Rickettsiae and rickettsial diseases

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This paper summarizes present knowledge on rickettsiae and rickettsial diseases, and on their epidemiological characteristics, control, and public health significance. There are many natural foci of rickettsial diseases, from where the disease may spread to other areas in the world under changing socioeconomic conditions. Because of rapid long-distance travel, sporadic cases of serious rickettsial diseases may today appear far from endemic areas where the infection occurred. Even in endemic areas the disease may be misdiagnosed and deaths may occur as a result of inadequate treatment. Rapid treatment of rickettsial infections (preferably with tetracyclines) is therefore most important. Epidemic louse-borne typhus, though no longer subject to the International Health Regulations, remains one of the diseases in the WHO epidemiological surveillance programme. This disease continues to be a major cause of morbidity and mortality in some parts of Africa and it is present also in parts of the Americas and of Asia. Scrub typhus remains a continuing and serious public health problem in areas of South-East Asia and in the Western Pacific. The annual number of reported cases of Rocky Mountain spotted fever in the USA showed an increase during the last two decades, which may be due to improved recognition as well as to increased outdoor activities and migration of people from the city centres to the suburbs. Related forms of tick-borne typhus occur in South America, the Mediterranean region, Africa, South-East Asia, the Far East, and the Western Pacific. Increasing in number, though still sporadic, are reports of serious illness from chronic Q fever infection in many parts of the world.

After a rather long period of stagnation, rickettsial diseases are now again the subject of interest and new approaches to their study are being developed, in part because of the recognition of rickettsial disease as a persisting and important cause of morbidity and mortality in certain countries. This paper is a synopsis of present knowledge on the epidemiological characteristics, control, and public health significance of rickettsiae and rickettsial diseases.

HOST RANGE AND PATHOGENICITY

Rickettsiae are generally transmitted to man by arthropod vectors, the only exception being Coxiella burnetii, the agent of Q fever.

Infected ticks and mites transmit rickettsiae primarily through their infected salivary glands directly into the bite. In lice and fleas, rickettsiae do not infect the salivary glands but multiply in the cells of the gut wall and are excreted in the faeces in large amounts, contaminating the skin area around the bite. Rickettsiae may gain entry into the body through bites or other breaks in the skin, or dried aerial suspensions of them may be inhaled or may infect the conjunctival mucosa. Dried tissue fluids or the excreta of mites and ticks may also be a source of infection.

Once rickettsiae have penetrated the skin, they multiply inside cells, reach the blood stream, and eventually become located in the endothelial cells of small veins, arteries, and capillaries. These infected endothelial cells enlarge, degenerate, and cause thrombus formation with partial or complete occlusion of the vascular lumen. Mononuclear leucocytes and plasma cells infiltrate the adventitia. Focal necrosis of the walls of small vessels leads to increased permeability, rupture, petechiae, and haemorrhages. The rupture of vessels and thrombosis interrupt the blood supply, causing macro- and micro-infarcts and necrosis of the tissues.
Localized cellular responses lead to the formation of nodules, commonly in the spleen, liver, kidneys, brain, heart, and skeletal muscles. Acute nonsuppurative myocarditis, both diffuse and local, is a common occurrence. Apart from vascular damage caused by the organism or its toxin, other lesions are rare. Rickettsiaemia is present throughout most of the acute febrile period. The overall pathological features are similar in most rickettsial diseases; however, the extent and degree of involvement vary and in general are indicated by the severity of the illness.

Fatalities occurring early in the acute phase of the illness are generally due to vascular collapse; when they occur later, they are related to chronic vascular damage producing thrombosis and necrosis.

The long survival of rickettsiae in various organs and lymphatic tissues after infection of both man and animals is a general characteristic in the pathogenesis of rickettsial disease.

**Classical typhus group**

This group includes *Rickettsia prowazeki* and *R. mooseri* (*R. typhi*), respectively the agents of louse-borne (epidemic) typhus and of flea-borne or murine (endemic) typhus. *R. canada*, antigenically related to this group, has recently been incriminated as a possible cause of infection in man (1).

Louse-borne typhus is essentially a human disease, and flea-borne typhus is a disease of rats occasionally involving man. Domestic cats and the cat flea, *Ctenocephalides felis*, have also been incriminated in the transmission of murine typhus.

Contradictory evidence has been put forward by some authors with regard to the possible role of domestic animals in maintaining the chain of infection with *R. prowazeki*.

