Erythema Migrans in the South

The conclusion by Kirkland et al[1] in their recent article that "In the southern United States, EM [erythema migrans]–like rash illness should no longer be considered definitive evidence of early Lyme disease" is both premature and unwarranted. As a clinician in Missouri who has identified, treated, followed up, reported, studied, presented, and published on these southern EM cases for a decade, I find this negative conclusion unsubstantiated by the authors' data. Proving a negative (null hypothesis) appropriately requires a high methodological standard, which was not met in the article by Kirkland et al.

Around the world, EM is considered the hallmark clinical finding associated with Lyme disease. It has been described in the literature at a minimum as "characteristic" and again and again as "pathognomonic,"[2] most recently in a January 1998 article coauthored by Dennis,[3] who is also a coauthor with Kirkland et al.

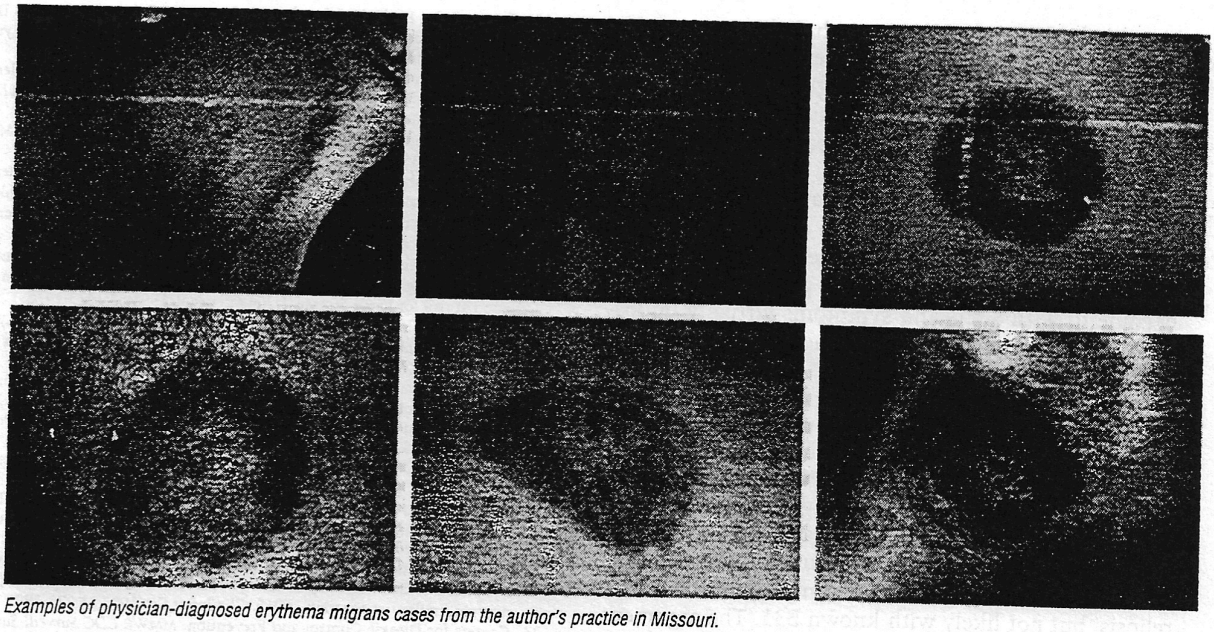
Absence of proof is not proof of absence. Remember when conventional wisdom told us that Lyme arthritis (disease) was caused by a virus, yielding the tenet "no arthritis, then no Lyme"; *Borrelia burgdorferi* in North America were homogeneous; there were absolutely no *B burgdorferi* in Missouri; *Ixodes dammini* was a separate tick species; and short-term low-dose antibiotic therapy was always effective in eradicating Lyme disease? We now know all of these dictums to be false.

