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Lyme Disease in Wisconsin: Epidemiologic, Clinical, Serologic, and Entomologic Findings

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In 1980-82, 80 individuals (71 Wisconsin residents) had confirmed Lyme disease (LD-c) reported; 39 additional patients had probable or possible LD. All cases of LD-c occurred during May-November; 73 percent occurred during June-July; 54 (68 percent) occurred in males. The mean age was 38.7 years (range, 7-77 years). Among LD-c patients, likely exposure to the presumed vector *Ixodes dammini* (ID) occurred in 22 different Wisconsin counties. Antibodies to the ID spirochete that causes LD occurred in 33 of 49 LD-c cases versus 0 of 18 in ill controls ($p < .001$) and in 13 of 26 LD-c cases treated with penicillin or tetracycline versus 16 of 19 LD-c cases not treated. Early antibiotic therapy appears to blunt the antibody response to the ID spirochete. Regional tick surveys conducted in Wisconsin during each November in 1979-82 have demonstrated regions of greater density of ID. Utilizing comparable tick collection in these surveys, increases were noted in the percentage of deer with ID from 24 percent (31/128) in 1979 to 38 percent (58/152) in 1981, in the standardized mean value of ID/deer from 1.0 in 1979 to 2.2 in 1981, in the percentage of ID of the total ticks collected from 13 percent in 1979 to 71 percent in 1981, or in the ratio of ID to *Dermacentor albipictus* ticks from 0.14 in 1979 to 2.44 in 1981. However, a reduction in the density of ID/deer was noted generally throughout Wisconsin in 1982 when compared to 1981. LD is widespread in Wisconsin, with ecologic and clinical features similar to those occurring along the eastern seaboard.

INTRODUCTION

Lyme disease (LD) is an immune-mediated inflammatory illness characterized by a distinctive primary skin lesion, erythema chronicum migrans (ECM), and in many cases concomitant or subsequent development of cardiac, neurologic, or arthritic complications [1,2]. It is caused by a tetracycline-, penicillin-, and erythromycin-sensitive spirochete [3-5] transmitted by ticks of the genus *Ixodes* [3-6], although

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other vectors may be involved. Since the early descriptions of Lyme disease in Connecticut in 1976 [1], LD has been recognized in at least 16 additional states in the East, the upper Midwest, and the West [7,8].

The first published report of ECM in the United States involved a patient who had been exposed to ticks in Taylor County, Wisconsin, in 1968 while grouse hunting [9]. The patient also had additional manifestations of LD. Subsequently, a description of the full complex of signs and symptoms of LD occurring in three patients in Wisconsin in 1978 [10] prompted a more intensive search. Since autumn 1979, the Wisconsin Division of Health (DOH) has been investigating suspect cases of LD to delineate the clinical illness and areas of LD risk in the state [11-13]. The purpose of this report is to present clinical, epidemiologic, serologic, and entomologic observations on LD in Wisconsin in the period 1980 to 1982.

MATERIALS AND METHODS

Surveillance for Lyme Disease in Humans

Reports of LD for this study were obtained through passive surveillance techniques stimulated by statewide mailings to physicians in each of the years 1980 to 1982. The mailings described the illness, and requested physicians to report suspect cases to the DOH and to submit paired serum specimens to the Wisconsin State Laboratory of Hygiene (SLH). Once a report was received or a request for LD-related laboratory studies at the SLH was made, the patient's physician was asked to complete a comprehensive case report form and initial and follow-up patient telephone interviews were completed by DOH personnel. The following information was requested: age, sex, race, county of residence, history of exposures to ticks and tick bites including location on the body, county of tick exposure or tick bites, travel history in the three weeks prior to illness onset; ECM onset and duration, location and number of ECM lesions, diameter of largest lesion, and other descriptive features of the rash; onset and duration of fever, headache, stiff neck, malaise, myalgia, nausea, vomiting, sore throat, joint abnormalities (individual joints specified) including recurrent joint abnormalities, neurologic abnormalities, cardiac abnormalities, other signs and symptoms; a request for results of laboratory tests; type, dose, and dates of antibiotic therapy and other medication prescribed, date of physician visit if any, and dates of hospitalization if any.

