Erythema Chronicum Migrans and Lyme Arthritis: Cryoimmunoglobulins and Clinical Activity of Skin and Joints

Abstract. *We report the presence of serum cryoimmunoglobulins in patients with attacks of a newly described epidemic arthritis—Lyme arthritis—and in some patients with a characteristic skin lesion—erythema chronicum migrans—that sometimes precedes the onset of the arthritis. Seven patients who had cryoimmunoglobulins at the time of the skin lesion have developed arthritis; four patients without them have not. The cryoglobulins in patients with the skin lesion consisted primarily of immunoglobulin M (IgM); those in patients with arthritis often included both IgM and IgG. These findings support the hypothesis that a common origin exists for the skin and joint lesions and suggest that circulating immune complexes may have a pathogenetic role in Lyme arthritis.*

A new epidemic form of inflammatory joint disease, called Lyme arthritis, has been occurring among children and adults in eastern Connecticut at least since 1972, with the incidence of new cases reaching a peak in the summer and early fall (*1*). From December 1975 through April 1976, we studied 51 residents—39 children and 12 adults—in three contiguous Connecticut communities, Old Lyme, Lyme, and East Haddam (total population, 12,000), who had an arthritis characterized by typically brief but recurrent episodes of asymmetric, oligoarticular swelling and pain in large joints, especially the knee, separated by longer periods of complete remission, with no permanent joint deformity as yet. The entity was recognized because of the tight geographic clustering of cases; 17 of the 39 affected children (44 percent) lived on four country roads where one in ten had the illness, and six families had more than one affected member. Epidemiologic analysis of the clustering suggested transmission of an agent by an arthropod vector. Furthermore, 13 of the 51 patients (25 percent) described an expanding annular skin lesion before the onset of the arthritis, consistent with an entity, erythema chronicum migrans, previously associated with arthropod bites but not with arthritis (*2*). Cultures of synovium and synovial fluid showed no growth or cytopathic effect, and serologic tests did not suggest infection with agents known to cause other forms of arthritis.

It should be emphasized that we learned about patients who had what was to become Lyme arthritis in November 1975 and that the initial, primarily retrospective, study of 51 patients took place between December 1975 and April 1976. Therefore, information about the initial attacks of arthritis and the preceding skin lesion came from extensive histories and from the records of other physicians. With the start of the 1976 summer "high season," we began a prospective study of patients with the characteristic skin lesion or arthritis. During a 3-month period, July through September 1976, 30 new patients with current or previous skin lesions were seen. Eleven were referred to us while the skin lesion was active, and seven of them have subsequently developed Lyme arthritis. Eleven others were referred during attacks of arthritis or arthralgia following the skin lesion, and eight others were referred when both the skin lesion and attacks of arthritis or arthralgia had come and gone, and no symptoms were present. We can now confirm the diagnosis of the skin lesion as erythema chronicum migrans and its importance as a unique marker for Lyme arthritis.

In the original study, 9 of 20 patients with active arthritis had low serum concentrations of the third component (C3) of complement (median, 61 mg per 100 ml); 31 asymptomatic patients had normal concentrations ($P < .005$). Because such a finding could result from the consumption of complement during an immune reaction, we began to look for immune complexes that precipitate in the cold (cryoimmunoglobulins) in the serums of the 30 new patients (*3*) (see Fig. 1). We grouped them according to whether (i) the skin lesion was active ("skin active"), (ii) the skin lesion had faded but arthritis or arthralgia was active ("joints active"), or (iii) both the skin lesion and the arthritis had become inactive ("both inactive"). Seven of the patients with active skin lesions had cryoimmunoglobulins, and four did not. All seven of those with cryoimmunoglobulins have developed arthritis, and all four without them have not. All of those with active arthritis or arthralgia had cryoimmunoglobulins except for one, and that patient had arthralgia rather than objective evidence of arthritis. The patients with active lesions had significantly higher levels of cryoglobulins than those whose lesions had become inactive ($P = .03$), and none of the serums of 14 normal controls had cryoimmunoglobulins (not shown in the figure). The cryoglobulins in patients with active skin lesions consisted primarily of immunoglobulin M (IgM); those in patients with arthritis often included both IgM and IgG, and two of them also contained IgA (0.01 and 0.02 mg per milliliter, respectively). None contained detectable C3 or C4 (*4*).