I believe the extraordinary import given the relatively few negative human cultures for *B burgdorferi* in the article by Kirkland et al is inappropriate. Not only do the authors report low numbers using a historically insensitive method that is not effective when proving nonexistence, we know that the standard culture medium (BSK-II) selects for specific genotypes of *B burgdorferi*. This alone destroys the value of a negative culture as proof of the absence of *B burgdorferi*. Why wouldn't atypical variants, especially if adapted to a different tick species, have atypical growth requirements? This differential growth or failure to grow in culture observed by nearly every researcher cultivating *B burgdorferi* and recently studied by Norris et al[4] has also been reported in England[5] and the northeastern United States.[6] Remember that when originally cultivating relapsing fever spirochetes, Kelly[7] had to use different media for *Borrelia* from different tick species. Given this precedent for variance in cultures of *Borrelia*, should we really accept the conclusion that its failure to grow in a complex culture medium is indicative of its absence? The triad of *Babesia*, *Borrelia*, and *Ehrlichia* is associated with *Ixodes scapularis* ticks. If these *Ixodes* ticks are not vectors of *Borrelia* or *Ehrlichia* in the South, then presumably they are not vectors of *Babesia* either. *Ehrlichia chaffeensis* in the South is associated with *Amblyomma americanum* (Lone Star) ticks, as are many southern cases of EM.[8] Recently, a new strain of *Babesia*, MO1, which is pathogenic to humans and presumably not vectored by *I scapularis* ticks, was identified in Cape Girardeau, Mo.[9] Notably, it appeared to have different growth requirements because multiple attempts using various known methods to grow other *Babesia* failed. It appears that this tick-vectored pathogen has adapted to a different tick and has growth requirements different from those of other *Babesia* species. Are the authors prepared to say they have proven this cannot happen with *B burgdorferi*?

Another troubling aspect of the article by Kirkland et al[1] involves the statement that *A americanum* is an incompetent experimental vector of *B burgdorferi*, without explaining that the studies cited used only 1 species of ticks at a time to feed on the animals, certainly not a requirement in nature. This is important because Mather et al[10] has presented data showing that when *Dermacentor* ticks (a less likely vector than *A americanum*) feed in conjunction with *Ixodes* ticks, the *Dermacentor* ticks can acquire and transmit *B burgdorferi*. We also know that using geographically mismatched spirochetes in *A americanum* in a laboratory setting, Ryder et al[11] showed a transstadial transmission rate of 1.6%, causing the authors to posit that *A americanum* ticks might be involved in occasional human cases. When attempting to disprove the importance of a global disease marker such as EM, a condition currently described by Nichol et al[3] as pathognomonic, it would be helpful to us clinicians who are trying to care for patients if authors would be as complete as possible with their information.

The study of EM in Missouri by Campbell et al[12] is also cited as evidence supporting the negative conclusion of Kirkland et al. Readers should be informed that the primary clinician (myself) who supplied most of the study patients and the state epidemiologist (Dr Donnell) who initiated that study declined authorship because of decisions to exclude data necessary for objective evaluation and other decisions about content and conclusions. This controversy is detailed in the June 1996 issue of the *Journal of Infectious Diseases*.[13] The data excluded from the study by Campbell et al were published by Donnell and myself[14] in *Missouri Medicine*, and we reached a different conclusion.

In their article, Kirkland et al also cite as evidence "not positive" serologic results based on criteria that are extremely specific for B31 *B burgdorferi*. There are 2 problems with this evidence. First, many of their serologic samples are also "not negative" in the sense of



Examples of physician-diagnosed erythema migrans cases from the author's practice in Missouri.

being consistent with negative uninfected controls. In fact, some of the serologic results from the Missouri patients were positive by other published criteria, and were distinguishable in other ways such as by positive whole-cell sonicated enzyme-linked immunosorbent assays, specific Western blot bands, numbers of bands, and weaker bands. In fact, the probability that some of the results of the tests run by the Centers for Disease Control and Prevention on patients from Missouri with EM were random within a negative control population were 1 in 25 million.[13,14] We know that strain variances can result in testing variances.[15,16] Kirkland et al provide sound data that southern physician-diagnosed EM is not all caused by B31 *B burgdorferi*. This brings me to problem number 2, which is that I do not know of anyone saying that is the case. That is truly a straw man argument extrapolated to apply to real people in the South with signs and symptoms that can only be explained by a borreliosis. Given the current data, it is expected that spirochetes differing from B31 may cause EM in the South, which is not evidence of Lyme disease nonexistence. It is already known that there is enormous heterogeneity of *B burgdorferi* in the South.[17-20] It is interesting that Wong et al[21] reported that *E chaffeensis* antigen (associated with *Amblyomma* ticks) lacks appropriate sensitivity to serve as a surrogate substrate for the detection of human granulocytic ehrlichiosis (associated with *I scapularis* ticks). If with the tick pathogen triad of *Ehrlichia, Babesia*, and *Borrelia*, we know that *Ehrlichia* and *Babesia* from different tick species test differently, is it prudent to assume without evidence that *Borrelia* do not, and that failure to test like B31 is definitive evidence of the absence of all *B burgdorferi*?

