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Lyme Disease:
The Up and Coming Disease of the 1990's

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Introduction

A significant discovery came about in 1975 because of two observant housewives. One of them, a physician's wife, noticed a tendency towards the diagnosis of juvenile rheumatoid arthritis within her community. She knew that this disease did not normally occur in clusters and decided to report the observation to the State Health Department. The other housewife reported the unusual occurrence of arthritis occurring from young to old in four of her family members.

Dr. Allen Steere, M.D., and co-workers decided to investigate their reports. They discovered that within three villages of Connecticut — Lyme, Old Lyme, and East Haddam — a high frequency of arthritis was reported. The high frequency suggested that some infectious agent was involved. They also noticed that the majority of cases occurred in the summer or early fall. This seasonal tendency implied involvement of an arthropod vector. At that time, not much more was learned about the disease. However, because of its geographic tendency, the disease was appropriately named Lyme Disease (LD).1

Etiologic Agent

The etiologic agent of LD was not discovered until 1982. At that time, Dr. Willy Burgdorfer found strong evidence to indicate that a spirochete causes LD and that the disease was spread by an arthropod vector. In his studies, the guanine-plus-cytosine content from isolates of the organisms isolated from the vectors and the blood, spinal fluid, and skin of human patients fit into the category of a Borrelia species. However, the DNA homology index was higher than that of other Borrelia. Since this spirochete did not fit into any species category of Borrelia, it was named after its founder, and came to be known as Borrelia burgdorferi.2

Vector

The theory originating in 1975 that LD is transmitted primarily by an arthropod vector has been confirmed. The main arthropod involved appears to be Ixodid ticks, however, the species of ticks that transmits the disease may vary with the geographical location. For instance, in the northeastern states (Connecticut, Delaware, Maryland, Massachusetts, New York, New Jersey, Pennsylvania, and Rhode Island) and Midwestern states (Minnesota and Wisconsin), Ixodes dammini is the primary vector. In the Western United States (California, Oregon, Nevada, and Utah) Ixodes pacificus is the tick that transmits the agent of LD. In Europe, USSR, and Scandinavia, Ixodes ricinus is the vector involved.3 Recently, a report claims that Ixodes persulcatus transmits LD in Japan.4 Lyme disease may also occur outside the normal recognized habitat of these ticks. There have been reports of LD occurring in Arkansas, Florida, Georgia, Kentucky, Indiana, Ohio, Montana, North Carolina, Vermont, Tennessee, Texas, Virginia, and Iowa.3,6 Some investigators have suggested that birds, which may be parasitized by some Ixodes ticks, may carry ticks outside their normal habitat. Other researchers isolated B. burgdorferi from ticks such as Amblyomma americanum, Dermacentor variabilis, and I. scapularis.2,4,5,6 It may also be possible that horse flies, deerflies, or mosquitoes act as secondary vectors of this disease.

Another interesting possible means of transmission was discovered when researchers studied deer mice (Peromyscus maniculatus) and found B. burgdorferi in their urine. It was determined

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that mice could be infected by ingestion of infected urine. In this way, it was hypothesized that contaminated feedstuffs could transmit the disease.\(^8\)

Despite these possible modes of transmission, the *Ixodes* tick is known to be a primary vector of LD. Therefore, the incidence and occurrence of the disease relies heavily on the propagation, life cycle, and distribution of this tick.

The *Ixodes* tick has a two-year cycle. In late winter and early spring the tick deposits its eggs. In late summer the larvae emerge and seek a blood meal from their preferred host, the mouse. The following spring, the larvae transform into nymphs, which feed on blood from a mouse or other available mammal. In late fall the nymphs become adults and usually feed on deer, their desired host. The female mates with the male and then engorges herself with blood, drops to the ground, discharges her eggs, and dies.

The tick can become infected with *B. burgdorferi* by feeding on an infected host at any point in this cycle. It can then transmit the disease to other animals when it feeds on them. The most common time for the tick to transmit the disease to humans or animals is during the nymph stage.\(^2\)

Ticks can also be infected with the agent of disease by transovarial transmission. This has been shown to occur with *I. ricinus* but has not been proven with other species.\(^3\)

**Incidence**

Since 1975, there have been reports of LD in 32 states as well as Europe, Australia, USSR, Ireland and Japan.\(^3,4,9-12\) Within the U.S. there have been over 6,000 reported cases since 1980.\(^13\) The Center for Disease Control (CDC) suspects that the number of cases is probably higher, because physicians are just starting to become aware of the disease.\(^14\) Most of the available statistical data is from cases involving humans.