Several animal species have been shown to be susceptible to infection with *R. prowazeki* and *R. mooseri* but only a few have practical use as laboratory models. The chick embryo is by far the most important of these and yolk sac cultures are routinely used for producing antigens and vaccines. White mice are useful in testing for and in titrating the toxin content of yolk sac preparations.

Guinea-pigs are somewhat less sensitive and less predictable than chick embryos and mice. However, they can be used for primary isolation. Intraperitoneal injection of infected human blood into guinea-pigs leads to rickettsiaemia and a characteristic fever pattern. *R. prowazeki* can be isolated from the blood, brain, suprarenal gland, or spleen of infected guinea-pigs.

Cotton rats and various species of African gerbils are highly sensitive to *R. prowazeki* and are ideal for isolation or research studies.

**Spotted fever group**

This group of rickettsiae, the agents of various forms of infection in man, has been divided into 4 subgroups on the basis of antigenic characteristics (8). Subgroup A consists of *R. rickettsii* and *R. siberica*, the agents of Rocky Mountain spotted fever (RMSF) and of north Asia tick typhus; subgroup B is formed by *R. conori*, the agent of fièvre boutonneuse, and by *R. parkeri*, which causes infection in guinea-pigs but has not been identified as a pathogen for man; subgroup C consists of *R. akari* and of *R. australis*, the agents of rickettsialpox (transmitted by mites, not by ticks) and of Queensland tick typhus; subgroup D includes only *R. montana*, a new species isolated from Dermacentor ticks in eastern Montana (USA) and not yet incriminated as a pathogen for man. All these rickettsiae multiply in the cytoplasm and in the nucleus of infected cells.

Rickettsiae are transmitted transovarially by ticks, which therefore represent both the reservoir and the vector of the agent. The infection may be transmitted to the vertebrate host by any of the larval stages and by the adult tick. Ticks remain infected for life, are not harmed by the rickettsiae, and pass them in their faeces. Transmission to man, however, is believed to occur primarily through the bite since rickettsiae also invade the salivary glands of the ticks. All the rickettsiae of this group pass through natural cycles in wild or domestic animals.

In man, RMSF may show very acute symptoms with intense vascular lesions. In contrast with other forms of tick typhus, eschars rarely develop at the site of the tick bite. The virulence of RMSF strains may vary considerably for man and for laboratory animals.

Rickettsialpox, the mildest of the rickettsial diseases of man, is caused by *R. akari* and transmitted by mites instead of ticks, and is mainly a disease of rodents. It is characterized in man by the presence of vesicular lesions superimposed on the initial papules.

**Scrub typhus**

Mite-borne scrub typhus, or tsutsugamushi, is caused by *R. tsutsugamushi* (*R. orientalis*), and is transmitted by a number of trombiculid mites that act both as vector and as reservoir, thus playing a
role similar to that of ticks in the transmission of the etiological agent; transovarial transmission has also been demonstrated. While the role of rodents and other animals is yet to be clarified, the variation in the virulence and antigenicity of strains is considerable.

Q fever

Q fever, caused by Coxiella burnetii, is primarily a zoonosis solidly established in domestic livestock the world over; it is a widely disseminated chronic infection involving many organs of the infected hosts. Of primary importance to transmission is infection of the uterus and udder tissue in female animals. The animal’s milk is thus infected, but of major importance is the fact that at parturition the infected products of conception contaminate the environment and remain for months or years as a source of infection for man, animals, and birds.

Man contracts Q fever usually by inhaling infectious dust generated from infected animals or their products. Clinically, Q fever in man is characterized by an interstitial pneumonia regardless of the site of entry of the infecting organism. C. burnetii can spread through almost all the organs of the body forming small lesions of varied character showing oedema, round cell infiltration, and patchy necrosis. Occasionally the liver or heart may become intensely involved leading to a frank hepatitis or a subacute endocarditis with vegetations. Although pathologic lesions may be widespread both in man and animals, fatalities are rare.

Ticks are an important element in the maintenance of the Q fever reservoir in nature and transovarial transmission of C. burnetii has been demonstrated in these arthropods. A wide variety of ticks have been shown to be infected and in view of the extensive host range of C. burnetii many different host–vector cycles probably occur.

Man to man transmission is rare. Recrudescence of latent infections in man may occasionally occur and Q fever can remain latent in the tissues for 2–3 years.

Strains of the Q fever agent with different degrees of virulence have been isolated.

