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## Erythema chronicum migrans – a tickborne spirochetosis\*

Short communication

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Erythema chronicum migrans (ECM) is a syndrome characterized by the formation of a small annular papule that expands centrifugally with indurated  $\frac{1}{2}$  to 2 cm wide borders and central clearing. First observed in 1908 by the Swedish physician, Arvid Afzelius, it has since been reported throughout Europe (Afzelius, 1921; Horstrup and Ackermann, 1973).

The causative agent has remained unknown although it was speculated that it may be a toxic substance, virus or rickettsia transmitted by ticks or other blood-sucking arthropods. Involvement of an infectious bacterial agent associated with hematophagous arthropods, particularly the ixodid tick, *Ixodes ricinus*, was suggested by transmission of the disease from man to man by implantation of affected skin (Binder et al., 1955) and by effective treatment with penicillin.

In the United States, a disease indistinguishable from ECM was first observed in Wisconsin in 1970 (Scriimenti, 1970) and in 1975 in southeastern Connecticut (Mast and Burrows, 1976). Clinical and epidemiological investigations of cases in the small community of Lyme, Connecticut, led to the description of Lyme arthritis or Lyme disease, an epidemic inflammatory disorder that usually begins with a skin lesion called erythema chronicum migrans (ECM) and weeks to months later may be followed by neurologic or cardiac abnormalities, migrating polyarthritis, intermittent attacks of oligoarthritis or chronic arthritis in the knees (Steere et al., 1977, 1979, 1980a, 1980b; Hardin et al., 1979;

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Reik et al., 1979). The causative agent, as in Europe, remained unknown. Epidemiological evidence, however, suggested involvement of an infectious agent transmitted by ticks of the genus *Ixodes*, namely *I. dammini* in the northeast and midwest, and *I. pacificus* in the west.

During a survey of spotted fever group rickettsiae in ticks from Shelter Island, New York – an area known for the occurrence of Lyme disease – we recently detected in 77 (61.1%) of 126 adult *I. dammini*, a cultivable spirochete whose antigenic relation to the hitherto unknown etiologic agent of Lyme disease, was suggested by the positive reactions of sera of patients with clinically diagnosed Lyme disease. White rabbits, fed on by infected ticks or inoculated with infected tick suspensions or cultured spirochetes, responded not only with high titers of antibodies but, in some instances, also with skin lesions resembling ECM, 10 to 12 weeks later. Since publication of these findings (Burgdorfer et al., 1982), spirochetes indistinguishable from the *I. dammini* spirochete were recovered from the blood of at least two patients with Lyme disease (A. C. Steere, Dr. J. L. Benach – personal communications).

Because of the clinical and epidemiological similarities between Lyme disease and ECM of Europe, we recently initiated a study to determine whether *I. ricinus*, the incriminated vector of ECM in Europe, is also a carrier of spirochetes.

In the spring of 1982, several hundred adult *I. ricinus* were collected by flagging vegetation in Seewald, a marshy forest on the east shore of the Lake of Neuchâtel in the canton of Bern, where according to practicing physicians, ECM cases had sporadically occurred. Upon collection, the ticks were shipped to the Rocky Mountain Laboratories where they were examined for spirochetes by (1) dark field examination of hemolymph, (2) direct fluorescence microscopy of dissected tissues using a conjugate prepared from sera of rabbits that had been immunized against the *I. dammini* spirochete (Burgdorfer et al., 1982), or by (3) feeding ticks on white rabbits.

Of 201 individually examined ticks, 73 (36.3%) were infected with spirochetes. The organisms were limited to the midgut in 69 ticks but were found in all the tissues including hemolymph in 4 ticks. As illustrated in Fig. 1, the spirochetes reacted strongly with fluorescein isothiocyanate-labelled antibodies to the *I. dammini* spirochete.

An additional 400 ticks, in pools containing 25 females and 25 males, were fed on each of 8 white rabbits. Upon repletion and oviposition, the surviving female ticks were dissected and examined as outlined above. Thirty-nine (21.7%) of 180 females were infected; two showed a generalized infection, the remaining 37 an infection limited to the midgut diverticula. The larval progeny of the 2 females with generalized infections were later examined to determine whether spirochetes had passed via eggs; one female produced 100% infected larvae, the other 60%.

