Lyme Disease

- **Lyme disease, caused by a tiny microorganism known as a spirochete, is transmitted by the tick *Ixodes dammini* in the Northeast and upper Midwest, and on the West coast by *Ixodes pacificus,* the western black-legged tick.**
- **Along the North Atlantic coast of the U.S., surveys indicate that 20 to 30 percent of *Ixodes* ticks have the Lyme disease spirochete in their gastrointestinal systems.**
- **In 1991, over 9,000 cases of human Lyme disease were reported to the U.S. Centers for Disease Control.**
- **Lyme disease has been reported in 49 U.S. states, as well as Canada, Europe, and Asia.**
- **While both people and animals are susceptible to the bite of the *Ixodes* tick, Lyme disease *cannot* be spread directly from animals to people.**

Lyme disease is a tick-borne bacterial disease that is most often contracted during the months of May through July. Since its discovery in 1975, it has become the most frequently diagnosed tick-transmitted illness in the U.S., if not the world. In the U.S., it is found primarily in the Northeast (in coastal areas), the northern Midwest (Minnesota and Wisconsin), and the West (parts of California, Oregon, Utah and Nevada). The disease is also found throughout Europe and has been recorded in Australia, the Commonwealth of Independent States, China, and Japan.

The symptoms of Lyme disease can be severe, ranging from acute headache and neck stiffness to neurological impairment and manifestations resembling rheumatoid arthritis. The discovery of this disease, from its recognition as a clinical entity to the identification of the causative agent, is a triumph of modern biomedical research.

Lyme disease was first reported in November 1975, when the Connecticut State Health Department received telephone calls from two mothers whose children had just been diagnosed with juvenile rheumatoid arthritis, a normally rare condition affecting only one in 100,000 children. In addition, a number of adults and children in the town of Lyme had also been diagnosed with rheumatoid arthritis, alarming health officials and

Massachusetts Society for Medical Research
1440 Main Street
Waltham, MA 02154-1649
(617) 891-4544

The Research Facts

prompting immediate research on this mysterious disease.

Researchers soon discovered that the disease was limited to three adjacent townships in eastern Connecticut — Old Lyme, Lyme and East Haddam. Most victims lived in heavily wooded areas and manifested symptoms during the summer months. One-fourth of patients interviewed reported having a strange expanding skin rash several weeks to several months before the arthritis-like symptoms. On the basis of these observations, researchers concluded that they were dealing with a new disease and named it Lyme disease after the town in which it was first observed.

In 1909 a skin lesion, called *erythema migrans* or EM, was described in Europe in individuals who had been bitten by the tick *Ixodes ricinus.* Based on this early work, researchers were able to identify the tick *Ixodes dammini,* a species closely related to *I. ricinus,* and confirm it to be the primary vector (or carrier) of the Lyme disease spirochete.

The search for the actual disease agent responsible for both EM and Lyme disease was aided by a Montana researcher, who isolated long, irregularly shaped spirochete bacteria in the intestinal tracts of *I. dammini.* The spirochetes were then grown in culture to obtain them in sufficient quantities for experimentation.

A direct test of the pathogenic (disease-causing) potential of the spirochete was carried out in rabbits. After placement of spirochete-infected ticks on the shaved skin of albino rabbits, microscopic examination of the skin at the site of tick attachment revealed the presence of live spirochetes. This work led to the isolation of the spirochetes from the blood, skin, and cerebrospinal fluid of Lyme disease victims.