Trench fever

R. quintana, the agent of trench fever, has a very limited host range. Besides man and the louse, several species of monkeys only have been shown to be infectable. The attempts to infect common laboratory animals have met with uniform failure.

Man is the only known reservoir and the body louse the only known natural vector. The faeces of lice become infectious 5–10 days after an infectious meal; after that the lice remain infectious for life although they are themselves unharmed. There is no transovarial passage of R. quintana in lice.

The disease in man leads frequently to a chronic rickettsiaemia, R. quintana having been isolated from the blood of patients up to 2 years after an acute attack. True relapses have occurred as long as 20 years after a primary attack. The chronic rickettsiaemia and late relapses are obviously important factors that help give rise to trench fever epidemics over long periods of time.

ANTIGENIC STRUCTURE

Classical typhus group

Three species belong to this group, R. prowazeki, R. mooseri, and R. canadensis. R. canadensis can be differentiated from R. prowazeki and R. mooseri by the toxin neutralization test and by the complement fixation test with mouse antiserum (9). The relationship between R. canadensis and the spotted fever group of rickettsiae, however, has not yet been clarified.

The nature of the soluble antigen and the antigenic properties of various rickettsial fractions have been reviewed (2). A thermolabile antigenic fraction capable of inducing protection after a single vaccination of animals was recently obtained from the classical soluble antigen. Vaccination of human beings with this antigen provoked no local or general reactions and was followed by the development of complement-fixing, haemagglutinating, and toxin-neutralizing antibodies (6).

The antigenic activities of intact R. prowazeki, and of its cell wall, protoplasm, and soluble antigens in complement fixation (CF) and mouse protection tests differ in several points. The protoplasm antigens show the greatest specificity and heat lability in the CF test. The cell wall and soluble antigens and intact rickettsiae contain more heat-stable CF antigens and tend to be more active than the protoplasm antigens in the mouse protection test. In vaccine potency tests, the soluble antigens released by ether treatment are the most active.

Spotted fever group

The division of this group into four subgroups has already been mentioned in the preceding section. This differentiation was made on the basis of toxin-neutralization and complement fixation tests with mouse species-specific sera.
Scrub typhus group

Except for the mouse cross-immunity tests, which show a close relationship among the strains of this group, other procedures, such as serum protection, complement fixation, toxin neutralization, and vaccination-challenge, reveal a considerable heterogeneity within the species. The impossibility of detecting antibody induced by a variety of antigenically dissimilar strains of *R. tsutsugamushi* represents a serious difficulty in the serologic diagnosis of scrub typhus. Serotypes Gilliam, Kato, and Karp were identified by complement fixation tests. The strains of *R. tsutsugamushi* recovered from patients can be a mixture of two or more antigenically distinctive types. Moreover, among the strains of *R. tsutsugamushi* in Thailand, 5 distinctive antigenic types have been recognized thus far: Gilliam, Karp, Kato, and 2 other types not previously described.

Coxiella burnetii

*Coxiella burnetii* is the only rickettsia showing phase variation. This phenomenon is similar in many ways to the rough–smooth variation of *Diplococcus pneumoniae*. In nature, *C. burnetii* has been found only in phase I; in the laboratory, the adaptation to growth in chick embryos produces phase II, which can be converted back to phase I by subsequent growth in laboratory animals. The essence of this phenomenon lies in the alternation of two main antigens. The strains in phase I possess both antigens and do not show positive results in a variety of serologic reactions with sera containing only antibodies against the phase II antigen. The vaccines prepared from a purified suspension of phase I, when tested in guineapigs, have 100–300 times the potency of those derived from phase II, provided that the immunity is tested by the use of a strain in phase I (14). With trichloroacetic acid it is possible to extract from coxiellae in phase I an antigen that resembles serologically the corpuscular phase I antigen.

This trichloroacetic acid extract of coxiellae can be used as a vaccine producing both phase II and phase I antibodies and it often produces allergic skin reactions. An antigenic component, with the serologic behaviour of phase I, can also be extracted with phenol from purified phase I suspensions.

The presence of antigen I in *C. burnetii* is related to its basic properties. The shift from the naturally occurring phase I to egg-grown phase II is accompanied by changes in antigenic composition, immunogenicity, density, autoagglutinability, staining properties, resistance to phagocytosis, and virulence.

There are only a few data concerning the antigenic differences among phase II strains. Antigenic differences among phase I strains have not yet been observed.

