ZOONOSES AND COMMUNICABLE DISEASES COMMON TO MAN AND ANIMALS

Third Edition

Volume II

Chlamydioses, Rickettsioses, and Viroses

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PROLOGUE

In recent years, zoonoses and communicable diseases common to man and animals have gained increasing attention worldwide. Human diseases that have their origins in infected animals, such as AIDS or Creutzfeldt-Jakob, have highlighted the need for a better understanding of animal diseases in terms of their epidemiology, mechanism of transmission to man, diagnosis, prevention, and control. Social and demographic changes have also contributed to the importance of gaining and disseminating knowledge about zoonoses. For instance, as people encroach further and further on ecological areas with which they had little contact and whose fauna may not be well known, their exposure to animals—and the infections they transmit—has increased. New knowledge is also being developed in the area of urban ecology. The ease and speed of modern travel also facilitates the spread of diseases once confined to specific geographic areas, as recently occurred with severe acute respiratory syndrome (SARS). Animal migration and trade pose a similar threat, as was shown by the outbreaks in the United States of West Nile fever, and most recently, monkeypox—two diseases not previously known in the Western Hemisphere. Each of these examples highlights the need for improved knowledge and surveillance of and response to zoonoses.

The negative effects of zoonoses are far reaching. High incidence rates continue to cause significant morbidity and mortality in both humans and animals. Their economic impact is seen in lost labor productivity due to illness; reduced travel and tourism to affected areas; reduced livestock and food production; death and destruction of affected animals; and restrictions on and reductions in international trade. Zoonoses can be a serious drain on a country's economy, which in turn can have wide repercussions for a society's health.

To help solve these problems, the Pan American Health Organization (PAHO)—an international public health organization that has devoted itself to improving the health and living conditions of the people of the Americas for over one hundred years—established the Veterinary Public Health Unit. The Unit's overall objective is to collaborate with PAHO's Member Governments in the development, implementation, and evaluation of policies and programs that lead to food safety and protection and to the prevention, control, or eradication of zoonoses, among them foot-and-mouth disease.

To this end, PAHO's Veterinary Public Health Unit has two specialized regional centers: the Pan American Foot-and-Mouth Disease Center (PANAFTOSA), created in 1951 in Rio de Janeiro, Brazil, and the Pan American Institute for Food Protection and Zoonoses (INPPAZ), established on November 15, 1991, in Buenos Aires, Argentina. INPPAZ's precursor was the Pan American Zoonoses Center (CEPANZO), which was created through an agreement with the Government of Argentina to help the countries of the Americas combat zoonoses, and which operated from 1956 until 1990.

Since its creation in 1902, PAHO has participated in various technical cooperation activities with the countries, among them those related to the surveillance, prevention, and control of zoonoses and communicable diseases common to man and

animals, which cause high morbidity, disability, and mortality in vulnerable human populations. PAHO has also collaborated in the strengthening of preventive medicine and public health through the promotion of veterinary health education in learning, research, and health care centers. An example of this work is the preparation of several publications, among which the two previous Spanish and English editions of *Zoonoses and Communicable Diseases Common to Man and Animals* stand out.

Scientific knowledge has progressed since the last edition was published in 1986. Also, the countries of the Americas have modified their livestock production strategies in recent years, which has affected the transmission of zoonotic infections and their distribution. The publication of this third edition is an attempt to address these changes. The third edition is presented in three volumes: the first contains bacterioses and mycoses; the second, chlamydioses, rickettsioses, and viroses; and the third, parasitoses.

We believe that this new edition will continue to be useful for professors and students of public health, medicine, veterinary medicine, and rural development; workers in public health and animal health institutions; and veterinarians, researchers, and others interested in the subject. We also hope that this publication is a useful tool in the elaboration of national zoonosis control or eradication policies and programs, as well as in risk evaluation and in the design of epidemiological surveillance systems for the prevention and timely control of emerging and reemerging zoonoses. In summary, we are confident that this book will contribute to the application of the knowledge and resources of the veterinary sciences for the protection and improvement of public health.

MIRTA ROSES PERIAGO
DIRECTOR

PREFACE TO THE FIRST EDITION

This book considers two groups of communicable diseases: those transmitted from vertebrate animals to man, which are—strictly speaking—zoonoses; and those common to man and animals. In the first group, animals play an essential role in maintaining the infection in nature, and man is only an accidental host. In the second group, both animals and man generally contract the infection from the same sources, such as soil, water, invertebrate animals, and plants; as a rule, however, animals do not play an essential role in the life cycle of the etiologic agent, but may contribute in varying degrees to the distribution and actual transmission of infections.

No attempt has been made to include all infections and diseases comprised in these two groups. A selection has been made of some 150 that are of principal interest, for various reasons, in the field of public health. The number of listed zoonoses is increasing as new biomedical knowledge is acquired. Moreover, as human activity extends into unexplored territories containing natural foci of infection, new zoonotic diseases are continually being recognized. In addition, improved health services and better differential diagnostic methods have distinguished zoonoses previously confused with other, more common diseases. A number of diseases described in this book have only recently been recognized, examples of which include the Argentine and Bolivian hemorrhagic fevers, angiostrongyliasis, rotaviral enteritis, Lassa fever, Marburg disease, and babesiosis.

The principal objective in writing this book was to provide the medical professions a source of information on the zoonoses and communicable diseases common to man and animals. Toward that end, both medical and veterinary aspects, which have traditionally been dealt with separately in different texts, have been combined in a single, comprehensive volume. As a result, physicians, veterinarians, epidemiologists, and biologists can all gain an overview of these diseases from one source.

This book, like most scientific works, is the product of many books, texts, monographs, and journal articles. Many sources of literature in medicine, veterinary medicine, virology, bacteriology, mycology, and parasitology were consulted, as were a large number of reports from different biomedical disciplines, in order to provide up-to-date and concise information on each disease. It is expected that any errors or omissions that may have been committed can, with the collaboration of the readers, be corrected in a future edition.

Where possible, explanations were attempted with special emphasis on the Americas, particularly Latin America. An effort was made, one which was not always successful, to collect available information on diseases in this Region. Data on the incidence of many zoonoses are fragmentary and frequently not reliable. It is hoped that the establishment of control programs in various countries will lead to improved epidemiologic surveillance and disease reporting.

More space has been devoted to those zoonoses having greatest impact on public health and on the economy of the countries of the Americas, but information is also included on those regionally less important or exotic diseases.

The movement of persons and animals over great distances adds to the risk of introducing exotic diseases that may become established on the American continent given the appropriate ecologic factors for existence of the etiologic agents. Today,

public health and animal health administrators, physicians, and veterinarians must be familiar with the geographic distribution and pathologic manifestations of the various infectious agents so that they can recognize and prevent the introduction of exotic diseases.

We, the authors, would like to give special recognition to Dr. Joe R. Held, Assistant Surgeon-General of the United States Public Health Service and Director of the Division of Research Services of the U.S. National Institutes of Health, who gave impetus to the English translation and reviewed the bacterioses sections.

We would also like to express our utmost appreciation to the experts who reviewed various portions of this book and offered their suggestions for improving the text. These include: Dr. Jeffrey F. Williams, Professor in the Department of Microbiology and Public Health, Michigan State University, who reviewed the chapters dealing with parasitic zoonoses; Dr. James Bond, PAHO/WHO Regional Adviser in Viral Diseases, who read the viroses; Dr. Antonio Pío, formerly PAHO/WHO Regional Adviser in Tuberculosis and presently with WHO in Geneva, and Dr. James H. Rust, PAHO/WHO Regional Adviser in Enteric Diseases, both of whom reviewed the bacterioses; and Dr. F. J. López Antuñano, PAHO/WHO Regional Adviser in Parasitic Diseases, who read the metazooses.

We would like to thank Dr. James Cocozza, PAHO/WHO Veterinary Adviser, for his review of the translation and Dr. Judith Navarro, Editor in the Office of Publications of PAHO, for her valuable collaboration in the editorial revision and composition of the book.

PEDRO N. ACHA
BORIS SZYFRES

PREFACE TO THE SECOND EDITION

The fine reception accorded the Spanish, English, and French versions of this book has motivated us to revise it in order that it still may serve the purpose for which it was written: to provide an up-to-date source of information to the medical profession and allied fields. This book has undoubtedly filled a void, judging by its wide use in schools of public health, medicine, and veterinary medicine, as well as by bureaus of public and animal health.

The present edition has been considerably enlarged. In the seven years since the first edition was published, our knowledge of zoonoses has increased broadly and rapidly, and new zoonotic diseases have emerged. Consequently, most of the discussions have been largely rewritten, and 28 new diseases have been added to the original 148. Some of these new diseases are emerging zoonoses; others are pathologic entities that have been known for a long time, but for which the epidemiologic connection between man and animal has been unclear until recently.

The use this book has had outside the Western Hemisphere has caused us to abandon the previous emphasis on the Americas in favor of a wider scope and geomedical view. Moreover, wars and other conflicts have given rise to the migration of populations from one country or continent to another. A patient with a disease heretofore known only in Asia may now turn up in Amsterdam, London, or New York. The physician must be aware of these diseases in order to diagnose and treat them. "Exotic" animal diseases have been introduced from Africa to Europe, the Caribbean, and South America, causing great damage. The veterinary physician must learn to recognize them to be able to prevent and eradicate them before they become entrenched. It must be remembered that parasites, viruses, bacteria, and other agents of zoonotic infection can take up residence in any territory where they find suitable ecologic conditions. Ignorance, economic or personal interests, and human customs and needs also favor the spread of these diseases.

Research in recent years has demonstrated that some diseases previously considered to be exclusively human have their counterparts in wild animals, which in certain circumstances serve as sources of human infection. On the other hand, these animals may also play a positive role by providing models for research, such as in the case of natural leprosy in nine-banded armadillos or in nonhuman primates in Africa. Of no less interest is the discovery of *Rickettsia prowazekii* in eastern flying squirrels and in their ectoparasites in the United States, and the transmission of the infection to man in a country where epidemic typhus has not been seen since 1922. A possible wild cycle of dengue fever is also discussed in the book. Is Creutzfeldt-Jakob disease a zoonosis? No one can say with certainty, but some researchers believe it may have originated as such. In any case, interest is aroused by the surprising similarity of this disease and of kuru to animal subacute spongiform encephalopathies, especially scrapie, the first known and best studied of this group. Discussion of human and animal slow viruses and encephalopathies is included in the spirit of openness to possibilities and the desire to bring the experience of one

field of medicine to another. In view of worldwide concern over acquired immuno-deficiency syndrome (AIDS), a brief section on retroviruses has also been added, in which the relationship between the human disease and feline and simian AIDS is noted. Another topic deeply interesting to researchers is the mystery of the radical antigenic changes of type A influenza virus, a cause of explosive pandemics that affect millions of persons around the world. Evidence is mounting that these changes result from recombination with a virus of animal origin (see Influenza). That this should occur is not surprising, given the constant interaction between man and animals. As a rule, zoonoses are transmitted from animal to man, but the reverse may also occur, as is pointed out in the chapters on hepatitis, herpes simplex, and measles. The victims in these cases are nonhuman primates, which may in turn retransmit the infection to man under certain circumstances.

Among emerging zoonoses we cite Lyme disease, which was defined as a clinical entity in 1977; the etiologic agent was found to be a spirochete (isolated in 1982), for which the name *Borrelia burgdorferi* was recently proposed. Emerging viral zoonoses of note in Latin America are Rocio encephalitis and Oropouche fever; the latter has caused multiple epidemics with thousands of victims in northeast Brazil. Outstanding among new viral disease problems in Africa are the emergence of Ebola disease and the spread of Rift Valley fever virus, which has caused tens of thousands of human cases along with great havoc in the cattle industry of Egypt and has evoked alarm around the world. Similarly, the protozoan *Cryptosporidium* is emerging as one of the numerous agents of diarrheal diseases among man and animals, and prob-ably has a worldwide distribution.

As the English edition was being prepared, reports came to light of two animal diseases not previously confirmed in humans. Three cases of human pseudorabies virus infection were recognized between 1983 and 1986 in two men and one woman who had all had close contact with cats and other domestic animals. In 1986, sero-logic testing confirmed infection by *Ehrlichia canis* in a 51-year-old man who had been suspected of having Rocky Mountain spotted fever. This is the first known occurrence of *E. canis* infection in a human. These two diseases bear watching as possible emerging zoonoses.

The space given to each zoonosis is in proportion to its importance. Some diseases that deserve their own monographs were given more detailed treatment, but no attempt was made to cover the topic exhaustively.

We, the authors, would like to give special recognition to Dr. Donald C. Blenden, Professor in the Department of Medicine and Infectious Diseases, School of Medicine, and Head of the Department of Veterinary Microbiology, College of Veterinary Medicine, University of Missouri; and to Dr. Manuel J. Torres, Professor of Epidemiology and Public Health, Department of Veterinary Microbiology, College of Veterinary Medicine, University of Missouri, for their thorough review of and valuable contributions to the English translation of this book.

We would also like to recognize the support received from the Pan American Health Organization (PAHO/WHO), the Pan American Health and Education Foundation (PAHEF), and the Pan American Zoonoses Center in Buenos Aires, Argentina, which enabled us to update this book.

We are most grateful to Dr. F. L. Bryan for his generous permission to adapt his monograph "Diseases Transmitted by Foods" as an Appendix to this book.

Mr. Carlos Larranaga, Chief of the Audiovisual Unit at the Pan American Zoonosis Center, deserves our special thanks for the book's artwork, as do Ms. Iris Elliot and Mr. William A. Stapp for providing the translation into English. We would like to express our most sincere gratitude and recognition to Ms. Donna J. Reynolds, editor in the PAHO Editorial Service, for her valuable collaboration in the scientific editorial revision of the book.

PEDRO N. ACHA
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INTRODUCTION

This new edition of *Zoonoses and Communicable Diseases Common to Man and Animals* is published in three volumes: I. Bacterioses and mycoses; II. Chlamydioses and rickettsioses, and viroses; and III. Parasitoses. Each of the five parts corresponds to the location of the etiologic agents in the biological classification; for practical purposes, chlamydias and rickettsias are grouped together.

In each part, the diseases are listed in alphabetical order to facilitate reader searches. There is also an alphabetical index, which includes synonyms of the diseases and the etiologic agents' names.

In this edition, the numbers and names of the diseases according to the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), are listed below the disease title. However, some zoonoses are not included in ICD-10 and are difficult to classify within the current scheme.

In addition, for each disease or infection, elements such as synonyms; etiology; geographical distribution; occurrence in man and animals; the disease in man and animals; source of infection and mode of transmission; role of animals in the epidemiology; diagnosis; and control are addressed. Patient treatment (for man or other species) is beyond the scope of this work; however, recommended medicines are indicated for many diseases, especially where they are applicable to prophylaxis. Special attention is paid to the epidemiological and ecological aspects so that the reader can begin to understand the determining factors of the infection or disease. Some topics include simple illustrations of the etiologic agent's mode of transmission, showing the animals that maintain the cycle of infection in nature. Similarly, other graphics and tables are included to provide additional information on the geographical distribution or prevalence of certain zoonoses.

The data on the occurrence of the infection in man and animals, along with data on the geographical distribution, may help the reader judge the relative impact that each disease has on public health and the livestock economy in the different regions of the world, given that the importance of different zoonoses varies greatly. For example, foot-and-mouth disease is extremely important from an economic standpoint, but of little importance in terms of public health, if animal protein losses are not considered. In contrast, Argentine and Machupo hemorrhagic fevers are important human diseases, but their economic impact is minimal, if treatment costs and loss of man-hours are not taken into account. Many other diseases, such as brucellosis, leptospirosis, salmonellosis, and equine encephalitis, are important from both a public health and an economic standpoint.

Finally, each disease entry includes an alphabetical bibliography, which includes both the works cited and other relevant works that the reader may consult for more information about the disease.