Case Definition

In this study we adopted and slightly modified a case definition that had been coordinated by Dr. George Schmid at the Centers for Disease Control in cooperation with other LD investigators. According to this definition, diagnostic categories were based on the occurrence of ECM and multisystem illness and on the geographic area of exposure to ticks. Specifically with regard to multisystem involvement the following abnormalities were included: (1) cardiovascular: atrioventricular conduction defects, electrocardiographic evidence of myocarditis or myopericarditis, or left ventricular dysfunction; (2) neurologic: clinical evidence of meningoencephalitis (headache and stiff neck), chorea, cerebellar ataxia, cranial or peripheral neuropathy, or myelitis; (3) joint: short (lasting at least one day), often recurrent, attacks of migratory polyarthritis or oligoarticular arthritis (swelling and pain). The case categories included:

1. *Confirmed case*

- A. *Exposure in a known endemic area:* ECM, with exposure occurring no more than 30 days prior to onset of the skin lesion; or

- B. *No exposure to a known endemic area:* ECM and two of the three systems described under multisystem involvement.
2. *Probable case*
 - A. *Exposure in a known endemic area:* (1) In the absence of ECM, typical involvement of at least two of the three systems as described under multisystem involvement with exposure occurring no more than 60 days prior to the onset of involvement of at least one system, or (2) If only one of the three systems as described in the multisystem involvement has been involved, then at least one of the following must also be found: (a) history of the tick bite occurring within 60 days prior to the onset of symptoms, or (b) geographic or family clustering, with at least one illness meeting the confirmed case definition for LD, or (c) an elevated serum IgM level or cryoglobulins containing IgM.
 - B. *No exposure to a known endemic area:* ECM with involvement of none or one organ system. Without ECM, there will be no probable cases in a non-endemic area.
3. *Possible case:* Any other case reported as LD not meeting the above criteria.
4. *Pending case:* Any non-confirmed case that cannot be classified as not a case in which additional information is pending.
5. *Not a case:* Any case clearly ruled out as being LD.

The definition for an endemic area used in this case definition in Wisconsin comprised the geographic region in which *Ixodes dammini* ticks had been identified through November 1981. The case definition was used, in part, to evaluate the accuracy of serologic findings in relation to clinical criteria; thus, the case definition did not include a laboratory criterion for confirmation.

Serologic Testing

Physicians were requested to submit, to the SLH, an acute serum specimen when available and at least one convalescent serum specimen from each reported patient. Specimens received at the SLH were stored at -70°C ; one ml aliquots were shipped in batches to the Rocky Mountain Laboratories (RML) in February, August, and November of 1982. Testing for antibodies to the *I. dammini* spirochete (Shelter Island isolate) that causes LD was performed at the RML using the log indirect immunofluorescent test methods previously described [3,14].

Entomologic Studies

In 1979 we initiated surveys of the distribution of *I. dammini* and *Dermacentor albipictus* in Wisconsin based on tick carriage by white-tailed deer (*Odocoileus virginianus*). Surveys completed in 1979 and 1980 were focal in nature, having been designed to evaluate the density of *I. dammini* in suspected endemic areas and to collect live ticks in which to search for an etiologic agent of Lyme disease. Surveys completed in 1981 and 1982 were designed to determine the distribution and relative density of *I. dammini* throughout the state. Each of the 1979–82 tick surveys was conducted on the first two days of the deer gun-hunting season, always the Saturday and Sunday preceding Thanksgiving. All ticks in any stage or material suspected of being a tick were collected from deer that had been killed no more than 24 hours prior to presentation at the deer kill registration station. Forceps were used to examine an approximately 300-square-inch area covering the entire right side or left side of the neck of a deer and extending distally from the ear to the top of the respective shoulder. The deer were usually examined in the position as presented in a transport vehicle. In the 1979–80 surveys, the ticks from each deer were placed live into indi-

