

THE DIFFICULT PROBLEM OF ONE IN 10 CASES OF LYME DISEASE:  
Is it co-infection? // Or factors unique to the patient? // Or bacteria-evading  
antibiotics? // Or are there other reasons why **it won't go away?**

# When Lyme Lingers

■ BY DAVID HOWARD //



he idea that he might have Lyme disease never crossed Ethan Robert's mind. His symptoms began in 2009 with pain in a sciatic nerve that ran down his left leg. After a month the pain went away, but the following year his shoulders and elbows hurt, and the pain migrated to different joints in his arms for about 18 months. Robert, who lives in Boston, wrote that off to overexertion at the gym.

Pain later flared in his hip and his jaw, and by last summer, he had developed marked swelling and pain in both knees and an ankle—four years after his ordeal began. When that siege of arthritis finally prevented him from walking to work, he called his doctor, who referred him to the rheumatology department at Massachusetts General Hospital. Robert wound up seeing Allen Steere, the researcher who produced the first conclusive account of Lyme disease in 1977 and is now lead investigator of the illness at the Center for Immunology and Inflammatory Diseases at MGH.

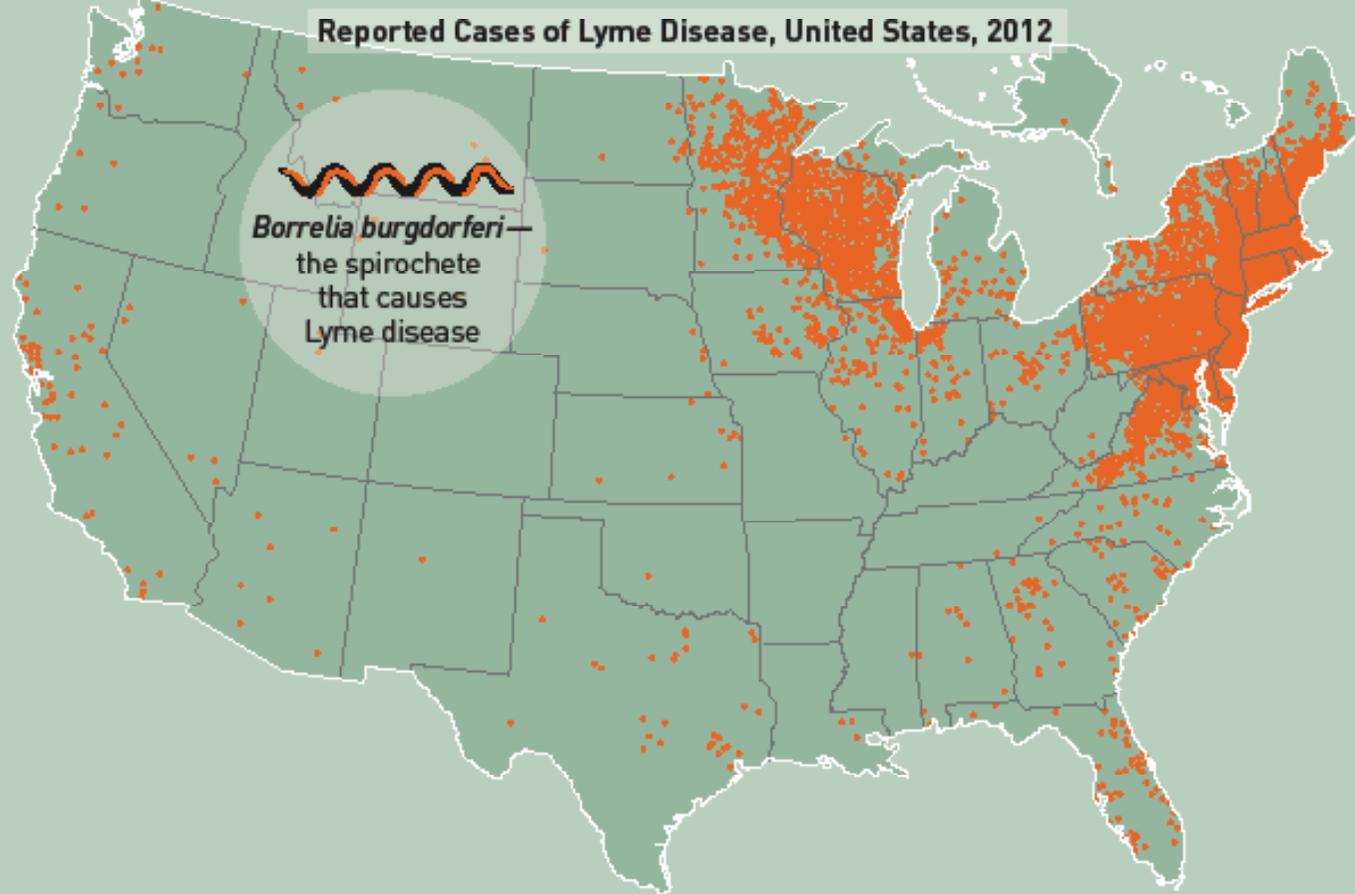
Tests showed that Robert did indeed have Lyme, and he was treated with antibiotics—first with oral doxycycline and then with intravenous ceftriaxone. Although his arthritis improved and tests for the bacterium that causes Lyme eventually came back negative, his joints were still inflamed. So he was prescribed methotrexate, an anti-inflammatory and immunosuppressive drug commonly used to treat rheumatoid arthritis. The joint inflammation finally went away, and he's now getting physical therapy to help regain mobility.

