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Close to Home: A History of Yale and Lyme Disease

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Yale scientists played a pivotal role in the discovery of Lyme disease and are credited as the first to recognize, name, characterize, and treat the affliction. Today, Lyme disease is the most commonly reported vector-borne illness in the United States, affecting approximately 20,000 people each year, with the incidence having doubled in the past 10 years [1]. Lyme disease is the result of a bacterial infection transmitted to humans through the bite of an infected deer tick, which typically results in a skin rash at the site of attack. While most cases, when caught early, are easily treated by antibiotic therapy, delayed treatment can lead to serious systemic side effects involving the joints, heart, and central nervous system. Here we review Yale's role in the discovery and initial characterization of Lyme disease and how those early discoveries are crucial to our current understanding of the disease.

RECOGNITION — LYME ARTHRITIS

The Yale Team

In the early fall of 1975, two mothers from Old Lyme, Connecticut, desperately sought medical help regarding the mysterious outbreak of arthritis and juvenile arthritis in their families and town. In the face of unexplainable symptoms and unsatisfying diagnoses, they reached out to the Connecticut State Department of Health and the Yale School of Medicine, sparking an investigation that would culminate in the characterization of what is now widely known as Lyme disease [2].

The initial studies carried out in Lyme, Connecticut, and two surrounding towns on the eastern bank of the Connecticut River in New London County were led by Allan C. Steere, MD, and Stephen E. Malawista, MD, from the Rheumatology section of the Yale School of Medicine, in conjunction

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†Abbreviations: ECM, *erythema chronicum migrans*; EM, *erythema migrans*; Osps, outer surface proteins; TROSPA, tick receptor protein.

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with David R. Snydman, MD, and Francis M. Steele, PhD, from the Connecticut State Department of Health, among others. Dr. Steere, the first author of the study, was a first-year fellow in rheumatology at the time. Dr. Malawista, then Head of the Rheumatology Section at Yale, continues to pioneer Lyme disease research at Yale.

The Investigation

In December 1975, Steere and Malawista led a surveillance study [3] to investigate the cause of a sudden outbreak of rheumatoid arthritis in and around Lyme. The study focused on the three contiguous towns of Old Lyme, Lyme, and East Haddam, where 51 residents were diagnosed with juvenile arthritis or arthritis of unknown cause (39 children and 12 adults) out of a total population of 12,000. The investigation consisted of thorough physical examinations and blood work of each patient on site at Yale. Additionally, detailed patient histories were collected through interviews with each patient's local physician and family members.

While the early physical examinations and laboratory tests revealed nothing out of the ordinary, the interview aspect was surprisingly informative. Approximately 25 percent of the patients in the study reported a skin lesion with an expanding bull's-eye pattern four or more weeks preceding the onset of arthritic symptoms. The authors found this to be particularly intriguing, as the lesion matched the description of *erythema chronicum migrans* (ECM), or *erythema migrans* (EM), a lesion previously reported in Europe that was thought to be a result of an infectious agent but had never before been associated with arthritis [4].

The mysterious arthritis also emerged in interesting patterns geographically and temporally. Most of the patients lived in close proximity within the towns — several children lived on a particular road, and the arthritis afflicted several members from the same family. The patients also exclusively lived in the rural wooded areas of town, with no cases present in the town centers. Notably, there was also a unique temporal clustering to the symptoms, with the majority of onset occurring from June through September. Rheumatoid arthritis, a known autoimmune disease leading to inflammation of the joints, had never before been, nor would it have been, expected to cluster geographically or temporally in this way.

The Skin Lesion-EM

The term *erythema migrans* (EM) was first mentioned in a presentation at the 1909 meeting of the Swedish Dermatological Society in Stockholm by Arvid Afzelius [2]. EM, also reported as *erythema chronic migrans* (ECM), was sometimes associated with a tick bite and was accompanied by nerve pain, paralysis, or meningitis. In Europe, doctors believed that EM might be caused by a bacterium, and penicillin and other antibiotics were moderately effective at treating it. This connection between ticks and EM led Steere and Malawista to hypothesize that Lyme disease might be transmitted by the bite of an arthropod such as a tick.

However, in the United States, there was little experience with EM, and in the European cases, EM never presented with arthritis. Intrigued by the EM lesion described by patients in their first study, Steere and Malawista eagerly awaited the next "high season." Indeed, during the summer of 1976, 30 new patients were identified, a survey of which strengthened the connection between the initial presentation of EM and the later development of arthritis [5]. The Yale team thus officially declared EM as the initial mark of infection and as the diagnostic hallmark of "Lyme arthritis," the initial name given for the disease by Yale investigators [6].