vidually labeled screw-cap vials. Ticks from the 1981–82 surveys were placed in individually labeled vials containing 70 percent ethyl alcohol. The 1979, 1981, and 1982 collections were shipped to Boston for speciation, staging, and sex determination by Dr. Spielman. The 1980 collection was shipped to Hamilton, Montana, for similar identification by Dr. Burgdorfer. For each deer examined, hunters provided the date, time, and precise location of the deer kill; the sex and the approximate age of the deer were recorded. The 1979 survey involved two sites in northwestern Wisconsin, and one site each in west central and south central Wisconsin. The 1980 survey included two sites in northwestern Wisconsin. The 1981 and 1982 surveys included 24 and 11 sites, respectively, widely distributed throughout the state.

While attempts were made to examine at least 50 deer at each site per survey, data in this report include sites where fewer than 50 deer were evaluated.

All collections at each study site were made by teams of individuals trained to use identical techniques of collection. Teams consisted of two to three individuals; 22 teams participated in the 1981 survey and ten teams participated in the 1982 survey.

RESULTS

Surveillance and Epidemiologic Features

Of 171 reports received for 1980–82, 80 (47 percent) met the case definition for confirmed LD, 16 (9 percent) for probable LD, 23 (14 percent) for possible LD, 39 (23 percent) were not cases, and 13 (7 percent) were pending. A comparison of 80 confirmed cases to 16 probable cases demonstrated these classifications to be very similar in demographic and clinical features (Table 1) with the exception of cardiac abnormalities, which were not observed in any probable case patients. Fourteen of the 16 probable cases were classified based on the criteria of ECM without a known exposure to ticks in an endemic area.

The ages of confirmed cases ranged from seven to 77 years with the following distribution: 0–9 years (4 percent), 10–19 years (14 percent), 20–29 years (18 percent), 30–39 years (18 percent), 40–49 years (16 percent), 50–59 years (15 percent), and 60 or more years (15 percent). Among patients with ECM, approximately 68 percent of known tick exposures occurred between May 16 and July 15, and approximately

TABLE 1
Erythema Chronicum Migrans/Lyme Disease in Wisconsin:
Demographic Features and Clinical Signs and Symptoms
Among Confirmed and Probable Cases, 1980–1982

	Confirmed	Probable
Number	80	16
Male (%)	54 (67.5)	12 (75)
Age: Mean (years)	38.7	32.5
Median (years)	37	29
Range (years)	7–77	1–71
ECM (%)	80 (100)	14 (87.5)
Arthritis (%)	26 (32.5)	6 (37.5)
Arthritis/Arthralgia (%)	55 (68.8)	11 (68.8)
Neurologic* (%)	30 (37.5)	4 (25)
Bell's palsy (%)	5 (6.3)	1 (6.3)
Cardiac (%)	6 (7.5)	0 (0)

*Headache plus stiff neck and/or Bell's palsy

TABLE 2
Erythema Chronicum Migrans/Lyme Disease in Wisconsin: Antibodies (IFA)^a to the *I. dammini* Spirochete

	Case Category			P ^b
	Confirmed(C)	Prob./Poss.	Negative(N) ^c	C vs. N
I. Seroconversion or fourfold change ^d	25/41	4/7	0/17	< .001
II. Convalescent antibody ^d (no acute tested)	8/8	2/4	0/1	
III. I and II ^d	33/49	6/11	0/18	< .001

^aIndirect immunofluorescent method of Burgdorfer et al. [3]

^bFisher's exact test

^cNegative = ill controls

^dPositive observations/total observations

73 percent of ECM onsets occurred between June 1 and July 31. Among confirmed cases with known tick bites, the mean interval from tick bite to ECM onset was 9.2 days (median, ten days; range, one to 21 days).