Part I

CHLAMYDIOSES & RICKETTSIOSES

RICKETTSIACEAE

This family includes the tribes Rickettsieae *and* Ehrlichieae. *When human ehrlichiosis was recognized in 1986, the disease was considered to be a zoonosis caused by* Ehrlichia canis. *However, findings in 1991 established that the human agent, although similar to* E. canis, *is actually a distinct species (Dawson et al., 1991). For this reason, ehrlichiosis falls outside the scope of the present volume.*

Rickettsiae, like bacteria, are prokaryotic intracellular organisms. However, because they lack certain enzymes, they are dependent on a eukaryotic cell of the host. An exception within the tribe Rickettsieae *is the genus* Rochalimaea, *which can be cultured in an axenic environment. Rickettsiae reproduce by binary fission within the cells of an arthropod or a human or animal host; both their DNA and RNA can be synthesized, and they are sensitive to antibiotics. They measure approximately 0.5 by 0.3 microns and may be either rod-shaped or spherical. They show up well with Gimenez and Macchiavellos stains but not as well with Gram stain (Weiss and Moulder, 1984; Mettler, 1991).*

In addition to the genus Rickettsia, *within the tribe* Rickettsieae *the genera* Coxiella *and* Rochalimaea *are also of interest.*

Organisms of the genus Rickettsia *may be divided into the following three groups: spotted fevers, typhus, and scrub typhus.*

The diseases in the spotted fever group are clinically similar and caused by related rickettsiae, and they are all transmitted by ticks.

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ASIAN IXODO-RICKETTSIOSIS

ICD-10 A77.2 Spotted fever due to *Rickettsia sibirica*

Synonyms: North Asian tick fever, Siberian tick typhus.

Etiology: *Rickettsia sibirica* (*Dermacentroxenus sibiricus*). This agent belongs to the spotted fever group of rickettsiae. *Dermacentor marginatus*, a variety of *R. sibirica* that was isolated from ticks in the former Czechoslovakia, is serologically distinct from *R. slovaca*, although the differences may not be sufficient to warrant establishing a separate species (Weiss and Moulder, 1984).

Geographic Distribution: Armenia, Kazakhstan, Kyrgyzstan, northern China, Mongolia, Siberia, and various islands in the Sea of Japan. *R. sibirica* has also been isolated from ticks and mammals in the former Czechoslovakia and in Pakistan.

Occurrence in Man: Sporadic. The disease occurs mainly in farmers, hunters, forestry workers, and people who enter the disease's natural foci in steppe and montane regions. Ticks may be carried from natural foci to populated areas via the fur of domestic animals, firewood, or by other means, and thus increase the possibility of infection.

Occurrence in Animals: The etiologic agent has been isolated from at least 18 wild rodent species that live in the disease's natural foci.

The Disease in Man: This is an acute, febrile, benign disease clinically similar to boutonneuse fever. It may also resemble the serious or moderate forms of Rocky Mountain spotted fever. It has an incubation period of two to seven days, and is treated with tetracycline.

The Disease in Animals: No information is available on the natural course of the disease in wild rodents or other species from which the rickettsia has been isolated; it is probably asymptomatic.

Source of Infection and Mode of Transmission: Man contracts the infection through tick bites. The principal vectors are ticks of the genera *Dermacentor*, *Haemaphysalis*, and *Rhipicephalus*. Nine species of naturally infected ticks have been found, and transovarial transmission has been confirmed in seven of them. The etiologic agent survives in the tick during hibernation. The continuous circulation of rickettsiae in natural foci is ensured by transovarial transmission from one arthropod generation to the next and by the presence of the infection in a wide variety of small mammal species.

At the end of hibernation and before egg laying, the ticks attach themselves to large domestic and wild mammals, and, accidentally, to humans who enter their habitat. Accordingly, the highest incidence of human disease occurs in spring, which is the period of greatest adult tick activity. It is usually the adult tick that attacks man, but larvae and nymphs of *Dermacentor nuttalli* and *Haemaphysalis concinna* may do so as well. The larvae and nymphs usually feed on small mammals, especially rodents, thus ensuring an additional reservoir and source of infection. Autumn brings a new generation of adult ticks, which may attach themselves to humans and produce cases of the disease.

Role of Animals in the Epidemiology of the Disease: Man is an accidental host; the reservoir consists of wild rodents and ticks. The latter play a key role in maintaining and transmitting the infection. Transstadial and transovarial transmission of *R. sibirica* has been confirmed in *D. marginatus* over a period of at least five years (Harwood and James, 1979). Domestic animals (cattle, horses, dogs) can serve as hosts for adult ticks.

Diagnosis: As with other spotted fevers, laboratory confirmation is obtained using such serological tests as complement fixation and microimmunofluorescence. The agent can be isolated in embryonated eggs or by inoculation in laboratory animals (guinea pigs, rats, hamsters).

Control: Control measures are directed against the vectors. They include the use of tickicides on domestic animals and in their environment, as well as the reduction of rodent populations, since rodents are the principal hosts of larvae and nymphs. Individuals who enter natural foci should wear protective clothing and use tick repellents.

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BOUTONNEUSE FEVER

ICD-10 A77.1 Spotted fever due to *Rickettsia conorii*

Synonyms: Marseilles fever, Mediterranean spotted fever, Mediterranean tick fever, African tick typhus, Kenya tick typhus, India tick typhus.

Etiology: *Rickettsia conorii* (*Dermacentroxenus conorii*). This microorganism belongs to the spotted fever group of rickettsiae. It can be differentiated from others in the group by serological and cross-immunity tests.

Geographic Distribution: The disease occurs in much of Africa, Southeast Asia, India, and areas of Europe and the Middle East adjacent to the Caspian, Mediterranean, and Black Seas.

Occurrence in Man: Sporadic. This is the most common rickettsial disease in South Africa. In Spain, the endemic area of Talavera de la Reina had 85 diagnosed cases in 1982 (España, Ministerio de Sanidad y Consumo, 1983). In Soria (Spain), 5% of 298 human sera samples were serologically positive for *R. conorii.* More than 90% of the cases were from the eastern part of the province, and 20% of the positive cases were found in a small area (Saz *et al.*, 1993). Similar results were obtained in Croatia on the Adriatic coast. The number of human cases in the Mediterranean basin has increased since the early 1980s, especially in Spain, France, Israel, and Italy. The number of cases in Italy rose from only 87 in 1974 to 1,128 in 1993 (personal communication, G. Federico, cited in Mansueto *et al.*, 1985). Most of the cases in the Mediterranean basin occur in summer, when ticks are most active.

Occurrence in Animals: In some areas, such as Kenya, serological studies have revealed a high proportion of reactors in several species of wild rodents (Heisch *et al.*, 1962). *R. conorii* has been isolated from many rodent species in South Africa and Kenya. Antibodies for spotted fever group rickettsiae were detected in a small sampling of sheep and goat sera examined in Ethiopia (Philip *et al.*, 1966) and also in nonhuman primates at the Kruger Reserve in South Africa (Kaschula *et al.*, 1978). The dog, principal host of the ixodid tick *Rhipicephalus sanguineus* (brown dog tick), has been the subject of seroepidemiological studies because the tick is both reservoir and vector of *R. conorii* disease in man. In western Sicily (Italy), where there are several endemic areas of boutonneuse fever, 81.5% of dogs examined were reactors in the indirect immunofluorescence test (Tringali *et al.*, 1986). In the south of France, this same test was used to examine the sera of 481 dogs; 80% were positive at a dilution of 1:32, and 45% at 1:128. The lower titers may indicate an old infection, and the higher titers, a recent infection. These data confirm that the disease is endemic in the south of France (Raoult *et al.*, 1985). In Israel, when sera from 92 dogs were examined using both the immunofluorescence and enzyme-linked immunosorbent assay tests on each sample, 30% were found to be positive. The prevalence of antibodies in dogs from two small communities where there had been cases of human disease caused by *R. conorii* was 2.8 times higher (82%–84%) (Keysary *et al.*, 1988).

The Disease in Man: Boutonneuse fever is usually benign. It is characterized by a primary lesion at the site where the tick was attached. The lesion consists of a small reddish ulcer covered by a small black scab (*tâche noire*), which may last throughout the course of the illness. Localized lymphadenitis is often seen. The fever appears 5 to 7 days after the tick bite and is accompanied by severe headaches and muscle and joint pain. A generalized eruption, at first macular and then maculopapular, appears on the fourth or fifth day of fever and lasts about a week. The disease takes a serious turn in approximately 5% of the cases. Of 142 cases treated at hospitals in Marseilles (France), 7 developed disease with purpuric exanthema, confusion, renal failure, hypoxemia, thrombocytopenia, hyponatremia, and hypocalcemia. Two patients died. Predisposing factors were advanced age, tobacco use, alcoholism, and respiratory insufficiency (Raoult *et al.*, 1986). Three fatal cases in children have been described in Israel. The

disease was characterized by irreversible shock, encephalopathy, renal failure, hemorrhagic tendency, and death within 24 hours of hospital admission. None of the children were known to have been bitten by a tick, nor was the black scab (*tâche noire*) observed. One child had no cutaneous eruption, and two had no antibodies. The diagnosis was based on isolation of *R. conorii* in the patients' blood or tissues, either by cell culture or inoculation in laboratory animals. These cases show that there is a grave form of boutonneuse fever in Israel (Yagupsky and Wolach, 1993).

Some investigators have attributed the spotted fever in Israel to a different species, *Rickettsia sharonii*, which would be antigenically different from the other rickettsiae in the spotted fever group and also from *R. conorii* (Goldwasser *et al.*, 1974). A clinical difference has also been pointed out, namely, the absence of the black scab in the Israeli patients.

The recommended treatment is tetracycline.

The Disease in Animals: Dogs infested with *R. sanguineus*, the main vector in the Mediterranean region, may have rickettsemia but show no clinical infection. Elsewhere, in wild rodents from which the agent has been isolated, the natural course of infection is unknown, but it is probably asymptomatic.

Source of Infection and Mode of Transmission: The vector of the infection in the Caspian, Mediterranean, and Black Sea basins is *R. sanguineus*. This tick is responsible for the focal nature of boutonneuse fever. All the human cases in this region correspond to the distribution of *R. sanguineus*. The tick completes its entire life cycle near human dwellings. *R. sanguineus* always prefers a dog as its host and only occasionally bites man, which would explain the small number of human cases of the disease despite the abundance of infected ticks. The causal agent is transmitted trans-ovarially from one tick generation to the next, so that the arthropod serves as both vector and reservoir. Dogs and their ticks are the main source of infection in man; wild rodents and their ticks are the reservoir in natural foci. In South Africa, the dog ticks *Haemaphysalis leachi* and *R. sanguineus* are the principal vectors of human infection. The agent has been isolated from many other tick species in their natural habitat, and they are probably involved in its primary life cycle in the wild. Studies carried out in Kenya and Malaysia confirm that in natural foci the agent circulates in a basic cycle between small wild animals and ticks. When ticks are crushed with the hand, the agent can penetrate via the conjunctival mucosa or the skin.

Role of Animals in the Epidemiology of the Disease: Man is an accidental host. The infection is maintained in nature by wild rodents and their ticks. Dogs play a very important role by introducing infected ticks into the human environment.

Diagnosis: Serologic tests are used for laboratory confirmation; the test used most often is microimmunofluorescence. A technique that could be performed easily is latex agglutination with *R. conorii* antigen, in much the same way as laboratories in the US use *R. rickettsii* antigen to diagnose Rocky Mountain spotted fever.

Cell culture (chick embryo fibroblasts, mouse L-cells, BHK-21, etc.) can be used to isolate *R. conorii* as well as other rickettsiae in the group. Recent infections can be distinguished from past ones by using specific anti-IgM and anti-IgG sera in the immunofluorescence test (Edlinger, 1979). A nested polymerase chain reaction assay on serum and tissue samples is useful for diagnosis, particularly in fatal cases (Leitner *et al.*, 2002).

Control: Control measures are directed against the vector and consist of using tickicides on dogs and their environment.

It is recommended that ticks not be crushed when they are detached.

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FLEA-BORNE TYPHUS

ICD-10 A75.2 Typhus fever due to *Rickettsia typhi*

Synonyms: Murine typhus, endemic typhus, urban typhus.

Etiology: *Rickettsia typhi* (*R. mooseri*), which belongs to the same group as *R. prowazekii*, the agent of endemic louse-borne typhus, and *R. canada* (not pathogenic to man), isolated from the tick *Haemaphysalis leporispalustris*. DNA:DNA hybridization between *R. typhi* and *R. prowazekii* is 70% to 79% (Myers and Wisseman, 1980). *R. typhi* is more virulent than *R. prowazekii* in guinea pigs. While some of the antigens are common to both species, others are species-specific. Immunologically, the two species can be differentiated by a cross-challenge of vaccinated guinea pigs or by the toxin neutralization test in mice (Weiss and Moulder, 1984).

Geographic Distribution: There are endemic areas throughout the world.

Occurrence in Man: Sporadic. Between 1963 and 1967, the average number of cases reported annually in the Americas was 241. Countries that reported cases during this period were Argentina, Brazil, Chile, Colombia (more than one-third of the total number of cases), Costa Rica, Ecuador, Mexico, Peru, USA, and Venezuela. In the US, there were some 42,000 cases between 1931 and 1946; after 1946, the incidence began to decline. There are fewer than 80 cases a year (Chin, 2000). Occurrence of the disease is associated with rat infestation. Although incidence of the disease has fallen sharply, especially in the developed countries, enzootic areas continue to exist on all the continents. In Texas (USA), there were 200 human cases between 1980 and 1984: 74% of the patients lived in the southern part of the state, and 85% had to be hospitalized (Taylor *et al.*, 1986). The island of Evia (Greece) is an endemic area; 49 cases were diagnosed at the general hospital in its capital city in 1985 (Tselentis *et al.*, 1992). A case of murine typhus appeared in Australia, after 30 years with no diagnosis of the disease (Graves *et al.*, 1992). In Kuwait, there were 254 cases between April and August 1978, most of them among the poorest members of the population, 80% of whose homes were rat-infested (Al-Awadi *et al.*, 1982). In southeast Asia, flea-borne typhus is an urban disease, since it is in the cities that man and rats, along with their fleas, share the same habitat. Scrub typhus, on the other hand, is endemic in rural areas. In Thailand, where murine typhus is endemic, a refugee camp was set up in 1985 to accommodate Khmers fleeing the civil war in neighboring Cambodia. Only eight months after the camp was constructed, 170 cases, including some of scrub typhus, were diagnosed at the camp hospital within a period of four months. At the same time, there was a sharp increase in the population of the rat *Rattus exulans* (Brown *et al.*, 1988). In Africa, Ethiopia is an endemic country, as is Myanmar (Burma) in Asia.

The incidence is greatest in summer and fall, when rat fleas are most active.

Occurrence in Animals: The most important reservoirs of infection are the domestic rats *Rattus norvegicus*, *R. rattus*, and *R. exulans*. The principal vector is the eastern rat flea *Xenopsylla cheopis*. The basic transmission cycle of the infection is rat-flea-rat and, accidentally, rat-flea-man. Many other species of wild and domestic animals, as well as some of their ectoparasites, have been found to be naturally infected or experimentally susceptible, but their role in the epidemiology of endemic

typhus does not appear to be important. Nevertheless, there are indications that there may be an independent cycle of the agent in addition to the basic cycle. Such would be the case of infestation of the cat and opossum by the flea *C. felis*. This flea often parasitizes the opossum in suburban and rural areas of southern California (USA), where the classic vector *X. cheopis* is absent and rats are serologically negative.

The infection rate in rats varies greatly from one enzootic focus to another.

The Disease in Man: The incubation period is 6 to 14 days. The symptomatology of the disease is similar to that of epidemic louse-borne typhus, but its course is shorter and more benign. It begins with fever, severe cephalalgia, and generalized pains. Five or six days after the onset of fever a macular eruption appears, first on the trunk and then on the extremities, but it does not affect the palms of the hands, the soles of the feet, or the face. The symptomatology also includes coughing, nervousness, nausea, and vomiting. In the refugee camp in Thailand, the main symptoms were persistent fever, retroorbital cephalalgia, and myalgia. In the 200 cases that occurred in southern Texas, only 58.1% of the patients manifested a cutaneous eruption, and only 44.9% experienced nausea. Complications are rare. When patients are not treated, convalescence can last several months. Case fatality increases with age; in the US, the rate is currently under 1% for all ages.

Treatment consists of administration of tetracycline or its long-acting analogs, such as doxycycline or minocycline. With this treatment, the fever subsides in a few days.