The Tick

While Steere and Malawista suggested the tick as the vector of Lyme arthritis as early as 1976 [3,5,6], in 1978 they showed epidemiological evidence for a tick vector by expanding their surveillance of the Lyme area across the Connecticut River [7]. They found that the incidence of Lyme arthritis was 30 times greater on the east side of the river, where Lyme is located, than it was on the west side, similar to the difference in deer and deer tick distribution in the area [8].

Scientists later confirmed that ticks indeed are the transmission vector of the infectious agent in Lyme disease. In the United States, Lyme disease is transmitted by the deer tick, or *Ixodes scapularis*, member of the *Ixodes* family. Other related *Ixodes* ticks have been found in Europe and Asia. The *Ixodes* tick can become infected at any point of its 2-year lifespan, which consists of three distinct stages — larvae, nymph, and adult [9,10]. The tick's survival depends on a feeding or "blood meal" at each stage of its life. The larvae hatched in late summer feed on small animals such as the white-footed mouse that can be infected but remain asymptomatic, serving as a continuous resource for infection. The larvae then molt into nymphs who feed again the following spring to early summer. Transmission to humans typically occurs by ticks in this stage, as increases in outdoor activity coincides with the nymph feeding cycle. The small size of the nymph, about the size of a poppy seed, allows them to go unnoticed. Furthermore, it has been shown that a tick must feed for 48 or more hours to transmit infection. In the fall, nymphs molt into adult ticks, which then feed on large animals, deer in particular. Adult ticks, which may actually mate on the deer itself, are transmitted by deer to the surroundings, usually leafy areas, where new larvae are hatched the following summer.

Deer thus play an important role in the tick life cycle by supplying a blood meal and potentially serving as a mating ground for adult ticks. Accordingly, the recent explosion of the United States deer population is thought to be responsible for the dramatic increase in the instances of Lyme disease, particularly in the Northeast [11]. Efforts to decrease the prevalence of *Ixodes scapularis* ticks and Lyme disease through the control of deer populations have proven successful [12] and is thought to be one possible Lyme disease prevention strategy.

LYME DISEASE — MORE THAN ARTHRITIS

To Steere and Malawista, it soon became clear that "Lyme arthritis" was actually only a small piece of a larger puzzle. Now that the EM skin lesion was confirmed as the initial mark of infection, the Yale team made a major effort to inform and educate the area near Lyme. The Yale team also asked local healthcare providers to refer patients to them soon after infection, enabling them to further characterize the disease and onset. As the result of these further studies, the team reports that Lyme disease can manifest in a variety of systemic ways, including those involving the nervous system [13], the heart [14], and the joints [15-19].

In 1984, the Yale School of Medicine brought together Lyme disease researchers from all over the world at the First International Conference on Lyme Disease in New Haven [10,20]. For the first time, professionals from a range of disciplines, including rheumatology, immunology, dermatology, and neurology, as well as public health officials and practicing physicians were gathered in recognition of this new complex and systemic disease. In 1985, Steere and Malawista were awarded the Ciba-Geigy International League Against Rheumatism Prize, an honor given once every 4 years, for the discovery and elucidation of Lyme disease. A group of Yale scientists continue to lead research efforts in various aspects of Lyme disease, including disease epidiomology (Durland Fish, PhD, and Eugene D. Shapiro, MD, from the Yale School of Public Health); the life cycle of the bacterium (Erol Fikrig, MD, Infectious Diseases, Yale School of Medicine); and inflammation and immunity (Linda Bockenstedt, MD, and Stephen Malawista, MD, Rheumatology, Yale School of Medicine).

Clinical Features

Today, Lyme disease is clinically described as either "early" or "late." Early Lyme disease initially presents itself with the characteristic bull's-eye patterned lesion, *erythema migrans* (EM). This lesion can last anywhere from several days to several weeks [21] and is most often accompanied by severe fatigue, myalgia, arthralgias, regional lymphodenopathies, and headaches or fever. The initial EM lesion can sometimes spread to produce smaller secondary

lesions 3 to 5 weeks after the primary lesion. Patients may further develop neurologic, cardiac, and rheumatogical symptoms in the early stage, the exact causes of which are still not fully understood.