Serologic Tests

Results of tests for antibodies to the *I. dammini* spirochete are presented in Tables 2 and 3. Results of testing of paired sera and of convalescent sera in the absence of available acute serum specimens, were available for 78 individuals (Table 2). Thirty-three (67 percent) of 49 confirmed cases as compared to 0 of 18 ill controls had a demonstrable seroconversion, a fourfold change in antibody titer, or evidence of antispirochete antibodies in convalescent sera ($p < .001$, Fisher's exact test). Evaluation of only results confined to testing of paired serum demonstrated the same significant differences. This trend was also noted when probable and possible cases were compared to non-cases.

TABLE 3
Erythema Chronicum Migrans/Lyme Disease in Wisconsin: The Effect of Penicillin (PEN) or Tetracycline (TET) Therapy on the Development of Antibodies (IFA)^a to the *I. dammini* Spirochete in Confirmed Cases

	Treatment Category ^b			P(Fisher's Exact)	
	A Early Rx	B Late Rx	C No Rx	A vs. C	A + B vs. C
I. Seroconversion or fourfold change ^c	8/18	5/8	16/19	.012	.016
II. Convalescent antibody (no acute tested) ^c			2/2		
III. I and II ^c	8/18	5/8	18/21	.007	.009

^aIndirect immunofluorescent method of Burgdorfer et al. [3]

^bA. Early treatment = received PEN or TET < 10 days after onset

B. Late treatment = received PEN or TET > 10 days after onset

C. No treatment = did not receive PEN or TET or related antibodies

^cPositive observations/total observations

We evaluated the effects of penicillin and tetracycline therapy on the development of antibodies to spirochetes by comparing results of serologic testing of confirmed LD patients who received penicillin or tetracycline early (less than ten days after illness onset) or late (more than ten days after illness onset) to those to whom antibiotics were not administered (Table 3). The late therapy data are too small to evaluate individually. However, 8 (44.4 percent) of 18 patients who received early penicillin or tetracycline and 13 (50 percent) of 26 patients who received early or late therapy, developed antibodies to spirochetes as compared to 18 (86 percent) of 21 who received no therapy ($p = .007$ and $.009$, respectively, Fisher's exact test).

Geographic Distribution of Cases and Entomologic Studies

The case definition used in this study depends on knowledge of exposure to a known endemic area to categorize cases. The distribution of the confirmed cases by county of documented or likely tick exposure is depicted in Fig. 1A. Such exposures were noted in 22 counties. The high prevalence of exposure in the northwest portion of Wisconsin corresponds geographically to the known distribution of *I. dammini* and to the origin of early reports of LD in Wisconsin. The difference in distribution of county of residence of these same confirmed case patients (Fig. 1B) is generally due to travel to or military training in endemic areas with individual onsets of illness often noted after return to home. Among confirmed cases, the county of residence differed from the county of known or likely tick exposure in 26/77 (34 percent) cases. However, only 16/77 (21 percent) of confirmed cases resided outside of areas where *I. dammini* is currently known to be present in Wisconsin. The counties of tick exposure in probable or possible cases (Fig. 1C) are more widely geographically dispersed.

The tick surveys conducted in 1979–82 during the autumn deer-hunting seasons have defined the distribution of *I. dammini* in Wisconsin and therefore potential areas for risk of LD in the state. Cumulatively, these surveys have permitted two types of comparisons. The first is a comparison of acarologic findings at three widely geographically separated locations in western Wisconsin (Table 4). In this component, *Dermacentor albipictus* represents a geographically established tick that can be found on deer in late autumn and winter and thus can be used for comparative purposes. Generally, from 1979 to 1981 there were increases in the percentage of deer examined on which one or more *I. dammini* were found, a decrease in the percentage of deer with one or more *D. albipictus* found in any stage, an increase in the mean number of *I. dammini* per deer, a large increase in the percentage of *I. dammini* among total ticks collected, and a reversal in the ratio of *I. dammini* to *D. albipictus* found in any stage on deer examined. This suggested that the density of *I. dammini* in western Wisconsin was increasing and that this increase may have covered a broad geographic area; however, specifically at the west central study sites, this trend was not noted. A confirming trend was not noted when 1982 survey data was compared to 1981 data; in fact, we observed a reduction in the density of *I. dammini* in 1982 in relation to 1981. However, a relative trend was noted to continue when comparing 1979 data to 1982 data.