Each year, the U.S. Centers for Disease Control and Prevention logs the cases of Lyme disease that physicians report—a total of about 30,000 every year. This makes it the nation's most commonly reported vector-borne illness (meaning a disease spread by a carrier such as a mosquito, tick or mammal) and the seventh most commonly reported infection overall. Knowing that Lyme disease is underreported, the CDC conducted three studies to estimate how many cases actually occur. They discovered that the number is closer to 300,000—“and even that may be a somewhat conservative estimate,” says Steere.

## The Disease Unchecked

When Lyme disease is undiagnosed and untreated, it can progress through different stages, often with remissions between them.

### Three Stages of Lyme



Not every patient experiences all stages of the disease. If the disease progresses, the symptoms of each stage improve and often resolve before the next stage begins.

Lyme disease occurs naturally in animals in a cycle involving deer; mice, chipmunks and other small rodents; and the deer tick. The adult tick's preferred host is deer, but in its immature nymphal stage, primarily responsible for transmitting Lyme to humans, the tick feeds on small rodents, usually in the late spring and summer. Human infection begins with a bite from an infected tick.

Steere was a 32-year-old rheumatologist when he and his colleagues discovered Lyme disease while investigating the outbreak of a mysterious illness in wooded eastern Connecticut; the malady was named for Lyme, Conn., where they conducted their research. Seven years later, Willy Burgdorfer, a medical entomologist at the National Institutes of Health's Rocky Mountain Laboratories, identified the cause: a previously unknown spirochete, or spiral-shaped bacterium, that was subsequently named for him: *Borrelia burgdorferi*.

When a deer tick transmits the bacterium, the most common symptoms include a slowly

expanding bull's-eye rash, often accompanied by headaches, neck stiffness and pain in joints, muscles and other soft tissues. But there isn't always a rash—approximately 30% of patients do not recall a rash—and Robert didn't have one. Lyme is easiest to treat if caught early, and patients who see the rash and go to the doctor will typically be prescribed a few weeks of the antibiotic doxycycline. That works about 90% of the time, and even if they're not treated, most patients with this earliest stage of Lyme disease will get better within several weeks. Others, though, may continue to have joint pain, fatigue or other symptoms for weeks or months, whether or not they received antibiotics.

For some who don't realize they have Lyme disease, a second and sometimes a third stage may bring increasingly severe symptoms. In stage 2, the bacterium often spreads to other parts of the body. Some two to 10 weeks after being infected, about 15% of untreated patients may get very sick, with

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neurological symptoms, which can include meningitis with intense headaches, facial palsy or other cranial nerve problems, or severe pain or paralysis of nerves radiating into the arms, legs or abdomen. That's what happened to Robert during stage 2, when his sciatic nerve was affected.