OTHER PROPERTIES OF RICKETTSIAE

Morphology

Rickettsiae can usually be visualized with the ordinary light microscope. They tend to be somewhat pleomorphic, varying in size and in shape from cocccoidal, to bacillary, to filamentous, depending on the species and the conditions of growth.

Electron microscopy has greatly contributed to knowledge of the structure of rickettsiae. Common to all studied so far are a trilamellar cell wall and a trilamellar cytoplasmic membrane. Both these show the typical "unit membrane" structure of bacterial cells. Intracytoplasmic invaginations of the plasma membrane, DNA strands, ribosomes, electrolucent spheres, vacuoles, and membranous organelles have been observed.

Chemical composition and metabolism

Comprehensive reviews of both the chemical composition and the metabolism of rickettsiae have been published by Paretски (15), Wiseman (18), and Ormsbee (13).

Rickettsiae possess complex cell walls, contain both ribonucleic and deoxyribonucleic acids, synthesize their own structural and functional constituents with their own enzymes, and generate high-energy phosphate bonds with energy derived from the oxidation of amino acids and carbohydrates.

Rickettsial cell walls closely resemble the cell walls of Gram-negative bacteria in complexity of structure and in the presence of muramic and diaminopimelic acid components. The purified cell walls of *R. mooseri* and *R. prowazeki* contain protein, polysaccharide, and phosphorus in excess of that from nucleic acid contamination. Further analyses show the presence of 12–15 amino acids, including both lysine and the distinctive diaminopimelic acid, and the presence of the amino sugars glucosamine and muramic acid. Teichoic acid has not been detected in *R. mooseri*.

The DNA of *C. burnetii* has been isolated and characterized and found to be significantly different from that of *R. prowazeki*. Several data suggest that the DNA of *C. burnetii* possesses a double stranded structure.

Energy production is apparently accomplished through the operation of part or all of the Krebs
cycle. The principal energy-yielding substrate is glutamate in the case of *R. quintana*, and pyruvate in *C. burnetii*. Oxidation is accompanied by phosphorylation. The electron transport system appears to utilize phosphopyridine nucleotides and cytochromes.

There is convincing evidence that rickettsiae possess enzymatic mechanisms for the breakdown of carbohydrates, the formation of high-energy phosphate bonds, and the synthesis of lipids and proteins. The host cell contribution probably includes primary substrates such as glutamate and pyruvate, factors such as ATP, NAD, and coenzyme A, and amino acids.

**Multiplication of rickettsiae**

Rickettsiae, except *R. quintana*, are obligate intracellular parasites. It is generally accepted that rickettsiae maintain their morphological integrity during growth and multiplication. Binary fission is considered to be the only mode of their multiplication; Kordová and her associates (reviewed in (3)), however, found "filterable particles" in *C. burnetii* and suggested some other form of replication. Koko-rin (7) studied various rickettsiae in tissue cultures and suggested the existence of two developmental stages: vegetative, dividing, and moving forms on the one hand, and resting, immobile forms on the other. Resting forms can persist in the cell for a very long period of time, thus providing a possible explanation for latency in rickettsial infections.

**DIAGNOSTIC PROCEDURES**

**Laboratory methods for isolation of rickettsial strains**

The procedures for the isolation of rickettsiae are well known. Guinea-pigs, mice, meriones, and cotton rats are the most useful animals for the isolation of rickettsial strains from patients and animals, and from ectoparasites with the exception of *R. quintana*. Tissue or cell cultures have been used for the propagation of various rickettsiae, but their value in primary isolation has not been confirmed.

*R. quintana* can be propagated from the blood of patients directly on blood agar. Erythrocytes (hemin) are essential components of media; in a liquid medium, fetal calf serum satisfied the requirement of *R. quintana* for a red blood cell lysate.

**Serologic methods for the study and diagnosis of rickettsial infections**

**Complement fixation test.** The most frequently used serologic method is the complement fixation test with soluble or particulate antigens. Louse-borne and murine typhus can be differentiated by means of washed corpuscular suspensions of *R. prowazekii* and *R. mooseri*. *R. canadensis*, a new member of the typhus group (9), shares common antigens with *R. prowazekii* and especially with *R. mooseri*. However, this new agent has been shown to be different from both *R. prowazekii* and *R. mooseri* when tested with antisera prepared in mice. The results of toxin neutralization tests confirmed that this was a new species of rickettsia. Several methods by means of CF and agglutination reactions allow the differentiation of primary from secondary (Brill-Zinsser disease) cases (10-12).

