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Lyme Disease Research Uncovers a Case of Delayed Recognition: Arvid Afzelius and His Successors

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The history, etiology, and treatment of Lyme disease are discussed. Despite the disease's relatively recent emergence as a health problem in the US, the skin condition known as erythema migrans, characteristic of the early stage of the disease, was first described in Europe nearly a century ago by Swedish researcher Arvid Afzelius, B. Lipschütz, and others. The delayed recognition of Afzelius's work is acknowledged, and the rapid growth of contemporary research on Lyme disease since 1980 is reviewed, including the highly cited work of Allen C. Steere, Tufts University School of Medicine, Boston, Massachusetts.

Since the first US cases of Lyme disease were described in 1977, the number of reported cases has escalated dramatically. From 1980 through 1988, over 13,700 cases have been reported nationwide.¹ In response to the increased incidence, Lyme disease has attracted a great deal of attention from the medical research community. Figure 1 illustrates the number of papers that have been published on Lyme disease since 1980, including projected data for 1989. The top journals publishing research on this disease reflect the multidimensional facet of this research field. Table 1 lists journals from such disparate fields as neurology, rheumatology, and epidemiology that have published at least 10 articles in the past five years on Lyme disease.

The lay press has also devoted much space to Lyme disease. These recent articles often give the mistaken impression that Lyme disease is a new problem that occurs only in the US. However, as was pointed out in a letter written in response to my recent essay on delayed recognition,² the skin rash that characterizes the early stage of the disease was first identified in Europe nearly a century ago. Björn Arvid Afzelius, Department of Ultrastructure Research, University of Stockholm, Sweden, wrote to me about his

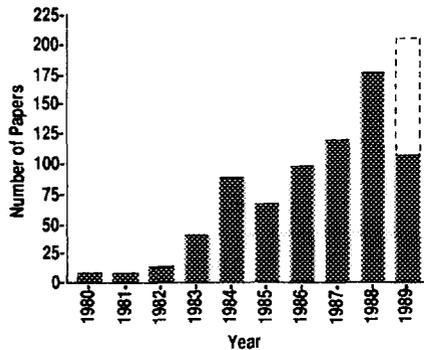
grandfather, Arvid Afzelius: "Eighty years ago my grandfather, Arvid Afzelius, reported on a severe skin rash that followed on the bites of the tick *Ixodes ricinus*.... My grandfather died before I was born and my father told me about this finding of a condition that my grandfather termed 'erythema chronicum migrans'."³

Early History of Lyme Disease

In a recent review article on Lyme disease, Gustave J. Dammin, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts, provided an excellent biography of Afzelius.⁴ Born in 1857 in Torstuna, Sweden, Afzelius received his medical degree from the Karolinska Institute. He then set up a dermatology practice and was one of the founders of the Dermatological Society, Stockholm.

At the October 28, 1909, meeting of the Dermatological Society in Stockholm, Afzelius described a case study in which he introduced the term "erythema chronicum migrans" to describe a circular skin rash. He first published his observations in 1910 in a German journal⁵ and again in 1921 in the Swedish journal *Acta Dermatovenereologica*.⁶

Figure 1: Distribution of papers on Lyme disease since 1980 with projection through 1989. Data taken from the *SCJ*[®].



As Dammin points out, Afzelius was not alone in studying this skin condition in the early part of this century. The most notable of his contemporaries was B. Lipschütz, an Austrian. Working in Vienna, independently of Afzelius, Lipschütz also reported a condition involving a progressively enlarging skin lesion. Lipschütz used the term that Afzelius had introduced, referring to the condition as “erythema chronicum migrans.” Afzelius also used this term as the title of his 1921 paper. As Dammin notes, Lipschütz and Afzelius referred to both “erythema chronicum migrans” and the shorter “erythema migrans” in their writings, with the longer term generally applied to chronic cases lasting months.⁴ Lipschütz, as much as Afzelius, should be remembered for his

Table 1: Journals publishing research on Lyme disease. A=title. B=1988 impact factor. First date of publication is included in parentheses after title.

A	B
American Journal of Epidemiology (1921)	3.11
Annals of Internal Medicine (1922)	8.47
Arthritis and Rheumatism (1958)	4.81
Deutsche Medizinische Wochenschrift (1875)	0.93
Infection and Immunity (1970)	3.21
Journal of Infectious Diseases (1904)	4.91
Journal of Medical Entomology (1964)	0.50
Neurology (1951)	2.97
New England Journal of Medicine (1812)	21.15
Yale Journal of Biology and Medicine (1928)	0.85

contributions to our current understanding of Lyme disease.