One of the most common features of late Lyme disease is arthritis, particularly asymmetric oligoarticular arthritis, involving large joints such as the knees. Arthritis arises when an inflammatory response occurs in the synovial tissue between the joints and leads to painful swelling in the affected area.

TREATMENT

In 1977, in the journal *Science* [5], Steere and Malawista reported the presence of common antibodies extracted from patients experiencing an active EM lesion or active arthritis, thereby suggesting a common origin for these two clinical symptoms. While it would be several years before the infectious agent that causes Lyme disease would be isolated, the Yale team had growing evidence for the role of a bacterial infection in the disease. In 1980, Steere and Malawista determined that antibiotic treatment "shortens the duration of ECM and may prevent or attenuate subsequent arthritis" [22]. The study consisted of 113 patients presenting the EM lesion. Half of the group did not receive treatment, while the other half were treated with antibiotics. In patients who did not receive antibiotics, the EM lesion and associated symptoms resolved within a median of 10 days after the initial visit. Those patients receiving antibiotic treatment experienced significantly faster resolution of EM, with a median of duration of 4 days. Furthermore, significantly fewer patients in the antibiotic group went on to develop arthritis compared to patients in the control group. Antibiotic therapy is still the major line of treatment for Lyme disease [23].

The Infectious Agent: B. burgdorferi

In 1982, Burgdorfer and colleagues isolated the infectious agent that causes Lyme disease that now bears his name: *Borrelia burgdorferi* [24]. The genus *Borrelia* is a member of the family *Spirochaetacaea*, also known as spirochetes, which are Gram-negative bacterium characterized by a wavelike body and flagella [21]. Burgdorfer and colleagues collected and dissected hundreds of *Ixodes* ticks from Shelter Island, New York (another location with a high prevalence of Lyme disease) and found that most of them contained spirochetes, specifically in the mid gut region. They further characterized the spirochetes with dark field and electron microscopy. Finally, indirect immunofluorescence revealed that antibodies extracted from serum of Lyme disease-infected patients reacted positively with the spirochete, while serum from control patients did not — thereby confirming the link between the tick-derived spirochete and Lyme disease. In the United States, Lyme disease is primarily caused by the spirochete *Borrelia Burgdorferi sensu stricto*. Other related genospecies of *Borrelia* such as *B. garinii*, and *B. afzelii* have been identified in Europe and Asia.

Outer Surface Proteins

B. burgdorferi's persistence inside the tick and transmission to its human host are thought to be a product of altered expression of outer surface proteins (Osps). When inside the tick host, expression of OspA enables *B. burgdorferi* to persist in the gut. More specifically, Erol Fikrig, MD, and colleagues at Yale have found that a tick receptor protein (TROSPA) expressed in the tick gut is responsible for tight binding to OspA [25]. During a tick's blood meal, expression of OspA is decreased, leading to dissociation from the gut, and expression of OspC is increased. OspC is thought to play a role in migration of the bacterium from the tick's gut to its salivary glands [26]. Fikrig and colleagues, along with Durland Fish, PhD, from the Yale School of Public Health, have since shown that the interaction of OspC with the tick salivary protein Salp15 enhances the infectivity of *B. burgdorferi* in its new mammalian host [27]. Once inside the human host, *B. burgdorferi* induces immune responses that lead to a variety of symptoms present in the disease. Vaccines incorporating OspA, a strong antigen that induces an

antibody response, have been developed but are currently off the market due to complications [28,29].

Diagnosis

Clear diagnosis of Lyme disease has been challenging. If the EM rash is present, then diagnosis is ameliorated, but since not all patients present with a purely characteristic rash and sometimes do not notice it in time, diagnosis remains difficult. Serological tests that indirectly test for antibodies produced against *B. burgdorferi* are often used, along with somewhat less accurate PCR assays. There is some controversy over misdiagnosis of Lyme disease and even the existence of long-term *chronic* Lyme disease [9,21,30] that is beyond the scope of this article. However, a regimen of antibiotic therapy is typically sufficient in treating the disease at any stage, with greatest efficacy seen for patients receiving treatment soon after the tick bite and associated EM lesion.

CONCLUSION

The massive efforts taken by Steere and Malawista toward the investigation of the clustering of arthritis in Lyme in the late 1970s and early 1980s have led to the discovery of a complex, multifaceted disease. The results of their studies have laid the foundation for our current understanding of the role of the infectious agent, the tick as vector for infection, the EM skin lesion, and the systemic clinical symptoms of late onset. Yale investigators continue to lead the field of Lyme disease research today.

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