In the spotted fever group the soluble antigen of each strain is group-specific whereas washed antigens allow for species differentiation. However, it was shown that antisera from white mice infected with various strains from the RMSF group contained species-specific complement-fixing antibody that did not react with the soluble, cross-reacting CF group antigen of heterologous rickettsiae of the same group.

In the scrub typhus group there is a high degree of antigenic heterogeneity among strains of *R. tsutsugamushi*. Purified or partly purified rickettsiae allow for differentiating between the antigenically representative Gilliam, Karp, and Kato strains. Recently satisfactory antigens were prepared from infected tissue cultures.

In Q fever, complement fixation is the test most frequently used for identifying Q fever antibodies although it is not the most sensitive method. Phase II antibodies are of primary diagnostic value for the detection of recent infection and phase II egg-adapted strains must therefore be used for the preparation of antigens.

Complement-fixing phase I antibodies are of little importance for the diagnosis of Q fever in man as they can only indicate past or present persisting infection. They are also found in cases of chronic Q fever endocarditis.

The CF test for trench fever provides a rapid diagnostic procedure, which can be used in conjunction with isolation of *R. quintana* from the patient's blood. Both particulate and soluble antigens can be prepared from whole *R. quintana* propagated on blood agar.

**Agglutination reaction.** The microagglutination test for typhus antibodies described by Fiset et al. (5) is a very reliable method for detecting typhus antibodies. The test appears to have the same limits of resolution as the standard tube agglutination tests and is more
sensitive than the CF test in distinguishing between murine and louse-borne typhus infections.

Infections of the spotted fever group can be detected by Giroud's slide microagglutination test with semipurified suspensions of R. conori.

In Q fever, highly purified haematoxylin-stained antigens are used in the method described by Fiset et al. (5). These are phase I antigens converted to phase II by treatment with trichloroacetic acid. The method has been further improved by Schramek et al. (17) producing phase II antigens by oxidizing the phase I antigens with periodate. Natural phase II strains cannot be used for this agglutination test as they tend to agglutinate spontaneously and are strongly agglutinated by normal serum.

Microagglutination on plastic plates with stained antigens is more sensitive than CF with phase II antigens. It is also suitable for demonstrating the phase I antibody with phase I antigen. During the past two decades several agglutination methods have been elaborated for detecting Q fever antibodies: the capillary agglutination test (CAT), the agglutination-resuspension test, and the radioisotope precipitation test (RIPT).

Other tests. These are useful in particular instances and include the following.

1. The passive haemagglutination test (PHT).

This test, which requires sheep or human group O erythrocytes sensitized with ESS (erythrocyte sensitizing substance), is sensitive, group specific, and appears to be particularly useful in detecting recent infections in both typhus and RMSF group rickettsioses.

In Q fever the passive haemagglutination test can be used for detecting phase I antibodies. The erythrocyte sensitizing factor consists of a phenol extract of the phase I antigen.

2. The toxin neutralization test.

A test of this type is used in cases of rickettsiae of the typhus and RMSF group. It is valuable for evaluating vaccine potency in the typhus group; in the spotted fever group this test is useful for studying antigenic structure.

3. The intradermal sensitivity test.

This involves a skin reaction of the delayed type. A positive skin test against C. burnetii is considered to be a contraindication for vaccination against Q fever.


The Weil–Felix reaction is still a useful test in all rickettsioses except for Q fever, trench fever, and rickettsialpox. However, it has several serious limita-

tions. It fails in approximately 75% of sporadic or recrudescence cases of typhus. In scrub typhus it may be positive in no more than 50% of cases.

5. The haemolymph (haemocyte) test.

This is an economical, rapid, and simple test for detecting rickettsiae in nature and in laboratory experiments (4,16). The presence of rickettsiae in ticks can be detected by examining the haemolymph obtained by amputating the distal portion of one or more legs. The smears are fixed by heat; stained by the Giménez method, and examined microscopically for the presence of rickettsiae or rickettsia-like organisms. If positive, additional smears from the same ticks are examined by the direct or indirect fluorescent antibody method with sera or immunoglobulins against the various rickettsial groups or against rickettsiae known or assumed to occur in the area. Adult ticks, both engorged and unengorged, may be used for the haemocyte test.

All tick-borne rickettsiae can be identified by the haemocyte test. In scrub typhus the indirect fluorescent antibody method has been reported to be group-specific, allowing the use of any strain for the diagnosis.

