A New Rickettsial Disease in the United States

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(See the article by Paddock et al. on pages 805–11)

The article by Paddock et al. [1] in this issue of *Clinical Infectious Diseases* demonstrates that we must be able to change our minds about traditionally established diseases such as Rocky Mountain spotted fever (RMSF) and tickborne rickettsioses. Paddock et al. [1] report the case of an American patient with fever, rash, and an inoculation eschar. The patient had antibodies to *Rickettsia rickettsii* and to *Rickettsia akari*. Culture of the eschar biopsy specimen yielded a rickettsia characterized by molecular biology as *Rickettsia parkeri*, which was discovered in ticks in the United States 60 years ago. This is the first report of an infection with this agent.

In the first part of the 20th century, it was established that a single organism, *R. rickettsii*, was the agent of RMSF. It was considered the only agent of tickborne rickettsial diseases in America. Any other rickettsia obtained from a tick was considered to be nonpathogenic. Among these were *R. parkeri* (first identified in 1939), *Rickettsia montanensis*, *Rickettsia canadensis*, *Rickettsia bellii*, and *Rickettsia rhipicephali*, and other isolates without formal description [2]. Even *Coxiella burnetii*, the agent of Q fever, was first considered to be a nonpathogenic rickettsia (named *Rickettsia diaporica*) because it was found first in a tick in the Rocky Mountain Laboratory (Hamilton, MT) [2]. In the rest of the world, the same simplification of causality was also observed, and tickborne rickettsial diseases were considered to be caused only by *Rickettsia conorii* in Europe, Africa, and Asia, by *Rickettsia sibirica* in Siberia, and by *Rickettsia australis* in Australia; a single species was considered the agent of all tickborne rickettsioses in a specific geographic area. Therefore, only 4 pathogenic species of tickborne rickettsioses were established.

Since World War II, the diagnosis of rickettsioses has been made mainly on the basis of serological testing, and indirect immunofluorescence assay has been the reference technique used [2]. After 1976, immunodetection in skin biopsy specimens was also proposed [3]. However, due to the widespread antigenic cross-reactions among tick-associated rickettsia, these techniques cannot discriminate among rickettsioses and are rarely able to formally identify new diseases. More sophisticated serological techniques, including cross-adsorption assays and Western blot testing, can differentiate between 2 identified species. However, serological tests can detect only antibodies to the suspected antigens of identified agents and not antibodies to unknown organisms [4].

Starting in 1991, with the introduction of cell culture and molecular biological testing methods, the spectrum of rickettsioses increased dramatically [5]. Eight new species (or new diseases) have been described since 1991: *Rickettsia japonica* in Japan, *Rickettsia honei* on Flinders Island (between Australia and Tasmania), *Rickettsia africae* in Africa and the West Indies, *Rickettsia slovaca* in Europe, *Rickettsia aeschlimannii* in Africa and Europe [6], *Rickettsia helvetica* in Europe and Asia, *Rickettsia helongianghensis* in Asia, and *R. parkeri* in the United States. Two new subspecies were also reported: *Rickettsia conorii astrakhan* in Russia, Africa, and Kosovo, and *Rickettsia sibirica mongolotimonae* in China, Europe, and Africa.

New rickettsial diseases have been found mainly under 3 conditions.

1. They sometimes have been identified in places where no tickborne rickettsiosis was previously known, such as Japan, Flinders Island, or Astrakhan (in Russia). In those cases, investigations were performed because the agent of the observed disease was unknown. However, the newly described diseases were typical of rickettsioses characterized by high fever, rash, and inoculation eschar.

2. In some other places, one rickettsial agent had already been identified, but active identification procedures allowed for the discovery of other agents. In France, for example, we now have 5 locally acquired tickborne agents (*R. conorii*, *Rickettsia helvetica*, *Rickettsia mongolotimonae*, *Rickettsia aeschlimannii*, and *R. slo-
vaca), and there are 4 in South Africa (R. conorii, R. africae, R. aeschlimannii, and Rickettsia mongolotimonae) and 2 in Australia (R. australis and R. honei). In these cases, the use of a broad spectrum of diagnostic techniques made it possible to identify unexpected agents. R. slovaca and R. aeschlimannii were identified in patients first by PCR, R. mongolotimonae was identified by culture, and R. helvetica was identified by serological testing. In the United States, the first documentation of a Rickettsia felis infection (a fleaborne spotted fever) also was obtained by PCR testing of a serum sample. In that study, investigators were testing patients with suspected murine typhus [7].

Of interest, in the United States in 1990, the molecular testing of an isolate from a patient in Ohio who died of a febrile disease showed that this isolate, considered to be R. rickettsii, was, in fact, indistinguishable from R. parkeri [8]. This fact was not considered significant enough to report a new pathogenic agent. It is retrospectively analyzed by Paddock et al. [1].

3. Some new clinical features have also stimulated the research of new agents. As a matter of fact, different rickettsial species are frequently associated with different clinical and epidemiological conditions. Atypical clinical situations should prompt the use of specific tools, including culture and molecular identification. Paddock et al. [1] describe a patient infected by R. parkeri who exhibited an eschar tache noire. This is highly unusual in cases of RMSF. On the basis of this finding, it should be investigated whether documented infections caused by R. rickettsii can, in fact, be associated with inoculation eschars. In Africa, R. conorii (the agent of Mediterranean spotted fever) and R. africae are prevalent, but clinical findings regarding patients infected with these agents are different. Patients infected with R. africae exhibit multiple eschars more commonly and exhibit a generalized rash less commonly than do patients infected by R. conorii. Moreover, vesicular eruption can be caused by R. africae but not by R. conorii [4]. Finally, grouped cases are much more common among R. africae infections. In Europe, R. slovaca causes a disease characterized by large scalp erythema and neck lymphadenopathies, but rarely by rash [9]. In this case, the disease does not appear to be a typical rickettsiosis. This shows that the spectrum of rickettsial disease is wider than previously thought and includes diseases not characterized by rash.

In conclusion, the article by Paddock et al. [1] challenges the old references for rickettsial diseases. The report shows that any tick isolate is a potential pathogen as soon as the infected tick bites a human being. (In the case of R. parkeri, it took 60 years to demonstrate this!) The report shows that atypical cases of febrile rash should be properly investigated using cell culture and/or molecular biological testing (samples from skin biopsies, and especially eschar biopsies, being the more potent [2]). It also shows that basic serological testing gives mainly confirmatory information, and this only on the tested antigens. In the case described by Paddock et al. [1], one might conclude, on the basis of serological testing, that the patient had RMSF or rickettsialpox, as he had antibodies to the causative agents of these diseases. Only cell culture makes it possible to identify the causative agent properly. Therefore, the results of serological testing are presumptive and should be interpreted with caution.

Finally, it is stimulating to show that many things remain to be discovered, even in classical diseases, and that infectious disease descriptions remain unchanged only when they are not challenged by new investigators.

References