On the basis of its DNA, the spirochete was determined to be a new species in the genus *Borrelia.* In 1984, to honor its discoverer, Willy Burgdorfer, it was given the full scientific name *Borrelia burgdorferi.*

B. burgdorferi is a gram-negative spirochete bacterium. It is a unicellular, loosely coiled, left-handed helix (i.e., it coils in a counterclockwise direction). Like most spirochetes, it is small and difficult to detect, allowing it to pass through many filters designed to retain bacteria. The spirochete has been found in the tissues of several mammals susceptible to bites by the tick *I. dammini,* including field mice, voles and deer. On the west coast of the U.S., the western black-legged tick *Ixodes pacificus* is the primary vector for transmission of *B. burgdorferi.* The dusky-footed woodrat is the primary animal reservoir of *I. pacificus.*

The life cycle of the tick *I. dammini* normally spans two years. Eggs are deposited in the spring and hatch into free-living larvae a month later. During the first summer, the larvae feed once on the blood of a host and then enter a resting stage in winter. The following spring the larvae molt, enter a nymphal stage and again attach themselves to an animal host to feed. The majority of ticks at this stage are found on the white-footed mouse. It is also at this stage that the ticks are most likely to attach themselves to humans.

At the end of the summer, nymphs molt into the adult stage. They can be found in brush about one meter above the ground, where they easily attach themselves to larger mammals. In the northeastern U.S., the adult *Ixodes* ticks are found predominantly on white-tailed deer. For this reason, they are often referred to as *deer ticks*.

Clinically, Lyme disease usually begins with the EM rash, which develops from 2 to 30 days after an individual has been bitten. The rash is often accompanied by profound fatigue, fever, chills, headache and backache, and secondary lesions may appear at various sites on the body. In some patients, however, none of these symptoms appear. It has also been documented that the symptoms of Lyme disease can disappear spontaneously, although the patient remains infected and the disease recurs intermittently.

Weeks later, some patients may develop neurological complications (meningitis or facial palsy, for example) or migratory musculoskeletal pain. A small percentage of patients develop cardiac difficulties lasting from three days to six weeks. These patients may experience palpitations, dizziness, or shortness of breath.

Months later, about 60 percent of untreated patients develop arthritis. Arthritis attacks usually last from a few days to a few weeks and primarily affect the knees and larger joints. Years later, patients may have late neurologic involvement, which manifests itself primarily as memory impairment or spinal pain.

Early Lyme disease can be treated successfully with antibiotics administered orally, most commonly doxycycline and amoxicillin. Neurologic complications usually require treatment with intravenous ceftriaxone or penicillin therapy.

Anyone who lives in or visits an area where Lyme disease is *endemic* (native to a particular region) is susceptible to the condition. The disease is indiscriminate, affecting both sexes and all age groups. There is currently no vaccine for the prevention of Lyme disease in humans.

Lyme disease has also rapidly become a veterinary problem. Dogs, horses, and cows in endemic areas have developed debilitating joint problems that veterinarians believe are caused by *B. burgdorferi.*

Canine Lyme disease is diagnosed with a blood test performed in conjunction with clinical signs of the disease. As physicians do with human Lyme disease patients, a veterinarian will generally recommend prompt treatment with antibiotics for a canine patient with the disease. A canine vaccine against Lyme disease is available through veterinarians, although the availability of the vaccine may vary from state to state. The efficiency of the vaccine in the field has not yet been proven.

In horses, chronic lameness, which variably affects multiple limbs, is frequently associated with Lyme disease. Variable joint swelling, weight loss despite adequate appetite and feed intake, neurologic disorders, and cardiac arrhythmias are also considered symptomatic.

How has animal research helped in the study of Lyme disease?

The identification of the spirochete *Borrelia burgdorferi* as the disease agent in Lyme disease was aided by animal models, most notably the rabbit. Albino rabbits, for example, were used to detect the presence of live spirochetes at the site of tick attachment.

Dogs were also used in the development of the first vaccine against canine Lyme disease. The vaccine is now licensed by the U.S. Department of Agriculture. While currently available to pet owners through their veterinarians, it is only recommended in highly endemic areas.

Is animal research still necessary to study Lyme disease?

Many patients with symptoms of chronic Lyme disease do not respond to antibiotic therapy. A mouse model of the disease is being used to determine the effectiveness of antibiotic therapy for the treatment of Lyme disease symptoms.