Some other tests may be used for special purposes such as cross-immunity tests (with live or killed rickettsiae for immunization), and the serum-protection test.

The formation of plaques by rickettsiae in some types of tissue cultures may lead to the elaboration of more precise methods for the titration of rickettsiae and their differentiation.

PUBLIC HEALTH SIGNIFICANCE

Louse-borne typhus

Epidemic louse-borne typhus, historically one of the major epidemic diseases, typically spreads during times of wars and civil disturbances. Since the agent is transmitted by body lice, the disease is still present where socioeconomic standards are low and where lice are abundant.

In the present century, the main foci of the disease have been in the highlands of northern and eastern Africa and in eastern Europe. The disease is also present in the mountainous regions of Central America, north-western South America, southern Asia, and of southern Africa.

During and immediately after the Second World War the disease spread again from its endemic foci in North Africa and eastern Europe through most of Europe causing very severe epidemics among pris-
oners of war and in concentration camps in Europe and in Asia.

Despite the existence of conditions favouring the spread of the disease, the development of persistent insecticides and their massive application to the control of the vectors made it eventually possible to limit somewhat the extent of epidemics. The development of specific vaccines prepared from rickettsiae grown in the yolk sac of embryonate eggs or in the lungs of laboratory animals significantly contributed to the effective control of the disease; this was further facilitated by the improvement in living conditions that occurred after the end of the Second World War.

Since then the number of countries from which cases are reported has considerably diminished. The great majority of the cases now reported are from the highlands of central and eastern Africa, namely from Burundi, Rwanda, and Ethiopia. A large number of cases of Brill–Zinsser disease (late relapses or recrudescence louse-borne typhus) are reported from some eastern European countries.

In Burundi, epidemic waves occurred in 1933–34, in 1939, and in 1945–46. During the latter period, 3752 cases and 429 deaths were recorded; in the endemic area the average number of lice on each person was approximately 40. A new epidemic started in Burundi in 1967, with a peak of 17,200 cases reported in 1970. The number of cases since then has decreased, but there were still 2,817 cases in 1973. Although the reported number of deaths caused by typhus ranged between approximately 1% and 3% of the number of cases, the mortality rate in 1971 from typhus was estimated by physicians practising in the country at 5–20%. Cases of louse-borne typhus started to be reported from neighbouring Rwanda in 1971 with a peak of 5,509 cases and 78 deaths reported for 1973. In Ethiopia 2,000–3,000 cases are usually notified every year from all provinces, but only a few deaths are reported. Most of the cases reported from other countries are from mountainous regions, where the climatic and socioeconomic factors facilitate a close association between the human population and the louse vector.

Resistance of the louse vector to the commonly used insecticides (DDT, gamma-HCH, and in a few cases organophosphorus compounds) has occurred in some areas as a consequence of their use for vector control or for agricultural purposes.

Although louse-borne typhus cannot be considered as a major risk from the point of view of its spreading to other countries from the regions where it is still present, it remains one of the most important causes of illness in some parts of Africa and a problem in parts of the Americas and of Asia. The development of tourism, rapid communications, and international travel in general make it possible for cases to occur far from endemic foci; if not recognized in time, it may present a considerable risk to the individual, if not to the community. Also, it must be emphasized that the very reasons allowing for the presence and dissemination of the infection and of the disease make it difficult to apply preventive and control measures.

Patients with Brill–Zinsser disease are a potential source of infection in other countries, but spread of the disease still requires that the patient be also infested with lice at the time of his relapse.

Other rickettsial infections

Murine typhus causes practically no public concern. It is in fact one of the relatively mild rickettsial diseases and its cycle in nature is relatively easy to interrupt. Xenopsylla cheopis, the normal vector of R. mooseri, being easy to control.

The number of reported cases of Rocky Mountain spotted fever in the USA, which slowly decreased from 1951 to 1960, has since risen from approximately 200 to 305 in 1967, 298 in 1968, 498 in 1969, 380 in 1970, 432 in 1971, and 528 in 1972. The majority of the cases are now reported from states east of the Mississippi river. This rise in reported cases may well be due to better recognition. However, mass migrations from the city centres to the suburbs have brought people into closer contact with the tick reservoir of the disease and this is believed by many to be responsible for the recent increases in the number of cases. Where the disease is relatively frequent, as for instance in Maryland, Virginia, and North and South Carolina, early recognition and treatment are the rule. Elsewhere in North America the disease is so infrequent that it is often misdiagnosed and a number of deaths occur each year because of inadequate treatment. Sporadic cases of the same type of disease, caused by the same agent (R. rickettsii), are also reported from South America.