These findings confirm and extend the

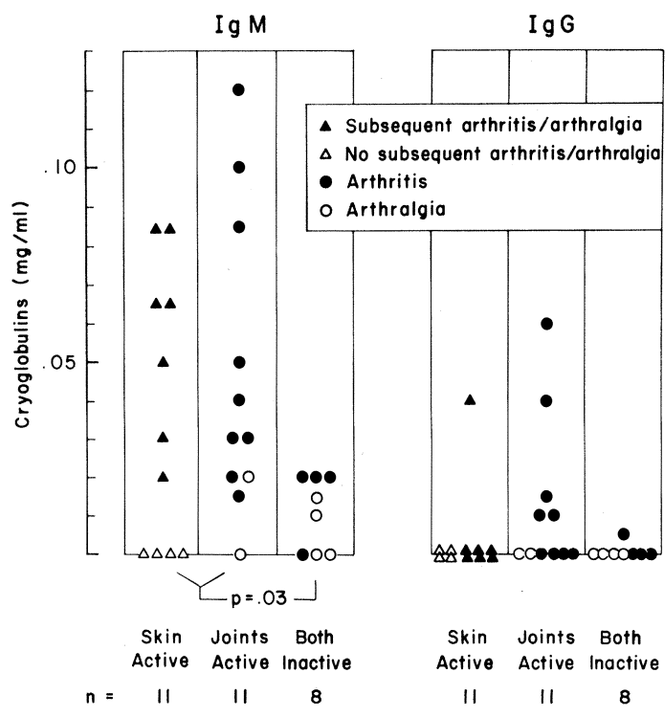

Fig. 1. Each point represents cryoglobulin from the initial serum of each of 30 patients with (i) active erythema chronicum migrans ("skin active," 11 patients), (ii) active arthritis following the skin lesion ("joints active," 11 patients), or (iii) previous skin and joint lesions, the latter inactive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

original epidemiologic evidence for the origin of Lyme arthritis. We postulate that an arthropod transmits the causative agent at the site where a skin lesion may appear. Those patients who develop cryoglobulins (primarily IgM to begin with) are at risk to develop subsequent Lyme arthritis, and this finding therefore has prognostic value. The presence of cryoglobulins (now both IgM and IgG) in almost all patients with active arthritis and their decrease or disappearance when the joint involvement has subsided, again support a pathogenetic role for circulating immune complexes in Lyme arthritis. Further support for this hypothesis can be obtained through the serial study of the individual patients, and possibly through the identification in the cryoprecipitates of an important antigen, or even of the causative agent itself (*5*).

Note added in proof: The presence of cryoglobulins in this illness may sometimes be associated with neurologic abnormalities (cranial nerve palsy, sensory radiculopathy, or aseptic meningitis) or with myocardial conduction abnormalities (*6*).

ALLEN C. STEERE
JOHN A. HARDIN
STEPHEN E. MALAWISTA
Section of Rheumatology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06510

References and Notes

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2. B. Lipschutz, in *Dermatology in General Medicine*, T. B. Fitzpatrick *et al.*, Eds.(McGraw-Hill, New York, 1971). pp. 709–711.
3. Blood samples (20 ml) were drawn and placed immediately at 37°C in a water bath for 1 hour. The clot was centrifuged at 400*g* for 10 minutes at room temperature; 5 ml of serum was obtained and kept at 4°C for 72 hours. Any precipitate that formed during this period was sedimented at 1000*g* for 20 minutes at 4°C, washed three times with ice-cold phosphate-buffered saline (*p*H 7.4), and resuspended in 0.5 ml of this buffer; most of the precepitate redissolves after 1 hour at 37°C. The concentrations of immunoglobulins were determined by radial immunodiffusion, and the presence of C3 and C4 was determined by double immunodiffusion in 1 percent agarose.
4. However, these and other complement components may still be present, and we are currently looking for them by more sensitive methods than double immunodiffusion.
5. Part of this work has appeared in abstract [A. C. Steere, J. A. Hardin, S. E. Malawista, *Arthritis Rheum.* **20**, 136 (1977)].
6. A. C. Steere, J. A. Hardin, S. E. Malawista, *Clin. Res.* **25**, 368A (1977); A. C. Steere, S. E. Malawista, J. A. Hardin, S. Ruddy, P. W. Askenase, W. A. Andiman, *Ann. Intern. Med.*, in press.
7. We thank S. B. Cretella for laboratory assistance. Supported by NIH grants AM-10493, AM-19742, AM-05639, AM-07107, AI-11785, AI-07033, and RR 00125, and grants from the Arthritis Foundation and its Connecticut chapter, and the Kroc Foundation.

