My Disease

LYME DISEASE

TEXAS DEPARTMENT OF HEALTH

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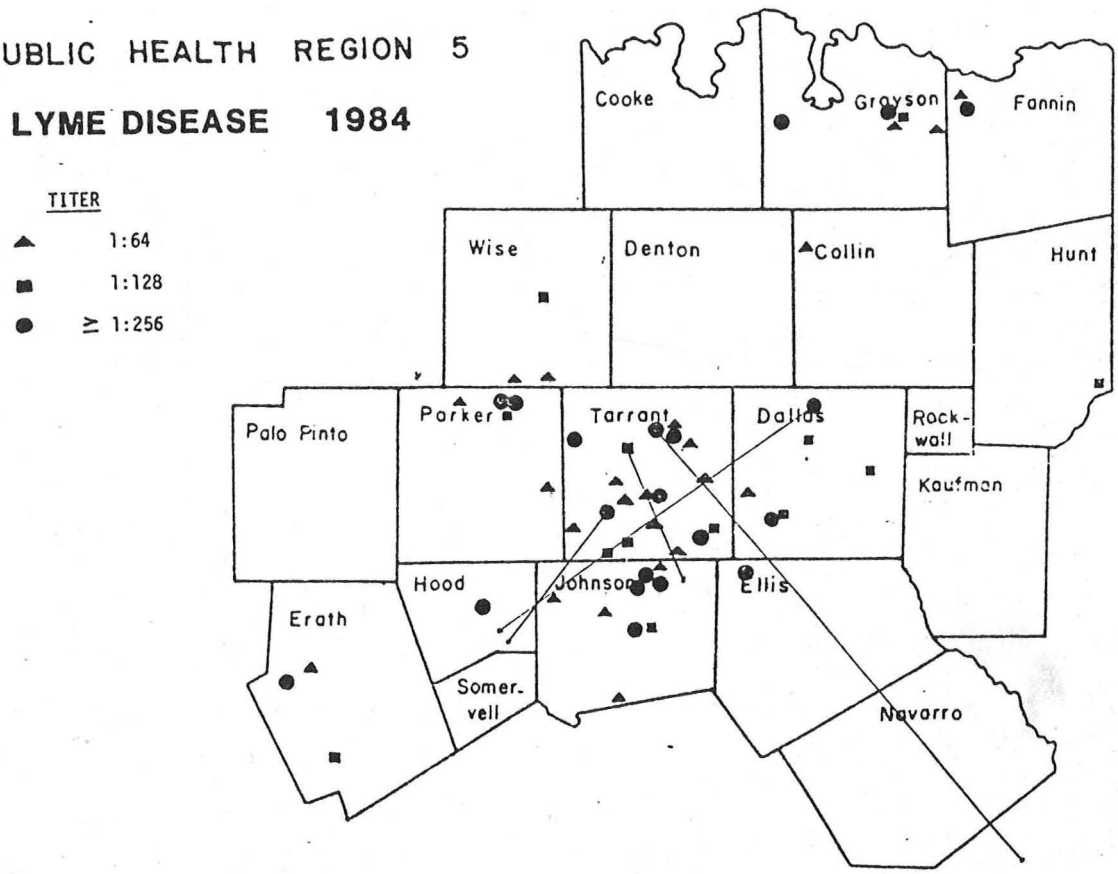
LYME DISEASE 1984



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INTRODUCTION

Lyme arthritis was first described in 1976 as an epidemic limited to three small communities situated east and at the mouth of the Connecticut River. Further characterization has revealed not only the clinical spectrum of the disorder, its infectious etiology, mode of transmission and optimal therapy, but also its world-wide distribution. The early reports clearly established the rheumatological aspects of the disease (1-10). With increasing experience in subsequent years, the multisystemic nature of Lyme arthritis became apparent. By 1979 it was rechristened "Lyme disease" (11-13). The methodical and scientific approach brought to this clinical problem by the Yale group led by Dr. Allen Steere along with numerous other U.S. investigators has combined a variety of immunologic, epidemiologic and molecular biologic techniques. Together these have elucidated the nature of a similar, if not identical syndrome first appreciated in Europe in 1909 (14). Because the chronic arthritis in some patients with Lyme disease resembles that seen in other more common arthritides, the approach used in elucidating the pathogenesis of Lyme disease has rekindled interest in the general relationship between infection and arthritis.

This review will encompass both the clinical description and epidemiology of this disorder, as well as the exciting experiments in which the etiologic agent was discovered and characterized. Because of new immunodiagnostic tests developed directly as a result of the identification of the etiologic agent in this disorder, a new awareness has arisen regarding the probability that Lyme disease or "Lyme-like" disease exists in Texas. The local experience therefore will be reviewed and contrasted with that described primarily by Steere and colleagues in their patients from the Northeast. Finally, an attempt will be made to relate clinical and pathogenetic aspects of Lyme disease to other more common forms of arthritis.

INITIAL DESCRIPTION

In 1975, two mothers from Old Lyme, Connecticut came forth to report to medical authorities at the State Health Department and the Yale Rheumatology clinic that an unusual clustering of individuals, mostly children had contracted a form of arthritis. The diagnosis of juvenile rheumatoid arthritis (JRA) was made in most of the pediatric cases. The number and clustering of the arthritis cases in this small community of 5,000 residents was unusual. Many lived close together, even on the very same roads. One of the mothers reported that she, her husband, two of their children and several neighbors were all affected with arthritis. This astounding epidemic came to the attention of Dr. Allen C. Steere, whose background in epidemiology at the Centers for Disease Control was brought to the fore. Thus began the first recognition of Lyme arthritis as a new entity (1,2).

The initial report by Steere et al described 51 residents of three contiguous Connecticut communities, 39 children and 12 adults (2). The annual peak incidence of cases was in the summer and early fall with the onset of the epidemic dating back to at least 1972. The arthritis was initially characterized as recurrent attacks of asymmetric swelling and

pain in a few large joints, especially the knee. Attacks were intermittent, lasting an average of 1 week, with episodes separated by several month periods. In the initial series of 51 cases, 25% had noted an erythematous papule that developed into an expanding red annular lesion approximately 1 month prior to the onset of arthritis. This characteristic rash was compatible with the entity called erythema chronicum migrans (ECM), described in the early 1900's in Europe where it has been shown to be transmitted by the sheep tick, Ixodes ricinus. In the Lyme patients the skin lesions lasted a median of 1½ weeks and were recurrent in 3 of 13 cases. One of the patients remembered having been bitten at the site of the skin lesion by a tick. This type of disease vector was consistent with the European ECM literature. The latter was also replete with description of associated neurologic manifestations (Bannwarth's syndrome or lymphocytic meningoradiculitis) and responsiveness of the skin lesion to penicillin (2). In contrast to the Lyme series, the European syndrome classically was not associated with arthritis. Subsequent cases of arthritis in association with ECM and neurologic involvement have been reported in Europe (15,16).

Steere and colleagues subsequently began a prospective study of 32 patients who were identified by the recent onset of erythema chronicum migrans, Lyme arthritis or both. In this second report (3), it was clear that skin involvement with or without joint involvement was more common than the development of arthritis alone. In this series, the skin lesions lasted about 3 weeks with approximately half of the patients developing more than one lesion. A minority of patients remembered tick bites at the site of the initial skin lesions, 4 to 20 days prior to their onset. Arthritis was present in 19 of the 32 patients. It was also clear in this report that 4 patients developed impressive neurologic abnormalities similar to those described by physicians in Europe, and 2 patients, in addition, developed myocardial conduction abnormalities of the atrioventricular node. Thus, by June, 1977, the full spectrum of Lyme disease was already appreciated and described. A characteristic sequence of symptoms and signs was noted in subsequent studies and has given rise to the division of Lyme disease into 3 stages (Tables 1,2),(17,18).

Table 1

LYME DISEASE: CLINICAL MANIFESTATIONS

STAGE 1	DERMATOLOGIC CONSTITUTIONAL
STAGE 2	CARDIAC NEUROLOGIC
STAGE 3	JOINT

Table 2

CHRONOLOGY OF LYME DISEASE

	Erythema Chronicum Migrans	Neurologic Symptoms	Cardiac Symptoms	Arthritis
Time of onset after tick bite				
Usual	2 wks	4 wks	5 wks	6 wks
Range	4 to 20 days	2 to 11 wks	3 to 21 wks	2.6 to 24 wks
Duration of symptom				
Usual	10 days*	3 wks	1 wk	8 days
Range	3 days to 1.5 yrs	2 to 32 wks	3 days to 6 wks	1 to 90 days
Recurrent episodes	Yes	Yes	No	Yes±

* Without penicillin or tetracycline treatment.

± Median number of attacks is three, range one to six, separated by remission of four weeks median duration.

CLINICAL FEATURES

Stage 1 Lyme Disease

A. Dermatologic Manifestations

1. Erythema chronicum migrans (ECM): In the review of 314 patients studied prospectively (19), a tick bite, recalled by 31%, was followed 3 to 32 days later (median, 7 days) by a gradual expansion of the redness around the papule. Particular sites of involvment included the thigh, groin and axilla. The maximum median diameter of the lesions rose to 15 cm., ranging between 3 and 68 cm. The lesions tended to have bright red outer borders, usually flat but occasionally raised, with partial central clearing that was flat. The lesions tended to look like a red ring. The center of the lesions occasionally became intensely erythematous and indurated, vesicular or necrotic. Occasionally, concentric rings were seen. Some lesions showed no central clearing. Approximately 50% of the patients described the lesion as burning or occasionaly pruritic and painful. Histologically, the skin biopsy showed dermal and epidermal involvement in the center of the ECM lesion, but only dermal changes at the periphery. Reports of ECM occuring in the U.S. in the absence of arthritis predated the description of Lyme disease (20-22).

2. Other skin manifestations: Approximately half the patients developed multiple annular secondary lesions within several days of the onset of the initial ECM leson. They tended to be smaller, migrated less, and lacked indurated centers. These lesions could occur anywhere except for the palms and soles. Thirteen percent of the patients were said to have a malar rash and 11% had conjunctivitis. In 55 patients not treated with antibiotics, the ECM and secondary lesions faded usually by 28 days, but could last as long as 14 months. In contrast, patients given antibiotic agents cleared their skin lesions within several days of therapy. Of the untreated patients, 9% had recurrences of ECM at the original site and 5% had recurrent secondary lesions. In contrast, antibiotic treated patients did not have recurrent skin involvement.

B. Early Signs and Symptoms

Nonspecific constitutional symptoms were prominent, including malaise, fatigue and lethargy in 80% of patients. Headache was present in 64% fever and chills in 59%, stiff neck in 48%, arthralgias in 48%, and lymphadenopathy in 61% of patients. In addition, myalgias present in 48% and backache in 26% were prominent symptoms. Fever tended to be low grade and intermittent but occasionally high, especially in children. True rigor was not observed, although chills were common. In addition to intermittent headache lasting hours, neck stiffness, mild encephalopathic changes with somnolence, memory difficulty and emotional lability and unusual clumbsiness were reported. Neck stiffness on examination was observed only on extreme flexion although Kernig's and Brudzinski's signs were absent. Spinal fluid examination during the first week of symptoms was normal. Approximately 10% of individuals had symptoms suggestive of hepatitis including anorexia, nausea, vomiting and right upper quadrant pain. Hepatomegaly was seen occasionally. All these signs and symptoms tended to be intermittent and rapidly changing over a period of several weeks, except for the constant fatigue and lethargy.