Another consideration is the recent study of heterogeneous tick isolates of proven *B burgdorferi*, including 1 from *A americanum* from the farm of one of my patients from Missouri with EM.[18] We believe that some southern ticks, including *A americanum*, may act as a bridge vector to humans, not unlike *Ixodes pacificus* in California. The Missouri isolates in this study are *B burgdorferi* sensu lato. However, just as genetic heterogeneity was first shown in Europe, *B burgdorferi* sensu lato has been implicated in human disease there. Notably, many of the patients with sensu lato "had variable and unpredictable serological responses, including an apparent lack of immunologic response despite disseminated disease."[22] Shouldn't we investigate this possibility further before we declare the South a Lyme-free and pathogenic *B burgdorferi*–free zone, especially when patients fulfill the diagnostic criteria for Lyme borreliosis? This could well be yet another dogma of conventional wisdom based on "definitive" evidence from some of the same sources that assured me with absolute confidence only a few years ago that *B burgdorferi* of any variety did not exist in Missouri.

We are clearly still on the front end of the learning curve of this complex disease. Suppose it is discovered that EM in the South is caused by *B burgdorferi* strain variants, or even new species of *Borrelia*? Would those variants still be related to Lyme disease, even if they could not be distinguished clinically? There are many *Borrelia* species, both tick borne and louse borne, that cause relapsing fever, and yet it is a consistent diagnosis of relapsing fever. Suppose a patient from Missouri goes to New York for a couple of days and then 2 weeks later develops a classic case of EM. He has had tick exposure, but does not remember the details. Does it make sense that if the treating physician guesses the patient contracted EM in New York, he has Lyme disease, but if the guess is he developed EM in Missouri, he does not have Lyme disease, when the lesions and clinical findings are indistinguishable? What about areas such as New Jersey, where *I scapularis* and *A americanum* ticks coexist and commonly

bite people. Suppose a patient with EM presents with a history of tick bites but does not remember the details. Is the physician going to have to guess at the tick species to make a diagnosis (if *I scapularis*, the patient has Lyme disease; if *Amblyomma*, the patient does not have Lyme disease)? Is Lyme disease, as the Centers for Disease Control and Prevention[23] and the world literature have stressed, really a clinical diagnosis? We have southern ticks with both identified and unidentified spirochetes that are biting our patients who then become ill with signs and symptoms virtually impossible to explain in the absence of a borreliosis. What is the diagnostic code for "Lymelike" disease?

After a decade of studying patients from the South (including Missouri), I am unaware of any way to clinically distinguish them from patients with Lyme disease elsewhere on the planet (**Figure**).[8] The article by Kirkland et al[1] did not change that because its negative conclusion is based primarily on the association of *A americanum* ticks, culture results unlikely with B31, and serologic results compatible with a borreliosis, but not likely with known B31. The argument against a homogeneous B31 spirochete population is strong. The argument ruling out the possibility of other *B burgdorferi* variants is woefully weak and certainly not definitive. The scientific whimper of the almost expected culture and serologic results claimed to support the negative conclusions of Kirkland et al pales in comparison with the evidentiary bang or explosion of clinical data supplied by hundreds of southern clinicians and other researchers.[2,13,14,18,19,24-26] The likelihood that *Borrelia*, possibly even atypical *B burgdorferi*, causes EM in the South has not been disproved, and the current evidence is inadequate to designate a new disease.

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