Today, the term “erythema migrans” (EM) has become widely used because of the number of similar cases found in both Europe and the US. Figure 2 shows the attention Afzelius’s 1921 paper has received in recent years after having been virtually ignored for most of this century.

This 1921 paper has helped researchers from this decade establish a relationship between this peculiar rash and the neurological and arthritis symptoms associated with what is now called Lyme disease. I have since asked Björn Afzelius to write a *Citation Classic*[®] commentary on his grandfather’s paper; that commentary appears at the end of this essay.

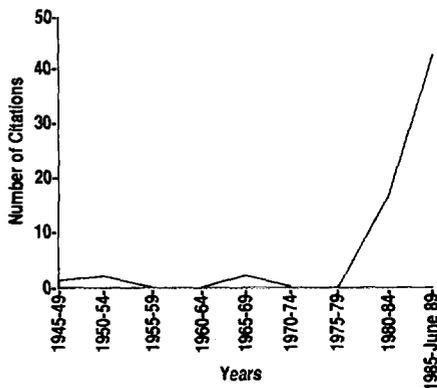
Recent History: The Connecticut Connection

The first US case of EM was documented in 1970. Rudolph J. Scrimenti, Department of Dermatology, Marquette University School of Medicine, Milwaukee, Wisconsin, reported the case of a 57-year-old physician with the rash who also complained of headaches and hip pain.⁷ Scrimenti’s case report showed familiarity with the European literature and is remarkable in that Scrimenti anticipated the later discoveries of the spirochete (bacterial) cause by treating his patient with penicillin.

In 1975 a clustering of children in the small community of Lyme, Connecticut, with symptoms similar to juvenile rheumatoid arthritis was brought to the attention of Allen C. Steere, then with the Section of Rheumatology, Department of Internal Medicine, Yale University, New Haven, Connecticut. In 1977 Steere and colleagues published a description of what they initially termed “Lyme arthritis,” a previously unrecognized disease characterized by a skin rash followed by recurrent attacks of swelling and pain in varied joints in the body.⁸

Later that same year, Steere and his colleagues published another paper that iden-

Figure 2: Distribution of SCI® citations to A. Afzelius *Acta Dermato-Venerol.* 2:120-5, 1921, from 1945 through June 1989.



tified EM as one of the clinical markers for this new disease. The authors also concluded that the illness had manifestations other than arthritis and was a multisystem disease.⁹

How the Disease Is Spread

As mentioned earlier, Afzelius hypothesized that EM was transmitted by the *I. ricinus* tick. But the complete outline of the various hosts and vectors for the disease was not fully identified until the 1980s.

In 1951 Einar Hollström reported successful treatment of EM cases with penicillin in Stockholm. Despite a lack of definitive evidence, Hollström concluded it "probable" that a tick-borne bacterium was the infective agent of this skin rash and its subsequent neurological, cardiac, and arthritic disorders.¹⁰

Confirmation that Lyme disease is caused by a bacterium transmitted by ticks was provided almost 30 years later. In 1982 Willy Burgdorfer, Epidemiology Branch, Rocky Mountain Laboratories, National Institute of Allergies and Infectious Diseases, Hamilton, Montana, and colleagues isolated a previously unrecognized spirochete that was later named *Borrelia burgdorferi* from the tick *I. dammini*,¹¹ already known to be a vec-

tor of Lyme disease.¹² (The tick was named in honor of Dammin, mentioned earlier.¹³) A short time later, a team led by Jorge L. Benach, Department of Pathology, State University of New York, Stony Brook, recovered spirochetes from the blood of two patients with Lyme disease.¹⁴ In the same issue of the *New England Journal of Medicine*, Steere and colleagues reported the recovery of spirochetes from the blood, cerebrospinal fluid, and skin of Lyme disease patients.¹⁵

Incidentally, the *Citation Classic* commentary that appears this week in several editions of *Current Contents*® deals with the cultivation of spirochetes—although the work discussed had no direct bearing on Lyme disease research. In 1964 Herman C. Ellinghausen and Willard G. McCullough, then at the Animal Disease and Parasite Research Division, US Department of Agriculture, Ames, Iowa, developed a medium of bovine albumin and oleic acid.¹⁶ As Ellinghausen notes in his commentary, this remains the medium of choice for the propagation of leptospire, another medically important spirochete.¹⁷