Stage 2 Lyme Disease

A. Cardiac Manifestations

Approximately 10% of patients developed cardiac abnormalities (23,24). Of 20 patients studied, 95% recalled previous ECM, 90% developed arthritis and 35% had neurologic involvement as well. Atrioventricular block was the most common feature. Whereas 98% of the patients showed 1st degree AV block, 40% Wenckebach block and 50% complete AV block, 38% required temporary pacemakers. Sixty-five percent of these patients showed more diffuse cardiac involvement, with ST segment depression or T wave inversion occuring in 55%, depressed left ventricular ejection fraction in 20%, cardiomegaly and pericarditis each in 5% of the patients. All cardiac involvement was transient, median duration less than one week, and did not recur.

B. Neurologic Manifestations

Approximately 11% of patients developed significant neurologic abnormalities (11,25-34). Most patients had a fluctuating course of symptoms, typically weeks to months, of meningitis and encephalitis. Affective and cognitive problems may be prominent but were usually mild. Rarely, movement disorders were seen (ataxia, chorea). Nearly one half of the patients had, in addition, unilateral or bilateral, Bell's palsy in association with recurrent meningoencephalitis. Occasionally, other cranial nerves were involved. Painful radiculopathies, peripheral neuropathy or mononeuritis multiplex were frequently superimposed. Transverse myelitis has been reported rarely. Neurologic signs and symptoms may mimic multiple sclerosis. Cerebrospinal fluid findings were consistent with an aseptic meningitis (lymphocytosis, normal glucose, normal to elevated protein and no bacteria). An increased IgG to albumin ratio and oligoclonal bands may be found. The presence of a CSF pleocytosis and lack of antibodies directed to neurons in Lyme disease help distinguish it from Guillain-Barré syndrome (29).

Stage 3 Lyme Disease

A. Joint Manifestations

1. Typical intermittent arthritis: As noted above, 50 to 60% of patients with ECM will develop transient, intermittent episodes of either monoarticular, oligoarticular or migratory polyarticular arthritis lasting up to a week, with disease free intervals of 4 weeks or more (2,8,9). The knee was most commonly affected in this form of arthritis, followed in decreasing order of frequency by the shoulder, elbow, temporomandibular joint, ankle, wrist, hip and small joints of the fingers and toes (Figure 1). The tendency to progress to less frequent but more sustained attacks has been noted.

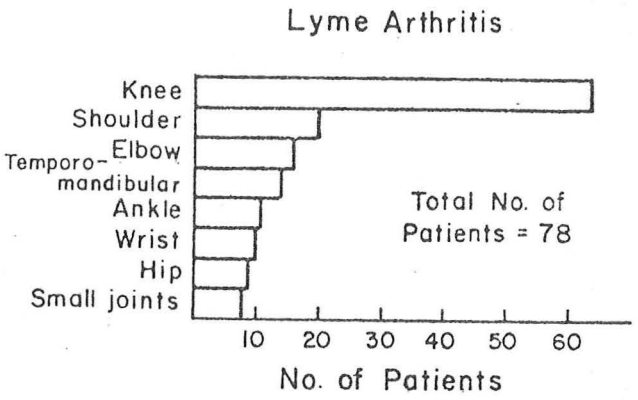

Figure 1
The frequency of joints involved in 78 patients with Lyme arthritis is seen. The knee, other large joints, and the temporomandibular joint are most often affected.

Figure 1 © AC Steere, JA Hardin, SE Malawista. Conn Med 42:353-357, 1978. Connecticut State Medical Society.

2. Chronic Lyme arthritis: Ten of 102 patients with Lyme arthritis developed joint involvement in the knees that had lost its typical intermittent character and had become chronic (9). Most of these patients had experienced short recurrent attacks for periods up to 24 months before developing a chronic pattern. Either one or both knees were involved. The knees were often intensely swollen with hypertrophied synovium that was palpable. The joints, however, were not as painful as might appear to the examiner. Thirty percent of the patients developed popliteal cysts that tended to dissect into the calf with the appearance of pseudothrombophlebitis. This complication of chronic knee effusions is not uncommonly seen in rheumatoid arthritis. However, in other respects, these patients denied morning stiffness and were negative for rheumatoid factor except in one patient. Joint fluid was typically inflammatory. White blood cell counts ranged widely, however, from 500 to 76,800 cells per mm^3, predominantly polymorphonuclear leucocytes. Synovial fluid total protein levels were elevated whereas C3 levels low. Cryoglobulins were present in all the joint fluids but in only 3 of the 10 sera. Only one patient had x-ray evidence of boney erosions in the femoral notch, confirmed at surgery one year after the onset of persistent involvement. Seven of the 10 patients had the HLA marker DR2, formerly called DRW2, compared to 22% of the normal population (9,35). Five of the patients with marked functional limitations had anterior synovectomies. Histologically the removed inflamed synovium showed pannus formation and underlying cartilage erosion. The synovial cells actively secreted prostaglandin E_2 and collagenase which have been implicated in the joint pathology of rheumatoid arthritis (43). Post-surgically, 4 of the 5 patients required additional manipulation of adhesions under anesthesia followed by prolonged physical therapy. However, all the knees remained non-inflammatory since surgery for periods up to 32 months. Whereas histologically the synovium resembled that seen in rheumatoid arthritis, these two entities are clearly distinguishable by clinical and laboratory features (Table 3). Of note, the predominant HLA associated predisposition in rheumatoid arthritis is DR4.

Table 3

COMPARISON BETWEEN LYME ARTHRITIS AND RHEUMATOID ARTHRITIS

CHARACTERISTIC	LYME ARTHRITIS	RHEUMATOID ARTHRITIS
PANNUS	YES	YES
BONE EROSION	OCCASIONAL	COMMON
LARGE JOINTS	COMMON	COMMON
SMALL JOINTS	RARE	COMMON
AM STIFFNESS	NO	YES
RHEUMATOID FACTOR	NO	YES
HLA	DR2	DR4

LABORATORY FEATURES

A. Early Findings

The commonest non-specific laboratory abnormalities were a high erythrocyte sedimentation rate, seen in 53% of the patients, an elevated serum IgM level in 33%, and an increased aspartate transaminase level in 19% (19). The creatine kinase was normal, but the alanine transaminase and lactate dehydrogenase also tended to be increased. The abnormalities returned to normal within a few weeks. Twelve percent of the patients were mildly anemic when first seen, but no evidence of hemolysis was noted. Only 8% had elevated leucocyte counts with shifts to the left in the differential count. Six percent had microscopic hematuria for up to 2 weeks, with occasional mild proteinuria, but normal values for creatinine and blood urea nitrogen. Antinuclear antibody and rheumatoid factor were almost always absent. Serum complement levels(C3, C4 and CH50) were normal.

B. Cryoglobulins and Circulating Immune Complexes

Nine of twenty patients with active arthritis in Steere's original study (4) had low serum concentrations of the third component of complement (C3). Because of this finding, it was hypothesized that circulating immune complexes may be involved in the pathogenesis of the arthritis. Cryoglobulins, i.e., cold-induced precipitable immunoglobulins, have often been used as a screen for circulating immune complexes. Thirty patients were studied who had either active skin disease, active joint

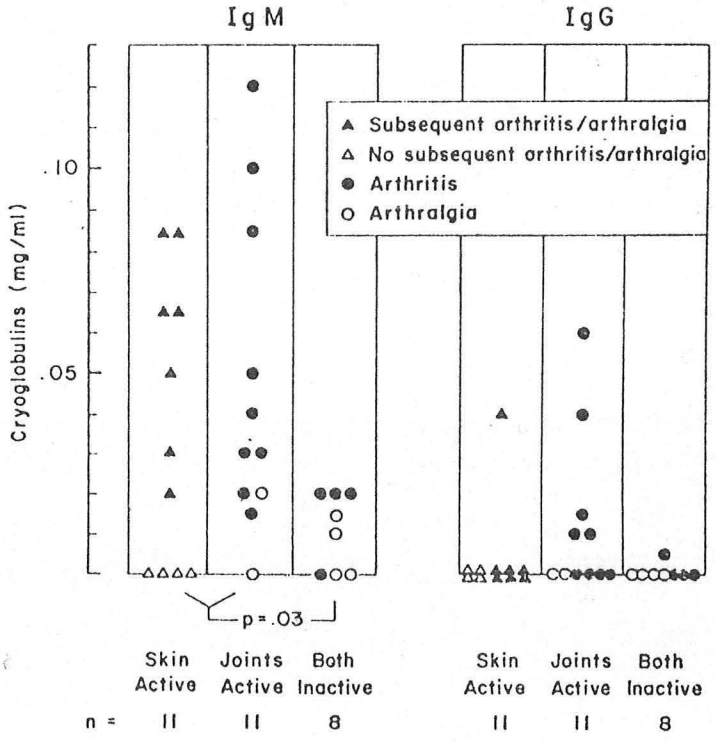

Fig. 1. Each point represents cryoglobulin from the initial serum of each of 30 patients with (i) active erythema chronicum migrans ("skin active," 11 patients), (ii) active arthritis following the skin lesion ("joints active," 11 patients), or (iii) previous skin and joint lesions, the latter inactive for 1 to 3 months ("both inactive," eight patients).

Figure 2 © AC Steere, JA Hardin, SE Malawista. Science 196:1121-1122, 1977, American Association for the Advancement of Science.

disease with resolved skin lesions, or those with inactive skin and joint lesions (4). As can be seen in figure 2, seven of the 11 patients with active skin lesions had cryoimmunoglobulins, and all seven subsequently developed arthritis. The four individuals without cryoglobulins did not develop arthritis subsequently. Ten out of 11 patients with active arthritis or arthralgia had cryoglobulins. The cryoglobulins in patients with active skin lesions consisted primarily of IgM, while those of patients with arthritis often had both IgM and IgG. Of some interest was the lack of detecting C3 or C4 in these cryoprecipitates.

Steere, et al reported a second series of patients in whom serum cryoglobulin levels were correlated with disease activity (8). Eighty-seven percent of patients with active ECM that was followed by subsequent neurological or joint involvement initially had cryoglobulins containing IgM, compared to only 13% of those patients who had active ECM, but no later symptoms. This study involved 48 patients with ECM followed prospectively in whom 26 patients developed no later symptoms, but 22 did develop arthritis and 9 neurologic complications.

Those individuals with IgM cryoglobulins had significantly lower serum C3 and C4 levels, although the complement levels were usually within the low-normal range. Sixty-seven percent of patients at the height of subsequent neurologic disease continued to have serum cryoglobulins, while 45% of patients continued to have cryoglobulins when their joint involvement was most severe. Only 11% of individuals in remission had positive tests for cryoglobulins. With time, the persistence of cryoglobulins in the serum of arthritis patients with active joint disease tended to wane. However, the cryoglobulins in joint fluid remained positive throughout the course. Of note, the amount of IgM in the cryoglobulins correlated directly with serum IgM.

The Yale group led by Hardin, et al (36) investigated in a more direct manner serum and joint fluid immune complex levels in patients with Lyme disease. Immune complexes detected by the C1q binding and C1q solid phase assays were positive in 45% of patients with ECM. Again, serum complement levels were within normal range even in these patients with positive tests for circulating immune complexes. A tendency to correlate C1q binding activity with cryoglobulin levels and activity of disease in the nervous system, heart and joints, was suggested by a case study.