The second comparison involved the 1981 and 1982 surveys at observation sites selected for a statewide representative geographic distribution (Fig. 2). Based on *I. dammini* density data, the state could be divided into three regions. The northwest (region I) was the region of highest density, the Wisconsin River Valley (region II) was the region of intermediate *I. dammini* density, and the rest of the state (region

TABLE 4
Wisconsin Tick Survey, November 1979 and November 1981: Comparison of Survey Data Utilizing Geographically Comparable Sites

	Geographic Location of Site							
	Southwest		West Central		Northwest		Total	
	1979	1981	1979	1981	1979	1981	1979	1981
Number of deer examined	18	50	35	52	75	50	128	152
% with <i>I. dammini</i> (ID)	11	36	34	15	23	64	24	38
% with <i>D. albipictus</i> (DA)	61	12	71	31	71	48	70	30
Mean ID/deer (\pm SD)	0.1 \pm .32	3.3 \pm 6.24	2.3 \pm 6.64	0.5 \pm 1.54	0.6 \pm 1.52	2.9 \pm 4.02	1.0 \pm 3.72	2.2 \pm 4.50
Mean DA/deer (\pm SD)	3.1 \pm 3.95	0.3 \pm 1.07	8.9 \pm 10.38	1.3 \pm 4.30	6.7 \pm 13.53	1.2 \pm 1.81	6.8 \pm 11.87	0.9 \pm 2.81
% ID of total ticks	4	92	20	27	8	72	13	71
Ratio ID/DA	0.04	11.71	0.25	0.38	0.09	2.53	0.14	2.44

