, by toxin neutralization tests and by the species-specific complement fixation test obtained with mouse antisera, which had proved useful in differentiating other closely related rickettsiae.<sup>31</sup> This new rickettsia, named *R. canada*, appears to belong in the typhus group on the basis of antigenic relationships even though it is apparently tickborne rather than carried by fleas or lice.

## 2. The Trombiculid Miteborne (OX K-Agglutinating) Group

*Rickettsia tsutsugamushi* is immunologically distinct from all other rickettsiae but shows considerable antigenic variation within the species. Three major antigenic types are generally recognized: Karp, Kato, and Gilliam,<sup>32</sup> but the recent work of Elisberg et al.<sup>33</sup> and others suggests that other antigenic variants occur naturally in Thailand and elsewhere. Much more work is needed before the highly complex antigenic properties within this group can be resolved. The uniqueness of *R. tsutsugamushi* among the Rickettsiae, however, is unquestioned.

## 3. The Tickborne "Spotted Fever" Group

The spotted fever (tickborne) rickettsiae form a heterogeneous group that can be defined immunologically on the basis of a common antigenic component. Lackman and Pickens<sup>34</sup> defined the group as one containing all rickettsiae having a soluble antigen which fixes complement in the presence of serum of guinea pigs convalescent from

Rocky Mountain spotted fever. The individual species can be distinguished by their reactions in one or more of the following tests:

1. Complement fixation, using washed rickettsial suspensions reacted with antisera prepared in guinea pigs inoculated with living rickettsial suspensions<sup>35</sup>
2. Cross-challenge, in guinea pigs immunized with either living or formalin-killed rickettsial suspensions<sup>36,37</sup>
3. Toxin neutralization<sup>38</sup>
4. Mouse protection against a toxic challenge<sup>39</sup>
5. Complement fixation using mice for the production of species-specific CF antibodies.<sup>31</sup>

Lackman et al.<sup>37</sup> clearly summarized the serological and immunological relationships between these rickettsiae and separated them into four distinct but related subgroups. *Rickettsia rickettsii* and *R. sibirica* are in subgroup A and *R. conorii* and *R. parkeri* in subgroup B on the basis of strong cross-reactions in the toxin neutralization test. The relationship between subgroups A and B is indicated by a slight cross-reaction between *R. sibirica* and *R. conorii* in the CF test. The various geographical strains of *R. conorii* (South African tick-bite fever, Kenya tick typhus, and Indian tick typhus) are antigenically identical to the agent of *fièvre boutonneuse*.<sup>38</sup> Subgroup C consists of *R. australis* and *R. akari* whose relationship is shown by the guinea pig cross-challenge test. Subgroup D contains *R. montana* and Western Montana U agent, an avirulent strain similar to *R. rickettsii*, on the basis of CF antibody studies in mice. More recent immunological groupings will be discussed in Volume I, Chapter 5.

### C. The *Proteus* Nonagglutinating Organisms

*Coxiella burnetii* and *Rochalimaea quintana* are antigenically distinct from all recognized species of *Rickettsia*. Exhaustive comparative serological and immunological studies have not been reported, but Vinson and Campbell<sup>40</sup> have shown that *R. quintana* and *C. burnetii* do not cross-react in the complement fixation test, nor does *R. quintana* immune rabbit serum contain antibodies to soluble *R. prowazekii* antigen. These two organisms appear to be as distinct antigenically from the main *Rickettsia* stem as they are distinct from it in many other characteristics. They will be discussed in greater detail in Volume II, Chapters 10 and 11.

## III. PHYLOGENETIC RELATIONSHIPS AND CLASSIFICATION ACCORDING TO VECTOR

Based on immunological criteria the rickettsia stem, divorced of *C. burnetii* and *R. quintana*, is composed of a rather homogeneous group of organisms (Table 2). Any natural classification will have to include the agents of typhus fevers (Group 1) and the tickborne agents (Group 3). The members of these antigenic groups are closely related phylogenetically and the phylogenetic relationship of *R. tsutsugamushi* to Groups 1 and 3 can be hypothesized, but may be rather remote. The relationships of the other "rickettsial" lines are less easily derived. These relationships as well as those of other families in the order will be explored in some detail in the following chapters.

### A. Terminology

A variety of terms commonly used to refer to rickettsiae and rickettsial diseases are sometimes used inaccurately, and their meaning often is not entirely clear. Common usage of certain terms over many years has made them household words in various



parts of the world, and they will continue to be used regardless of the fact that they may be etymologically incorrect. Generally, two sets of terms are necessary to clearly distinguish between the organism and the disease it causes in man. Specific terms to refer to individual organisms are also required in some instances. The context in which terms are used often determines their exact meaning, but this is not always the case. In the following discussions, I have attempted to minimize the confusion by sticking wherever possible to a standard set of terms to refer to the rickettsiae and the diseases they cause. In some cases, terms that are widely used and whose meanings are clear may be used interchangeably if there is no chance for confusion. In general, the terminology suggested by Traub and Wisseman<sup>41</sup> will be used throughout. This terminology recognizes the fact that infection is not always (perhaps seldom) associated with disease. Thus, infection of whatever nature is referred to as a "rickettsiosis." The type of rickettsiosis is indicated by prefixing the name of the common vector or arthropod maintaining host when relevant or known. When referring to the organisms themselves as a group, the term rickettsia (with a small "r") with the appropriate prefix is employed.