However, the disease does affect other species. LD has been reported in raccoons (*Procyon lotor*), white-tailed deer (*Odocoileus virginianus*), opossums (*Didelphis virginiana*), eastern chipmunks (*Tamias striatus*), gray squirrels (*Sciurus carolinensis*), white-footed mice (*Peromyscus leucopus*), rabbits, passerine birds, dogs, horses, and cattle.\(^15-20\)

**Lyme Disease in Humans**

Lyme disease in humans is a multisystemic complex disorder that can result in dermatologic, neurologic, cardiac and joint abnormalities. The clinical syndrome has been divided into three stages. The first stage involves the development of an annular erythematous macule or papule at the tick bite site, often with an area of central clearing. This lesion, referred to as erythema chronicum migrans (ECM), is regarded as the hallmark sign of LD in humans. According to the Minnesota Health Department, ECM is present in 70 percent of the LD cases.\(^14\) Other symptoms which may or may not occur with ECM include fever, muscle aches, headache, stiff neck, lethargy and sore joints. These symptoms can be accompanied by "...high erythrocyte sedimentation rate and total serum IgM titer, cryoglobulinemia, abnormal Cl-1 binding activity and circulating immune complexes in both blood and spinal fluid."\(^2\)

The second stage of the disease involves neurologic and cardiac abnormalities. Usually within weeks to months after onset of the first stage signs, neurologic signs such as meningitis, cranial and peripheral neuropathies, can develop. Some investigators feel that the signs closely resemble Alzheimer’s disease and multiple sclerosis.\(^21\) The cardiac sequelae, including lymphoplasmacytic interstitial myocarditis, are characterized by varying degrees of heart block that typically resolve within one to six weeks.\(^2\)

The third and final stage presents as arthritis. Although it is possible to see arthritis in the earlier stages of LD, it is not usually clinically apparent until several months after onset of the disease. This part of the disease can be confused with other causes of arthritis such as systemic lupus erythematos, rheumatoid arthritis, trauma, or other infectious agents.\(^2\)

Recently, concern about Lyme disease and pregnancy has been brought to the attention of the Center for Disease Control (CDC). A 1986 study showed that "of the 19 pregnancies, five had adverse outcomes, including syndactyly, cortical blindness, intrauterine fetal death, prematurity and rash in the newborn".\(^22\) These problems occurred when women were infected during various stages of their pregnancy, however this study could not directly link these problems to the *B. burgdorferi* infection. Despite this, officials advise pregnant women not to take any chances and visit their physicians if they have signs consistent with LD.\(^23\)

**Diagnosis**

LD may be suspected in humans with the
clinical signs discussed above and a history of possible exposure. Confirmation of LD is based upon direct and indirect observation of the etiologic agent, culture and identification of the etiologic agent and serologic tests.

Microscopic examination of certain samples may potentially provide a rapid diagnosis. The spirochete may be seen in synovial fluid, blood, CFS, or ocular fluid samples when direct dark field microscopy is used. The organism may also be identified when tissue specimens stained with aniline dyes or silverstains are microscopically examined. Direct fluorescent antibody techniques have been used on tissue specimens in an effort to enhance detection. However, the success rate of diagnosis using these direct methods is low; a negative result does not rule out the possibility of disease.3

The organism can be cultured using Modified Kelly’s medium. Growth requires a microaerophilic environment for up to eight weeks, and the medium should be checked weekly for the presence of spirochetes. This is a low yield process and the medium is costly and difficult to prepare. The process is also labor intensive making it impractical for the practitioner.24 Current research, directed at developing a test to detect B. burgdorferi in the urine, may enable the practitioner to obtain a rapid diagnosis.14

Presently, serology is the major diagnostic tool used to diagnose LD. There are two techniques currently used to detect serum antibodies to B. burgdorferi: indirect fluorescent antibody (IFA) and enzyme-linked immunosorbent assay (ELISA). Positive results for the IFA are titers greater than or equal to 1:62 and positive results for the ELISA are greater than or equal to 1:160.25,26 The CDC claims that both of these tests are “...equally sensitive in their ability to reveal half of all cases of Lyme Disease in its early stages and essentially all late complicated cases.”12 Some reports claim that the ELISA is slightly more sensitive. This, plus the fact that the test is objective and can be automated, makes the ELISA technique more desirable.25,26

There are basically two drawbacks in the use of the serologic methods for diagnosis. First, false positives have resulted in humans with yaws, pinta, and syphilis.2 Secondly, LD in its early stages cannot be consistently detected serologically. Antibody titers to B. burgdorferi are not detectable serologically until one or two weeks post-infection, since it takes that long for the body to start producing IgM. The IgM levels usually peak around the third to sixth week and may persist for months or years after the disease onset. IgG levels tend to rise more slowly and are not detectable until the fourth to sixth week of the disease. IgG levels are highest months to years after infection and may remain elevated for years after clinical remission.27 Since the IgG and IgM levels rise slowly, early diagnosis of LD is based on clinical signs and response to therapy.