Isolation of the *I. ricinus* spirochete was accomplished by inoculating the

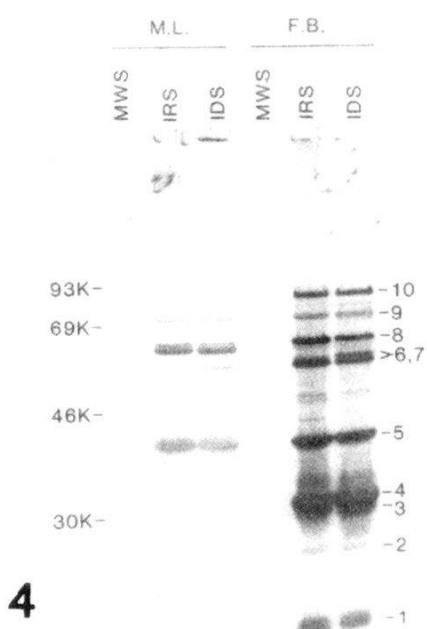
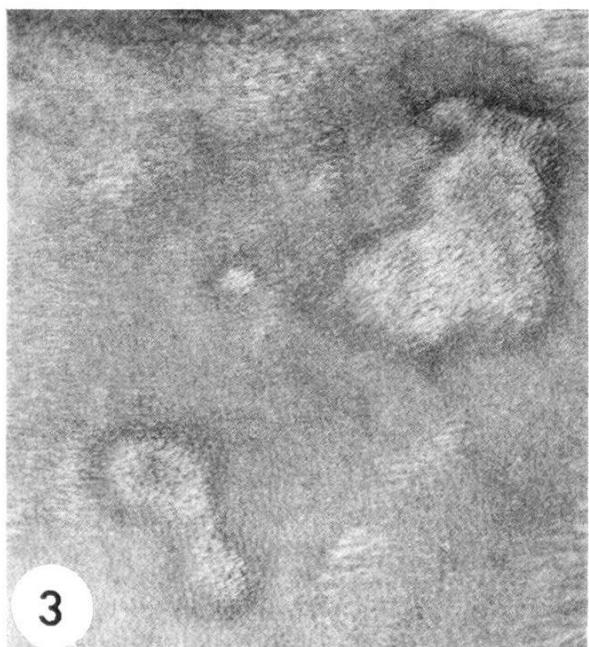
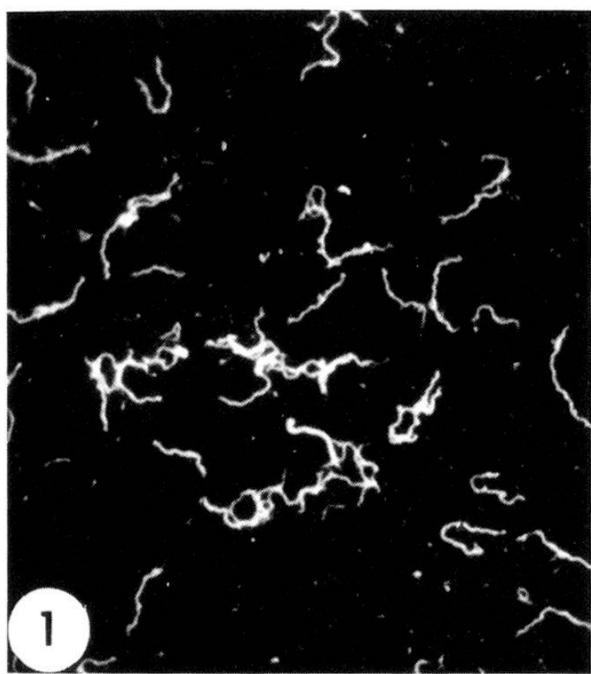


Fig. 1. Spirochetes in midgut smear of *I. ricinus*. Direct fluorescent antibody staining with a conjugate prepared from sera of rabbits immunized against the *I. dammini* spirochete (750 $\times$ ).

Fig. 2. *I. ricinus* spirochete negatively stained with 2% ammonium molybdate (bar = 2.0  $\mu$ m).