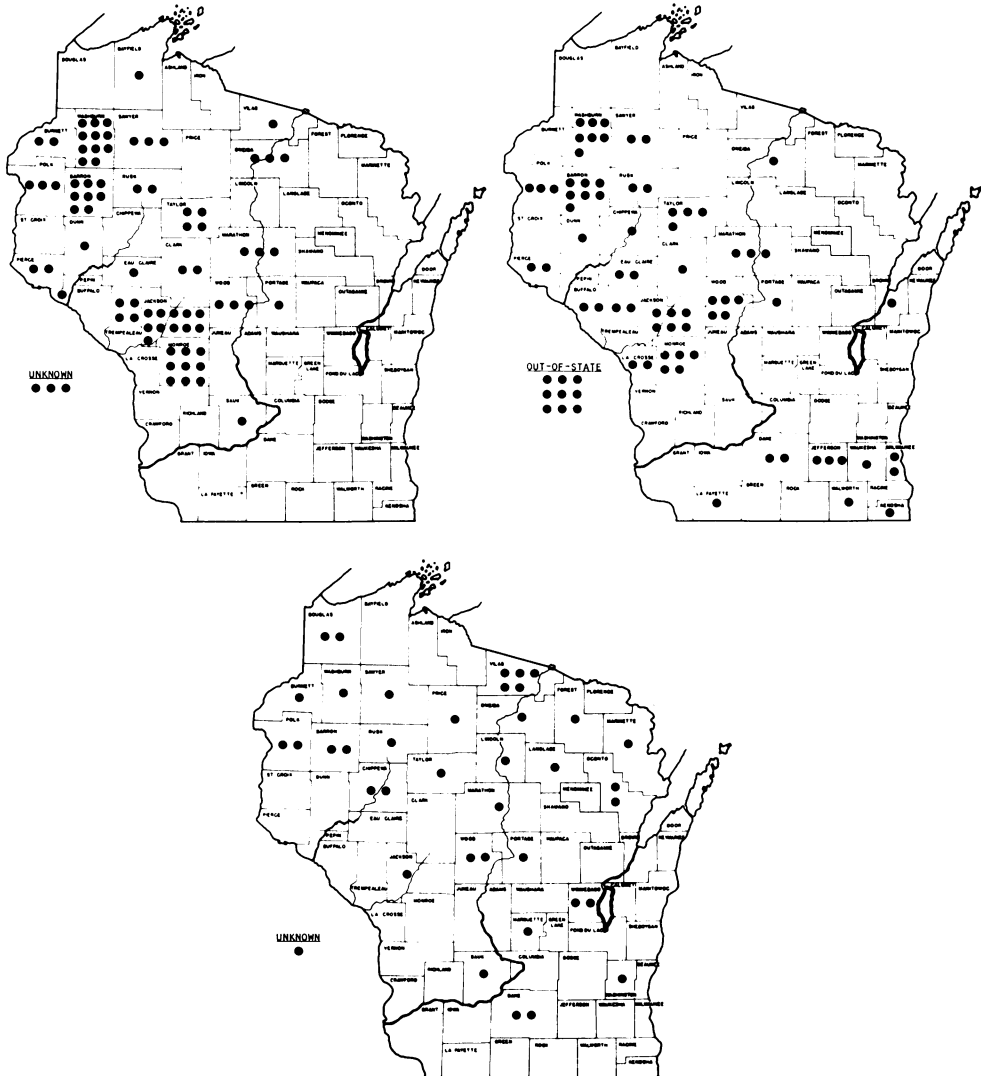


FIG. 1. County of tick exposure and county of residence for confirmed, possible, and probable cases of Lyme disease; Wisconsin, 1980–1982. (above left) A. County of tick exposure for confirmed cases only; Wisconsin, 1980–1982. (above right) B. County of residence for confirmed cases only; Wisconsin, 1980–1982. (below) C. County of tick exposure for probable and possible cases only; Wisconsin, 1980–1982.

TABLE 5
Wisconsin Tick Survey, November 1981 and November 1982: Comparison of Mean Densities of *I. dammini* (ID) per Deer by Region Utilizing Geographically Comparable Sites

Region ^a	1981		1982	
	No. of Deer	Mean ID/Deer (\pm SD)	No. of Deer	Mean ID/Deer (\pm SD)
I	127	2.32 \pm 3.51	141	0.58 \pm 1.61
II	189	0.88 \pm 3.50	209	0.23 \pm 0.75
III	121	0.01 \pm 0.09	134	0.01 \pm 0.09

^aRefer to Fig. 2.