Also during stage 2, about 5% of patients who don't get treatment will have heart block (a disease of the heart's electrical system). This stage, too, is likely to respond to a course of antibiotic pills taken for up to a month. If there are neurologic problems or complete heart block, a patient may get an intravenous antibiotic. But even for patients who have progressed to stage 2 of Lyme disease, symptoms are likely to go away within several months, with or without antibiotics.



In stage 3, which may happen if Lyme remains undetected and untreated, some six in 10 patients develop intermittent attacks of arthritis affecting one or more joints. Eventually one or both knees may become inflamed and the arthritis more persistent. Stage 3 can be harder to treat than the earlier stages of Lyme disease, although most patients are helped by a longer, four- to eight-week course of antibiotics. In a few cases, though—and this is what happened to Robert—patients will suffer inflammation in a knee for months or even several years after the spirochetal bacterium is gone, a condition known as antibiotic-refractory Lyme arthritis.

This complex and variable course of Lyme disease has helped sow considerable confusion about the disorder. There is even a post-Lyme disease syndrome that's similar to conditions such as fibromyalgia or chronic fatigue syndrome that are common in the general population. Any of those may arise not only after someone has had Lyme disease but also following other infections or stressful life events. "Chronic Lyme disease" can be a catch-all diagnosis for such syndromes—even when there's little or no evidence that a patient was ever infected with Lyme.

That diagnosis has spawned a class of “Lyme literate” doctors who will prescribe long-term antibiotics—stretching a year or more, sometimes without any sign of *Borrelia* infection past or present. That approach and the phrase “chronic Lyme” itself are extremely controversial, with many physicians and public health officials asserting that such treatment is irresponsible and even dangerous. “The chronic Lyme ideology,” Steere says, “has been very seductive for someone who has gone to doctors who can’t explain what’s wrong and then finds one who says, ‘You have Lyme, and I will make you well.’”

**T**o untie the Gordian knot that is Lyme, begin with diagnosis. The most common test is often negative during the first several weeks of infection. That’s because it’s designed to detect the antibodies the body generates to battle the bacteria, and those antibodies don’t initially show up in sufficient quantities to produce a positive test result, says Ben Beard, coordinator of the CDC’s national programs on Lyme disease, plague and tularemia. A patient who notices a bull’s-eye rash might test negative, even if she does have Lyme.

Next, factor in the possibility of co-infection. Scientists have identified at least four other disease-causing pathogens in the ticks that carry Lyme. It’s possible that these bacteria behave differently in combination and may cause more severe early infections. Add to that the vast array of possible hosts—people who are young or old, who are healthy or have compromised immune systems—and the resulting symptoms are quite variable and can range from mild to severe.

The bacterium at the root of Lyme disease, *Borrelia burgdorferi*, is an organism with a remarkable ability to mask its presence so that it won’t be attacked by the human immune system, says Monica Embers, an assistant professor in the Division of Bacteriology and Parasitology at the Tulane University Health Sciences Center. The bacterium may, for example, bind with human proteins on its surface, thus appearing to be made up of

human cells. The bacterium also can mask itself when presented with an immune response; as soon as the host starts to attack, it changes its expression—its genetic appearance—to thwart the assault. “It keeps doing this throughout the infection,” Embers says, “so the immune system can’t keep up.”

Embers, using a monkey model, recently led an intriguing study into Lyme bacteria in which uninfected ticks were fed on an infected monkey, then analyzed to determine whether they had become infected. The research was a follow-up to [work at University of California, Davis](#) showing that the DNA of the *Borrelia* spirochetes sometimes persisted in mice after antibiotic treatment. In the study by Embers’ team, [published in the journal PLOS ONE in 2012](#), three rhesus macaques were infected with the Lyme spirochete and treated with a course of oral doxycycline four months later. Then the researchers let laboratory-raised, Lyme-free ticks feed on the primates and they found a few spirochetes in ticks removed from two of the three animals. But it’s not clear whether those organisms were capable of infecting a new host.