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Licking Behavior: Evidence of Hypoglossal Oscillator

Abstract. *Action potentials and slow waves were recorded from the hypoglossal nucleus of rats during licking of water from a drinking tube. Periods of licking and of rhythmic neural activity were usually highly correlated, as were their frequencies. Neural activity sometimes continued after cessation of licking; at other times, it stopped during a short interruption of licking and resumed in rhythm with licking. These observations are consistent with an oscillatory model of the control of licking.*

Mammalian licking behavior is a highly stereotyped, rhythmic process. The tongue and jaw movements in such behavior represent an especially clear example in a mammal of the stereotyped rhythmic motor activity that repeatedly has been observed in invertebrates (*1*). A central oscillator has been proposed as the basis for the observed rhythmicity; the typical rate of sustained licking in the laboratory albino rat is five to seven licks per second (*2, 3*). From this model it is predicted that rhythmic neural activity can continue while motor output is temporarily suspended. We report data on action potentials and slow waves recorded from the hypoglossal nucleus, which contains the cell bodies of the motoneurons that are efferent to the muscles of the tongue, during licking by conscious, unrestrained animals. The neural and behavioral responses corresponded both in periodicity and in general pattern. During interruptions of licking, we found evidence for the oscillatory nature of the control of licking behavior.

Data were obtained from six male albino rats (Charles River) between 3 and 6 months of age, weighing 300 to 500 g. Under barbiturate anesthesia, an electrode device that permitted multiunit and, occasionally, single-unit recording (*4, 5*) was implanted above the hypoglossal nucleus or surrounding hindbrain areas (*5*). All recordings were made at least 7 days after implantation from animals that were deprived of water for 23 hours. The rats, while in their living cages, were placed individually into an electrically shielded enclosure for recording of water licking and hypoglossal activity (*6*). Licking behavior was monitored by means of circuitry which produced a pulse when tongue contact with the drinking tube was terminated.

Multiunit responses were recorded

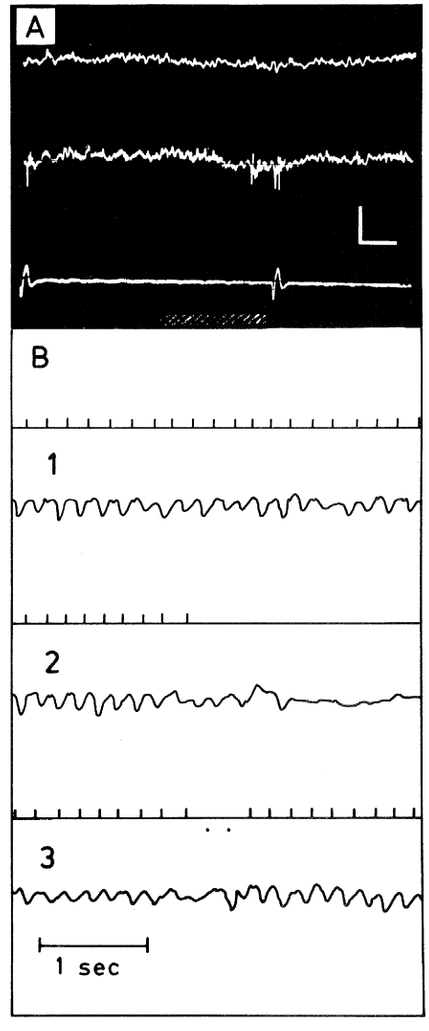

Fig. 1. (A) Neuronal activity recorded simultaneously with licking in an unanesthetized rat. Upper and middle traces are multiunit activity recorded in the hindbrain during two successive licks. The upper trace was recorded from a control electrode in the principal vestibular nucleus; the middle trace, from an electrode in the radiations of the hypoglossal nucleus. The voltage calibration for upper and middle traces is 200 μv. The lower trace, from an electrical sensor on the drinking tube, shows two pulses that correspond to termination of tongue contact. The horizontal bar below the lower trace shows the lick contact duration of 70 msec expected for the observed licking rate of 5.5 licks per second (*2, 6*). Calibration time for all three traces is 25 msec. (B) Licking patterns and slow waves from the hypoglossal nucleus. The upper trace of each pair consists of lick termination pulses; the lower trace is simultaneously recorded slow-wave bioelectric activity of the hypoglossal nucleus. All traces were produced from tape-recorded activity as displayed on an inkwriter. Action potentials were filtered by the frequency response of the inkwriter (0 to 25 hertz). In trace pair 1, steady licking is accompanied by rhythmic waves from the hypoglossal nucleus. In pair 2, cessation lick contact precedes the disappearance of the slow waves by about 500 msec. In pair 3, rhythmic licking shows a brief pause. The expected times of the missing lick termination pulses are marked by dots. There is corresponding disruption of slow waves from the hypoglossal nucleus.