A subsequent more complete analysis of 78 patients (37) revealed that abnormally high serum C1q binding activity was present in virtually all cases with ECM. Circulating immune complexes persisted in those patients who had subsequent nerve and heart involvement, whereas after three months in those with only arthritis, the complexes disappeared from the serum. However, as seen with the cryoglobulin determinations, and noted above, C1q binding activity persisted in the joints (Figure 3). This second study revealed additional information regarding the

relationship between cryoprecipitates and immune complexes. Cryoglobulin levels were good, but insensitive predictors of the presence of immune complexes. The C1q binding assays, but not the Raji cell assay were far more sensitive. This study also determined that immune complexes persisted in the sera of patients with neurologic disease, in contrast to cryoglobulins, which resolved with time in these individuals. It appeared from the study that the immune complexes themselves were not responsible for the cryoprecipitability of serum in that levels of significant C1q binding activity were found in sera lacking cryoprecipitability, and certain cryoprecipitable sera lacked C1q binding activity. Of note, is the fact that only 26% of the total cryoprecipitable protein was of an immunoglobulin nature, and the composition of the rest of these cryoprecipitates remains to be determined.

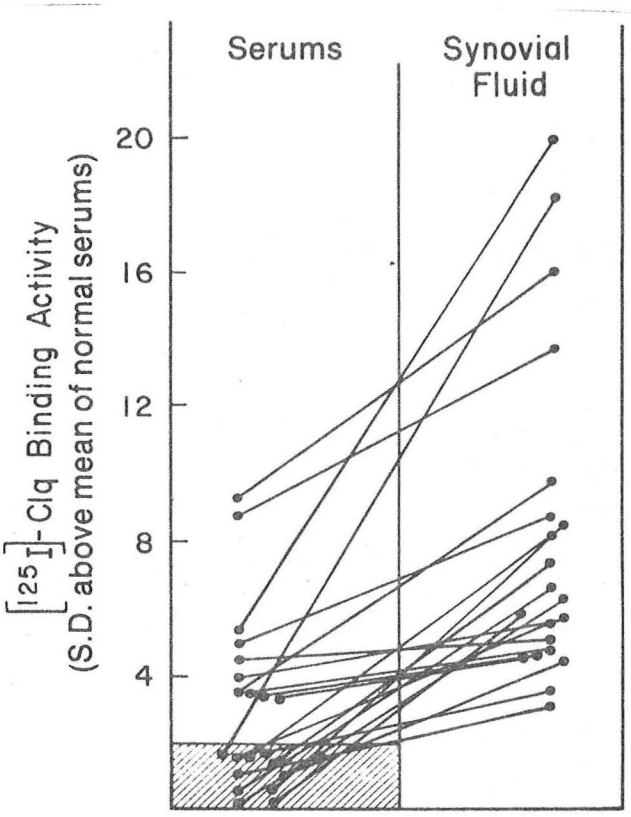

Figure 2. Comparison of Serum and Synovial-Fluid C1q Binding Activity.

The C1q binding activity of 21 corresponding serum and synovial-fluid samples from 12 patients is shown. The shaded area denotes the range of normal. Abnormal C1q binding activity was present in all the synovial fluids but in only about half the serums. Moreover, synovial fluid always bound more C1q than did serum.

Figure 3 © JA Hardin, AC Steere, SE Malawista. N Engl J Med 301:1358-1363, 1979. Massachusetts Medical Society

In summary of these tests, circulating immune complexes appeared to be more sensitive indicator of ongoing activity. The investigators

strongly suggested that these components of sera and joint fluid are responsible for much of the organ system involvement that typifies active Lyme disease.

EPIDEMIOLOGY

The marked seasonal and geographic clustering of cases of Lyme disease suggested the probability of an infectious agent. Of 39 affected children initially studied, 17 lived on four country roads where one in 10 had the illness, and six families had more than one affected member. This seasonal clustering suggested transmission of an agent by an arthropod vector. The finding of erythema chronicum migrans, as described above, was also suggestive of an arthropod vector and several of the patients related the onset of the lesion to an antecedent bite.

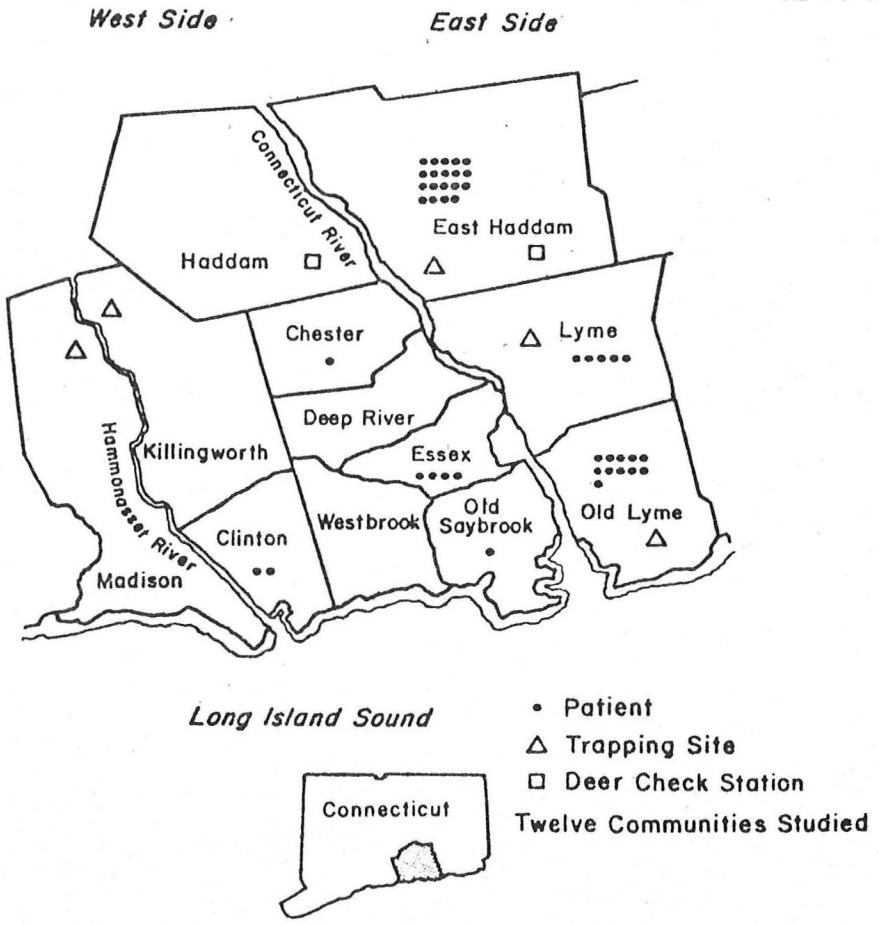

FIGURE 1. Map of the study area in southcentral Connecticut with locations of the mammal trapping sites and the deer check stations in the nine west communities and the three east communities.

Figure 4 © RC Wallis et al. Am J Epidemiol 108:322-327, 1978. The Johns Hopkins University School of Hygiene and Public Health.

The initial complete report by Steere, et al (2) contained serologic evidence that failed to implicate recent infection with numerous of viruses and other microorganisms. The Yale group then went on to identify specifically the vector for this disease in an effort to secure access to the presumed infectious agent (38). One patient produced a tick associated with his skin lesion and it was identified as Ixodes scapularis. Patients were noted to have significantly greater number of cats and farm animals and had noted ticks on their pets and tick bites on themselves.

The incidence of Lyme disease was thirty-fold more on the east side of the Connecticut River compared to the west side (38). A concomitant field study of ticks (39) revealed that Ixodes scapularis was much more abundant on the east side of the Connecticut River than the west, 13 times more abundant on white-footed mice and 16 times more abundant on white-tailed deer (Figure 4). In addition, all active stages of the life cycle of this tick were found on humans in the east communities of Lyme, Old Lyme and East Haddam. Because of distinct entomologic differences between Ixodes scapularis and the tick transmitting Lyme disease, the latter was renamed Ixodes dammini, after Dr. Gustave J. Dammin, of Harvard Medical School (40). Steere and Malewista reported a striking correlation with the natural distribution of Ixodes dammini and Lyme disease, not only in Connecticut and other parts of New England and Long Island, but also in the upper Midwest (12). In addition, cases in Oregon and California were correlated with the presence of a similar vector called Ixodes pacificus.

A current hypothesis (Dr. A.C. Steere, personal communication) contends that Lyme disease was introduced to the Northeast U.S. by a migration of deer in the 1920's. The native deer population on the East Coast had become extinct by the early 1900's and the government sponsored a repopulation on the that region with deer herds from Wisconsin. It is thought that the spirochete and Ixodes dammini ticks may have been introduced along with this migration.

By 1982, cases of Lyme disease had been reported from 38 states, as well as Australia, Switzerland, Germany, France and Sweden (15-17, 28,41-67)). More recently, Amblyomma americanum, another hard tick, also called the Lone Star tick, was identified as a vector for Lyme disease in New Jersey (68).

TICKS AND TICK ASSOCIATED DISEASES

Ticks are of two basic types (69). The Ixodidae, or hard ticks, attach for prolonged periods to hosts, but are not usually felt at the time of feeding. Lesions after the bite are frequent and associated with an inflammatory response. The ticks transmitting Lyme disease invariably have been of this type. The other major class of ticks are the Argasidae, or soft ticks, which mainly feed for brief periods and often at night. Of note to physicians in Texas, relapsing fever or borreliosis, is transmitted by a soft tick, whereas Rocky Mountain Spotted Fever, a rickettsial disease, is transmitted by the hard tick, Dermacentor variabilis, the American Dog tick. Table 4 outlines common ticks and the diseases with which they are associated.

Table 4

TICKS AND TICK ASSOCIATED DISEASES

DISEASE	SPECIES	COMMON NAME
Lyme	Ixodes dammini	-
	Ixodes pacificus	-
	Ixodes scapularis	blacklegged tick
	Ixodes ricinus	sheep tick
	Amblyomma americanum*	Lone star tick
	Amblyomma maculatum*	Gulf coast tick
Rocky Mountain Fever	Dermacentor variabilis*	American dog tick Spotted
Relapsing Fever	Ornithodoros hermsi	-
Boutonneuse Fever	Rhipicephalus sanguineus*	Brown dog tick

*Suspected, but not proven to transmit Lyme disease in Texas

TREATMENT OF LYME DISEASE

Because of the reports from Europe claiming that penicillin treatment lessened the course of erythema chronicum migrans, antibiotics were given to Lyme disease patients in America.

Reports by Mast and Burroughs (70,71) revealed not only resolution of the ECM with penicillin or erythromycin, but prompt relief of a monoarticular arthritis with penicillin. More extensive studies were carried out by Steere, et al, who initially reported in 1980 (13) that ECM responded to either penicillin or tetracycline, lasting 4 and 2 days, respectively, whereas in untreated patents it lasted a median of 10 days. Erythromycin, of note, had no effect on the course of ECM in this series. Patients were treated with penicillin-G, 250,000 units four times a day; a significant protection from the development of subsequent arthritis, although not absolute, was seen. In the patients given tetracycline, none developed neurologic involvement subsequently, in comparison to such sequelae in both oral penicillin and no-treatment groups. However, the number of individuals treated with tetracycline was too small to show a statistically significant protection.