The Disease in Animals: Rickettsemia occurs in rats during the first week of infection. The agent remains viable in the brain and other organs for long periods. The infection is asymptomatic.
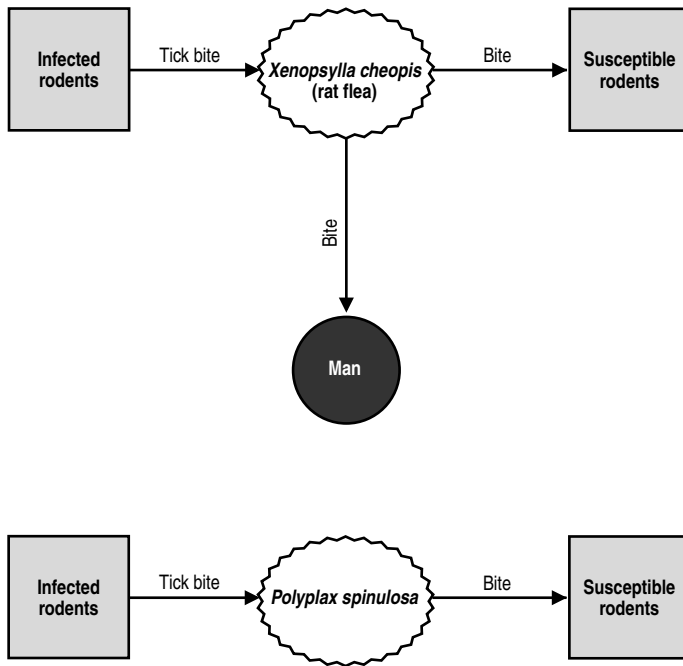
Source of Infection and Mode of Transmission (Figure 1): The most important reservoir of *R. typhi* is the rat, and the main vector is its flea, *X. cheopis*. Fleas become infected by feeding on the host when it has rickettsemia. The agent multiplies in the flea's intestine and Malpighian tubules without causing any apparent damage. The vector eliminates *R. typhi* in its feces throughout its lifetime, but not in its saliva. *X. cheopis* does not transmit the infection to its progeny, and the infection of new generations of fleas requires that they feed on a rickettsemic host. In other species of fleas, the infection follows the same pattern.

The infection is transmitted from rat to rat by means of the flea *X. cheopis* and the louse *Polyplax spinulosa*. The agent can survive for a long time in flea feces and in contaminated rodent burrows. The infection can be produced by contact with the mucous membranes of the conjunctiva and the mouth, or by inhalation.

Man becomes infected when the rat flea, or another flea, such as *C. felis,* bites him and defecates on his skin. When he scratches himself, he can introduce the contaminated fecal matter through the bite or some other skin abrasion. He exposes himself to the same process if he swats a flea against his skin. Man can probably acquire the infection by other routes as well, such as the conjunctiva or by inhalation, though these modes of transmission are of little importance.

The spread of the disease in man depends on the extent of the enzootic in rats and the degree of contact he has with these animals and their fleas. Although the disease used to occur primarily in rat-infested buildings in urban areas, it is now seen in rural areas as well.

**Figure 1. Flea-borne typhus *(Rickettsia typhi)*.
Transmission cycle.**

Role of Animals in the Epidemiology of the Disease: This is an infection in rats that is accidentally transmitted to man by fleas. Cats and opossums can also carry the infected flea *C. felis* into the human environment. The infection is not transmitted from one person to another.

Diagnosis: The agent can be isolated by inoculating the blood of a febrile patient into male guinea pigs and embryonated eggs. In guinea pigs, the infection produces the Neil-Mooser reaction (adhesion of the tunica vaginalis testis that prevents reintroduction of the testicles into the abdomen). This reaction occurs both with the agent of murine typhus and also with those of the spotted fever group.

The complement fixation and indirect immunofluorescence tests are both very useful, though the latter is employed more often. The disadvantage of the complement fixation test is the appearance of anticomplementary sera. Also, the immunofluorescence test has the advantage that it can be adapted to distinguish IgM and IgG antibodies (Wisseman, 1982). The antibodies appear at the end of the second week of the disease, reach their peak two weeks later, and then gradually decline (Elisberg and Bozeman, 1979). Group specificity is good, although with human patients it is difficult to distinguish murine typhus from epidemic typhus, which is not the case in rodents. This distinction can be made with the complement fixation test if washed species-specific antigens are used.

Control: Control measures should be directed first against the vector and then against rodents. To decrease the number of fleas on rats, residual action insecticides are applied to rat runs, nests, and holes. Once the fleas have been dealt with, the next step is to control the rat population through the application of raticides. In addition, environmental sanitation measures can be taken, such as the elimination of rat holes and possible sources of food, as well as the construction of rat-proof buildings.

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INFECTIONS CAUSED BY *BARTONELLA HENSELAE*

Etiology: *Bartonella henselae* is a recently described species belonging to the family Rickettsiaceae. The genera *Rickettsia* and *Bartonella* are genetically related, as demonstrated by the fact that there is 25% to 33% DNA hybridization between *B. henselae* and *Rickettsia prowazekii*. The type species of the genus *Bartonella* is *B. quintana*, the agent of trench fever, which affected approximately 1 million soldiers in World War I and reemerged to a more limited extent in World War II. Some sporadic cases still occur. It is believed that the primary reservoir of *B. quintana* was a vole, probably *Arvicola terrestris,* which became independent of the zoonotic cycle and began to circulate between man and the louse *Pediculus humanus* (Weiss and Moulder, 1984).

The genus *Bartonella* currently includes four species: *B. quintana*, *B. vinsonii*, *B. elizabethae*, and *B. henselae* (Groves and Harrington, 1994). The species of greatest interest as an emerging agent of new zoonotic diseases is *B. henselae*. This rickettsia is bacilliform, curved slightly inward, and measures 1 to 2 microns long by 0.5 to 0.6 microns in diameter. It is gram-negative and stains well with Gimenez stain. The genus *Bartonella* differs from the genus *Rickettsia* most notably by the fact that it does not need eukaryotic cells in order to develop. It can be grown in noncellular culture media such as tryptose soy agar or brain-heart infusion agar containing 5% sheep's blood incubated at 35°C in a humidified stove in an atmosphere of 5% carbon dioxide. The first culture develops slowly and may take as long as five weeks (Welch *et al.*, 1992; Regnery *et al.*, 1992a).

The reservoir of *B. henselae* is the domestic cat, and the diseases that it causes are bacillary angiomatosis, bacillary parenchymatous peliosis, cat-scratch disease (CSD), and recurrent rickettsemia.

Geographic Distribution: Unknown, except for CSD, which appears to occur worldwide (Benenson, 1990).

Occurrence in Man and Cats: It is estimated that in the US, some 22,000 cases of CSD are diagnosed each year, and that more than 2,000 patients are hospitalized (Jackson *et al.*, 1993). The etiologic agent of CSD is not yet known for certain, but there is definite evidence that *B. henselae* plays an important role. It is still difficult to determine the relative role played by *B. henselae* and *Afipia felis* in the etiology of the disease (see "Cat-scratch Disease" in Volume I: Bacterioses and Mycoses). However, research points to *B. henselae* as the causative agent. In one serologic study, 88% of 41 patients were positive for *B. henselae* in the indirect immunofluorescence test, whereas only 25% of the same group reacted positively to *Afipia felis* (Regnery *et al.*, 1992b).

The number of cases of bacillary angiomatosis is unknown. Bacillary peliosis has been observed in isolation and in association with angiomatosis. As of 1982, there were approximately 100 cases of this condition on record (García *et al.*, 1982).

Researchers at the University of California at San Francisco (USA) conducted an epidemiologic study of four patients with bacillary angiomatosis in an effort to discover the source of infection. The four patients had been in contact with seven cats, and *B. henselae* was isolated from both the cats' blood and their fleas. Blood samples were taken from 61 cats in the San Francisco metropolitan area, living both in homes and at an animal shelter, and *B. henselae* was isolated from 41% of the samples.

The Disease in Man: *B. henselae* infection produces a broad range of clinical and pathological varieties: CSD (see "Cat-scratch Disease" in Volume I: Bacterioses and Mycoses), recurrent rickettsemia, bacillary angiomatosis, and bacillary peliosis.

Bacillary angiomatosis is a vasoproliferative reaction observed in histological sections taken from lesions of the skin, bones, lymph nodes, and brain. The presence of a large number of bacillary forms in the lesions can be detected with Warthin-Starry argentic stain or an electron microscope. Although the disease is seen most often in immunodeficient patients, especially those infected with the human immunodeficiency virus (HIV), it also occurs in immunocompetent patients. The most common skin lesions are painful, angiomatous papules, which can be mistaken for Kaposi's sarcoma, but which histologically resemble epithelioid hemangiomas. In the disseminated form of bacillary angiomatosis, patients experience fever, weight loss, discomfort, and increased volume of the affected organs (Koehler *et al.*, 1992; Groves and Harrington, 1994). The etiology of bacillary angiomatosis is apparently shared between *B. henselae* and *B. quintana*. Koehler *et al.* (1992) isolated *B. quintana* from three patients with cutaneous and osseous lesions of bacillary angiomatosis. A DNA:DNA hybridization assay with the type species demonstrated 99% to 100% relatedness (strains with over 70% relatedness are considered to belong to the same species) (Koehler and Brenner, 1993).

Bacillary peliosis is a pathological entity specific to the solid internal organs (liver, spleen, abdominal lymph nodes, and bone marrow), which is expressed in the form of small blood-filled cysts. In some cases it can also affect the kidneys, pancreas, and lungs. Most cases are seen in individuals who are weak and chronically ill, such as HIV-infected tuberculosis patients, those with cancer, and those on systemic anabolic steroids. The clinical symptoms are fever, weight loss, nausea, diarrhea, abdominal pain, and lymphadenopathy.

In a group of 48 patients with bacillary angiomatosis or peliosis studied by Tappero *et al.* (1993), 42 were HIV-positive.

Another clinical form is recurrent rickettsemia, which is rare. In immunocompetent individuals, the rickettsemia is recognized clinically by its sudden onset, fever, muscle and joint pains, and sometimes, headache, meningism, and photophobia (Lucey *et al.*, 1992). In immunodeficient patients, the disease develops slowly, with manifestations of fatigue, asthenia, discomfort, and weight loss. In AIDS patients, *B. henselae* can cause inflammatory disease without angiomatosis or peliosis, which can be demonstrated using immunocytochemical techniques on autopsy specimens of infected tissue (Slater *et al.*, 1994). The authors describe three cases of AIDS patients without neoangiogenic lesions on their organs but whose pathological changes were caused by *B. henselae*, as was demonstrated by immunocytochemistry.

The recommended treatment for bacillary angiomatosis, bacillary peliosis, and recurrent rickettsemia is the administration of erythromycin, rifampicin, or doxycycline for six weeks. In bacillary angiomatosis, if the lesions are limited to the skin, surgical excision alone is sufficient. With recurrent rickettsemia, the recommended treatment is intravenous gentamicin and ceftriaxone, followed by oral ciprofloxacin (Groves and Harrington, 1994). For the treatment of CSD, see "Cat-scratch Disease" in Volume I: Bacterioses and Mycoses.

The Infection in Cats: Although cats are the reservoir of *B. henselae*, they are asymptomatic, except for persistent and prolonged rickettsemia. This may be because of the agent's long adaptation to the animal host.

Source of Infection and Mode of Transmission: The reservoir is the domestic cat. In a study carried out in California (USA), *B. henselae* was isolated from blood in 25 (41%) of 61 cats from family homes and animal shelters (Koehler *et al.*, 1994). It was also demonstrated that the rickettsemia is prolonged: the agent was isolated from a naturally infected cat for 18 weeks after the infection was first detected serologically (Regnery *et al.*, 1992b). These data indicate that immunocompetent individuals are not very susceptible to *B. henselae* infection and that other factors lower their resistance and contribute to the development of bacillary angiomatosis or peliosis. On the other hand, the agent was not observed to be opportunistic in CSD.

In CSD, the causal link to the scratch or bite of a cat, especially one under 12 months old, is a salient fact in the epidemiology of this disease. With other human diseases caused by *B. henselae*, except for recurrent rickettsemia, it is clear that they are contracted directly from the scratch or bite of a young cat, or via their fleas (Groves and Harrington, 1994). Little is known about cat-to-cat transmission, but it is assumed to be through fleas, bites and scratches during play among young cats, or fights between tomcats.

Diagnosis: The most certain method of diagnosis is isolation of the agent in culture media (see the section on etiology), but this technique takes too long; serological methods are more practical. An indirect immunofluorescence test (Regnery *et al.*, 1992b) has been developed for diagnosis of CSD. The test showed that CSD patients had high titers to *B. henselae* antigens. Of 41 CSD patients, 88% tested positive, whereas in a group of 107 controls only 3% were positive. A diagnosis can also be obtained using immunocytochemistry on pathological specimens (Slater *et al.*, 1994).

Control: The epidemiology of diseases caused by *B. henselae* is just beginning to be understood and there are still many areas to explore before any rational foundation can be established for their prevention and control. Transmission to man could be reduced by controlling cat fleas and perhaps by treating infected cats with antibiotics. Any wound inflicted by a cat should be promptly washed with soap and water and disinfected.

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Q FEVER

ICD-10 A78

Synonyms: Pneumorickettsiosis, Balkan influenza, coxiellosis, abattoir fever, Australian Q fever, hiberno-vernal bronchopneumonia, nine-mile fever, quadrilateral fever, infection due to *Coxiella burnetii*.

Etiology: *Coxiella burnetii* (*Rickettsia burnetii*). The agent differs from other rickettsiae in its filterability and high degree of resistance to physical and chemical agents (it is more resistant than most nonsporogenic microorganisms). It does not produce agglutinins in the Weil-Felix test, nor does it cause a cutaneous rash in man, and it can be transmitted without the intervention of a vector.

C. burnetii is bacilliform and measures 0.4–1 by 0.2–0.4 microns. In order to develop, it requires the presence of eukaryotic cells, where it tends to take up residence in the phagolysosomes, rather than the cytoplasm or the nucleus as the *Rickettsia* species do. It shows up well with Gimenez stain (Weiss and Moulder, 1984). It has been found to have several different plasmids, the functions of which are not yet understood.

C. burnetii can be highly pleomorphic when it reproduces inside the phagolysosomes of an invaded host cell. Two different forms can be distinguished under an electron microscope: one, large and bacilliform, and the other, coccoid, which develops from the former and has greater electronic density (McCaul and Williams, 1981). A third form appears in the large cells after passage through embryonated eggs or BGM cell cultures when they have been kept in suboptimal temperature conditions or fresh medium has not been added. These small, high-density forms are similar to spores (Aitken *et al.*, 1987). The morphogenesis is comparable, but not identical, to cell differentiation in the formation of endospores. These small forms are responsible for the high resistance of the Q fever agent to environmental factors and many disinfectants.

C. burnetii has two antigenic phases (I and II), much like the S-to-R variation in salmonellae or brucellae. When harbored in the animal or tick organism, it is in phase I. After several passages through the yolk sac of embryonated eggs, it converts to phase II, which is avirulent. This antigenic variation is important for diagnosis and prophylaxis.

Geographic Distribution: Worldwide. The infection is endemic in many areas and its presence has been confirmed in at least 51 countries. Although the Nordic countries were previously believed to be free of Q fever and that the few cases seen there were imported, in the 1990s, the disease was recognized as endemic in Sweden.

Occurrence in Man: Q fever appears in the form of sporadic cases or outbreaks. The human infection is often asymptomatic, and its mild form can be mistaken for other febrile diseases. For this reason, sporadic cases often go undiagnosed and the true incidence of the disease is unknown. Moreover, the indiscriminate use of antibiotics in febrile patients hampers the clinical identification of Q fever as well as other rickettsioses and bacterioses. In Australia, which is considered an endemic area, there were some 2,000 cases in 1979–1980 (Hunt *et al.*, 1983), and the United Kingdom has at least 100 laboratory-confirmed cases each year (Heard *et al.*, 1985).