Life Cycle of the Tick

The life cycle of the tick that transmits Lyme disease was eventually defined and was recently reviewed by Steere. Briefly, tick eggs are laid in the spring. The larval stage emerges in August and September and feeds on small animals, most commonly the white-footed mouse *Peromyscus leucopus*, known to be a carrier of *B. burgdorferi*. The larval stage ticks then enter a resting phase through the winter and do not become active until molting occurs in the spring. The newly molted nymphs feed on a variety of vertebrates, but most frequently the white-footed mouse.¹⁸

The involvement of the white-footed mouse provides an opportunity to limit the spread of the disease by curtailing the tick population on the mice. Indeed, a patent has been issued for a special device, described

in our *IST® Press Digest* section this week.¹⁹ A cardboard tube, containing cotton saturated with an insecticide, is left where the mice nest. The mice use the cotton to build their nests; the insecticide kills the ticks during the winter.

Otherwise, as the normal cycle continues, the tick nymphs molt at summer's end to emerge as adults and feed on larger mammals, such as the white-tailed deer *Odocoileus virginianus*. These adult ticks mate, the female lays her eggs in the spring, and the cycle continues. Only the nymph and adult stages of the tick can transmit the disease to humans.¹⁸

Diagnosis and Treatment

Steere also reviews the three distinct stages of Lyme disease that occasionally overlap in some patients. As mentioned earlier, EM is the hallmark of the first stage of the disease. This skin rash begins as a small red bump and expands into an ever wider red circle, sometimes growing as large as 15 inches in diameter. Eventually, the skin in the center of the rash may clear, leaving a red, circular ring. While EM is common, 10 to 20 percent of patients diagnosed with the disease never develop the rash. Often headaches; chills; fever; stiff, aching muscles; or nausea occur in this early stage.

The symptoms of the second stage of the disease may not develop for weeks or months after EM has occurred. As Steere notes, the list of possible manifestations is long, but infection at this stage is often characterized by symptoms in the skin, nervous system, and musculoskeletal system. Patients may suffer debilitating malaise and fatigue. Cardiac problems, including myocarditis (inflammation of the heart muscle), pericarditis (inflammation of the membranes surrounding the heart), irregular heartbeats, or fainting spells, may develop, lasting for days to weeks. A variety of neurological

symptoms also may occur, including Bell's palsy (paralysis of a facial nerve), meningitis, or encephalitis.

The third stage of Lyme disease is characterized by painful, swollen joints; aching muscles; and inflamed tendons. These arthritic problems may occur intermittently at first but eventually become chronic.¹⁸

Current serological testing for antibodies using an enzyme-linked immunosorbent assay (ELISA) or indirect immunofluorescence assay is the standard method used to confirm diagnosis of Lyme disease. But according to Alan G. Barbour, Department of Microbiology and Medicine, University of Texas Health Science Center, San Antonio, these tests are still poorly standardized and often result in false-negative or false-positive results. Furthermore, patients in the early stages of the disease may prove seronegative because it can take several weeks after exposure for antibodies to be detected.²⁰

Oral antibiotics given for 10 to 21 days shorten the duration of the skin rash and other symptoms in the early stages of the disease. For men, nonpregnant women, and children over age eight, doxycycline or tetracycline HCl has been found effective. For pregnant or breast-feeding women and children under eight, amoxicillin is preferred. Those with more severe cardiac or neurological symptoms may require larger doses of antibiotics for longer periods. And anti-inflammatory therapy, such as aspirin or prednisone, is usually combined with antibiotics to treat arthritic symptoms.^{18,21}

Highly Cited Author

One of the most-cited authors in Lyme disease research is Steere, now with the Division of Rheumatology, Tufts University School of Medicine, Boston. Steere coauthored 11 of the 39 core papers for the research front on "Diagnosis of Lyme disease" (#88-0169), including the aforementioned 1977 paper that was the first to document a cluster of the disease in the US.⁸

Table 2: The *SCF*[®] research fronts on Lyme disease, 1983-1988. A=number. The first two numbers indicate the year of the research front. B=research-front name. C=number of core papers. D=number of citing papers for the year indicated.

A	B	C	D
83-2362	Clinical manifestations of Lyme disease	10	58
84-0839	Epidemiology of Lyme disease	21	153
85-0164	Ticks, spirochetes, and diagnostic tests for Lyme disease	15	93
86-0159	Clinical, serological, and radiographic aspects of Lyme borreliosis	18	129
87-0072	Lyme disease spirochete and <i>Borrelia burgdorferi</i> infection	45	248
88-0169	Diagnosis of Lyme disease	39	225

This groundbreaking paper has been cited over 200 times.