Other forms of tick-borne typhus are of recognized minor public health significance in localized geographic areas: boutonneuse fever in the Mediterranean region, African and Indian tick typhus, Queensland tick typhus in Australia, and Siberian tick typhus in North-Eastern Asia. The incidence of the disease is generally low and the clinical features so
mild that there is very little public interest in control measures.

Rickettsialpox is the mildest of all the rickettsial diseases. In the USA at the time when the disease was first discovered in the mid-1940s, over 160 cases were reported from New York. For several years thereafter about 180 cases were reported annually from New York City alone, but more recently only occasional sporadic cases have been reported from North America. Reports of the rickettsialpox organism occurring in Korea and Russia as well as in the USA indicate that it may have a worldwide distribution. Rickettsialpox poses a minor public health problem only because it could appear in an epidemic form if there should be a large buildup of infected vectors and their hosts in close association with man.

Scrub typhus poses a continuing serious and important public health problem. While the disease may be mild, the severe clinical form is common, with a 20–60% mortality if not treated in time. Since the ubiquitous mite serves as both vector and reservoir and has numerous small animal hosts, *R. tsutsugamushi* appears to be not eradicable at least with the mite control measures now available. In the scrub typhus endemic area of South-East Asia and the Pacific Islands there is always the possibility of sporadic cases or localized outbreaks, and no vaccine is available to help in control. As a result of travel, sporadic cases of the disease may appear in any part of the world.

Q fever is a continuing and significant public health problem. While there are not many human cases reported in the literature, pilot serologic surveys in certain high-risk groups and in animals indicate that many undiagnosed cases occur. There is widespread seeding of domestic livestock throughout the world with *C. burnetii* and in many areas the incidence of infection in animals is rising. The disease in man occurs in livestock handlers and processors of animal products, especially in abattoirs and textile plants. The milk of infected animals contains *C. burnetii*, but there is conflicting evidence as to how much infection as well as how much overt disease is transmitted through milk.

There are an increasing number of reports, although still sporadic, of serious illnesses such as endocarditis, pericarditis, and hepatitis resulting from chronic Q fever infection.

The only known epidemics of trench fever occurred during the First and Second World Wars. The virtual disappearance of the disease from public notice for nearly 50 years combined with the mild character of the human illness when it does occur accounts for the absence of any public health interest in this disease.

**CONTROL MEASURES**

*Treatment of human rickettsioses*

The broad-spectrum antibiotics, namely the tetracyclines and chloramphenicol, are the drugs of choice for the specific treatment of all rickettsial diseases. Tetracyclines are preferred to chloramphenicol because of the higher risk of untoward reactions with the latter. The treatment should be prolonged to avoid the occurrence of relapses upon withdrawal of the antibiotic.

A new tetracycline, doxycycline, better absorbed and more slowly excreted than other compounds of this group, has recently been used successfully for the treatment of louse-borne typhus in endemic areas.

The development of resistance to antibiotics commonly used in the treatment of rickettsial diseases has been induced under laboratory conditions, but as far as is known it has not been observed in the field.

Chemoprophylaxis requires even more special attention than chemotherapy with regard to the dosage and the duration of treatment in order to obtain suppression of overt symptoms and the development of active protection. A combination of chemoprophylaxis and vaccination with killed vaccine has been successfully used against scrub typhus.

*Vector control*

Since all rickettsial diseases (Q fever excepted) are transmitted to man through the bite or excreta of infected arthropods, the obvious control measure would be the elimination of the vectors. Although theoretically the control of lice and fleas is relatively easy because of their close association with man and his immediate environment, it is much more difficult to control transmission by ticks and mites. These arthropods in natural environments have life cycles associated with a multitude of wild animals that are themselves difficult to eliminate or to control.

Rickettsialpox is the only mite-borne rickettsial disease that appears to be controllable by attacking its vector, *Allodermanysus sanguineus*, or its host, the house mouse, or both.

Resistance to pesticides may present a severe problem. The resistance to chlorinated hydrocarbons is stable and so high that it excludes its routine use in many areas. Resistance to malathion is not a stable characteristic and depends on continual exposure.
Some new organophosphorus compounds and other rapidly degradable pesticides are therefore being sought.