This latter protective effect of tetracycline with regard to neurologic, cardiac, and joint sequelae was reported subsequently (72). None of 39 patients given tetracycline developed later complications, i.e., stage 2 or 3 disease, compared to three of 40 penicillin-treated patients and four of 29 erythromycin-treated patients. Thus, by 1982 it was clear that tetracycline, 250 mg four times a day, for a ten day course, given during erythema chronicum migrans (Stage 1 disease), was protective in all cases, and was, therefore, the drug of choice for the treatment of the early manifestations of Lyme disease (Table 5).

Table 5

OUTCOME OF TREATMENT IN PATIENTS WITH ERYTHEMA CHRONICUM MIGRANS

	Children	Adults				
					1982	
	1980-1982 Penicillin (n = 27)	Penicillin (n = 40)	Erythromycin (n = 29)	Tetracycline (n = 39)	Tetracycline 10 days (n = 25)	20 days (n = 24)
No late disease	17	16	14	22	17	16
Minor late disease						
Facial palsy	1	1	1	0	1	0
Supraventricular tachycardia	0	0	0	1	0	0
Brief arthritis (< 2 weeks)	1	1	2	2	0	1
Musculoskeletal pain	5	20	11	14	8	7
TOTAL	7	20	11	17	8	8
Major late disease						
Myocarditis	0	0	0	0	0	0
Meningoencephalitis	1	1	2	0	0	0
Recurrent arthritis	2	2	3	0	0	0
TOTAL	3	3	4	0	0	0

Steere, et al have reported the successful treatment of recurrent neurologic syndromes in Lyme disease with high-dose intravenous penicillin, 20 million units per day, for a ten day course (73) (Table 6). Similarly, Steere reported recently the successful treatment of chronic Lyme arthritis with this same intravenous penicillin regimen (74). An alternate regimen of oral tetracycline 500mg g.i.d. for 30 days was recommended for patients allergic to penicillin. Since tetracycline is contraindicated during childhood, alternative regimens have been recommended by Steere, et al (Table 7).

Additional studies by the Yale and other groups have also employed the antimalarial agent, hydroxychloroquine and corticosteroids. Hydroxychloroquine had a beneficial effect in one patient with Lyme arthritis (75). Prednisone has also been used, particularly for neurologic involvement, and has been shown to be far less effective in ameliorating the painful symptoms associated with radiculoneuritis than was penicillin (73). Motor deficits, however, took up to six to eight weeks to resolve with either high-dose intravenous penicillin, or prednisone therapy, presumably due to delay in remyelination of the affected nerves (Table 6). The Yale group has advocated the use of steroids acutely within 24 hours of onset of the development of Bell's palsy, in addition to antibiotics. However, it is unlikely that individuals correctly diagnosed during Stage 1 disease and treated with tetracycline will require either high-dose penicillin or steroids.

The efficacy of treating Lyme disease with antibiotics is powerful evidence to suggest the involvement of an antibiotic-sensitive infectious organism in the etiology of the disorder. While viruses were suspected early on (2), this telling and consistent experience of patients responding to antibiotics led to subsequent studies that have succeeded in identifying the causative agent in this desease.

Table 6

RESULTS OF TREATMENT

	Patients Treated with Penicillin	Patients Treated with Prednisone	p Value
Duration from treatment to resolution (mean ± SD), wks.			
Neurologic pain (headache, stiff neck, or radicular pain)	**1 ± 0.5**	**29 ± 11**	**0.000001**
Motor deficits due to cranial or peripheral neuropathy)	**8 ± 10**	**7 ± 9**	**NS**

Table 7

LYME DISEASE: TREATMENT RECOMMENDATIONS

Stage	Adults	Children
1	Tetracycline 250 mg P.O. q.i.d. ≧10 days (up to 20 days if sx persist or recur)	Phenoxymethyl Penicillin 50 mg/kg/day (divided) (≧ 1 g/d ≦ 2g/d) for 10 days or *Erythromycin 30mg/kg/d (divided) for 15-20d
2 or 3	**Penicillin G 20 million units/d I.V. for 10 days or *Tetracycline 500 mg P.O. for 30 days	No specific recommendations other than for adults available in the literature

*For penicillin-allergic individuals **Brief course of prednisone for acute Bell's palsy

IDENTIFICATION OF THE ETIOLOGIC AGENT IN LYME DISEASE

In November 1981, Dr. Willy Burgdorfer of the Rocky Mountain Laboratories of the National Institute of Allergy and Infectious Diseases, discovered the etiologic agent of Lyme disease (76). Adult Ixodes dammini ticks were collected and dissected. Seventy-seven of 126 ticks contained spirochetes distributed mainly in the midgut, but occasionally also seen in their hindgut and rectal ampulla. These organisms stained well with Giesma. They moved sluggishly on wet mount preps examined by darkfield microscopy. On electron microscopy, fine structural features were appreciated and recorded. Using a modified Kelly's medium, the Ixodes dammini spirochete was grown in culture.

In addition to the identification of the spirochetes in the well established tick vector, this study by Burgdorfer et al reported two other significant observations (76). First, infected ticks were allowed to feed on New Zealand white rabbits who after 10-12 weeks developed lesions resembling erythema chronicum migrans. Histologic sections and culture of biopsy material from the skin of these rabbits, however, did not reveal spirochetes. Second, an indirect immunoflorescence assay was designed to detect antibodies to the spirochetes in infected individuals. The sera of rabbits infected with ticks showed very high titers of antibody to the spirochetes. In addition, sera from patients with Lyme disease revealed significant titers of antibody to the spirochete.

This study revolutionized the area of Lyme disease reseach, demonstrating that the agent could be visualized and cultured, and that immunodiagnostic techniques were now available to study patients. In addition, the domestic rabbit appeared to be a suitable experimental model for study of Lyme disease. This paper was published in June of 1982.

On March 31, 1983, two papers demonstrated the isolation of spirochetes from patients with Lyme disease. Steere, et al were able to recover spirochetes in three out of 56 patients with Lyme disease (77). Positive cultures included one from blood, one from a skin biopsy, and one from cerebrospinal fluid. This study also recognized that the IgM antibody to the spirochete peaked between the third and sixth week after the onset of the disease, whereas specific IgG antibody rose more slowly, peaking months later in association with arthritis. High IgM levels were seen in most of the patients with ECM, whereas high IgG antibody was found during Stage 2 and 3 disease. Only three control patients with infectious mononucleosis had elevated IgM titers, whereas none of the controls had elevated IgG titers, specific for the Lyme spirochete. The authors concluded that the Ixodes dammini spirochete was the causative agent of Lyme disease. The other paper in the New England Journal by Benach, et al reported the isolation of spirochetes from the blood of two of 36 patients from New York who had Lyme disease (78). In both patients there was a rise in specific anti-spirochetal antibodies in several specimens of sera. The conclusion of this study was the same as the accompanying one by Steere, et al. A timely editorial reviewing the rapid progress made in Lyme disease research accompanied these two papers (79).

Additional studies in the dermatopathology literature have demonstrated spirochetes in the lesions of erythema chronicum migrans in patients (80,81). Spirochetes have subsequently been isolated from Ixodes ricinus ticks from Switzerland by Barbour et al (82), and from Amblyomma americanum in New Jersey by Schulze, et al (68) (Table 8). The natural reservoirs for the spirochetes in the animal kingdom have been determined (83). The preferred natural hosts of Ixodes dammini are the white-footed mouse and the white-tailed deer. Spirochetes were isolated from these animals on Shelter Island, New York. Five of 77 mice and nine of 12 deer showed spirochetemia.

Table 8

DISTRIBUTION OF TICKS CAPABLE OF TRANSMITTING LYME DISEASE

Tick	Location
Ixodes dammini	Northeast, Midwest U.S., Ontario
Ixodes pacificus	U.S. West Coast, Utah
Ixodes scapularis	U.S. East Coast, Southeast, Texas
Ixodes ricinus	Western Europe
Amblyomma americanum	New Jersey, Southern U.S., Texas

Similar studies were done in Connecticut (84). Spirochetes were isolated from a raccoon and a white-footed mouse. Ticks isolated from these animals revealed infected, unengorged, immature nymphs. This finding suggests the possibility that the spirochete is transmitted by transovarial passage without the need for feeding on an infected host for the tick to harbor the spirochete. The isolation of spirochetes from infected ticks has been facilitated by selective medium in which kanamycin and 5-fluorouracil are added to inhibit contaminant bacterial overgrowth (85).

The suitability of the New Zealand White rabbit as an animal model for Lyme disease has been extended recently by Burgdorfer (86), Benach et al (87) and Kornblatt et al (88), who were able to recover spirochetes in the blood of infected rabbits, either by intradermal innoculation with cultured spirochetes, or by infection with Ixodes dammini ticks harboring the spirochete. Lesions in these rabbits developed within 11 days of tick bite. Typical ECM lesions were not noted in a previous study (89), probably because of the fact that the ticks used were not infected with the spirochete.

CLASSIFICATION OF THE LYME DISEASE SPIROCHETE

Spirochetes comprise five genera, three of which are pathogenic for humans. These include Leptospira, Borrelia and Treponema. Morphologically, and by growth characteristics, the Lyme agent appeared to resemble Treponema and Borrelia more than the Leptospira. The Lyme agent has flagellae, resembling Treponema, whereas it grows in modified Kelly's medium like Borrelia. In order to characterize the infectious agent in Lyme disease more rigorously, DNA hybridization studies were performed in two laboratories and published simultaneously in August of 1984 (90,91).

Both studies came to the same conclusions, namely that the Lyme agent more closely resembles Borrelia than Treponema or Leptospira. This was shown by measuring the guanine and cytosine molar percentage in the DNA of Lyme disease spirochetes from various sources, as well as from representatives of the other types of spirochetes. With respect to the guanine and cytosine molar percentage, the Lyme disease spirochete most closely resembled Borrelia hermsii, the agent of relapsing fever. DNA hybridization studies also revealed that the DNA in the Lyme spirochete resembles that of the Borrelia hermsii to a greater degree than that of various species of Treponema or Leptospira. The study by Hyde and Johnson, in addition, reported the detection of plasmids (self-replicating cytoplasmic DNA fragments) in both Lyme disease spirochetes and North American Borrelia (90). It is possible that these plasmids code for functions that are important in determining the pathology seen in Lyme disease.

The spirochete isolated from Ixodes ricinus appeared in these DNA studies to be identical to that from Ixodes dammini, even though the clinical manifestations resulting from infections by these organisms appear to differ, particularly with regard to the degree of arthritis seen in infected individuals. Certainly they are the same species, but perhaps not identical. It is possible that variation in

extrachromosomal DNA might mediate effects that determine the difference in disease expression between these bacteria. In addition, a bacteriophage has been isolated in the Ixodes dammini spirochete and might be responsible for some of the toxicity induced during infection by this organism (92).

Finally, the Lyme disease spirochete has been officially named Borrelia burgdorferi because of the contributions made by Dr. Willy Burgdorfer in these series of studies (93).

The Western European Experience

As noted above, the spirochete-induced disease in Europe and the United States appears to differ in some respects. This may be explained by subtle differences in the DNA content between the bacteria, differences in the degree to which clinicians appreciate the arthritis in Europe, or the well established clinical use of penicillin in Europe for erythema chronicum migrans. The latter in Dr. Steere's studies clearly has the capacity to mitigate the development of arthritis. It is also possible that subtle changes in antigenic structure of the organisms may exist and this possibility will be discussed below. In addition, the predisposition toward the neurologic syndrome, meningoradiculitis, might well be preventable by the use of tetracycline but not by low dose oral penicillin.