Several epidemic outbreaks have occurred in abattoirs and wool-processing plants. In Uruguay, 310 of 630 workers and veterinary inspection personnel in a meat-packing plant fell ill in a single month in a 1976 epidemic. Cases were most concentrated among workers involved in bone-milling and the collection of animal wastes, such as placentas, fetuses, and viscera. The outbreak was attributed to aerosols, probably generated by the handling of placentas and amniotic fluid. Three more outbreaks occurred, apparently in that same meat-packing plant, in August and October 1981 and in 1984, with 25, 17, and 46 cases, respectively. Most of the affected personnel worked in slaughtering and deboning (Ortiz Molina *et al.*, 1987). According to the same authors, there have been 15 more outbreaks in abattoirs since 1976, mostly involving cattle. Epidemics have occurred among slaughterhouse workers in other parts of the world as well. In Quebec (Canada), an outbreak in the 1950s affected 62 employees (36.5% of the company's total workforce) within a

period of 18 days (Pavilanis *et al.*, 1958. Cited in Lang, 1989). In Australia, 110 workers contracted the disease in a rural goat slaughterhouse (Buckley, 1980), and in Romania, 149 workers in a municipal abattoir contracted the infection (Blidaru *et al.*, 1982).

Other high-risk groups are ranch hands and persons living on farms where cattle, sheep, and goats are raised. A sudden outbreak on a dairy cooperative in Romania during the calving season affected 45 persons. The source of infection was traced to cows that had been acquired elsewhere to open up a new dairy establishment (Blidaru *et al.*, 1980). Q fever outbreaks have also occurred in scientific institutes that use sheep as models for the study of human diseases. In addition to outbreaks at two universities in 1969 and 1971, four other outbreaks affected a large number of persons, many of whom were not working directly with animals (Spinelli *et al.*, 1981; Meiklejohn *et al.*, 1981; Hall *et al.*, 1982). In 1992, there were 86 cases of Q fever in Berlin (Germany), which mainly affected staff and students at a veterinary clinic. The infection was traced to sheep that had been brought to the clinic with nonspecific symptoms. That was the largest outbreak in Germany in 28 years (Schneider *et al.*, 1993). There was also an outbreak in a human pathology institute at a German university following the autopsy of a patient; all the people involved in the autopsy were affected, plus seven others who worked in other buildings (Gerth *et al.*, 1982). During World War II, there were numerous Q fever epidemics, both large and small, among German and Allied troops stationed in southern and southeastern Europe. Major epidemics also occurred in the postwar years in the civilian population in Germany, with 2,000 confirmed cases, and in Italy, where an estimated 20,000 cases occurred in a two-year period (Babudieri, 1959).

Hundreds of serologically confirmed cases of Q fever have been reported in Bulgaria since the beginning of the 1990s. The increase in the number of cases is thought to be linked to the tripling of the number of goats in the country and to increased contact between the animals and their owners, as well as increased consumption of raw goat milk and its products (Serbezov *et al.*, 1999). Raoult *et al.* (2000) recorded 1,070 acute and 313 chronic cases of Q fever in a retrospective study conducted in France.

In addition to cattle, sheep, and goats, which are the principal sources of the infection in man, parturient cats and newborn kittens can also cause outbreaks. In Canada, an outbreak in a truck repair shop affected 16 of 32 employees. One of them had kept a cat in the shop that gave birth to kittens two weeks before the animal's owner got sick. The wife and son of the cat's owner also developed the disease. The authors assume that the outbreak started with the employee's contaminated clothing (Marrie *et al.*, 1989).

There have also been epidemics that were not linked to any direct contact with animals or their viscera. In Switzerland, an outbreak in the fall of 1983 produced 415 confirmed cases of acute Q fever (21% of the population of the towns involved) along a route that had been followed by 12 herds of 850 to 900 head each descending from alpine pastures to the valley below. Five of the herds had seropositivity rates ranging from 46% to 93%. The infection was transmitted to man by inhalation of dust in the road, which was no doubt contaminated with excreta from the animals (Dupuis *et al.*, 1987). Because it is so highly resistant, the agent can cause an outbreak far away, as occurred in Switzerland, where the disease was contracted by 19 workers who unpacked a machine from the US that had been packed in contaminated straw (Stoker

and Marmion, 1955). A similar outbreak occurred among art students in Great Britain who unpacked sculptures packed in straw (Harvey *et al.*, 1951). Another example of indirect transmission was reported among British air force personnel who cleaned a shed that had been occupied by sheep (Holland *et al.*, 1960).

Occurrence in Animals: The infection has been found in almost all species of domestic animals and many wild animals, including birds. In India, the agent was also isolated from amphibians (Kumar and Yadav, 1981) and a python. From the public health standpoint, the most important sources of infection for man are cattle, sheep, and goats.

Serologic surveys conducted in some endemic areas have revealed a sizable proportion of reactors in the bovine, ovine, and caprine population. In a seroepidemiologic study in Colombia, 57% of 482 dairy cows produced antibodies in the complement fixation test (Lorbacher and Suárez, 1975). In California (USA), serologic studies of 2,097 sheep and 1,475 goats from different sources gave reactor rates of 24% and 57%, respectively, for the two species (Ruppaner *et al.*, 1982). Serologic surveys in France revealed reactor prevalence rates of 15% for cattle and 20% for sheep and goats in some departments. In Ontario (Canada), infection rates in dairy cattle have risen sharply, from 2.4% in a 1964 serologic survey to 67% in 1984 (Lang, 1989). Of 103 flocks of sheep in Ontario, 22 had one or more serologic reactors (Lang *et al.*, 1991).

In the Upper Nile province of southern Sudan, where the prevalence of serologic reactors in the human population was 39%, a survey of the animal population showed that 40.4% of 52 sera from cattle were positive, as were 53% of 42 sera from goats, and 62.5% of 32 sera from sheep (Reinthaler *et al.*, 1988). In New Brunswick and Prince Edward Island (Canada), a survey was conducted of the cat population, since it is believed that these animals play a role in the transmission of *C. burnetii* to man. In New Brunswick, 19.2% of 104 cats, and on Prince Edward Island, 6.2% of 97 of them, reacted positively in the immunofluorescence test (Higgins and Marrie, 1990).

It is also common to find antibodies to *C. burnetii* in wild animals. In a series of sera from 759 rodents (representing 15 species) that were examined by microagglutination, 3% were seropositive, and 20% of 538 free-living birds were reactors (Riemann *et al.*, 1979). In India, 1.2% of 342 birds and 14.3% of 91 wild land animals tested positive (Yadav and Sethi, 1980). In Bialowieza National Park (Poland), microagglutination testing of sera from 47 aurochs (wild oxen) showed that 76.5% were reactors. Of 39 people working in the forest, 10.2% were positive as well (Ciecierski *et al.*, 1988).

The Disease in Man: The incubation period ranges from two weeks to 39 days, with an average of 20 days. The disease has a sudden onset, with fever, chills, profuse sweating, malaise, anorexia, myalgia, and sometimes nausea and vomiting. The fever is remittent and usually lasts from 9 to 14 days. A prominent symptom of the disease is severe cephalalgia, and retroorbital pain is common. In about half the patients, X-ray examination reveals pneumonitis, which manifests itself clinically in the form of a slight cough, mild expectoration, and, occasionally, chest pain. About 50% of patients have gastrointestinal problems, such as nausea, vomiting, or diarrhea. Acute hepatitis can also occur. In contrast to the other rickettsioses, Q fever does not cause a cutaneous rash. The disease ranges in severity, but in most cases it is benign. Many human infections are mild and inapparent and thus go undetected.

Q fever rarely attacks children under 10 years old. However, in the Netherlands, 18 cases in children under 3 years old were reported within a 16-month period (Richardus *et al.*, 1985). The disease is more serious in adults over 40. The case fatality rate for acute Q fever is less than 1%. A retrospective study of Q fever patients in France (1,070 acute cases during 1985–1998) found that different clinical forms of acute Q fever were associated with different patient statuses. Isolated fever occurred more frequently in females, hepatitis occurred among younger patients, and pneumonia occurred in older or immunocompromised patients (Raoult *et al.*, 2000).
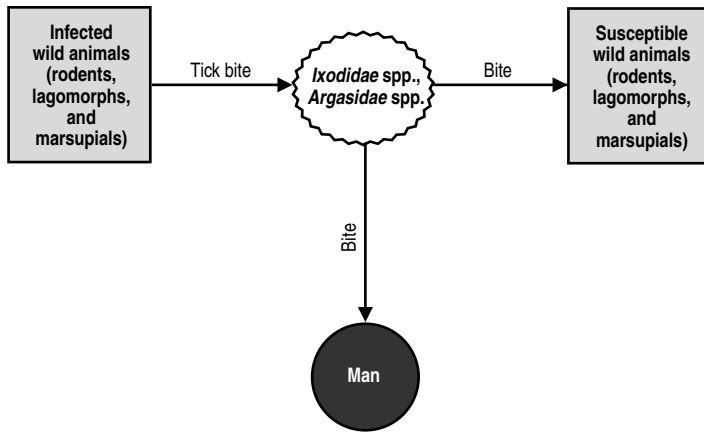
When the disease takes a chronic course, it mainly affects the cardiovascular system. The case fatality rate for chronic Q fever is approximately 65%. In Great Britain, out of 839 confirmed cases of Q fever, 92 (11%) had endocarditis and 10 had liver disease (Palmer and Young, 1982). Of the 313 chronic Q fever patients in the retrospective study in France, 259 had endocarditis; most patients had previous valvulopathy (Raoult *et al.*, 2000). Endocarditis is the most serious complication and is often fatal. It most often occurs among adults, with males being more frequently affected than females. Endocarditis develops slowly and usually manifests between 1 and 20 years after the acute disease. Sawyer *et al.* (1987) have summarized the characteristics of 28 cases from several different countries: 89% of the patients had a history of valve disease; the aortic valve alone was the site in 46% of the 28 cases; and the clinical signs were fever (86%), hepatomegaly (60%), splenomegaly (68%), and microscopic hematuria (80%). One study estimated the risk of developing endocarditis to be 39% among Q fever patients with valvular defects (Fenollar *et al.*, 2001).

Most cases of acute disease heal spontaneously; nevertheless, given the possibility that it could become chronic, treatment is recommended. It consists mainly of the administration of tetracycline or one of its derivatives, particularly doxycycline for two to three weeks (Chin, 2000). Several regimens have been tried for the treatment of chronic Q fever—for example, tetracycline combined with trimethoprim-sulfamethoxazole and rifampicin with doxycycline. Chronic Q fever endocarditis requires prolonged treatment (several years) with tetracycline, or doxycycline in combination with quinolones or hydroxychloroquine.

The Disease in Animals: As a general rule, the infection in domestic animals is clinically inapparent. In ruminants, after *C. burnetii* has invaded the bloodstream, it becomes localized in the mammary glands, the supramammary lymph nodes, and the placenta. Many cows get rid of the infection after a few months, but others become carriers, with the agent localized in the mammary glands and eliminated throughout many lactation periods. During calving, a large number of rickettsiae are shed with the placenta, and, to a lesser degree, the amniotic fluid, feces, and urine. The agent's strong resistance to environmental factors ensures its survival, as well as the infection of new susceptible animals and man. Activation of the infection during calving, with massive shedding of the agent in various secretions and excretions, explains why many sporadic outbreaks in man coincide with that period. Usually, neither milk production nor development of the fetus or the newborn animal is affected by the infection.

In Cyprus, there was an epizootic of Q fever-related abortions in sheep and goats during hostilities on the island in 1974. Twenty-one outbreaks of abortions in these

Figure 2. Q fever. Transmission—wildlife cycle.

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│   Infected   │   Tick bite    │ Ixodidae    │      Bite      │  Susceptible │
│ wild animals │ ─────────────> │  spp.,      │ ─────────────> │ wild animals │
│  (rodents,   │                │ Argasidae   │                │  (rodents,   │
│  lagomorphs, │                │   spp.      │                │  lagomorphs, │
│     and      │                ╰─────────────╯                │     and      │
│  marsupials) │                       │                       │  marsupials) │
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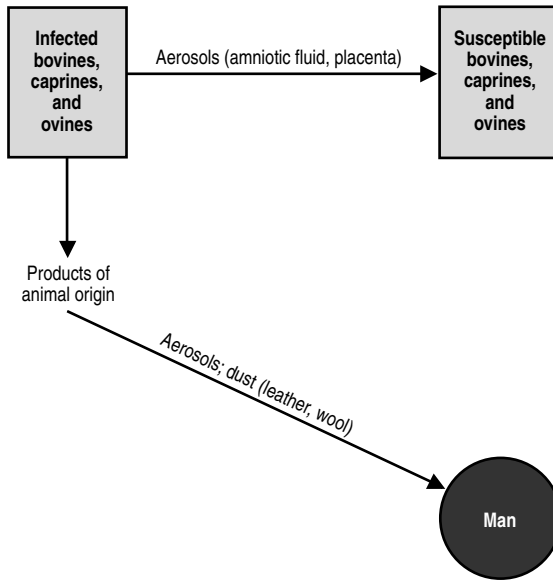
animals were recorded, all in the southeastern part of the island. At the same time, there were also 78 cases of Q fever among British soldiers stationed at the Eastern Sovereign Base Area. It is quite probable that the large concentration of livestock in this part of the island and the shortage of proper feed were factors contributing to the abortions (Crowther and Spicer, 1976). In the US, abortion in domestic animals is rarely associated with *C. burnetii* infection, and it has been observed that dairy cows with heavily infected placentas have given birth to normal calves. In Europe, on the other hand, especially in France, *C. burnetii* is thought to be responsible for 2% to 7% of all abortions in cattle and a similar proportion in sheep. So far no explanation has been offered to account for this difference between the US and Europe.

In Canada, there was an outbreak of abortions in a goat herd between January and April 1992. The fetuses appeared normal. The most remarkable lesion was a purulent inflammation of the cotyledons. Eleven of 33 pregnant goats aborted. *C. burnetii* was isolated, and 34 of the 40 adult female goats reacted positively in the enzyme-linked immunosorbent assay (ELISA). An epidemiological investigation to track down the origin of the infection revealed that 8 of the 11 goats that aborted had been at a livestock fair. Moreover, it was learned that at least six persons developed Q fever in the 12 months following the fair (Sanford *et al.*, 1993). Also, Canada has seen an increase in the rate of abortions and stillbirths in infected domestic ungulates (Marrie, 1990), and it is possible that this trend is occurring in other countries as well.

Little is known about the course of the natural infection in wild animals.

Source of Infection and Mode of Transmission (Figures 2 and 3): Two cycles of infection can be distinguished in nature: one in domestic animals (mainly cattle, sheep, and goats), and the other in natural foci, where the agent circulates between wild animals and their ectoparasites, especially ticks.

Figure 3. Q fever. Transmission—domestic cycle.

Many wild animal species, including marsupials, rodents, and lagomorphs, have been found to be infected. The natural infection has also been observed in more than 40 species of ticks from the families Ixodidae and Argasidae, as well as other arthropods that feed on animals. However, even if infected, not all tick species are able to serve as vectors and transmit the infection to vertebrates.

The relationship between the two cycles of infection is not well studied. There are indications that domestic animals may contract the infection through infected ticks coming from natural foci, but the infection in domestic animals is not dependent on this mechanism; it can be perpetuated independently. The most common mode by which the infection is transmitted between domestic animals is through the inhalation of aerosols from contaminated placental material, amniotic fluid, and excreta. The placenta of infected animals can contain as much as 10^9 g of the causative agent, which can be transported long distances via inert material (see the section on the disease in man for information about other outbreaks). Because of its strong resistance, the agent can be isolated from the soil as long as six months after infected animals have left the area. New foci of infection are created when an infected animal joins a disease-free herd.

The main sources of human infection are domestic animals and their contaminated products (leather and wool). In abattoirs, aerosols are generated by the handling of fetuses, placentas, uteruses, hide, and wool. The main mode of transmission is by aerosols. People who are in close contact with infected animals or their products because of their occupation or residence are most likely to be affected. Although the agent is shed in milk, there are few reported cases of human infection stemming from the consumption of contaminated milk. It seems that man can be infected via the digestive tract, but infection by that route is seldom clinically appar-

ent, probably because of the high titer of antibodies found in milk. Although humans can acquire the infection by entering a natural focus and getting bitten by an infected tick, such cases are rare.