## B. Tickborne Rickettsiae

All the organisms which are maintained naturally by ticks are included in the term tickborne rickettsiae, (singular, rickettsia). The most common synonyms for this group are tick typhus rickettsiae or spotted fever rickettsiae. The organisms in this group and the diseases they cause in man are

<i>Rickettsia conorii</i>	<i>Fievre boutonneuse</i>
<i>R. sibirica</i>	North Asian (Siberian) tick typhus
<i>R. rickettsii</i>	Rocky Mountain spotted fever, spotted fever
<i>R. australis</i>	Queensland tick typhus
<i>R. akari</i>	Rickettsialpox
<i>R. canada</i>	No disease known
<i>R. parkeri</i>	No disease known
<i>R. montana</i>	No disease known
<i>R. rhipicephali</i>	No disease known
<i>R. slovaca</i>	No disease known

This classification suffers from the same problem inherent in all generalizations. Lumped together are organisms which can be readily separated into distinct categories of their own on the basis of other biological criteria. *Rickettsia canada*, although tickborne, is antigenically related to the insectborne typhus group rather than to the spotted fever or tick typhus group. Also, *R. akari* technically is not tickborne, but is maintained naturally by a mesostigmatic mite even though it is antigenically and biologically close to the spotted fever group. The mesostigmata (mites), however, are closely related phylogenetically to the Metastigmata (ticks) and in many respects, they resemble tiny ticks. Since *R. akari* is the only rickettsia known to be associated with mesostigmatic mites, and because of its other biological properties, it is included in the tickborne rickettsiae.

The Wolbachiae are symbiotes of ticks and other arthropods and they do not infect vertebrates as far as is known. The tickborne members of this group may be phylogenetically related to the tickborne rickettsiae, but there is reason to believe that the insectborne Wolbachiae are phylogenetically unrelated (Volume II, Chapter 8).

The association of members of the Ehrlichiae with arthropods is not so well established as for the Rickettsiae and Wolbachiae, and phylogenetic relationships are ten-

uous at best. In one species, *Neorickettsia helminthoeca*, the natural invertebrate host appears to be a trematode worm, not an arthropod at all (see Volume II, Chapter 9).

In the family Anaplasmataceae, there are organisms whose association with ticks is reasonably well-established, others for which it is debatable, and still others for which it doesn't exist at all. The phylogenetic relationship of the anaplasmas with the rickettsiae may be very remote at best (see Volume II, Chapter 11).

*Coxiella burnetii*, although it may be tickborne, is not included in this group for reasons that will be discussed in Volume II, Chapter 10.

### C. Insectborne Rickettsiae

The rickettsiae maintained in or closely associated with insects are classed as the insectborne rickettsiae and include *R. typhi*, fleaborne (endemic or murine) typhus, and *R. prowazekii*, louseborne (epidemic or classical) typhus. *Rochalimaea quintana*, the etiologic agent of trench fever in man, might logically be included in this group since its natural host is the human body louse, but there are important reasons to doubt its membership in the Rickettsiales (Volume II, Chapter 11).

One of the three species in the small family Bartonellaceae, *Bartonella bacilliformis*, is biologically associated with phlebotomine flies and thus may be considered to be arthropodborne. The other two species are not associated with arthropods at all. All three species grow well on nonliving bacterial media and in many other ways are not rickettsial in nature (see Volume II, Chapter 11).

### D. Trombiculidborne Rickettsiae

The rickettsiae maintained by trombiculid mites, the numerous serotypes of *R. tsutsugamushi*, are classified as trombiculidborne rickettsiae. The infection they cause is termed chiggerborne rickettsiosis in recognition that only the larvae (chiggers) of the trombiculid mites are parasitic on vertebrates, and only they can transmit the rickettsiae (see Volume II, Chapter 7).

## IV. NATURAL CLASSIFICATION OF THE RICKETTSIAE

Development of a natural or phylogenetic classification of the rickettsiae is not an impossible or impractical task. The obligate association of most members of the group with vertebrates and arthropods suggests a long-term, perhaps evolutionary, relationship so that the origin, development, and divergence of the rickettsiae may be traced through the origin, development, and divergence of their arthropod and vertebrate hosts. This approach is utilized in the present review and discussion of rickettsial ecology and evolution.

Documentation of facts and statements is provided whenever possible by citing the original references. Most of the Russian literature cited was seen as translations through the generosity of Dr. Harry Hoogstraal, U.S. Navy Medical Research Unit No. 3, Cairo, Egypt. Considerable use also was made of Hoogstraal's multivolume *Bibliography of Ticks and Tickborne Diseases*<sup>42</sup> and the *Index-Catalogue of Medical and Veterinary Zoology* compiled by Doss et al.<sup>43</sup>

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