Treatment

Certain antibiotics have been found to be highly effective in the treatment of LD. Tetracycline, penicillin, and erythromycin are the most useful drugs.9,14,28 A recent article also describes another drug, ceftriaxone, as being effective as a treatment for LD.14 If the disease is recognized early, oral antibiotics are effective. However, prolonged oral therapy or intravenous therapy may be indicated if the disease is not recognized until the later stages.

Prevention

Prevention of this disease involves common sense. Endemic or tick infested areas should be avoided whenever possible. If not, protective clothing and tick repellent may prevent exposure. If any clinical signs of LD are present, a physician should be consulted.9,23,29

Lyme Disease in Dogs

Lyme disease in dogs does not appear to have three distinct stages as it does in humans. To date, there have been no reports of ECM in dogs. This may suggest that the lesion does not occur or that owners do not see the lesion because of the animal’s hair coat. There also have been no reports of neurologic problems directly associated with LD, however, myocarditis similar to that seen in human Lyme carditis, has been recently reported.30

The major clinical sign seen with LD in dogs appears to be arthritis.31,32 In a recent study performed by Magnarelli et al., 271 dogs were examined that were suspected of having borreliosis.31 In this study, 91 percent showed signs of lameness, 53 percent were anorexic, 44 percent has fever, 29 percent showed signs of fatigue, 5 percent has lymphadenopathy, and 2 percent of the dogs experienced renal impairment. Males and females appeared to be equally affected. Lameness was often intermittent, affecting the carpal, digital, tarsal, elbow, shoulder, stifle, cervical or lumbar

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regions. Serologic conformation of borreliosis was made in 68 percent of the 243 lame dogs. However, 78 dogs clinically diagnosed as having LD were seronegative.

**Diagnosis**

This fairly high incidence of seronegative animals in clinically diagnosed dogs brings about an important point. All other differential diagnoses need to be ruled out before a definitive diagnosis of LD can be made. Differential diagnoses would include degenerative joint disease, septic arthritis, trauma, rheumatoid arthritis, and systemic lupus erythematosus (SLE). Physical examination, laboratory findings and radiography should rule-out trauma or degenerative joint disease. Giemsa stains and culture of synovial fluid will help rule out septic arthritis. Systemic lupus erythematosus is usually associated with other organ involvement. Antinuclear antibodies or LE cells can be detected in SLE. For rheumatoid arthritis, radiographs, arthrocentesis and cytology, and rheumatoid factor may aid in diagnosis.

Direct methods of diagnosis, such as dark field microscopy and culture, are infrequently diagnostic. Measurements of serum antibodies to *Borrelia burgdorferi* using ELISA or IFA techniques are the best methods available to reach a definitive diagnosis. Antibody titers rise slowly from onset of infection. In the dog, IgM levels peak at about one month; IgG levels rise more slowly but persist for months. By the time arthritis develops IgG levels are generally detectable. In the dog, there seems to be no problem with cross reaction to *Leptospira*.

**Treatment and Prevention**

Little research has been done with respect to treatment of animals with LD. Tetracycline, penicillin, and erythromycin are effective in humans, and these drugs are currently being used with success in dogs as well. As with humans, precautions should be taken when a dog is in a tick infested area. Tick collars and powders may be useful. When a dog has spent time outside, it should be checked carefully for ticks.

**Lyme Disease in Horses**

Lyme disease has recently been reported to occur in horses in endemic areas. Reports have been less common than in man or dogs but similar clinical signs are associated with the disease. Positive titers (greater than 1:64) have been found in both clinically normal horses and in horses with signs attributed to the disease. Survey reports from endemic areas found 24-36% of general horse population to have positive titers. Nine clinical cases were identified in Connecticut with signs including arthralgia, lameness, laminitis and myalgia and with positive titers ranging from 1:64 to 1:1024. Eight of these were treated with antibiotics and phenylbutazone and all recovered. An equine clinician in Lyme, Connecticut reports seeing approximately 12 clinical cases of LD per 1,000 horses per year (1.2%).

**Diagnosis**

Diagnosis of LD in horses is largely based on clinical signs ruling out other diseases and response to antibiotic therapy. The clinical signs reported in horses include lethargy, low grade fever, multiple swollen painful joints, stiffness and reluctance to move, laminitis, skin hypersensitivity and myalgia, uveitis and various central nervous system signs, suggestive of encephalitis. The classic ECM lesion of humans has not been reported in horses although areas of hair loss and flaky skin around suspected tick bites may occur.