An indication of the fast growth in this field is its immediacy rating, a measure of how quickly a paper becomes a standard reference in the field. Six of the 39 core publications from this research front have been published since 1985, giving this front a high immediacy rating, a sign of rapid advance.

Research front #88-0169 is included in Table 2, which shows the progression of Lyme disease research from 1983 to 1988. The table includes the research-front name, the number of core articles, and the number of citing papers. These fronts are linked by the continuity of the core literature from year to year. If the same core publications are cited at the required thresholds in two adjacent years, a cluster linkage is established.

Europe Versus the US

Lyme disease is certainly not unique to the US. Indeed, G. Stanek, Hygiene Institute, University of Vienna, and colleagues have found that most European countries report thousands of new cases each month.²² European cases tend to progress slightly differently from their US counterparts. Although the basic clinical symptoms are the same, European cases are usually milder. Steere notes that the bacteria causing European Lyme disease are related to the US bacteria but have a slightly different morphology, outer surface proteins, and DNA make-up. These differences may account for the milder clinical symptoms.¹⁸

Researchers are puzzled about the recent increased incidence of Lyme disease on both continents. Writing in *Experimental and Applied Acarology*, Franz R. Matuschka, Free University of Berlin, Federal Republic of Germany, and Andrew Spielman, Harvard School of Public Health, Boston, theorize that the dramatic increase in Lyme disease cases has coincided with the recent increase of deer in both Europe and the US. In this century, more and more farmland has been allowed to revert to woodland, improving the habitat for deer.²³ Incidentally, *Experimental and Applied Acarology* (acarology being the scientific study of ticks and mites) was only started in 1985.

Our knowledge concerning Lyme disease is a result of research developed over the last century. By linking EM to the *Ixodes* tick, Afzelius set the stage for researchers on two continents to identify new neurological, dermatological, and arthritic conditions related to this rash. This is a case where world events shaped scientific recognition. If it were not for the increased swell of Lyme disease cases in this decade, it would seem unlikely that the 1921 paper by Afzelius would ever have reached noticeable citation levels.

* * * * *

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This Week's Citation Classic®

Afzelius A. Erythema chronicum migrans. *Acta Dermato-Venereol.* 2:120-5, 1921.

During a dermatological meeting in Stockholm in 1909 a patient was presented who, after a tick bite, had a circular erythema with a peculiar mode of spreading. The clinical picture of this condition, termed *erythema chronicum migrans*, is very characteristic: It starts as a fairly small round plaque and spreads peripherally to form ½-2 cm wide red bands that expand whereas the center again turns pale. The erythema may last from a few weeks to over a year. This condition, once called Afzelius's disease, is now regarded as a form of Lyme disease. [The *SCI*® indicates that this paper has been cited in over 65 publications since 1945.]

Afzelius's Disease—Or Is It Lyme?

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August 21, 1989

Eighty years ago my grandfather, Arvid Afzelius, reported on a severe skin rash that followed bites of the tick *Ixodes ricinus*. The report was given at a meeting in the Swedish language, but somewhat later, in 1910, it was published in German,¹ and again, and more fully, in 1921. These two scientific papers were practically the only ones that my grandfather published, and I did not pay much attention to them. My grandfather died before I was born, and it was my father who told me about the tick bites and the conditions that followed thereof and that

my grandfather had termed *erythema chronicum migrans*. My ignorance of these tick bites and their potential pathological importance was, however, so profound that I did not understand that this was the condition that was referred to when some colleagues told me that they had seen the term *Afzelius's disease* in a textbook of pathology.

As I am working in science myself, and because I find it useful to look in the *Science Citation Index*® for any references that may appear on topics that I have published, I started in the 1960s to use this source of information. In the first two decades, I did not notice any references to papers by an A. Afzelius, except for some to the pupil of Linnaeus, Adam Afzelius, who was a cousin of the great-grandfather of my grandfather Arvid. There was also an occasional reference to some of my own papers that had been quoted with my first initial omitted. From 1983 references to my grandfather's papers started to appear and they are still quoted fairly frequently. I now believe they will continue to be so for many years to come.

During my last visit to the US, I saw a reference to my grandfather and his work in *Newsweek*.² I then got an explanation as to why he is now so highly quoted. The discovery by my grandfather has lately turned out to be very important. Lyme disease in the US and the less severe chronicum erythema migrans in Europe are sister diseases caused by the infection of related spirochaetes injected by ticks.³ Both diseases are of economic importance. Lyme disease emerged in its epidemic form in 1975 and is now considered to be a potentially serious and debilitating disease. Last year over 5,000 cases were reported in the US.

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