Two other dermatologic conditions in Europe have been associated with Ixodes ricinus tick bites (94,95). These include lymphocytoma cutis of the ear lobe, particularly in children, and acrodermatitis chronicum atrophicans. Lymphocytoma cutis appears mostly as a red indurated ear lobe, whereas the second condition is a violaceous discoloration of the skin affecting especially distal upper extremities. Titers to the Lyme spirochete are very high in both of these conditions, as reported by Weber (86). Since these dermatologic complications are not seen in the United States, a different spectrum of disease may well be based on subtle differences between the Borrelia in European and United States ticks.

A difference in the specific neurologic syndromes on the two continents has also been noted (11). First, in Europe, cerebral involvement, i.e., encephalitis is rare, but in the Connecticut series it was common, though mild. It is possible that the subtle mental changes called encephalitis by the Yale group were merely ascribed to the meningitis in the European cases. Second, European reports have not emphasized the recurrent nature of the meningoencephalitis. Third, the radicular pain in European but not in U.S. cases was associated with the dermatomal segment where the tick-induced ECM lesion was observed. Despite these clinical distinctions, antibody titers were elevated in 6 of 9 European patients with Bannwarth's syndrome presumably before they received antibiotic therapy (28).

IMMUNE RESPONSE TO BORRELIA BURGDORFERI

A. Humoral Immunity

The definitive identification of Borrelia burdorferi as the causative agent in Lyme disease has sparked a new phase of study of the immune response that patients undergo during infection with this organism. The initial antibody test involved the use of whole spirochetes isolated from Ixodes dammini ticks as a substrate for an indirect immunofluorescence assay (76,96,97). In this assay, washed spirochetes are layered onto glass slides featuring numerous wells which are coated with the organisms. After the slides are dryed and fixed in acetone, patients' sera in various dilutions are added. A second step consists of adding fluorescein conjugated anti-human immunoglobulin, a polyvalent reagent. The slides were then analyzed in a fluorescence microscope. Monospecific antisera conjugated to fluorescein can also be used to identify specific IgM, IgG, or IgA antibody to the Lyme spirochete. A second antibody test was developed using the ELISA technique. The antigen used in this test is a sonicate of the Lyme spirochete. After the primary incubation of this antigen with patient serum, a goat IgG antibody linked to alkaline phosphatase and specific for human immunoglobulin is added during a second step along with p-nitrophenyl phosphate. The optical density at 410 nm is then read. This value is usually compared with a known positive serum containing antibody to the Lyme agent in order to obtain a specific OD ratio of test serum to positive control.

Several studies have been carried out to evaluate the relative specificity and sensitivity of these respective antibody tests. These studies have shown that specific IgM antibody is elevated during early disease (stage 1) but that specific IgG antibody is present during stage 2 and 3 (neuritis and arthritis) and these IgG titers remain elevated after months of remission. The ELISA assay appeared to be more sensitive and specific than was the immunofluorescence assay. Cross-reactivity was seen in patients with other treponemal diseases such as syphilis, yaws, and pinta. The Lyme disease patients, however, gave negative tests in the rapid reagin screening tests for syphilis. The anti-Lyme agent titers in patients with erythema chronicum migrans alone tended to be low and the antibody tests were felt to be somewhat insensitive. CDC accepts a titer of 1:256 or greater in the indirect immunofluorescence assay to be a true positive for exposure to the Lyme disease agent (54). CDC criteria for the diagnosis of Lyme disease are listed in Table 9. Not surprisingly, patients with relapsing fever tended to have significant titers in this assay because it is induced by a Borrelia, whereas leptospirosis patients tended to be negative. As mentioned above, patients with acute infectious mononucleosis did have IgM antibody to the Lyme agent, which was felt to reflect polyclonal B cell activation.

Table 9

DIAGNOSTIC CRITERIA FOR LYME DISEASE

A. Endemic Area
   1. ECM
   2. Antibody titer ≧1:256 and involvement of ≧1 organ system*

B. Nonedemic Area
   1. ECM with antibody titer ≧1:256
   2. ECM with involvement of ≧2 organ systems*
   3. Antibody titer ≧1:256 and involvement of ≧1 organ system

*Either musculoskeletal, neurological or cardiac.

Subsequent studies principally by Dr. Alan Barbour and colleagues (98) and Dr. Steere's group (99), have asked the question of what antigens on the Borrelia burgdorferi are recognized by these antibodies present in Lyme disease patients. The approach has been two-fold. First, cell surface proteins from the Borrelia burgdorferi have been extensively separated and analyzed by a variety of immunochemical techniques. These have included separation of membrane components by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), transfered to nitrocellulose and reacted with patients serum in a technique known as a western blot. It has been demonstrated that Lyme disease patients have antibodies that identify chiefly two components with apparent molecular weights of 41,000 and 60,000. By this analysis control individuals as well as patients with rheumatoid arthritis, systemic lupus erythematosus and other connective tissue diseases are negative.

Dr. Barbour and colleagues have gone on to develop at least three monoclonal antibodies with the hybridoma technique using the cells from spirochete-immunized mice. The first monoclonal antibody recognized a 31,000 molecular weight (31 kilodalton (Kd)) protein that was present in both spirochetes from Ixodes dammini ticks as well as those from Ixodes ricinus ticks (100). This protein was present on the cell surface of the organism. A second cell surface protein of 34 Kd size was recognized by two additional monoclonal antibodies (101). There was more variation in expression of the bacterial antigens recognized by these monoclonal antibodies when spirochetes of various sources were assayed. With such techniques a variation in expression of this major cell surface protein on the spirochete was appreciated. This sort of antigenic variation was reminiscent of that expressed by other Borrelia, such as those responsible for relapsing fever (102). This property seems to promote the organism's ability to elude host defense mechanisms and persist in the infected mammal. These monoclonal antibodies did not react with either the spirochetes from Ixodes ricinus ticks nor did they react with a variety of Borrelia species. A recent abstract by Craft et al from Yale (99) similarly found that the 34 Kd antigen was not present on the proteins isolated from Ixodes ricinus spirochetes nor on Borrelia hermsii. It was hypothesized that this 34Kd antigen may be associated only with arthritogenic Borrelia species.

B. Cell Mediated Immunity

Two recent reports from Yale have provided evidence for specific changes in cell mediated immunity and Lyme disease. A tendency to respond less well than normal to the mitogens phytohemagglutinin (PHA) and pokeweed mitogen was observed during the first six weeks of disease (103). Patients with chronic arthritis tended to respond better than average to these mitogens when their peripheral blood mononuclear cells were analyzed. Reactivity by peripheral blood cells to the Lyme disease spirochete antigen was observable in arthritis patients but not in controls or patients with only erythema chronicum migrans. This response was enriched when the cells in joint fluid were tested. The lymphocyte proliferative response to the Lyme spirochete antigen was even greater than to mitogens or to Borrelia hermsii. This suggested strongly that the causative spirochete or antigen derived from it was present in affected joints, perpetuating a chronic immune response reflected in lymphocyte reactivity.

The second study established that during stage 1 disease, the mitogenic response to PHA was in the normal range, but that a suppressor cell function was increased (18). Whether this assay of spontaneous suppressor cell activity reflected the activities of T cells or other types of suppressors was not stated in this publication. As disease progressed, in those patients with active neuritis, carditis or arthritis, there was a tendency to generate a high PHA response as well as less suppression than normal. In addition, this study confirmed the observation that serum IgM levels correlated directly with disease activity and inversely with the number of T cells. Those individuals with early disease that had high IgM levels tended to have an increased PHA response as well as decreased suppressor cell activity. This study concluded that a impairment in suppressor cell activity may prepetuate a chronic immune response.

C. Miscellaneous Aspects of Immunity to Borrelia Burgdorferi.

The ability of the Lyme spirochete to induce various immunologic responses by phagocytic cells has been studied in detail by Dr. Benach and coworkers at the Department of Pathology, SUNY, Stony Brook, New York. This organism was found to be a very potent inducer of interleukin 1, otherwise known as endogenous pyrogen (104). Interleukin 1 has wide-spread effects on both the induction of fever and the state of activation of both B and T lymphocytes (105) (Figure 5). A recent discovery at Stony Brook (G Habicht, personal communication) has revealed that the organism contains a potent lipopolysaccharide (endotoxin) which is mitogenic for both human and murine lymphocytes and is pyrogenic in rabbits. Among other effects, endotoxin has the capacity to directly activate chondrocytes and result in cartilage degradation (106). The capacity of this organism to induce the proliferation of lymphocytes and the production of interleukin 1 probably is very important for its induction of a vigorous immune response that leads to pathologic consequences.

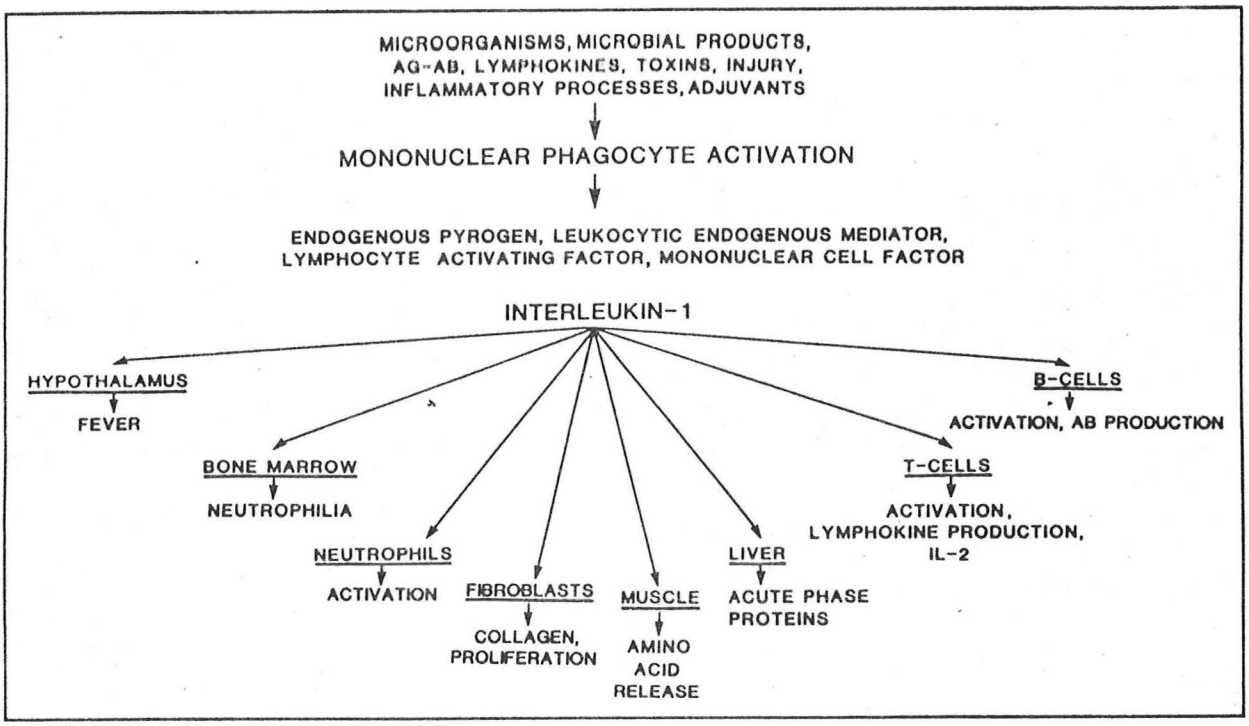

Figure 1. The Multiple Biologic Activities of Interleukin-1.
AG denotes antigen, AB antibody, and IL-2 interleukin-2.