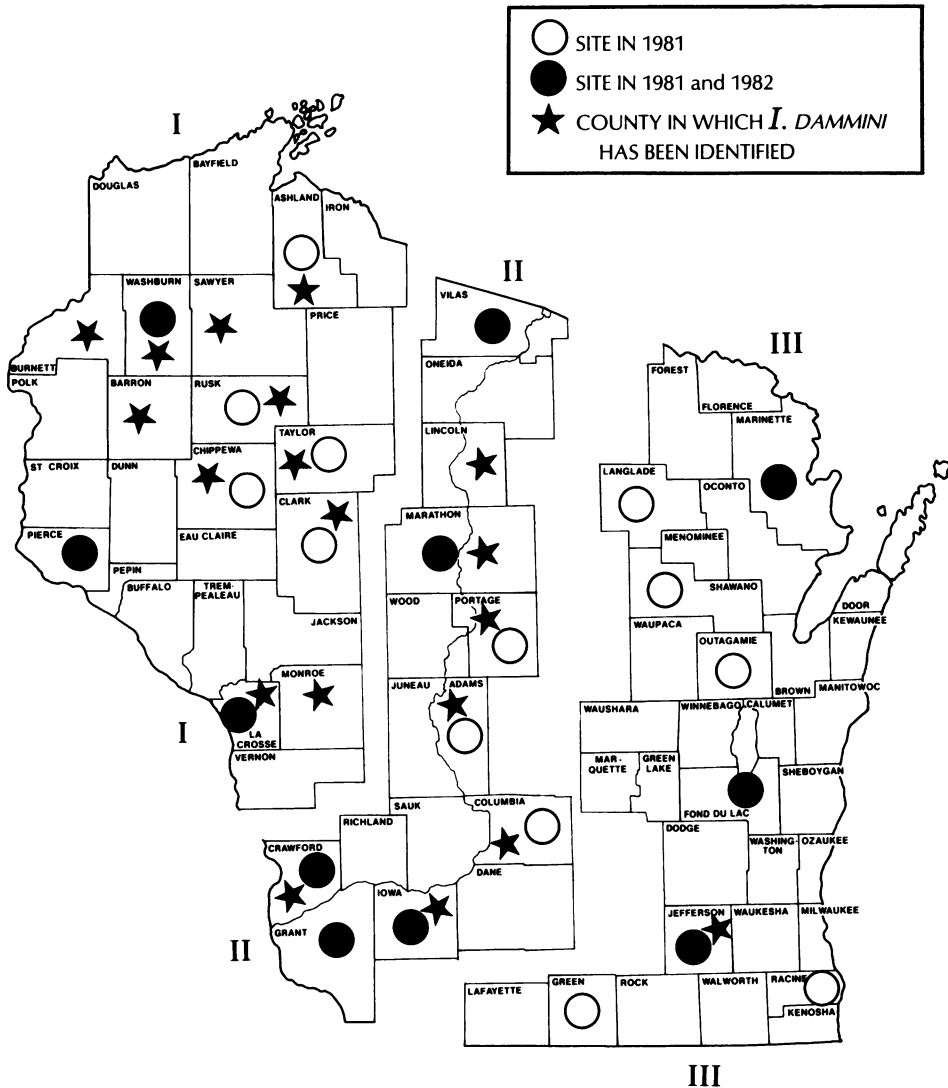


FIG. 2. Wisconsin tick survey, November 1981 and November 1982; distribution of study sites by region and distribution of counties in which *I. dammini* has been identified.

III), had a virtual absence of *I. dammini*. While the relative differences in *I. dammini* densities between regions were the same in 1981 and 1982, the actual density by region decreased from 1981 to 1982 (Table 5).

DISCUSSION

Lyme disease and its vector have been present in Wisconsin for at least 15 years. The 1968 case report of ECM in the grouse hunter in Wisconsin conforms to the case definition of confirmed LD used in this study. In addition to having ECM, joint, and neurologic abnormalities, the patient had a history of a tick bite in Taylor County prior to onset of illness [9]. The northern variety of *I. scapularis*, now reclassified as *I. dammini* [15], was documented to be present in Taylor County during

an acarologic study conducted in 1968 [16]. All ticks collected in the 1968 study have been reclassified as *I. dammini* [Dr. Andrew Spielman: personal communication]. While both the disease and the vector had been documented in Wisconsin as early as 1968, and were again recognized in 1978, the magnitude of the LD problem in Wisconsin during the intervening ten years is unknown. In addition to the early recognition of *I. dammini* and ECM in Wisconsin, the breadth of the area in which *I. dammini* currently can be found in Wisconsin is considerable, approximately 36,240 square miles.

Data presented in this report represents a continuum of LD and acarologic surveillance in Wisconsin at first limited to northwestern and west central Wisconsin and then expanded to a statewide effort by 1981. All reports of human disease were obtained by use of a heightened passive surveillance system in which clinicians were frequently reminded of the condition and apprised of available resources, but were not called regularly to stimulate new reports of illness. In addition, we screened reports of clinical illness accompanying specimens to be tested at the SLH for a variety of rash illnesses, and for illnesses suggestive of meningoencephalitis, carditis, or arthritis. Our series might thus include a disproportionate number of complicated cases and not be fully representative of LD as it occurs in Wisconsin. However, the demographic features, seasonal occurrence, and distribution of clinical signs and symptoms in this series are very similar to those initially reported by Steere and colleagues [1,2]. More exhaustive studies of early clinical manifestations of disease published subsequent to the time that our study was conducted provide a definitive, comprehensive listing and discussion of early signs and symptoms of LD [17].