Fig. 3. ECM-like lesions on the trunk of a rabbit fed on by infected *I. ricinus* 12 weeks previously.

Fig. 4. Western blot analysis of antigens in the *I. ricinus* (IRS) and *I. dammini* (IDS) spirochetes. Proteins in whole cell lysates were separated by SDS-PAGE (Laemmli and Favre, 1973), then transferred to nitrocellulose, incubated with 1:100 dilutions of sera from ECM patient M. L. and Lyme disease patient F. B., and probed with  $^{125}$ I-labelled protein A. Molecular weight standards (MWS) are indicated on the left. Intensely emitting bands in the F. B. serum are arbitrarily numbered 1 to 10. Note the close similarities of reactions of sera for both the IRS and IDS spirochetes.

suspensions of 4 ticks into BSK medium (Barbour et al., 1983). Tubes inoculated with infected tick suspensions were positive as early as 7 days after inoculation. At 35°C, the organisms grew well with a generation time of about 12 hours.

Morphologically, including fine structural analysis by electron microscopy, the *I. ricinus* spirochete was found to be indistinguishable from the *I. dammini* spirochete. Irregularly coiled, it ranges from 10 to 30  $\mu\text{m}$  in length and from 0.18 to 0.25  $\mu\text{m}$  in diameter (Fig. 2). Its ends are also tapered, and from 6 to 8 filaments are inserted subterminally at each end with insertion points being located in a row paralleling the cell's long axis.

Of the 8 rabbits that served as blood donors for the 200 *I. ricinus* females, 7 were fed on by one to 19 infected ticks. When tested for antibodies by indirect immunofluorescence 28 days after the engorged ticks had dropped, all 7 rabbits had titers ranging from 1:40 to  $>1:1,280$ . The rabbit fed on by negative ticks did not have antibodies. As early as 4 weeks after tick feeding, multiple lesions, similar to those elicited by *I. dammini* spirochetes, appeared on the back and lateral trunk of each seropositive rabbit (Fig. 3). Small annular papules at first, they gradually enlarged to annular or irregularly-shaped erythematous lesions, 3–5 cm in diameter, that were surrounded by a narrow, dark-red border. By the 12th week after tick feeding, these lesions were still detectable in some rabbits, but had disappeared in others.

The close similarity of the *I. ricinus* and *I. dammini* spirochetes was also established immunologically by indirect immunofluorescence and by polyacrylamide gel electrophoresis (Barbour et al., 1982). Sera of rabbits immunized by exposure to ticks infected with the *I. ricinus* spirochete and from patients diagnosed as having had ECM had antibodies that reacted in a similar often identical way to both the *I. ricinus* and *I. dammini* spirochetes. The same was true for rabbits fed on by infected *I. dammini* and for patients with Lyme disease. Also very similar were the PAGE-Coomassie blue-protein profiles of the two spirochetes (Barbour et al., 1983).

Shared antigenic determinants were also demonstrated by Western blot analysis (Towbin et al., 1979; Barbour et al., 1982) of sera from an ECM patient (M. L.) of Switzerland and from a Lyme disease patient (F. B.) of Connecticut. As illustrated in Fig. 4, there were only minor differences between the *I. ricinus* spirochete and the *I. dammini* spirochete in the antigens that reacted with the immunoglobulins of the two sera. The serum of patient M. L. contained antibodies that detectably bound to fewer antigens than F. B.'s antibodies. Sera from two Swiss controls and two Connecticut controls did not contain antibodies that detectably reacted with spirochete components in blots (data not shown).

In conclusion, it appears that the spirochete detected in and isolated from the ixodid tick, *I. dammini*, in the United States is not only the etiologic agent of Lyme disease in that country but also the cause of ECM in Europe where it is transmitted to man by *I. ricinus* and possibly other bloodsucking arthropods. Our data also support the long-advanced hypothesis (Reik et al., 1979; Gerster

et al., 1981) that ECM and Lyme disease are expressions of the same infectious process. As yet, little is known about the relation of these spirochetes to their tick vectors. Studies are in progress in our laboratories to determine the development of the spirochetes in *I. ricinus* and *I. dammini* and to clarify the transmission mechanism(s) to a host.

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