Figure 5 © CA Dinarello. N Engl J Med 311:1413-1418, 1984. Massachusetts Medical Society.

This same group at Stony Brook has examined the requirements for phagocytosis of the Lyme spirochete. A critical role for Fc receptor-mediated phagocytosis of the organism was shown (107,108). Antibodies directed to Fc receptors blocked phagocytosis of opsonized organisms. Heat inactivation of the serum used in this experiment did not affect the level of phagocytosis, indicating that heat labile complement components were not necessary. Non-opsonized spirochetes were ingested, although at a much lower level. Similar findings were recently reported by Petersen et al (109) who also showed an enhanced phagocytosis when the organism was reacted with specific antibody. However, optimal levels of uptake of the organisms within the phagocytic cells were seen without antibody if the cells were incubated long enough with the organisms. A role for the Fc receptor in the mediation of efficient, rapid phagocytosis has therefore been shown. Benach et al have speculated that the propensity of DR2 positive individuals to develop stage 2 and 3 disease relates to the studies by Kimberly et al showing defective Fc mediated phagocytosis in such individuals (110). Again, the Fc-dependent phagocytic defect in DR2 individuals was only partial.

LYME DISEASE IN TEXAS

Texas, particularly North Central and North East Texas, is an endemic area for tick borne diseases. Rocky mountain spotted fever is not an uncommon occurence during the summer months (111,112). Because of the awareness of physicians in Texas of the possibility of spotted fever, sera are often submitted to the State Health Department in Austin for

testing for antibodies to Rickettsiae. When such tests are negative for spotted fever, the etiologic diagnosis in such cases is uncertain. Recently, Julie Rawlings, MPH, a microbiologist at the Texas Department of Health has made available the indirect immunofluorescence test for the Lyme spirochete. In a retrospective study of 403 sera submitted since April, 1984, primarily to test for Rocky mountain spotted fever exposure but also including several cases of aseptic meningitis, 9 patients had titers in the Lyme assay greater than or equal to 1:512 and 20 had titers of 1:256 (113) (Table 10). Those patients whose sera were positive appeared mostly from the North Central and North East Texas areas (Public health regions 5 and 7). The Dallas /Fort Worth area is in region 5.

Table 10

TEXAS DEPARTMENT OF HEALTH 1984 RETROSPECTIVE STUDY

Antibodies To Lyme Disease Agent*	Number Sera
≧1:512	9
1:256	20
1:128	42
1:64	55
≦1:64	277
Total	403

*Titer by indirect immunofluorescence assay (IFA)

A breakdown of 50 cases seen locally is shown on Figure 6. Most of the cases were those of children. They tended to have small rashes, often less than a centimeter, but in some cases rashes up to 13 inches were noted. Unfortunately photos of such patients are not available. Most individuals whose sera were submitted, received antibiotics early on because of suspicion of spotted fever. Recurrent neurologic symptoms have been seen in 13% of patients and recurred joint symptoms in 23% of cases. Objective documentation of whether true arthritis (by physical signs, joint fluid analysis) exists in these patients is not yet available. The vector for Lyme disease in Texas is not really known, although ticks from 3 patients with antibody to the Lyme disease agent have been identified. These have included Dermacentor Variabilis, the American dog tick, and Rhipicephalus sanguineus, the brown dog tick. It is possible that these were not the true vectors transmitting infection. Only an analysis of such ticks to determine whether they harbor spirochetes will be able to settle the point. Dermacentor has been analyzed in North Eastern studies and was found not to harbor spirochetes even when isolated from the skin of an infected host which also carried Ixodes dammini species (83). In addition, Amblyomma americanum has been implicated in one case in Tyler (Dr. Wiley Tanner, personal communcation) and this tick has been a proven vector in New

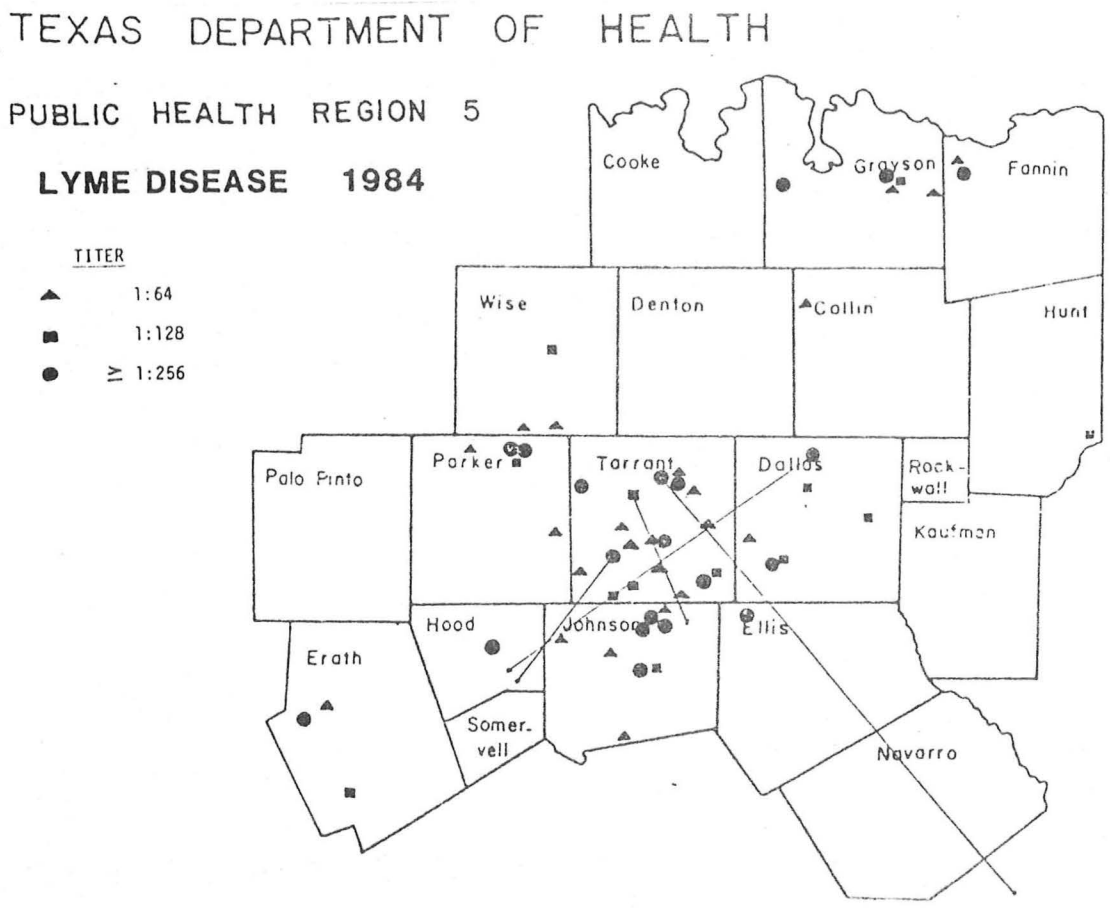

Figure 6

Jersey (68). Also Amblyomma maculatum, the Gulf Coast tick, has been implicated in Houston. It is clear that Ixodes scapularis, the black-legged tick, which has been a proven vector in other states, can be found in Texas. Studies such as those done in the Northeast to isolate spirochetes in ticks, deer and other wildlife remain to be performed in Texas. Only when isolates are grown and analyzed can they be assessed fully for characteristics of Borrelia burgdorferi, i.e., the known antigenic expression and reactivity with defined monoclonal antibodies. No isolates have been obtained from blood submitted on Texas patients with the positive immunofluorescence assays. Much field work and epidemiologic work remains to be done in Texas to establish the true significance of the serologic data gathered to date. However it is possible that Lyme disease has been present in Texas for a considerable period and that its expression has been aborted by the appropriate use of antibiotics given for suspected Rocky Mountain spotted fever. Whether cases of chronic arthritis of unknown etiology seen by rheumatologists locally will become linked to this disease is an exciting possibility remaining to be explored.

LYME ARTHRITIS: CURRENT CONCEPTS OF PATHOGENESIS

The finding of cellular reactivity within the joint fluid mononuclear cells cited above as well as the prompt response of chronic arthritis to high dose intravenous penicillin treatment, both suggest the possibility of ongoing infection in the joint. Cultures to date of synovial tissue from Lyme disease patients have not revealed growth of the organism. An exciting recent study from Yale, however, has demonstrated the presence of intact spirochetes in 5 of 19 synovial specimens obtained at total or subtotal synovectomy (114). The organisms have been revealed by silver stain of the synovial material. Material obtained by needle biopsy to rule out the possibility of suppurative arthritis uniformly has not revealed the organism by histologic methods. The organisms therefore are sparse in number. This is consistent with recent findings in experimental Lyme disease in animals in which positive cultures are obtained from a variety of tissues which, however, reveal few organisms histopathologically (P. Duray, personal communication). The organisms seen in the human samples were up to 35 microns long and resembled in every respect the cultured spirochetes from ticks and extraarticular sites from patients. The synovium in addition, was rich in complement, immunoglobulin and fibrin deposition. Actually more fibrin was seen in Lyme disease synovium than in synovial tissue from patients with either rheumatoid arthritis or Reiter's disease. Another significant finding by Dr. Duray's group at Yale is the observation of an obliterative endarteritis in the synovium, a microangiopathic process seen in 6 of 15 cases. This is reminiscent of old descriptions of syphilitic microangiopathic changes described in the 19th century and is distinct from changes seen in the chronic synovitis of rheumatoid arthritis or Reiter's disease.

A case that presented to an orthopedic surgeon in Connecticut with a history of trauma was taken to arthroscopic surgery for repair of suspected meniscal injury. The 1½ year involvement of the knee in this 29 year old man suggested to the orthopedic surgeon the possibility of Lyme disease in this endemic area. Routine histology was performed on the surgical specimens and revealed a microangiopathic process reminiscent of the Lyme disease pattern. In this individual, serum revealed high titers to the Lyme disease agent and, in addition, spirochetes were observed by silver stain of the synovial specimen. This case highlights the possibility that many chronic arthritides especially those that are monoarticular, may have an infectious etiology. If the synovial tissue is examined carefully for characteristic histopathologic patterns, an etiologic diagnosis may be suggested and confirmed by appropriate testing. In the individual described, antibiotic therapy resulted in a good outcome.

The precise role that live organisms, in contradistinction to immune complexes involving spirochetal antigens might play in the pathogenesis of the joint inflammation is still a matter of speculation. The successful treatment with antibiotics suggests that the organisms need to be present to perpetuate the arthritis. Whatever bacterial debris remains after the organisms are killed by the antibiotic can be removed with a resolution of joint inflammation. This model contrasts those proposed by others including Bennett (115) and Hadler (116) who have

suggested that phlogistic debris from bacteria are retained for prolonged periods within the joints, long after the organisms are not viable leading to a chronic immune response and arthritis (Table 11). It is possible that infectious triggers in common arthritides like rheumatoid arthritis and Reiter's disease can persist in the joint (117,118) and antibiotic therapy might be of benefit in these conditions. No widely accepted positive results with such an approach, however, have been reported in these conditions. An intense search for infectious triggers for rheumatoid arthritis and ankylosing spondylitis and the other seronegative spondyloarthropathies is now being conducted world-wide. Of interest is the finding in a recent study that both rheumatoid factor positive and seronegative rheumatoid arthritis patients were found to have elevated titers to the Lyme spirochete (119). This provocative finding needs to be further evaluated in view of earlier reports showing that rheumatoid arthritis patients' sera were negative in the Lyme spirochete antibody assay (98).