Role of Animals in the Epidemiology of the Disease: Human-to-human transmission is rare. However, an outbreak of 38 cases at a hospital in Frankfurt (Germany) was traced to a staff member who worked with *C. burnetii* and was confirmed by isolation of the microorganism from his sputum. A similar episode originating in an autopsy room has been recorded.

As a general rule, man acquires the infection from domestic animals. Q fever is a zoonosis.

Diagnosis: Few laboratories have adequate installations and equipment to safely isolate *C. burnetii*, and it is therefore preferable to rely on serologic tests. Diagnosis is based on the difference between the titer of a sample taken during the acute stage of the disease and that of a sample taken during the convalescent stage. With serology it is important to take into account the differences between the phases. Strains of *C. burnetii* that have been recently isolated or maintained by passage in laboratory animals are in phase I. After a (varying) number of passages in embryonated eggs, the strains convert to phase II. The tests used most often are complement fixation and indirect immunofluorescence. Comparison studies have shown that with the complement fixation test, the highest titers are obtained at three months, while with indirect immunofluorescence, similar titers are reached at one or two months and maintained for at least a year. A disadvantage of complement fixation is that anticomplementary sera can sometimes develop. This does not happen with the indirect immunofluorescence test, which is also more versatile because it can distinguish several immunoglobulin isotypes. Specific IgM antibodies indicate a recent infection and can be detected the second week after the disease's onset. However, care should be taken to remove the rheumatoid factor before performing the test (Sawyer *et al.*, 1987). High IgA and IgG titers against phase I antigens are indicative of chronic disease (endocarditis) (Aitken *et al.*, 1987).

Use of the complement fixation test with phase II antigens will detect the infection in about 65% of the patients during the second week and about 90% of them by about the fourth week. When there are no complications, patients rarely react to the complement fixation test with phase I antigens. On the other hand, because phase I titers are high in cases of endocarditis, this test is useful for discovering possible complications during convalescence.

Various agglutination tests are also available: standard agglutination, microagglutination, agglutination-resuspension, and capillary agglutination. In about 50% of the patients, the presence of agglutinins can be detected at the end of the first week of the disease, and in 92%, during the second week. The Luoto capillary agglutination test, which uses phase I antigens stained with hematoxylin, is especially useful for epizootiologic studies because it can be used on milk samples. When serum from the acute stage of the disease is not available to test for seroconversion and compare with serum obtained during convalescence, the indirect immunofluorescence test for IgM antibodies, which uses both phase I and II antigens, can be useful. In an experiment carried out in Australia, all Q fever patients reacted positively at about two weeks after onset of the disease, and thus it was possible to obtain a diagnosis using only one serum sample (Hunt *et al.*, 1983).

The agent can be isolated from febrile blood and sometimes from sputum and urine in humans, as well as from substances such as milk, placentas, and amniotic fluid from animals. These materials are inoculated into laboratory animals (guinea pigs and mice) and embryonated eggs. However, as pointed out earlier, isolations should only be performed in laboratories that have high-safety equipment and supplies.

Control: Several vaccines have been developed to protect high-risk occupational groups such as workers in laboratories, abattoirs, wool-shearing sheds, and on farms, as well as patients with heart valve implants and immunodeficient individuals. One of these vaccines was tested on volunteers with good results (Ascher *et al.*, 1983). The most well-known vaccine is a formalin-inactivated whole-cell preparation made with phase I antigens, which confers much greater protection than those made with phase II antigens. The disadvantage of using whole-cell vaccines with phase I antigens is that they can cause undesirable side effects, such as local erythema, induration, granulomas, sterile abscesses, and systemic reactions in persons previously exposed to *C. burnetii* infection. The whole-cell vaccine should not be used in persons who have had a positive serologic or cutaneous reaction. To address these problems, a phase I cell chloroform:methanol residue vaccine (CMRV) has been developed (Williams *et al.*, 1992). Though the whole-cell and CMRV vaccines are not commercially available in the US, persons at risk can request vaccination. A Q fever vaccine is commercially available in Australia.

In a clinical trial in Australia, a whole-cell formalin-inactivated vaccine was administered to 4,000 abattoir workers and related groups over the period 1981–1984. The side effects observed were erythema and pain at the inoculation site and, sometimes, a passing headache. The protection conferred by the vaccine was very satisfactory and lasted for five years. Eight cases of Q fever were observed, but they were all in persons who were already incubating the illness before they were vaccinated, so that there was no time to establish immunity. On the other hand, there were 97 cases in unvaccinated individuals who worked or visited the participating abattoirs (Marmion *et al.*, 1990). In a random double-blind trial conducted at three abattoirs in Queensland (Australia) the formalin-inactivated vaccine was administered to 98 persons and an influenza vaccine to 102 persons; 15 months later, there were 7 cases in the group vaccinated against influenza and none in the group vaccinated against Q fever (Shapiro *et al.*, 1990). A Q fever vaccine is licensed in Australia.

Sheep used for experimental purposes should undergo serologic testing before they are accepted at research institutes. Measures aimed at combating infection in the animal reservoir (domestic animals) are difficult to implement because Q fever does not cause obvious economic losses and livestock owners are reluctant to invest in prophylaxis. When practicable, it is recommended to separate gravid females before they give birth and to bury or burn the placenta and all material surrounding the fetus.

Raw milk should not be consumed.

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QUEENSLAND TICK TYPHUS

ICD-10 A77.3 Spotted fever due to *Rickettsia australis*

Etiology: Despite its name, this disease belongs to the spotted fever group, and its agent is *Rickettsia australis*. A new agent from the same group was isolated on Flinders Island, northeast of Tasmania. The genetic difference between this rickettsia and *R. australis* is significant (Baird *et al.*, 1992).

Geographic Distribution: The original disease is limited to the area between Queensland and Sydney, in New South Wales (Australia), while the new spotted fever has been found on Flinders Island, Tasmania, and in Gippsland, Victoria, in southeastern Australia (Graves *et al.*, 1993).

Occurrence in Man: The disease caused by *R. australis* is sporadic. The disease caused by the new agent is not fully understood. On Flinders Island (population 1,000), annual incidence is nearly 1%. Between October and December 1989, there were 17 new cases. In all, 24 cases have been diagnosed on Flinders Island and in southeastern Australia (Graves *et al.*, 1993).

Occurrence in Animals: A serological study of wild animals in an area of Queensland revealed reactors in several species of marsupials and rodents. In southeastern Australia, where the Flinders variant of *R. australis* predominates, a study using indirect immunofluorescence showed that 11.2% of 312 domestic and farm dogs had antibodies to *R. australis*. While control dogs in New Zealand were negative, 15% of the dogs on Flinders Island were positive.

In a set of serum samples from species of native vertebrates captured in Gippsland, Victoria, particularly the rat *Rattus fuscipes*, 89% were positive in the competitive enzyme-linked immunosorbent assay (ELISA). On Flinders Island, the same test was used to examine sera from 37 wild animals (placental and marsupial mammals), and 8 (22%) proved to be positive (Graves *et al.*, 1993).

The Disease in Man: *R. australis* produces a benign macular disease similar to boutonneuse fever and Asian ixodo-rickettsiosis. An eschar is often seen at the site where the larval or adult tick was attached. Painful regional adenopathy is also observed. The eruption, which appears during the first week of the disease, disappears soon after the fever subsides. The clinical aspects of Flinders Island spotted fever (FISF) differ very little from those of Queensland tick typhus. Only a small proportion of patients have an eschar left by the tick, and the frequency of lymphadenopathy is also low.

Treatment consists of administering of tetracycline or doxycycline.

The Disease in Animals: Little is known about how the infection develops in marsupials or rodents, nor have signs of the disease been observed in dogs bitten by infected ticks. In the case of a dog inoculated experimentally with *R. australis*, a series of tests failed to reveal rickettsemia (Sexton *et al.*, 1991).

Source of Infection and Mode of Transmission: The natural history of *R. australis* is not well understood. In a focus in southeastern Queensland, either *R. australis*, the new variant, or the agent that produces FISF was isolated from two species of ticks: *Ixodes holocyclus* and *I. tasmani*. Another tick associated with the infection is *I. cornuatus*. No infected ticks from these species have been found on Flinders Island. A patient from the island with laboratory-confirmed rickettsiae had been bitten by *Aponomma hydrosauri* nine days before the onset of his illness, but it is not certain that this tick was the vector. The human infection has long been associated with the bite of *I. holocyclus*, a species that feeds on a large variety of vertebrate animals and often bites man.

Diagnosis: The disease must be distinguished from scrub typhus (*R. tsutsugamushi*), endemic murine (flea-borne) typhus (*R. typhi*), and Q fever, which also occur in Australia.

R. australis can be isolated by inoculating the blood of febrile patients into suckling guinea pigs and mice. In the complement fixation test, sera from convalescent mice inoculated with material containing *R. australis* had species-specific antibodies that could be distinguished from antibodies to other rickettsial antigens of the spotted fever group. Seeding the agent on plaques of Buffalo green monkey kidney cells has yielded satisfactory results after a month of incubation in carbon dioxide at 34.5°C.

Control: Control measures are similar to those used against infections caused by other spotted fever group rickettsiae.

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RICKETTSIALPOX

ICD-10 A79.1 Pustular rickettsiosis due to *Rickettsia akari*

Synonyms: Vesicular rickettsiosis, Kew Garden fever, gamaso-rickettsiosis varicelliformis.
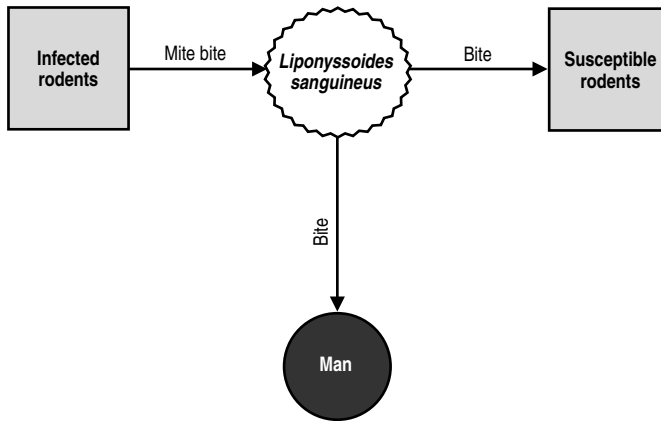
Etiology: *Rickettsia akari* (*Dermacentroxenus murinus*). This microorganism belongs to the group of rickettsiae that produce spotted fever. *R. akari* is a small coccobacillus that can be seen in the nucleus and cytoplasm in stained histological sections of infected mouse tissue.

Geographic Distribution: The disease has been found in New York City and other cities in the US. A similar disease has also been reported in Ukraine, where the agent was also isolated from household rats. On the basis of clinical observations, it is suspected that this rickettsiosis occurs among natives of equatorial Africa and in South Africa (where there is serologic evidence as well). In addition, a serologic study conducted in Central America suggests that the disease has occurred in Costa Rica. In Korea, *R. akari* has been isolated from a vole (*Microtus fortis pelliceus*). The agent was isolated from a patient in Croatia, too (Radulovic *et al.*, 1996).

Occurrence in Man: Occasional. In 1946, an outbreak affected 144 persons in Kew Gardens, a neighborhood in New York City. For a while thereafter, about 180 cases were reported each year in the US, but then the incidence dropped off sharply. In 1979, there was a small outbreak of five cases in New York among persons living in two apartments in the same mouse-infested building (Brettman *et al.*, 1981). Also in Ukraine, where the infection was once widespread in the Donets basin, there has been a marked decline in the incidence of the disease.

Occurrence in Animals: The natural host of *R. akari* in the US is the house mouse (*Mus musculus*), and in Ukraine it is the rat (*Rattus* spp.). The infection is transmitted by the mite *Liponyssoides sanguineus* (*Allodermanyssus sanguineus*). The frequency of infection in rodents is unknown.

The Disease in Man: The disease has a benign course. It starts with a cutaneous lesion at the site of the mite bite (*L. sanguineus*) and continues with a week of

Figure 4. Rickettsialpox *(Rickettsia akari)*. Transmission cycle.

fever accompanied by a varicelliform eruption. Symptoms appear 9 to 24 days after the bite. The initial cutaneous lesion, a small papule that develops a vesicle in the center and later forms a dark crust, appears about one week before the fever and leaves a small scar. The febrile period is characterized by chills, profuse sweating, intermittent fever, cephalalgia, and myalgia. Some patients may experience nasal discharge, cough, nausea, vomiting, or abdominal pain. A maculopapular eruption appears between the first and the fourth day of the fever and then becomes a maculovesicular eruption that disappears at the end of the week, leaving no scars. The eruption is painless and can appear on many parts of the body, but it does not affect the palms of the hands or the soles of the feet. Leukopenia and mild lymphocytosis are present during the early days of the febrile period (Brettman *et al.*, 1981).

Although the disease has a benign course and is eventually self-limiting, antibiotics are recommended to reduce the duration of the symptoms. The preferred treatment is 250 mg of tetracycline every six hours for two to five days (Brettman *et al.*, 1981).

The Disease in Animals: The natural course of the infection in mice and other rodents is unknown. Laboratory mice are highly susceptible to artificial infection. Intranasal inoculation causes a pneumonia that is often fatal. Intraperitoneal inoculation causes peritonitis with a sanguinolent exudate, lymphadenitis, and splenomegaly. Death occurs between 9 and 18 days postinoculation. Strains of *R. akari* vary in terms of virulence.

Source of Infection and Mode of Transmission (Figure 4): The main reservoirs are the domestic mouse and the mite *L. sanguineus*, which can pass on the rickettsia by transovarial transmission. In the US, the nymphs and adult mites feed on domestic mice and may attack other animals and man (Weiss and Moulder, 1984). It is possible that there is also a wild cycle, as suggested by isolation of the agent from a wild

rodent in Korea. The disease is also believed to occur in the "bushveld" of South Africa (level, steppe-like grassland with abundant shrubs and thorny vegetation).

Both in the US and in the Russian Federation, rickettsialpox has occurred in cities and affected people living in rodent-infested dwellings. The etiologic agent is transmitted from one mouse to another by the mite *L. sanguineus* and, accidentally, to man. This mite is probably the main reservoir of the agent. Thus, *L. sanguineus* would be the vector of the infection and also serve as its reservoir. Although house mice are the preferred hosts, the vector also feeds on rats and other rodents. *L. sanguineus* does not remain permanently on the host; it only stays for one or two hours in order to feed. Large numbers of nymphs and adult mites are found in buildings located near rodent nests and paths (Harwood and James, 1979; Bell, 1981).

Role of Animals in the Epidemiology of the Disease: The infection is perpetuated by rodents and by the mite *L. sanguineus*; man is an accidental victim.

Diagnosis: Laboratory confirmation is accomplished by isolating the agent from blood taken during the febrile period and inoculating it in mice, then performing the complement fixation test using sample sera obtained during the acute phase of the disease, and then again three to four weeks later. The indirect immunofluorescence test is also useful in diagnosing the disease.

Control: Control measures target the vector and the rodents. They consist of applying acaricides in the infested area, followed by rodenticides. Trash should be incinerated to eliminate mice and rat havens in buildings. The sharp drop in incidence among persons in New York City is attributed to changes in waste-handling practices (Benenson, 1990).

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ROCKY MOUNTAIN SPOTTED FEVER

ICD-10 A77.0 Spotted fever due to *Rickettsia rickettsii*

Synonyms: Spotted fever, petechial fever, macular fever (Brazil), tick-borne typhus, New World spotted fever, North American tick typhus, São Paulo fever, Choix fever, pinta fever (Mexico).

Etiology: *Rickettsia rickettsii* (*Dermacentroxenus rickettsii*). This microorganism is the prototype of the spotted fever group rickettsiae. Although it is the most pathogenic of the group, its strains differ in terms of their virulence. Some of its antigens are shared by the entire group, and it also has species-specific antigens, which can be demonstrated by applying the microimmunofluorescence test to mouse sera. The agent penetrates human skin through a tick bite and travels through the body via the bloodstream and lymphatic system, attaching to endothelial cells along the way and eventually involving the lungs. It enters the cells by phagocytosis and then moves from the phagosome to the cytoplasm, and sometimes the nucleus, where it reproduces by binary fission (Raoult and Walker, 1990).