As stated, the case definition in this study did not include a criterion for laboratory confirmation in order to evaluate the accuracy of clinical criteria in relation to serologic findings. The high rate of development of antibodies to the Shelter Island isolate of the *I. dammini* spirochete among confirmed cases and the virtual absence of antibodies among ill controls who clearly did not have LD, provide additional data to support the spirochetal etiology of LD. (Much of this study was conducted prior to reports of isolation of the spirochete from clinical material obtained from LD patients [4,5] which provide the most compelling and definitive etiologic evidence.)

Some patient sera may have lacked an antibody response for any of several reasons. Spirochete strains present in ticks along the eastern seaboard may show antigenic variations from those in Wisconsin. If cross-reactivity between the strains is indeed incomplete, it is possible that serologic confirmation of Wisconsin LD infections may be missed by using the Shelter Island antigen. This issue can be resolved by testing of patient sera against a Wisconsin-derived spirochete and by comparative antibody studies on a variety of (human- and non-human-derived) *I. dammini* spirochete strains obtained from a variety of regions in the United States, Europe, and elsewhere. Regional differences in *I. dammini* ticks might be another factor that could modify spirochete activity and alter infectivity in humans or other mammals. Differences in microbial symbiotes known to be present in ticks [18] could theoretically affect virulence or transmissibility.

Another factor bearing on the antibody response is antibiotic therapy. Steere et al. have shown that penicillin and tetracycline therapy can significantly shorten the duration of ECM and its associated symptoms and prevent or attenuate the subsequent arthritis [19,20]. Our finding suggesting blunting of the specific antibody response to the spirochete with early and appropriate antibiotic therapy demonstrates that serologic diagnosis of LD may be difficult in treated cases. Fortunately,

ECM is an excellent clinical marker [17]; however, serologic evaluation becomes more critical in patients where ECM is missed or not present, additional manifestations of LD persist, and the patient may have received penicillin or tetracycline for treatment of the illness. The case definition did have proven utility as none of 18 non-case patients serologically evaluated had evidence of antibodies against the *I. dammini* spirochete.

The definition of an endemic region in the case definition used in this study was arbitrarily established as the region inclusive of counties in which *I. dammini* had been documented as of November 1981. The distribution of possible and probable cases in our study reflects the lack of accurate demarcation of the LD endemic region in the state and the circular nature of defining the endemic region based on the documentation of *I. dammini* in a given county.

The location and identification of *I. dammini* (*I. scapularis*, reclassified as *I. dammini*) in six Wisconsin counties in 1968 was thought at that time to be associated with potholes or depressions resulting from glacial outwash which are common in the northern lowland forests of Wisconsin [16]. The investigators did not document any *I. dammini* in the prairie hardwood forests of southern Wisconsin. If we consider comparable sites of tick collection from 1979 to 1982, the most striking result is the number of *I. dammini* identified on deer in 1981 and 1982 as compared with 1979, particularly in southwestern and west central Wisconsin. This, along with the earlier acarologic observations in Wisconsin, would suggest that *I. dammini* is spreading in a southerly direction in Wisconsin. It is interesting to note that although *I. dammini* ticks have been identified in the southern third of Wisconsin, particularly in the western part of the state, very few cases of LD have been documented to originate in that region. The gradient of increasing *I. dammini* density as one moves from east to west in the state is notable; however, the ecologic factors that control this phenomenon have yet to be determined. It will take additional years of observation to fully understand the dynamics of *I. dammini* distribution and LD occurrence in Wisconsin.

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