The mouse model has been shown to closely resemble the disease in humans. SCID mice, afflicted with a disease called severe combined immune deficiency, are virtually born without an immune system. These mice are being used to study the mechanism by which Lyme disease attacks the heart and joints. These experiments point to a possible genetic component in susceptibility to the disease. Evidence of a genetic susceptibility comes from experiments and epidemiological studies in dogs. One

study has shown that many dogs in endemic areas exhibit the presence of antibodies to *B. burgdorferi,* an indication that they have been infected with the spirochete. However, follow-up studies on these dogs months later showed no progression of Lyme disease when compared with dogs not exposed to the spirochete. In addition, when dogs are experimentally infected with the Lyme disease spirochete using ticks, many develop self-limiting arthritis, suggesting that the immune system may have arrested the condition in these dogs.

Clinical signs of Lyme disease in horses are variable, and skin lesions are seldom seen. A blood test to diagnose Lyme disease in horses is currently under development. The pony is one experimental model being used to study the condition in horses.

What lies ahead in research on Lyme disease?

In 1991 a long-term study of the effects of Lyme disease was begun in the town of Ipswich, Mass. 100 participants have volunteered for the study, half of whom have contracted the disease and half of whom have not. The work is being modeled after the Framingham Heart Study, which has followed the lives of residents of Framingham, Mass. for years in order to monitor the effects of lifestyle on heart disease. A similar study is being conducted in Lyme, Conn. and has been on-going for the past 16 years.

The immune system protein interleukin-1 (IL-1) is synthesized primarily by white blood cells called *macrophages.* It is a regulator of the body's immune response against a variety of foreign invaders. Among other things, IL-1 coordinates the body's reaction to bacterial infection and trauma by regulating the onset of fever, the release of neutrophils from bone marrow, and the proliferation of connective tissue cells called *fibroblasts.*

One of the most powerful stimuli for the release of IL-1 is a lipopolysaccharide (LPS), a complex of sugar and lipid molecules found in the outer envelope of the cell walls of all gram-negative bacteria. Since *B. burgdorferi* is a gram-negative bacterium, some researchers speculate that the LPS contained in the cell wall of the spirochete can trigger the release of IL-1, producing powerful effects on the body. To prove the effects of LPS on the body, experiments are being conducted by injecting rabbits with pure LPS.

Researchers are making progress toward a vaccine to combat Lyme disease. Among the promising candidates is one based on a protein, called OspA, from the surface of the *B. burgdorferi* bacterium. OspA has been identified as the protein responsible for conferring immunity to the disease. Mice vaccinated with this protein have been

shown to successfully fight off infection from tick bites. Even more, the antibodies triggered by the vaccine in the mice were also found to kill off the spirochetes in the ticks that bit them. Based on this finding, an experimental vaccine has been developed, which consists of a genetically engineered piece of OspA lifted from the outer coat of *B. burgdorferi.* Researchers are currently investigating the application of this technique to a human vaccine. A major pharmaceutical company is now developing this product for human clinical trials.

Hamsters are also being used as a model to develop a human vaccine against Lyme disease. In this work, a killed version of the whole *B. burgdorferi* bacterium is being studied for the ability to confer immunity on the host.

In addition to symptoms of Lyme disease that mimic those of humans, veterinarians are finding that a small fraction of canine Lyme disease patients develop a progressive and fatal kidney syndrome that is unresponsive to treatment. Understanding this serious condition is work being undertaken through experiments in dogs.

Also under investigation is the possibility of limiting the spread of Lyme disease by immunizing deer and mice in the wild, a method now being tried to combat rabies among wild raccoon populations.

Lyme disease is a widespread and debilitating condition in both humans and animals. But much remains to be learned about its development, prevention and cure. Animal research remains an important element to winning the battle against this debilitating disease.

For further information contact the MSMR or:

Tufts University School of Veterinary Medicine,
200 Westboro Road, North Grafton, MA 01536
(508) 839-5302

Massachusetts Society for Medical Research
1440 Main Street
Waltham, MA 02154-1649
(617) 891-4544