Geographic Distribution: The disease has been found in Brazil (states of Minas Gerais, Rio de Janeiro, and São Paulo), western Canada, Colombia, Costa Rica, the western and central areas of Mexico, Panama, and the US. In the US, it occurs everywhere except in the states of Alaska, Hawaii, Maine, and New Hampshire. The infection has not been identified outside the Americas.

Occurrence in Man: Sporadic. In the US, where the disease is the subject of epidemiological surveillance, there were 528 cases a year on average from 1970 to 1973. This figure rose considerably over the rest of the decade, and during 1977–1980, there were 4,411 cases, for an annual average of 1,103. However, the trend reversed in the next decade, falling from 1,170 cases in 1981 to 603 in 1989, with an incidence of 0.25 per 100,000 population. At the same time, the case fatality rate fell from 4.7% in 1982 to a low of 1.1% in 1989 (CDC, 1990). In 1990, a total of 649 persons contracted the disease, and case fatality increased by 7.6% (CDC, 1991).

In the US, which is the country most affected, there has been a notable eastward shift in the distribution of case incidence. From 1910 to 1930, the largest numbers of cases (between 100 and 600 a year) were reported in the Rocky Mountain region, where the tick *Dermacentor andersoni* is found. Today, however, the highest numbers are reported from the southeastern seaboard and the central southwest (the region corresponding to the dog tick *Dermacentor variabilis*). Of the 603 cases reported in 1989, 224 (37.1%) were from the southeastern seaboard and 100 (16.6%) from the central southwestern states. The incidence was highest in the state of Oklahoma (1.9 per 100,000 population), followed by North Carolina and Montana (1.8 per 100,000 population) (CDC, 1990). The cases occur mainly in the spring and summer, when the ticks are most active. In a series of 487 cases, 63% of the patients were males. The rate was highest in children 5 to 9 years old and lowest in persons age 20 and over (CDC, 1990). Geographically, overall national incidence was 5.2 cases per 1,000,000 population, and the highest incidence was in the southeast. Most cases occur between mid-April and mid-September, and are mainly seen in children and young adults, with males predominating (Bernard *et*

al., 1982). No recent figures are available on the incidence of this zoonosis in Latin America.

Occurrence in Animals: In Brazil, *R. rickettsii* has been isolated from dogs, opossums, and wild rabbits (*Sylvilagus* spp.). In the endemic areas of the US, it has been found, as elsewhere, in dogs, opossums, and wild rabbits, and also in many species of wild rodents. Rickettsemia is short-lived in wild animals (Weiss and Moulder, 1984; Raoult and Walker, 1990).
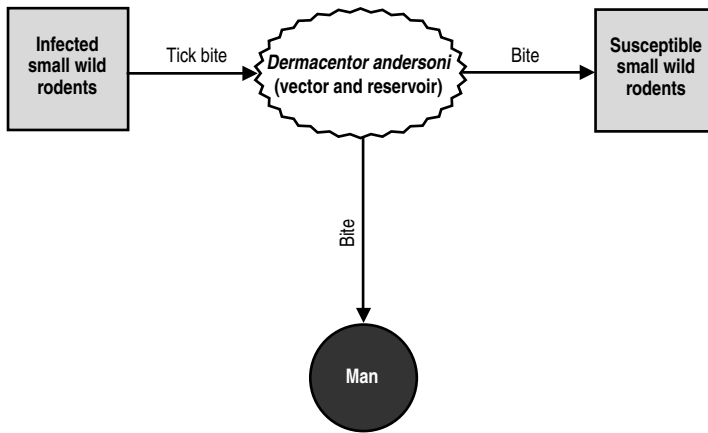
Serological studies in the US have confirmed that many species of wild mammals have antibodies for *R. rickettsii*. Since dogs infested with the tick *D. variabilis* are an important link in transmission of the infection to man, it is of interest to know the extent to which they are exposed to infected ticks. Several serological studies have found a high rate of reactors among dogs in endemic areas. The highest prevalence of seroreactors was reported in Columbus, Ohio, where 45.2% of 73 dogs tested by microimmunofluorescence were positive (Smith *et al.*, 1983).

The disease occurs sporadically in both dogs and humans. An outbreak was reported among a group of Siberian huskies kenneled in a makeshift building on a high pasture where ticks were known to be present. Within five days, 7 of the 12 dogs had fallen sick (Breitschwerdt *et al.*, 1985).

The Disease in Man: Clinical symptoms appear 2 to 14 days after the tick bite. The disease has a sudden onset and is characterized by fever, chills, headache, and pain in the muscles, joints, and bones. Fever of about 40°C lasts until the end of the second week of illness. Also, before the skin rash develops, there is often a phase of gastrointestinal upset with nausea, vomiting, and diarrhea (Raoult and Walker, 1990). A generalized macular rash appears three to six days after the onset of fever; at first it resembles measles, but it often becomes petechial. This rash, which starts around the wrists and ankles, is the most characteristic sign of the disease and is present in more than 80% of the cases. Involvement of the nervous system, with such symptoms as agitation, insomnia, delirium, or even coma, may develop at the end of the first week. During the second week there may be circulatory and pulmonary complications. Also, gangrene was reported in about 30 patients, a number of whom had to have a limb and/or digit amputated (Kirkland *et al.*, 1993). The period of convalescence can be short for patients who receive treatment, but when the disease is allowed to progress untreated, it can last for weeks or months. In the US, case fatality declined from 4.5% to 1.2% (CDC, 1990).

The Disease in Animals: The infection is inapparent in most of its wild hosts. Dogs infected either experimentally or in nature may have clinical symptoms. In a group of four dogs that had been diagnosed serologically, three had high fever, abdominal pain, depression, and anorexia. Two of them displayed lethargy and nystagmus, and the third had conjunctivitis and petechial hemorrhages in the oral mucosa. The fourth dog had no clinical symptoms. It is possible that dogs in endemic areas are exposed to *R. rickettsii* at an early age and that maternal antibodies protect them from a severe form of the disease. Thus, by the time they are re-exposed later on, they may have become actively immune and therefore resistant to clinical infection (Lissman and Benach, 1980).

In an outbreak described by Breitschwerdt *et al.* (1985), the following symptoms of the disease were observed: lethargy, anorexia, ocular and nasal discharges, inco-
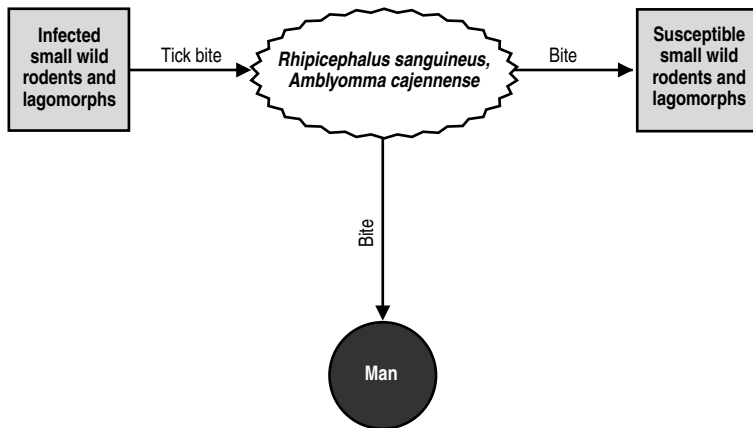
Figure 5. Rocky Mountain spotted fever. Transmission cycle in the US.

ordination, scleral blood vessel injection, fever, lymphadenomegaly, splenomegaly, and increased bronchovesicular sounds. In a report of four cases, in addition to suffering from various signs of the disease, the dogs developed necrotic skin lesions in such areas as the scrotum, earflap, nose, nipples, and the limbs (Weiser and Green, 1989). In 11 dogs with a serologically confirmed diagnosis, 9 had mild ophthalmic lesions that healed after the dogs were given parenteral oxytetracycline or oral tetracycline for a minimum of two weeks (Davidson *et al.*, 1989). Since dogs have much more exposure to ticks than humans do, they can serve as an indicator of the prevalence and location of disease foci (Feng *et al.*, 1979).

Source of Infection and Mode of Transmission (Figures 5 and 6): The natural reservoir is a complex of ticks of the family *Ixodidae* and small wild mammals. In the US, there are two main vectors and reservoirs: *D. andersoni* in the Rocky Mountain region, and the dog tick *D. variabilis* in the east and southeast. Currently, *D. variabilis* is much more important as a vector because most of the human cases occur in the eastern part of the country. In the endemic areas of Latin America, the principal vector is *Amblyomma cajennense*. This tick attaches to humans at any stage in its development, whereas *D. andersoni* and *D. variabilis* do so only as adults. In Mexico, the brown dog tick *Rhipicephalus sanguineus* is also a vector. In Costa Rica, the agent was isolated from *Haemaphysalis leporispalustris*, which infests the wild rabbit *Sylvilagus braziliensis*. This tick has no special preference for man and is not believed to be a vector for human disease (Fuentes *et al.*, 1985).

The agent circulates in natural foci via ticks, which transmit it to small rodents when they attach themselves in order to feed. Uninfected ticks, in turn, can then acquire the infection by taking a blood meal from infected wild animals (field mice, squirrels, etc.). Although wild rabbits (*Sylvilagus* spp.) were once thought to be a primary reservoir, doubts have been raised about how readily they can transmit the

**Figure 6. Rocky Mountain spotted fever.
Transmission cycle in Latin America.**

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┌──────────────┐                                          ┌──────────────┐
│ Infected     │   Tick bite   ⟨ Rhipicephalus      ⟩  Bite │ Susceptible  │
│ small wild   │ ───────────▶  ⟨ sanguineus,        ⟩ ──────▶│ small wild   │
│ rodents and  │               ⟨ Amblyomma cajennense⟩      │ rodents and  │
│ lagomorphs   │                                          │ lagomorphs   │
└──────────────┘                                          └──────────────┘
                                    │
                               Bite │
                                    ▼
                                 ( Man )
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NOTE: Transovarial transmission of *Rickettsia rickettsii* in ticks may possibly perpetuate the infection by itself.

infection to ticks (Burgdorfer *et al.*, 1980). Ticks play an important role not only as biological vectors but also as reservoirs, because they can pass *R. rickettsii* to their offspring by transovarial transmission.

The rate of infection in ticks is low, even in highly endemic areas, and it varies from year to year. Nevertheless, the infection can be maintained in nature by transovarial transmission alone. In this situation, ticks would be the main reservoir of the infection, and animals to which they attach would serve only to feed them.

The role of other animals as reservoirs capable of maintaining the infection in nature has not been established, since the rickettsemia that they experience is brief. As for dogs, even though they play a very important role in the epidemiology of the disease by introducing infected ticks into the human environment, it is doubtful that they can infect ticks under natural conditions.

Man becomes infected through the bite of a tick, which must remain attached to the body for at least four to six hours in order for the rickettsiae to "reactivate" (pass from the avirulent to the virulent stage). It is also possible, though less common, for rickettsiae in a tick's feces, or in pieces of its tissue that rupture at the time it is detached, to enter the body through a break in the skin.

Humans contract the infection either by entering tick-infested areas or through contact with ticks carried by dogs to suburban homes. The human infection is seasonal, coinciding with annual periods of greatest tick activity.

Role of Animals in the Epidemiology of the Disease: Man is an accidental host. The dog is a key link in the transmission of the infection to man because it introduces infected ticks into the human environment—specifically, such species as *D. variabilis*, *A. cajennense*, and *Rhipicephalus sanguineus*.

Diagnosis: Laboratory confirmation of the clinical diagnosis is based on isolation of *R. rickettsii* from the patient's blood during the first week of fever and inoculation of a coagulated blood suspension into male guinea pigs or embryonated eggs. Stained smears of the tunica vaginalis testis can be examined microscopically four to six days after inoculation. Although isolation of the agent is the most reliable way to diagnose the disease, due to the risk of contaminating the environment and exposing personnel to the infection, it is imperative that the test be performed only in reference laboratories equipped for the procedure.

It is very important to have an early presumptive diagnosis. If the disease is suspected because of the clinical signs and epidemiological antecedents, treatment should be started immediately without waiting for laboratory results. The Weil-Felix test is no longer used because of its low sensitivity and specificity. The main tests now used are indirect immunofluorescence and indirect hemagglutination. Complement fixation, latex agglutination, and microagglutination are specific but not sufficiently sensitive. The tests are performed on acute- and convalescent-stage sera. A four-fold rise in titer is considered positive. Sometimes *R. rickettsii* antigen can be detected in eruptive skin lesions using direct immunofluorescence (50%–70% sensitivity) (CDC, 1990). Diagnosis was obtained using polymerase chain reaction to amplify ribosomal DNA of *R. rickettsii* in blood clots from four of five patients, but in three of the cases reamplification was needed. This would indicate that the test is not sufficiently sensitive and has limitations for clinical diagnosis (Sexton *et al.*, 1994). Moreover, the value of serological tests for diagnosing *R. rickettsii* is limited by the fact that seroconversion cannot be demonstrated until at least six days after onset of the disease (Clements *et al.*, 1983a).

Control: Control measures include the application of tickicides in limited areas to exterminate or reduce the vector population, use of protective clothing and repellents (diethyltoluamide and dimethylphthalate) for individual protection, inspection of clothing twice a day to get rid of unattached ticks, and careful removal of attached ticks. It is also important to apply residual tickicides to dogs, kennels, and dwellings at two-week intervals.

Vaccines to protect individuals at high risk of exposure (laboratory workers and ecologists) have not given very satisfactory results. An improved, chick embryo cell-derived formalin-inactivated vaccine was tested on volunteers and evaluated. The vaccine conferred only partial protection (25% efficacy), but the volunteers who did become ill had a milder form of the disease (Clements *et al.*, 1983b).

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SCRUB TYPHUS

ICD-10 A75.3 Typhus fever due to *Rickettsia tsutsugamushi*

Synonyms: Tsutsugamushi disease, mite-borne typhus fever, tropical typhus, and various local names.

Etiology: *Rickettsia tsutsugamushi* (*R. orientalis*) belongs to the typhus group. In Greek, the word *typhos* means "stupor caused by a fever." There is a high degree of antigenic heterogeneity among the different strains. Eight antigenic prototypes are recognized, and there may even be more. Immunity against the homologous strain is long-lasting, but against the heterologous strains it is only temporary. Where several serotypes coexist in an endemic area, one of them may predominate (Shirai and Wisseman, 1975). In a series of 168 isolations obtained from various species of *Leptotrombidium* mites in Malaysia, 68.5% contained only one type, with the Karp prototype predominating (Shirai *et al.*, 1981). The different strains of *R. tsutsugamushi* vary in their virulence.

R. tsutsugamushi, a bacillus, is one of the smallest rickettsiae, averaging 1.2 microns in length. It can be seen with Giemsa stain or a modified version of Gimenez stain. It grows well in cell cultures and in the viteline sac of embryonated eggs. It is found in the perinuclear region of eukaryotic cells (Weiss and Moulder, 1984).

Geographic Distribution: From Primorski Krai, in the far eastern part of the Russian Federation, to southeast Asia, India, Afghanistan, Pakistan, northern Australia, and islands of the eastern Pacific. In these areas, the infection is found in a wide range of ecological conditions: primary jungle, semidesert, mountainous desert, and the alpine meadows of the Himalayas. Its distribution is uneven, since it depends on the presence of the agent and the vector/reservoir complex, the latter consisting of trombiculid mites and the small mammals, especially rodents, on which they feed. When all these elements come together, they form "typhus islands." Focalization occurs when the vector's larvae and the reservoir *Leptotrombidium* spp. are found in the same place.