Table 11

FOUR GENERAL MECHANISMS BY WHICH INFECTIOUS AGENTS CAN INITIATE SYNOVITIS

CLASSIFICATION OF ARTHRITIS ASSOCIATED WITH INFECTIONS

I	Multiplication of the agent within a joint space
II	Infectious agent or its derived antigens localize in the joint space and initiate an immune response
III	Infectious agent or its derived antigens at a distant site, but the associated immune response causes arthritis
IV	Infectious agents produce "arthritogenic toxins"

It is clear that a more careful examination of synovium for patterns of pathologic changes, staining for various organisms and reexamination of the epidemiologic factors in all forms of arthritis will be spurred on by the Lyme disease experience. Whereas a viral etiology for rheumatoid arthritis is still being pursued (120) bacterial triggers certainly have not been ruled out. The HLA predisposition to rheumatoid arthritis and the seronegative spondyloarthropathies, DR4 and HLA B27 respectively contrast the associated DR2 in Lyme disease. What specific host defense factors might be determined by these respective HLA genes remain to be defined. Perhaps a defective clearing of organisms predisposing to their prepetuation within tissue and a compensatory, exaggerated immune response is at the basis of some of these lesions and syndromes. Which

specific antibody reactions to certain cell surface structures on the bacteria and which cell mediated immune responses prepetuate these reactions will have to be worked out for each disease. It is clear, however, that in the eight years since the first description of Lyme arthritis, much progress has been made in establishing a link between some forms of chronic arthritis and infection.

REFERENCES

1. Steere AC,SE Malawista, DR Syndman, WA Andiman. A cluster of arthritis in children and adults in Lyme, Connecticut. Arthritis Rheum 19:824, 1976.(Abstract).

2. Steere AC, SE Malawista, DR Syndman, RE Shope, WA Andiman, MR Ross, FM Steele: Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis Rheum 20:7-17, 1977.

3. Steere AC, SE Malawista, JA Hardin, S Ruddy, PW Askenase, WA Andiman. Erythema chronicum migrans and Lyme arthritis: the enlarging clinical spectrum. Ann Int Med 86:685-698, 1977.

4. Steere AC, JA Hardin, SE Malawista. Erythema chronicum migrans and Lyme arthritis: cryoimmunoglobulins and clinical activity of skin and joints. Science 196:1121-1122, 1977.

5. Steere AC, JA Hardin, SE Malawista. Erythema chronicum migrans and Lyme arthritis: related problems recently recognized in Connecticut. Conn Med 42:353-357, 1978.

6. Calabro JJ, LJ Del'Italia, SA Leers, M Yunus, FJ Kildaff, GW Hazard. Lyme arthritis. Arthritis Rheum 21:167, 1978.

7. Steere AC, JA Hardin, SE Malawista. Lyme arthritis: a new clinical entity. Hosp Practice 143-158, 1978.

8. Steere AC, JA Hardin, S Ruddy, JG Mummaw, SE Malawista. Lyme arthritis: correlation of serum and cryoglobulin IgM with activity, and serum IgG with remission. Arthritis Rheum 22:471-483, 1979.

9. Steere AC, A Gibofsky, ME Patarroyo, RJ Winchester, JA Hardin, SE Malawista. Chronic Lyme arthritis: clinical and immunogenetic differentiation from rheumatoid arthritis. Ann Int Med 90:896-901, 1979.

10. Steere AC, CE Brinckerhoff, DJ Miller, H Drinker, ED Harris, Jr., SE Malawista. Elevated levels of collagenase and prostaglandin E2 from synovium associated with erosion of cartilage and bone in a patient with chronic Lyme arthritis. Arthritis Rheum 23:591-599, 1980.

11. Reik L, AC Steere, NH Bartenhagen, RE Shope, SE Malawista: Neurologic abnormalities of Lyme disease. Medicine 58:281-294 1979.

12. Steere AC, SE Malawista. Cases of Lyme disease in the United States: locations correlated with distribution of Ixodes dammini. Ann Int Med 91:730-733, 1979.

13. Steere AC, SE Malawista, JH Newman, PN Spieler, NH Bartinhagen: Antibiotic therapy in Lyme disease. Ann Int Med 93:1-8, 1980.

14. Afzelius A: Erythema chronicum migrans. Acta Derm Vernereol (Stockh) 2:120-125, 1921.

15. Ackermann R, U Runne, W Klenk, C Dienst: Erythema Chronicum migrans with arthritis. Dtsch Med Wochenschr 105:1779-1781, 1980.

16. Mallecourt JM, M Landurean, AM Wirth: Lyme's disease: a clinical case observed in western France. Nouv Presse Med 11:39, 1982.

17. Schrock CG. Lyme disease: additional evidence of widespread distribution. Am J Med 72:700-702, 1982.

18. Moffat CM, LH Sigal, AC Steere, DH Freeman, JM Dwyer. Cellular immune findings in Lyme disease: correlation with serum IgM a disease activity. Am J Med 77:625-632, 1984.

19. Steere AC, NH Bartenhagen, JE Craft, GJ Hutchinson, JH Newman, DW Rahn, LH Sigal, PN Spieler, KS Stenn, SE Malawista. The early clinical manifestations of Lyme disease. Ann Int Med 99:76-82, 1983.

20. Scrimenti RJ. Erythema chronicum migrans. Arch Derm 102:104-105, 1970.

21. Wagner L, G Susens, L Heiss, R Ganz, J McGinley, Erythema chronicum migrans. West J Med 124:503-505, 1976.

22. Naversen DN, LW Gardner. Erythema chronicum migrans in America. Arch Dermatol 114:253-254, 1978.

23. Steere AC, WP Batsford, M Weinberg, J Alexander, HJ Berger, S Wolfson, SE Malawista. Lyme carditis: cardiac abnormalities of Lyme disease. Ann Int Med 93:8-16, 1980.

24. Bedell SE, BM Pastor, SI Cohen. Symptomatic high grade heart block in Lyme disease. Chest 79:236-237, 1981.

25. Meissner HC, SE Gellis, JF Milliken, Jr. Lyme disease first observed to be aseptic meningitis. Am J Dis Child 136:465-467, 1982.

26. Hindfelt B, PG Jeppsson, B Nilsson, et al: Clinical and cerebro-spinal fluid findings in lymphocytic menango-radiculitis (Bannwarth's syndrome). Acta Neurol Scand 66:444-453, 1982.

27. Wulff CH, K Hansen, P Strange Et al. Multiple mononeuritis and radicultis with erythema, pain, elevated CSF protein and pleocytosis (Bannwarth's syndrome). J Neurol neurosurg Psychiatry 46:486-490, 1983.

28. Ryberg B, B Nilsson, W Burgdorder, et al: Antibodies to Lyme disease spirochete in European lymphocytic meningoradiculitis (Bannwarth's syndrome) Lancet 2:519, 1983.

29. Ryberg B, B Hindfelt, B Nilsson, JE Olsson: Antineural antibodies in Guillain-Barr syndrome and lymphocytic meningoradiculitis (Bannwarth's syndrome). Arch Neurol 41:1277-1281, 1984.

30. Darras BT, D Annuziato, RJ Leggiadro: Lyme disease with neurologic abnormalities. Ped Infect Dis 2:47-49, 1983.

31. Sterman AB, S Nelson, P Barclay: Demyelinating neuropathy accompanying Lyme disease. Neurology 32:1302-1305, 1982.

32. Donaldson JO, RA Lewis: Lymphocytic meningoradiculitis in the United States. Neurology 33:1476-1479, 1983.

33. Barza M. Case records of the Massachusetts General Hospital. Case 29-1984. N Engl J Med 311:172-181, 1984.

34. Putkonen T, KK Mustakallio, A Salminen. Erythema chronicum migrans with meningitis: a rare coincidence of two tick-borne diseases? Dermatologica 125:184-188, 1962.

35. Steere AC, A Gibofsky, JA Hardin, RJ Winchester, SE Malawista. Lyme arthritis: immunologic and immunogenetic markers. Arthritis Rheum 22:662-663, 1979. (Abstract)

36. Hardin JA, LC Walker, AC Steere, TC Trumble, KSK Tung, RC Williams, Jr., S Ruddy, SE Malawista. Circulating immune complexes in Lyme arthritis. J Clin Invest 63:468-477, 1979.

37. Hardin JA, AC Steere, SE Malawista. Immune complexes and the evolution of Lyme arthritis: dissemination and localization of abnormal Ciq binding activity. N Engl J Med 301:1358-1363, 1979.

38. Steere AC, TF Broderick, SE Malawista. Erythema chronicum migrans and Lyme arthritis: epidemiologic evidence for a tick vector. AM J Epidemiol 108:312-321, 1978.

39. Wallis RC, SE Brown, KO Kloter, AJ Main Jr. Erythema chronicum migrans and Lyme arthritis: Field study of ticks. Am J Epidemiol 108:322-327, 1978.

40. Spielman A, CM Clifford, J Piesman, MD Corwin. Human babesiosis on Nantucket Island, USA: description of the vector, Ixodes (Ixodes) dammini, N. Sp. J Med Entomol 15:218-234, 1979.

41. Burgdorfer W, JE Keirans. Ticks and Lyme disease in the United States. Ann Int Med 99:121, 1983.

42. Williams DN, JC Vance, C Hedberg, C Foley, M Osterholm: Lyme disease and erythema chronicum migrans in Minnesota. Minn Med 65:217-221, 1982.

43. Harris Ed Jr., JM Evanson, DR DiBona, SM Krane: Collagenase and rheumatoid arthritis. Arthritis Rheum 13:83-94, 1970.

44. Gerster JC, S Gucci, H Perrod, R Boret: Lyme arthritis appearing outside the U.S.: a case report from Switzerland. Brit Med J 283:951-952, 1981.

45. Ward LC: A case of "Lyme disease" acquired in New Jersey. J Med Soc NJ 78:469-470, 1981.

46. Slade JD, PP Lenz: Lyme disease in New Jersey: a cluster of frour cases of eleven sporadic cases. J Med Soc NJ 79:496-500, 1982.

47. Kerns JW. Was it Lyme disease? Virg Med 110:390-391, 1983.

48. Pegram, Jr., PS, CN Sessler, WL London. Lyme disease in North Carolina. Southern Med J 76, 740-742, 1983.

49. Steward A, J Glass, A Patel, G Watt, A Cripps, R Clancy. Lyme arthritis in the Hunter Valley, Med J Aust 1:139, 1982.

50. Thurlby RW. Lyme arthritis, report of a case in Arkansas. J Ark Med Soc 78:152-154, 1981.

51. Hanrahan JP, JL. Benach, JL Coleman, EM Bosler, DL Morse, DJ Cameron, R Edelman, RA Kaslow, Incidence and cumulative frequency of endemic Lyme disease in a community. J Infect Dis 150:489-495, 1984.

52. Kaslow RA, CL Samples, DG Simon, JN Lewis. Occurrence of erythema chronicum migrans and Lyme disease among children in two noncontiguous Connecticut counties. Arthritis Rheum 24:1512-1516, 1981.