Several procedures are useful in the diagnosis of LD. In cases of arthritis, septic or traumatic causes should be ruled out with radiographs and synovial fluid analysis. A predominance of lymphocytes, plasma cells and villous proliferation are the common joint characteristics reported in horses with LD. When anterior uveitis is present, LD must be differentiated from disease such as onchocerciasis or leptospirosis. With signs of encephalitis, various viral encephalitides, protozoal myelitis or traumatic disorders must be ruled out with the help of CFS fluid analysis, viral titers and radiographs.

Serologic testing for *B. burgdorferi* antibodies can be very helpful in confirming LD. Both IFA and ELISA tests are available. False negative findings can occur, especially early in the clinical course and some cross reactivity with *Leptospira* organisms may result in false positives. For this reason most labs consider only titers greater than or equal to 1:64 to be indicative of LD. Since some normal horses have positive titers in endemic areas, serology alone does not confirm the diagnosis. Demonstration of a rising titer from paired samples obtained during clinical disease, plus good response to therapy are necessary to make a defini-
tive diagnosis.

Spirochetes can be identified on dark field microscopy or by culturing from blood, synovial fluid or urine. Timing and handling of samples is critical and these procedures are usually not successful. Histopathologic findings from kidney, eye, stomach, reproductive tract, synovium and brain may show lymphocyte and plasma cell infiltrates. Krajian silverstain can be used to visualize spirochetes in the anterior chamber of the eye. Direct IFA should be used on brain tissue from animals suspected of *B. burgdorferi* infection.

### Treatment and Prevention

Horses have been successfully treated with antibiotics and non-steroidal anti-inflammatories. Most commonly used are tetracycline, ampicillin or procaine penicillin G for 10-14 days. Phenylbutazone may be given concurrently. This therapy usually results in abatement of the clinical signs, although a recurrent episode a few months after therapy has been reported in one case. It is unclear if this therapy completely clears the infection or if a carrier state may be created. It is currently presumed that a latent infection persists if the antibody titer remains high for a year or more. This may be difficult to distinguish from titers resulting from repeated exposure in endemic areas.

Prevention relies on insect control and avoiding endemic areas. The pattern of clinical disease in the horse is still unclear but seems to parallel those of the human. Therefore, any horse with undiagnosed disorders involving joints, heart, the nervous system, eyes, abortions or fetal anomalies should be considered a suspect for Lyme Disease.

### Lyme Disease in Cattle

Lyme disease has recently been reported in cattle. In a report submitted by Burgess et al, a heifer with LD had "...chronic weight loss, bilateral distension of the carpal joints, lameness, and inability to rise without aid". Investigators suggest that deer mice may play a vital role in transmission of this disease, since these mice are frequent habitors of barns. For this reason, grain should be stored so that it cannot be contaminated by the urine of these mice.

### Diagnosis

Histopathologic examination of heart, kidney, lung, and liver has been used to diagnose LD in cattle. Lymphocytes, plasma cells, and eosinophils were seen in cardiac and renal tissue of a cow diagnosed with LD. Immunofluorescent evaluation of liver and lung has aided in visualizing *B. burgdorferi* spirochetes. IFA and ELISA serologic titers have been particularly useful in diagnosis. It is possible to find positive titers to *B. burgdorferi* in serum, synovial fluid, and milk.

### Treatment and Prevention

At this time, there have been no reports of controlled studies on treatment in the bovine.

### Conclusion

Throughout the years, the numbers of cases of Lyme Disease have been on the rise. There are currently so many human cases reported that Schwan and Burgdorfer from the National Institute of Allergy and Infectious Disease have claimed LD to be "...the most prevalent human arthropod-borne disease in this country." Animal cases of LD are just beginning to be recorded. Dogs and horses are the most extensively studied domestic animals infected with the disease. Recently, cattle have been added to the list.

Despite all the incoming data little is known about the disease. There have been a few reports of inconsistencies in the questions about the role of *Ixodes* tick as the primary vector. The exact pathogenesis of the disease is not known.

Additionally, diagnostic procedures and tests need to be refined to adequately diagnose LD. Direct staining, phase contrast dark field microscopy, and isolation techniques are not sensitive tests. Even though the ELISA and IFA test results have a higher yield, the results are not always absolute. The urine test, which is currently being developed, may help improve some of the inconsistencies in diagnosis.

The paucity of diagnostic tools may allow LD to be overlooked. Exposure to a tick infested area, knowledge of a tick bite, and clinical signs are useful bits of information. The clinician can guard against an oversight by being observant, ruling out other diseases and making maximum use of available diagnostic tests available.

The history of exposure to a tick-infested area, knowledge of tick bites, or clinical signs consistent with LD should alert the clinician to the possibility of this tick-borne disease.
REFERENCES