Occurrence in Man: During World War II, scrub typhus was a serious problem for both the Allied and the Japanese forces in the southwestern Pacific and the India-Burma-China theater of operations. It is estimated that the Allied troops had some 18,000 cases. Case fatality in the various outbreaks ranged from 0.6% to 35.3%, depending on the area. The disease continues to be a public health problem in some
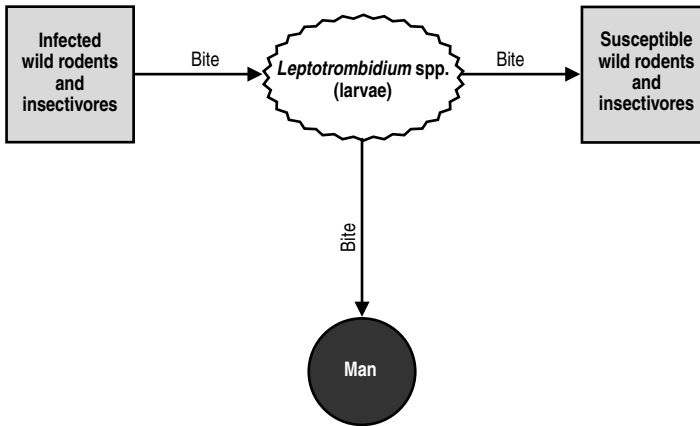
endemic areas. In most cases it occurs sporadically. Although the recorded incidence of clinical cases in Malaysia between 1967 and 1974 was very low (averaging about 55 a year), the real incidence of the disease was thought to be much higher. In a study conducted in two communities of peninsular Malaysia, the monthly incidence of infection was estimated at 3.9% in one community and 3.2% in the other. The lack of adequate laboratories in rural areas makes it difficult to distinguish scrub typhus from other febrile diseases (Brown *et al.*, 1978). In some areas, the disease in humans can disappear and then reappear many years later. That was what happened in Chiba Prefecture (Japan), where it was first recognized in a patient in 1950, and then disappeared, only to appear again in 1982 and resume its upward climb. A total of 152 cases were recognized in 1989, and the following year the number increased to 157. Ninety percent of these cases occurred in November and December. Of six isolations typed with monoclonal antibodies, five were of the Kawasaki type and one was Kuroki (Kaiho *et al.*, 1993). In recent years, new disease foci have been found in Korea and Australia's North Territory. Of 113 isolations from Korean patients, which were typed using polyclonal and monoclonal sera, 88 had an antigenic determinant that was not found in the Karp, Kato, and Gilliam prototype strains, and they also had antigens in common. The authors (Chang *et al.*, 1990) concluded that a new serotype, related to the Karp type, is prevalent in Korea.

The rate of serologic reactors can be very high in areas of great endemicity. For example, an indirect immunofluorescence study conducted in a Thai village revealed that 77% of the adults in the community were reactors. Similar results were found in Malaysia, especially among jungle aborigines, with much lower rates among the people living in villages. No doubt the population in endemic areas is constantly exposed to the infection.

Occurrence in Animals: Natural infection has been observed in many mammal species. Rats (*Rattus* spp.) and, in some regions, voles and field mice (*Microtus* spp. and *Apodemus* spp.), as well as arboreal shrews, are of particular interest. The species of infected mammals vary depending on the zoogeographic region in which the natural foci of infection are found.

The Disease in Man: One to three weeks after being bitten by a larval mite of the genus *Leptotrombidium*, the patient develops a fever, headache, conjunctival congestion, and generalized aches coupled with lymphadenopathy that is painful to the touch. Interstitial pneumonitis is also common. The temperature can rapidly rise to 40–40.5°C within the first few days (Saah, 1991). A skin ulceration with a black scab at the site of the bite is often found among patients of the Caucasian race but rarely among Asians. A macular eruption occurs at the end of the first week of fever and can last from just a few hours to as long as a week, in which case it assumes a maculopapular form and turns dark purple. Convalescence is long. The severity of the disease depends on the infecting strain and, above all, the amount of inoculum received. Within these parameters, the clinical picture can range from very mild to very severe. Some patients may experience delirium, tremor, psychomotor excitation, hypoacusis, and stiffness of the neck. In a group of 87 American soldiers who developed the infection, only 30 (34%) had a cutaneous eruption, and for 85% of them, the most common sign was adenopathy (Berman and Kundin, 1973; Saah, 1991). In untreated patients, pulmonary, encephalic, or cardiac complications can occur, often with fatal results. As with the other rickettsioses, the basic pathologic

Figure 7. Scrub typhus *(Rickettsia tsutsugamushi).*
Transmission cycle.

lesions may be found in the smaller blood vessels. The case fatality rate can range from 0% to 30% (Wisseman, 1982), and is much higher in older persons.

The classic treatment consists of oral tetracyclines: a high initial dose, followed by four daily doses over the course of a week. If the treatment is started during the first three days of the disease, a relapse may occur. In Malaysia and the Pescadores Islands (Taiwan), administration of a single dose of 5 mg/kg of doxycycline on the seventh and fifth days, respectively, was found to be effective (Benenson, 1990).

The Disease in Animals: In natural hosts, the infection is inapparent or relatively mild.

Source of Infection and Mode of Transmission (Figure 7): The most important vectors of *R. tsutsugamushi* are several mite species of the genus *Leptotrombidium,* most notably *L. akamushi*, *L. arenicola*, *L. deliense*, *L. fletcheri*, *L. pallidum*, and *L. pavlovsky*. The vector species differs depending on the particular ecosystem. For example, in Japan *L. akamushi* is found in partially cultivated fields that flood in spring and early summer, whereas *L. deliense* is associated more with jungles. The mites are often found in tightly circumscribed foci (belts or islands) in areas of scrub vegetation, hence the name of the disease. Only the larvae of these mites attach themselves to vertebrate hosts for feeding, and in the course of this act transmit the infection. During its other phases of development (egg, nymph, and adult), the mite lives in the surface layers of the soil. *Leptotrombidium* species serve not only as the vector but also as the reservoir, since they pass the agent to their offspring by transovarial transmission. This occurs at a very high rate and perpetuates the infection from one generation to the next. Another indication that *Leptotrombidium* species are probably the principal reservoir is that the larvae feed on animals or man only once (Saah, 1991). Shortly after the eggs emerge, the six-legged larvae remain on top of the soil or climb a few centimeters up a plant and wait for an animal or person to pass by so that they can attach to its skin. Once they have fed, the larvae return to the soil, where

they continue their life cycle (Weiss and Moulder, 1984). Wild vertebrates are also a possible reservoir, but their main role is that of food source for the mites.

The mite larvae transmit the infection to wild vertebrates (rodents and insectivores) and, accidentally, to man. The latter becomes infected when he enters the natural foci of infection. The highest incidence has been found among soldiers participating in military operations and farmers who enter the ecological niches of the agent. Military operations conducted in brush and jungle areas have led to epidemics affecting 20% to 50% of the troops over periods of several weeks or months.

It is suspected that some bird species that are frequently parasitized by the larvae of trombiculid mites may serve as transporters thereof, thereby giving rise to new foci of infection. Otherwise it would be difficult to explain how the infection has managed to spread to islands that are separated from other land areas by large bodies of water.

Role of Animals in the Epidemiology of the Disease: Man is only an accidental host of *R. tsutsugamushi*. In natural foci, the infection is circulated among small mammals by the trombiculid vector. However, there is some doubt as to whether these animals are indispensable to maintaining the infection in nature, since the mite alone could perform this role.

Diagnosis: A presumptive diagnosis, based on a rise in the titer during the course of the disease, may be obtained using the Weil-Felix test with *Proteus* OX-K as the antigen. However, this technique is not very sensitive and gives negative results for approximately half the cases.

The indirect immunofluorescence and immunoperoxidase tests are more sensitive and specific than the Weil-Felix test. The difficulty with the first is that a fluorescent microscope is not always available in rural hospitals. In such circumstances, the indirect peroxidase test is more practical (Yamamoto and Minamishima, 1982; Kelly *et al.*, 1988). Using the polymerase chain reaction combined with microplate hybridization, a system has been developed that yields a diagnosis within six hours (Sugita *et al.*, 1993). The etiologic agent can be isolated from blood by inoculating it in mice.

Control: Control measures consist of applying residual acaricides on land to be used for agriculture or military operations. Individual protection can be achieved by using clothes impregnated with acaricides (benzyl benzoate) in conjunction with repellents. When camps are set up in endemic areas, it may be helpful to burn the vegetation or apply herbicides.

There is no effective vaccine available, mainly because of the agent's wide antigenic heterogeneity. However, in a study conducted among 1,125 soldiers destined for the Pescadores Islands of Taiwan, a hyperendemic area, chemoprophylaxis with 200 mg of doxycycline per week proved to be effective (Olson *et al.*, 1980).

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ZOONOTIC CHLAMYDIOSIS

ICD-10 A70 *Chlamydia psittaci* infection

Synonyms: Psittacosis (in birds of the family Psittacidae), parrot fever, ornithosis (in other birds).

Etiology: Within the genus *Chlamydia* the following three species are currently recognized: *C. trachomatis*, *C. pneumoniae* (formerly TWAR strain), and *C. psittaci*. A fourth species, *C. pecorum* (Fukushi and Hirai, 1992; Kuroda-Kitagawa *et al.*, 1993), has been proposed. Chlamydiae are intracellular microorganisms with a characteristic reproductive cycle that goes through two phases, only one of which is infectious. It is now agreed that they are bacteria, but with certain exceptional characteristics—e.g., strict intracellular parasitism, metabolic and structural differences, and a distinct evolutionary cycle.

The infectious element is the elementary body, which binds to and is internalized by susceptible cells in the columnar epithelium of the mucosa. At six to eight hours, the internalized elementary body differentiates into a noninfectious reticulate body. The reticulate body then divides by binary fission, and after another 18 to 24 hours the new bodies undergo another reorganization, which condenses them and turns them into elementary corpuscles 0.2 to 0.3 microns in diameter. Hence, the intracellular inclusion bodies contain not only the elementary bodies (0.2 to 0.3 microns), but also the reticulate bodies, which are more than twice as large (0.8 microns). When the host cell disintegrates, the elementary bodies are released and the infection cycle starts anew. The elementary body is metabolically inert; the reticulate body is active, but parasitizes the host animal's cell because it cannot synthesize high-energy compounds, such as adenosine triphosphate and guanosine triphosphate.

C. trachomatis is the causative agent of trachoma (a keratoconjunctivitis) and the human genital tract infection. The agent of pneumonitis in mice is a biotype of this chlamydial species. *C. pneumoniae* causes human pulmonary disease. *C. psittaci* is the agent of psittacosis/ornithosis in birds and of several diseases in mammals, and it can accidentally infect humans. The new species, *C. pecorum*, has been isolated from cases of bovine encephalitis, pneumonia, and enteritis, and also from ovine polyarthritis. All *Chlamydia* species share a common antigen which, as in the case of gram-negative bacteria, is a lipopolysaccharide.

This chapter will deal only with *C. psittaci*, which can be transmitted from animals to humans. *C. psittaci* strains fall into two broad groups with very different characteristics, namely, the agents of avian psittacosis, and those of mammalian psittacosis.

According to endonuclease restriction analysis, *C. psittaci* has at least five biotypes, and the avian biotype has at least four serotypes. One of these avian serovars is responsible for infection and disease in psittacine birds and another one causes psittacosis in turkeys. The latter has been associated with outbreaks in both turkeys and humans (Andersen and Tappe, 1989). The avian strains of *C. psittaci* have varying degrees of virulence. The more virulent strains, usually isolated from turkeys (turkey serovar), can cause outbreaks in turkeys, with mortality ranging from 5% to 30%. These strains have also been isolated from asymptomatic wild birds. Humans, especially if they work with or are otherwise exposed to these birds, can also be victims of the disease. The less virulent strains are mainly isolated from pigeons and ducks, and occasionally from turkeys and free-living birds (Grimes and Wyrick, 1991). The virulence factors have yet to be determined.

There is even greater diversity among *C. psittaci* strains in mammals. One study (Spears and Storz, 1979) divides the mammalian strains into eight groups. The proposed species, *C. pecorum*, is an offshoot of the mammalian strains. It shares less than 15% DNA:DNA homology with other members of *C. psittaci*, *C. trachomatis*,

and *C. pneumoniae*, compared with 88% homology with the members of the proposed new species. Three serotypes of the species have been identified (Fukushi and Hirai, 1992).

Geographic Distribution: Worldwide.

Occurrence in Man: Generally sporadic. Most human cases of *C. psittaci* are transmitted by birds; cases transmitted by mammals are rare. Between 1929 and 1939, there was an epidemic that spread to 12 countries (in North Africa, Argentina, the US, and a large part of Europe) and caused some 1,000 cases and 200 to 300 deaths. The outbreaks were attributed to the importation of psittacines from South America (Schachter, 1975). The epidemic is believed to have originated in the province of Córdoba (Argentina). Since then, several outbreaks have also occurred among workers in turkey-processing plants. In the US, there were four outbreaks in the state of Texas in 1974, followed in 1976 by an outbreak in Nebraska that affected 28 out of 98 workers, and another in Ohio in 1981 that affected 27 out of 80 workers (CDC, 1982). A 1978 outbreak affecting 21 people at The College of Veterinary Medicine, in New York, is believed to have been associated with the autopsying of turkeys (Filstein *et al.*, 1981). Another outbreak occurred among workers engaged in turkey slaughtering and processing in central Minnesota. Between June and November 1986, a total of 186 suspected cases were identified, of which 122 (66%) were confirmed by serology (complement fixation) (Hedberg *et al.*, 1989). Another area in which workers are at risk is the raising, slaughtering, and processing of ducks. Between 1949 and 1963, a total of 1,072 human cases were identified in the former Czechoslovakia (Caffarena *et al.*, 1993). In 1985, an outbreak in a duck-processing plant in England affected 13 out of 80 workers (16%) (Newman *et al.*, 1992). At present, *C. psittaci* infection in the US is largely an occupational disease related to working with turkeys, whereas in central and eastern Europe it is found among employees who work with ducks.

In the UK, there were 150 suspected cases of psittacosis in Cambridgeshire County (population 300,000) between 1975 and 1983 (Nagington, 1984). The US had 1,136 cases and 8 deaths between 1975 and 1984 (Williams, 1989). Many sporadic cases go undiagnosed or are attributed to other diseases.

In Argentina, there were 26 cases in 1976, followed in 1977 by an outbreak of 180 suspected cases (of which 71 were confirmed), with 3 deaths. Between 1977 and 1981, there were 949 suspected cases of psittacosis, of which 387 (41%) were confirmed by complement fixation. Among these cases, there were two in which human-to-human transmission could be assumed, and 25% of the confirmed cases apparently had no connection with birds (Planes *et al.*, 1986). A 1989 outbreak of 12 cases in the city of Necochea originated at a store where psittacines were sold (Caffarena *et al.*, 1993). During 1992–1993 and the first three months of 1994, the Francisco Javier Muñiz Hospital for Infectious Diseases in Buenos Aires registered 55 cases of psittacosis, all of them serologically confirmed by indirect immunofluorescence, with 2 fatalities. In Uruguay, 22 cases were reported during 1962–1970 and 6 during 1987–1988 (Caffarena *et al.*, 1993).

Few human cases have been traced to the disease in mammals. In 1969, a man acquired acute follicular keratoconjunctivitis from his cat, which had pneumonitis (Schachter *et al.*, 1969). A cat was also linked to a human case of endocarditis with associated glomerulonephritis (Regan *et al.*, 1979). In Great Britain, some 10 cases

of severe infection in pregnant women were traced to *C. psittaci*, which causes enzootic abortions in sheep (Hadley *et al.*, 1992). Also, a case occurred in a pregnant woman in France who had assisted in birthing in a herd of goats, one-third of which had aborted (Villemonteix *et al.*, 1990).