Vaccination

Dead and live vaccines have been prepared against louse-borne typhus. A single dose of the dead vaccine (Cox type) may prepare for a booster effect at any time within 15 years. However, there are significant problems in the methods of assay for standardizing this vaccine. Soluble antigen vaccines may offer some advantages as the antibody response appears earlier. With the live vaccine (strain E) there is the problem of late reactions (more properly termed mild disease) that occurred in 0–14% of the vaccinees in different studies. A reversion to virulence after passage in laboratory animals has been reported from one laboratory, but was not fully confirmed by two others.

A killed vaccine against Rocky Mountain spotted fever is available and is indicated for persons at high risk (such as laboratory workers).

Killed crude C. burnetii vaccines are available but severe and persistent local reactions have contraindicated their use. Purified phase I and live vaccines are under experimental study. A trichloroacetic-acid extract from the phase I purified suspension promises to be very effective in preventing human disease.

Other methods

In general, the only practical measure against tick- and mite-borne typhus is personal protection against the arthropod vector with repellents or by means of adequate clothing to prevent the attachment of the vectors.

Health regulations

Louse-borne typhus was one of the six quarantinable diseases subject to the International Sanitary Regulations. These have been replaced as of 1 January 1971 by the new International Health Regulations to which only cholera, plague, yellow fever, and smallpox will henceforth be subject.

Louse-borne typhus, however, remains one of the diseases in the WHO epidemiological surveillance programme, together with relapsing fever, influenza, paralytic poliomyelitis, and malaria. Under this programme, Member States are requested to inform the Organization of the occurrence of any outbreak of the disease, providing pertinent details, and the Organization is responsible for the dissemination to Member States of such information received. In order to facilitate the implementation of this programme a technical guide for typhus surveillance has been prepared by WHO (19).

RÉSUMÉ

RICKETTSIES ET RICKETTSIOSES

Dans la présente étude sont résumées les connaissances actuelles concernant les rickettsies et les rickettsiose, et notamment leurs caractéristiques épidémiologiques, leur importance en santé publique et les moyens de lutte à leur opposer.

Il existe de nombreux foyers naturels de rickettsioses, à partir desquels elles peuvent se propager dans d’autres régions du monde à la faveur de changements des conditions socio-économiques. La rapidité des voyages à longue distance fait que l’on assiste aujourd’hui à l’apparition de cas sporadiques, parfois graves, dans des endroits très éloignés des zones d’endémie. Même dans ces dernières, il arrive que ces affections ne soient pas diagnostiquées et des décès peuvent survenir si un traitement correct, de préférence par les tétracyclines, n’est pas appliqué rapidement.

Les rickettsies sont généralement transmises à l’homme par des arthropodes (poux, puces, tiques et acariens); seule Coxella burnetii, agent de la fièvre Q, fait exception. Pour certaines espèces de rickettsies, le cycle naturel d’infection fait intervenir comme réservoirs des animaux domestiques ou sauvages. La transmission transovarienne chez les arthropodes, démontrée pour les rickettsies du groupe de la fièvre pourprée (chez des tiques) et du typhus de brousse (chez des acariens) joue un rôle important dans la persistance des infections dans les foyers naturels. Pour la fièvre des tranchées, l’homme est le seul réservoir connu; des infections persistantes chez l’homme et chez le pou assurent le maintien du cycle malgré l’absence de transmission transovarienne de Rickettsia quintana chez le pou.

Le typhus épidémique à poux, bien que rayé de la liste des maladies soumises au Règlement sanitaire international, reste l’une des maladies figurant au programme de surveillance épidémiologique de l’OMS; cette affection est responsable d’une morbidité et d’une mortalité importantes dans certaines parties de l’Afrique, et des cas sont signalés localement dans les Amériques et en Asie. Le typhus de brousse pose toujours un sérieux problème de santé publique en certains endroits de l’Asie du Sud-Est et du Pacifique Occidental. Aux Etats-Unis d’Amérique, le
nombre annuel de cas signalés de fièvre pourrée des montagnes Rocheuses a augmenté pendant les deux dernières décennies; les raisons possibles en sont de meilleurs diagnostics et une migration accrue de populations du centre des villes vers les faubourgs. Des affections apparentées, transmises par des tiques, sont observées en Amérique du Sud, dans la région méditerranéenne, en Afrique, en Asie du Sud-Est, en Extrême-Orient et dans le Pacifique Occidental. Bien que sporadiques, les cas d'affections graves dues à une infection chronique par la fièvre Q sont en augmentation dans beaucoup de régions du globe.

REFERENCES