53. Editorial. Lyme disease: a new entity. N Zeal Med J 96:388-389, 1983.

54. MMWR 33: May 18, 1984/Update: Lyme Disease-United States, JAMA 251:2916-2919, 1984.

55. Editorial. Lyme disease challenges Australian clinicians. Med J Aust: 101-102, 1982.

56. Dryer RF, PG Goellner, AS Carney. Lyme arthritis in Wisconsin. JAMA 241:498-499, 1979.

57. Danilevicius Z. Lyme arthritis: not confined to the east coast. JAMA 241:504, 1979.

58. Zakem JM, BF Germain. Lyme arthritis in Florida. J Florida M.A. 66:281-283, 1979.

59. Bowen GS, M Griffin, C Hayne, J Slade, TL Schulze, W Parkin. Clinical manifestation and descriptive epidemiology of Lyme disease in New Jersey, 1978 to 1982. JAMA 125:2236-2240, 1984.

60. Campagna J, PE Lavoie, NS Birnbaum, DP Furman. Lyme disease in northern California. West J Med 139:319_323, 1983.

61. Editorial. Lyme disease. S Afr Med J 58:465-466, 1980.

62. Editorial. Lyme disease: a new entity. N Zea Med J 388-389, 1983.

63. Editorial. Spirochete isolated in tick vectors of Lyme disease. Hosp Prac 46-55, 1982.

64. Gundy P. Lyme disease: spirochetes up to old ticks? JAMA 248:812-813, 1982.

65. Bruhn FW. Lyme disease. AKDC 138:467-470, 1984.

66. Meyerhoff J. Lyme disease. Am J Med 75:663-670, 1983.

67. Williamson PK, JJ Calabro. Lyme disease - a review of the literature. Sem Arth Rheum 13:229-234, 1984.

68. Schulze TL, GS Bowen, EM Bosler, MF Lakat, WE Parkin, R Altman, BG Ormiston, JK Shisler, Amblyoma americanum: A potential vector of Lyme disease in New Jersey. Science 601-604, 1984.

69. Harwood RF, MT James: Ticks and tick-associated diseases, in Entomology In Human and Animal Health. 7th edition, MacMillian, New York, 1979, pp 371-416.

70. Mast WE, WM Burrows, Jr. Erythema chronicum migrans in the United States. JAMA 236:859-860, 1976.

71. Mast WE, WM Burrows. Erythema chronicum migrans and "Lyme arthritis". JAMA 236:2392, 1976.

72. Steere AC, GJ Hutchinson, DW Rahn, LH Sigal, JE Craft, ET DeSanna, SE Malawista. Treatment of the early manifestations of Lyme disease. Ann Int Med 99:22-26, 1983.

73. Steere AC, AR Pachner, SE Malawista. Neurologic abnormalities of Lyme disease: successful treatment with high dose intravenous penicillin. Ann Int Med 99:767-772, 1983.

74. Steere AC, J Green GJ Hutchinson, DW Rahn, R Schoen, LH Sigal, SE Malawista. Curing Lyme arthritis: sucessful antibiotic therapy of established joint involvement. Arthritis Rheum 27:S26, 1984. (Abstract).

75. Coblyn JS, P Taylor. Treatment of chronic Lyme arthritis with hydroxychloroquine. Arthritis Rheum 24:1567-1569, 1981.

76. Burgdorfer W, AG Barbour, SF Hayes, JL Benach, E Grunwaldt, JP Davis. Lyme disease a tick-borne spirochetosis? Science 216:1317-1319, 1982.

77. Steere AC, RL Grodzicki, AN Kornblatt, JE Craft, AG Barbour, W Burgdorfer, GP Schmid, E Johnson, SE Malawista. The spirochetal etiology of Lyme disease. N Engl J Med 308:733-740, 1983.

78. Benach JL, EM Bosler, JP Hanrahan, JL Coleman, GS Habincht, TF Bast, DJ Cameron, JL Ziegler, AG Barbour, W Burgdorfer, R Edelman, RA Kaslow. Spirchetes isolated from the blood of two patients with Lyme disease. N Engl J Med 308:740-742, 1983.

79. Harris, Jr. ED. Lyme disease - success for academia and the community. N Engl J Med 308:773-775, 1983.

80. Berger BW, OJ Clemmensen, AB Ackerman. Lyme disease in a spirochetosis. Am J Dermatopath 5:111-124, 1983.

81. Waldo Ed, GS Sidhu. The spirochete in erythema chronicum migrans. Am J Dermatopath 5:125-127, 1983.

82. Barbour AG, W Burgdorfer, SF Hayes, O Peter, A Aeschlimann. Isolation of cultivable spirochete from Ixodes ricinus ticks of Switzerland. Current Microbiology 8:123-126, 1983.

83. Bosler EM, JL Coleman, JL Benach, DA Massey, Natural distribution of the Ixodes dammini spirochete. Science 220:321-322, 1983.

84. Anderson JF, LA Magnarelli, W Burgdorfer, AG Barbour. Spirochetes in Ixodes dammini and mammals from Connecticut. Am J Trop Med Hyg 32:818-824, 1983.

85. Johnson SE, GC Klein, GP Schmid, GS Bowen, JC Feeley, T Schulze. Lyme disease: a selective medium for isolation of the suspected etiological agent, a spirochete. J Clin Microbiol 19:81-82, 1984.

86. Proceedings of the First International Symposium on Lyme Disease. Yale J Biol Med 57:No. 4, 1984, in press.

87. Benach JL, EM Bosler, JL Coleman, GS Habicht. Experimental transmission of the Lyme disease spirochete to rabbits. J Infect Dis 150:786-787, 1984.

88. Kornblatt AN, AC Steere, DG Borwnstein: Experimental Lyme disease in rabbits: spirochetes found in erythema migrans and blood. Infect Immun 46:220-223, 1984.

89. Krinsky WL, SJ Brown, PW Askenase. Ixodes dammini: induced skin lesions in guinea pigs and rabbits compared to erythema chronicum migrans in patients with Lyme arthritis. Experimental Parasitology 53:381-395, 1982.

90. Hyde FW, RC Johnson, Genetic relationship of Lyme disease spirochetes to Borrelia, Treponema, and Leptospira spp. J Clin Microbiol 20:151-154, 1984.

91. Schmid GP, AG Steigerwalt, SE Johnson, AG Barbour, AC Steere, IM Robinson, DJ Brenner. DNA characterization of the spirochete that causes Lyme disease. J Clin Microbiol 20:155-158, 1984.

92. Hayes SF, W Burgdorfer, AG Barbour, Bacteriophage in the Ixodes dammini spirochete, etiological agent of Lyme disease. J Bacteriol 154:1436-1439, 1983.

93. Johnson RC, GP Schmid, FW Hyde, AG Steigerwalt, DJ Brenner. Borrelia burgdorferi sp. nov.: etiologic agent of Lyme disease. Int J Systematic Bacteriol 34:496-497, 1984.

94. Weber K. Treatment of Lyme disease. Ann Int Med 94:137, 1981.

95. Burgdorf WHC, WI Worret, O Schultka. Acrodermatitis chronica atrophicans. Int J Derm 18:595-601, 1979.

96. Russell H, JS Sampson, GP Schmid, HW Wilkinson, B Plikaytis. Enzyme-linked immunosorbent assay and indirect immunfluorescence assay for Lyme disease. J Infect Dis 149:465-470, 1984.

97. Craft JE, RL Grodzicki, AC Steere. Antibody response in Lyme disease: evaluation of diagnostic tests. J Infect Dis 149:789-795, 1984.

98. Barbour AG, W Burgdorfer, E Grunwaldt, AC Steere. Antibodies of patients with Lyme disease to components of Ixodes dammini spirochete. J Clin Invest 72:504-515, 1983.

99. Craft JE, DK Fischer, JA Hardin, M Garcia-Blanco, AC Steere. Spirochetal antigens in Lyme disease. Arthritis Rheum 27:S64, 1984. (Abstract).

100. Barbour AG, SL Tessier, WJ Todd. Lyme Disease and Ixodid tick spirochetes share a common surface antigenic determinant defined by a monoclonal antibody. Infect Immun 41:795-804, 1983.

101. Barbour AG, SL Tessier, SF Hayes: Variation in a major surface protein of Lyme disease spirochetes. Ifect Immun 45:94-100, 1984.

102. Southern Jr., PM, JP Sanford. Relapsing fever: a clinical and microbiological review. Medicine 48:129-149, 1969.

103. Sigal LH, AC Steere, JM Dwyer. Evolution of cellular reactivity to the Lyme spirochete: concentration in joint fluid. Arthritis Rheum 27:S36, 1984. (Abstract).

104. Beck G, JL Benach, JL Coleman, DK Leichtling, GS Habicht. Production of IL-1 by mouse and human macrophages stimulated by Borrelia burgdorferi. Fed Proc 43:1438, 1984. (Abstract).

105. Dinarello CA. Interleukin-1 and the pathogenesis of the acute-phase response. N Eng J Med 311:1413-1418, 1984.

106. Jasin HE. Bacterial lipopolysaccharade induced in vitro degradation of cartilage matrix through chondrocyte activation. J Clin Invest 72:2014-2019, 1983.

107. Benach JL, HB Fleit, GS Habicht, JL Coleman, EM Bosler, BP Lane. Interactions of phagocytes with the Lyme disease spirochete: role of the Fc receptor. J Infect Dis 150:497-507, 1984.

108. Fleit HB, JL Benach. Polymorphonuclear leukocyte phagocytosis of Lyme dsease spirochetes is inhibited by a monoclonal anti-Fc receptor antibody. Fed Proc 43:1914, 1984. (Abstract)

109. Peterson PK, CC Clawson, DA Lee, PJ Garlich, PG Quie, RC Johnson: Human phagocyte interactions with the Lyme disease spirochete. Infect Immun 46:608-611, 1984.

110. Kimberly RP, A Gibofsky, JE Salmon, M Fotino. Im paired Fc-mediated mononuclear phagocyte system clearance in HLA-DR2 and MT1-positive healthy young adults. J Exp Med 157:1698-1703, 1983.

111. Helmick CG, KW Bernard, LJ D'Angelo. Rocky mountain spotted fever: clinical, laboratory and epidemiological features of 262 cases. J Infect Dis 150:480-488, 1984.

112. Woodward TE. Rocky mountain spotted fever: epidemiological and early clinical signs are keys to treatment of reduced mortality. J Infect Dis 150:465-468, 1984.

113. Rawlings J: Lyme disease in Texas. Texas Preventable Disease News. Week No. 43, October 27, 1984.

114. Johnston Y, P. Duray, AC Steere et al: Spirochetes found in microogropathic synovial lesions in Lyme arthritis. Am J Pathol, 1984, in press.

115. Bennett JC. The Infectious etiology of rheumatoid arthritis. Arthritis Rheum 21:531-538, 1978.

116. Hadler NM, DA Granovetter. Phlogistitic properties of bacterial debris. Semin Arth Rheum 8:1-16, 1978.

117. Goldings EA, HE Jasin. Arthritis and autoimmunity in animals. In Arthritis and Allied Conditions, DJ McCarty, ed., Lea and Febiger, Philadelphia, Tenth Edition, in press.

118. Goldenberg DL. Postinfectious arthritis: new look at an old concept with particular attention to disseminated gonococcal infection. Am J Med 74:925-928, 1983.

119. Lavoie PE. W Burgdorfer. Serologic reactivity to Lyme disease spirochete in rheumatoid arthritis patients. Arthritis Rheum 27:S70, 1984. (Abstract).

120. Simpson RW, L McGinty, L Simon, CA Smith, CW Godzeski, RJ Body. Association of parvoviruses with rheumatoid arthritis of humans. Science 223:1425-1428, 1984.