Occurrence in Animals: Natural chlamydial infection has been found in 130 species of domestic and wild birds, more than half of them from the family Psittacidae. For practical purposes, all avian species may be considered potential reservoirs of chlamydiae. In addition to psittacines, the disease is common in fringillids, pigeons, turkeys, and ducks, and somewhat less frequent in chickens. Between 1960 and 1987, more than 20 outbreaks, mainly among turkeys, were reported in the US (Grimes and Wyrick, 1991). The infection rate is generally lower in wild birds. In the state of Florida, *C. psittaci* was isolated from 20% of 287 pet birds (250 of them psittacines) that had died (Schwartz and Fraser, 1982). A similar study of dead and dying birds in Japan yielded *C. psittaci* isolations in 19 (24.7%) of 77 psittacines and 12 (26.1%) of 46 passerines (Hirai *et al.*, 1983). On the other hand, among wild pigeons in Japanese residential areas, the agent was only isolated from 6 (0.8%) of 716 birds, even though 37% of 568 specimens yielded antibodies in the complement fixation test (Fukushi *et al.*, 1983). *C. psittaci* also parasitizes many wild and domestic mammalian species. It is difficult to determine the frequency of *C. psittaci* and *C. pecorum* in mammals. Some of the diseases have been diagnosed in only a few countries, for example, placentopathy and ovine enzootic abortion have only been known to occur in Germany, the US, France, Great Britain, and Hungary; sporadic bovine encephalomyelitis, only in the US and Spain; and ovine polyarthritis, only in the US (Timoney *et al.*, 1988). However, estimates have been received from Great Britain regarding two diseases of zoonotic interest. In a study of enzootic abortion in sheep conducted in Scotland in 1987–1991, specimens from ovine abortions were received from 30.7% of the herds; 28% of the reporting herds had evidence of *C. psittaci* infection, for an estimated prevalence of 8.6% (Leonard *et al.*, 1993). The prevalence of *C. psittaci* infection in cats from different habitats was also studied in Great Britain. Among pet cats, the agent was found in 30% of 753 conjunctival swabs collected; among feral cats, the infection was enzootic in 2 of 3 colonies studied; and cats living on sheep-raising farms were serologically positive at 10 of 22 establishments (Wills *et al.*, 1988).

The Disease in Man: The incubation period lasts one to two weeks, and sometimes longer. Many infections evolve asymptomatically, while with others the symptoms can vary widely in severity. Mild forms of psittacosis may be mistaken for common respiratory illnesses and often go unnoticed. The disease can have a sudden onset, with fever, chills, sweating, myalgia, loss of appetite, and headaches. In the 1986 outbreak in Minnesota, the symptoms of a large number of patients were quantified: 91% had headaches; 80%, chills; 88%, fever; 83%, weakness; 69%, coughing; and 58%, sweating (Hedberg *et al.*, 1989). On the other hand, there are cases in which the disease's onset is more insidious. The symptoms last for 7 to 10 days. When atypical pneumonia is present, radiography shows infiltrations at first, and less often, patches of consolidation in the lower part of the lungs, which may develop into bronchopneumonia. At first there may be a dry cough; later there is some expectoration of mucoid sputum that becomes mucopurulent. The most acute forms of the disease are seen in patients over the age of 50. The most serious cases

may have enlargement of the liver and spleen, vomiting, diarrhea, constipation, insomnia, disorientation, mental depression, and even delirium. The infection contracted from mammals almost always produces systemic disease, but fortunately these cases are rare. Pregnant women, at any point in the pregnancy, are susceptible to contracting the infection from sheep in countries where enzootic abortion occurs in these animals, or in goats infected with *C. psittaci* (see the section on occurrence in animals). In the cases described in Great Britain, all patients but one aborted and experienced fever, kidney and/or liver dysfunction, and disseminated intravascular coagulation. In two of the cases in England, the women had had no direct contact with sheep, but lived on a sheep farm (Hadley *et al.*, 1992).
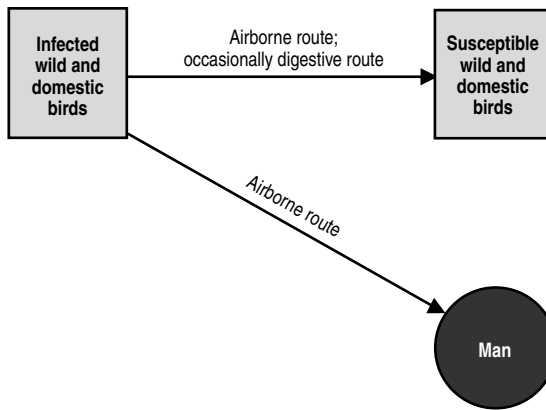
Early treatment is important in order to shorten the duration of the disease and prevent complications. Tetracycline should be given as long as the patient has fever and for 10 to 14 days thereafter. Erythromycin may be used with pregnant women or children under the age of 8, for whom tetracyclines are contraindicated (Benenson, 1990). Case fatality is less than 1% when patients receive proper treatment.

The Disease in Animals: Most infections in birds are latent and inapparent. The disease usually appears when the birds' overall resistance has been lowered because of stress (brought on by such factors as overcrowding, concurrent infections, unsanitary conditions, nutritional deficiencies, prolonged transport, etc.). Outbreaks have occurred in establishments that sell pet parrots and parakeets, or, more often, during the shipment of these animals, and the disease has also been reported in pigeons, turkeys, and ducks. The symptoms—fever, diarrhea, loss of appetite, emaciation, and respiratory distress—are uncharacteristic. Conjunctivitis is common, with severity ranging from mere conjunctival congestion to necrotic obstruction of the orbit. Autopsy may reveal inflamed serous membranes with fibrinous exudate, edematous or hyperemic areas in the lungs, and an enlarged and striated liver. Enlargement of the spleen is common in psittacine birds, and epicarditis and myocarditis are seen in turkeys. In chickens, however, the infection is almost always inapparent.

C. pecorum, the proposed new species, causes encephalitis, pneumonia, and enteritis in bovines and polyarthritis in sheep. The mammalian strains of *C. psittaci* are the strains that cause abortion, keratoconjunctivitis, and other diseases. Trials with parenteral inoculation of chlamydiae from ovine polyarthritis have reproduced the disease in turkeys, while chlamydiae associated with ovine enzootic abortions have been fatal for sparrows and have caused infection in pigeons. However, when chlamydiae from domestic mammals were given orally to several species of wild birds, no seroconversion was observed, nor was the agent detected in feces (Johnson and Grimes, 1983). The avian strains are not transmitted to domestic mammals, nor are mammalian strains communicable to birds. However, a case was described of conjunctivitis in a cat which had probably been contracted from a macaw (*Ara ararauna*) that its owner had acquired a month earlier, from which *C. psittaci* was isolated in a conjunctival scraping and also in a sample taken from the cloaca (Lipman *et al.*, 1994). Human infection from mammalian strains is accidental.

Source of Infection and Mode of Transmission (Figure 8): Wild and domestic birds are the natural reservoirs of *C. psittaci*. Except for the strains of *C. trachomatis* that are proper to man, the *C. trachomatis* biotype that causes pneumonitis in mice, and *C. pneumoniae*, also proper to man, the chlamydiae found in mammals belong to the species *C. psittaci* and *C. pecorum*. The mammalian strains of *C.*

Figure 8. Zoonotic chlamydiosis (psittacosis, ornithosis). Transmission cycle.

psittaci that cause enzootic abortion in sheep and goats are shed in large quantities through the feces and the placenta. Pregnant women can become infected by handling these materials at birthing stations or in abattoirs. The infection is probably also present in women who are not pregnant and persons who come in contact with these animals in the course of their work, which could be demonstrated in seroprevalence studies done by veterinarians. In the case of feline pneumonitis, large amounts of the agent are shed through the conjunctiva and the nose. This infection, which causes conjunctivitis and rhinitis, is common in cats, but human cases of the disease (conjunctivitis), despite frequent exposure, are rare (Schachter, 1989). The mammalian strains of *C. psittaci* are seldom pathogenic for man; only a few cases of human infection from this source have been contracted in the laboratory or in nature (Schachter and Dawson, 1979).

Humans contract the infection from birds by inhaling the airborne agent in contaminated environments. Sporadic human cases have been associated mainly with psittacines and other companion or decorative birds. However, in some places turkeys or ducks may outrank psittacines and pigeons as the main source of infection. Chlamydiosis of avian origin is largely an occupational disease of workers in turkey-processing plants, duck and geese pluckers, pigeon breeders, and employees at establishments that trade in exotic and pet birds. In the former Czechoslovakia and the former East Germany, there were more than 1,000 cases of infection (one-third of them with clinical disease) among workers engaged in plucking ducks and geese. Other occupational groups at risk are laboratory personnel and veterinarians.

In birds, the infection is primarily gastrointestinal and the agent is shed through the feces. Sick birds frequently suffer from diarrhea and release large quantities of chlamydiae into the environment through their feces, which give off aerosols as they dry. Chlamydiae are also spread through contamination of the plumage. The strains isolated from birds vary widely in terms of their virulence, and this fact, coupled

with variations in the extent of exposure to the agent, accounts for the range in severity of human disease.

Transmission between birds can also take place by inhalation, and in some cases via the digestive tract (coprophagy, cannibalism). Domestic fowl—turkeys, ducks, geese, and sometimes chickens—may be infected by wild birds, which represent a large reservoir of the infectious agent. Migrating birds can give rise to new foci of infection (Grimes, 1978). Little importance has been given to transovarial transmission, which has been confirmed in ducks, or to mechanical transmission by arthropod vectors.

Role of Animals in the Epidemiology of the Disease: Human *C. psittaci* infection is a zoonosis, and, as with most zoonoses, man is an accidental host. Human-to-human transmission is rare and has only been seen in a few nurses who had cared for psittacosis patients.

Diagnosis: The following serological techniques are regularly used: direct complement fixation (DCF), modified complement fixation (MCF), and latex agglutination (LA). The advantages of DCF are its relative sensitivity and the fact that it can be used for a large number of species, though not all of them. The most common technique is microprocedure. However, this test does not distinguish between IgM and IgG, and it is therefore necessary to resort to paired samples. The MCF test adds 5% (v/v) normal chick serum to guinea pig complement. By increasing the sensitivity of the test in this way, it is possible to use it for sera from birds that would not normally fix guinea pig complement (Grimes and Wyrick, 1991). The latex agglutination test is easy to perform, specific, and detects IgM only; a positive result indicates that the bird has an active infection. The LA test also makes it possible to assess the efficacy of treatment: if it is successful, the titer falls rapidly. The disadvantages of the method are its low sensitivity and that apparently it cannot be used with all avian species (Grimes, 1989). In the case of individual birds, it is best to use more than one method. The complement fixation test is generally used for the diagnosis of chlamydiosis in humans. Diagnosis can also be confirmed by isolating the agent from sputum or blood taken during the febrile stage of the disease and inoculating it in embryonated eggs, mice, or cell cultures. Several passages may be necessary. Early treatment of the patient with tetracyclines may interfere with isolation and with the formation of antibodies.

To isolate the agent it is best to use several organs at once—for example, the spleen, the liver, and intestinal contents. Serotyping can be done using a panel of 10 serovar-specific sera in the indirect immunofluorescence test (Andersen, 1991a).

A quick preliminary diagnosis can be obtained with samples taken from serous membrane exudate, spleen, liver, and lung, and stained by the Macchiavellos, Gimenez, or Giemsa method.

Isolations, whether from humans or animals, should only be performed in laboratories that adhere to the highest safety standards.

Control: Eradication cannot be considered due to the large number of hosts, including many free-living birds, nor are there effective vaccines for controlling the disease. The control strategy that has yielded the best results is giving tetracycline-based chemoprophylaxis to psittacine and other birds—specifically, 1% chlortetracycline and up to 0.7% calcium included in their feed. In the event of a chlamydio-

sis outbreak in an establishment where birds are sold, their sale should be suspended until the appropriate measures have been taken. Chlortetracycline should be added to the birds' feed for 45 days, and the cages and premises should be cleaned and disinfected with quaternary ammonium chloride. In the case of imported birds, chlortetracycline should be added to their feed for 45 days as a preventive measure, either in the country of origin or upon arrival at their destination. Mass treatment has also been given on turkey farms. Epidemiological surveillance is necessary. This should include serological screening to identify infected farms, placing the establishments under quarantine, and administering tetracycline in the turkeys' feed for a period of four weeks.

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ZOONOTIC TYPHUS CAUSED BY *RICKETTSIA PROWAZEKII*

ICD-10 A75.0 Epidemic louse-borne typhus fever due to *Rickettsia prowazekii*

Synonyms: *R. prowazekii* wild typhus, louse-borne typhus, classic typhus fever, typhus exanthematicus.

Etiology: *Rickettsia prowazekii.* The agent was isolated from the eastern flying squirrel, *Glaucomys volans volans*, in Florida (USA). This rickettsia is not distinguishable antigenically or by the toxin neutralization test from the classic strains of the etiologic agent of epidemic louse-borne typhus (Bozeman *et al.*, 1975).

Geographic Distribution: Worldwide, but as a cause of zoonosis, the agent is of greatest interest in the US. It has been isolated from flying squirrels or their ectoparasites in Florida, Maryland, and Virginia (USA). However, the geographical origin of the human cases that have been seen would suggest that the distribution is much wider. The distribution of the natural host, the flying squirrel, reaches across the entire eastern part of the US and northward into southern Canada (McDade *et al.*, 1980).

Occurrence in Man: Sporadic. Between 1976 and 1979, a total of 1,575 sera specimens were tested for antibodies to rickettsiae at the US Centers for Disease Control and Prevention (CDC). Of these sera, 1,349 (85.7%) were negative for all rickettsial antigens and 226 (14.3%) were positive for various rickettsial diseases. Of the latter, eight (3.5%) were positive for *R. prowazekii*—five from the state of Georgia and one each from Massachusetts, Pennsylvania, and Tennessee. These patients had not been parasitized by human lice, nor did any of their contacts become ill; therefore, the classic transmission cycle of man-louse-man did not apply. Two of the patients reported having had contact with flying squirrels (McDade *et al.*, 1980). Between July 1977 and January 1980, seven more sporadic cases were diagnosed in the states of North Carolina, Virginia, and West Virginia, none of which were associated with human lice (Duma *et al.*, 1981).

Occurrence in Animals: Serological studies carried out between 1972 and 1975 showed that 54.2% of 557 flying squirrels captured in Florida, Maryland, and Virginia were positive for the agent. The highest seroconversion rates for these animals were seen in the autumn and early winter, when the ectoparasites are in greatest abundance on the squirrels. The infection spreads rapidly among the young animals in autumn, when they begin to congregate in nests in which the vector is present. No other infected animal species were found in these habitats (Sonenshine *et al.*, 1978).

The Disease in Man: The disease has a sudden onset, with fever, headache, muscular aches, and rash. Except in a few severe cases, the disease appears to be more benign than classic louse-borne epidemic typhus (Duma *et al.*, 1981). Some patients also experience nausea, vomiting, and diarrhea. Four of eight patients in a study had a rash. The disease lasted two to three weeks in patients who did not receive appropriate treatment, while its course was shorter for those who received tetracycline or chloramphenicol (McDade *et al.*, 1980).

The Disease in Animals: The natural course of the infection in flying squirrels is unknown. Rickettsemia lasted two to three weeks in animals infected experimentally (Bozeman *et al.*, 1981). Animals inoculated intraperitoneally with high doses of the agent died on the seventh day.

Source of Infection and Mode of Transmission: The last outbreak of epidemic louse-borne typhus in the US was in 1922. A laboratory-confirmed case in 1950 was contracted outside the country. Recrudescent typhus (Brill-Zinsser disease) has been observed only in concentration camp survivors and immigrants from Eastern Europe (McDade *et al.*, 1980).

Unlike classic epidemic louse-borne typhus, the recent cases of human *R. prowazekii* infection have been zoonotic in character.

The reservoir (probably unique) of wild typhus is the flying squirrel, *Glaucomys volans volans*, which has a high rate of infection and rickettsemia lasting several weeks. Experiments have shown that cohabitation is not a factor in the transmission of infection among these animals. Of the many ectoparasites that infest them, the louse *Neohaematopinus sciuropteri* is the vector responsible for transmission. The mode of transmission to man is not yet fully understood. The squirrel louse, *N. sciuropteri,* does not feed on man. On the other hand, the squirrel flea, *Orchopeas howardii,* which can become infected, cannot transmit the infection to susceptible squirrels. It is possible that this flea, which bites man, may transmit the infection if it is squashed against broken skin, or that man may become infected via aerosols originating from the feces of the squirrel louse, especially during more intense epizootic periods (Bozeman *et al.*, 1981).

The cases described up to now have occurred largely among rural inhabitants, some of whom said they had had contact with flying squirrels. The time of the year when the human cases occurred (November to March) coincides with the period of heaviest transmission among squirrels.

Diagnosis: So far, human cases have been diagnosed using such laboratory tests as complement fixation, indirect immunofluorescence, toxin neutralization, and cross-absorption.

Control: Given the small number of confirmed human cases, no special measures are warranted.

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