Then, in February, researchers at the [National Institutes of Health and Tufts University](#) [published a human study in which](#) they allowed lab-raised ticks to feed on a positive control patient and 10 previously infected patients who now had post-Lyme disease symptoms. Only two ticks, one removed from the control patient and the other from a post-Lyme patient, subsequently tested positive for *Borrelia burgdorferi* DNA, but not for active spirochetes. In their conclusions, the authors warned that this work doesn’t prove that live spirochetes persist despite antibiotic treatment.

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**M**eanwhile, Steere and his team are working to find out why patients may have persistent arthritis after antibiotic therapy appears to have eradicated the spirochetal bacterium from the affected joint. Steere's team recently [published a study](#) on a strain of *Borrelia burgdorferi* found in the Northeast that induces more extreme inflammation than is caused by any other strain, especially in people with a certain genetic predisposition. About half of the Caucasian test subjects possessed a gene mutation that, when confronted with this strain of Lyme, set off an overwrought inflammatory reaction that was most intense in joints. In studies by other researchers, only 8% of African-Americans and no one of Asian descent had this mutated gene.

Looking back on how such a genetic variation might have evolved, Steere believes something happened in Europe that killed off people who didn't have the mutated gene, which may have helped others survive the plague or another deadly contagion. But it's a disadvantage with *Borrelia burgdorferi* because it leads to greater inflammation that may not be dampened even when antibiotics have killed off the spirochetes.

Intense inflammation in joints and the difficulty in controlling it set the scene for a third complication: the potential for an autoimmune reaction. In studies published in the journal *Arthritis & Rheumatism* in [2013](#) and [2014](#), MGH researchers reported the identification of the first autoantigen known to trigger autoimmune damage in some patients with antibiotic-refractory Lyme arthritis. An autoantigen is a human protein that comes under attack from a patient's own immune system. That never happens under normal circumstances, but it may occur within an area of intense inflammation, and in Lyme arthritis, this immune attack can obliterate small blood vessels within the joint.

In another puzzling development, someone who has had Lyme disease will develop pain, neurocognitive symptoms or fatigue, a condition sometimes called post-Lyme disease syndrome. In some patients, symptoms of headache, joint pain and fatigue, which typically occur with early Lyme disease, may persist for weeks or months after standard antibiotic therapy and then go away. However, unlike patients with antibiotic-refractory

Lyme arthritis, these patients don't have swollen, inflamed joints.

In still another variation, a small percentage of patients, after feeling well for several months following treatment, will have diffuse pain, difficulty concentrating, or incapacitating fatigue that continues indefinitely. Here, too, standard tests don't show inflammation, and anti-inflammatory therapies often don't help much. Four double-blind, placebo-controlled trials involving such patients failed to show sustained benefits of additional antibiotic therapy. That leaves few options for effective treatment.

**M**uch recent research into Lyme only adds to its complexity. But as a public health official, Ben Beard of the CDC is also interested in progress on other fronts—for example, preventing people from getting the disease in the first place. The CDC recently contracted with Allylix, the manufacturer of a natural insecticide, nootkatone, a component of the essential oils of Alaskan yellow cedar and citrus fruits, to create a new kind of tick repellent that while toxic to ticks, is considered by the Food and Drug Administration to be a “food-grade product”—in other words, it's thought to be safe for people, Beard says. The CDC has a licensing agreement in place and hopes to move into commercial production within five years, he says.

Also on the prevention front, public health officials hope for the return of a Lyme vaccine. In 1998, SmithKline Beecham (now GlaxoSmithKline) introduced a vaccine that was about 80% effective after three doses for at least one year. But the Advisory Committee on Immunization Practices, which advises the CDC on vaccine use, gave a tepid recommendation, suggesting use of the vaccine only in high-risk locations. Then a group of volunteers from studies of the vaccine reported arthritic symptoms. The rate of arthritis in the volunteers was the same as in the control group that didn't get the vaccine, but sales plummeted, and the drug was withdrawn in 2002.

The CDC is currently working with Colorado State University to identify diagnostic

biomarkers for Lyme—for example, a test that could detect the presence of proteins of the Lyme bacteria. But beyond these practical steps, much Lyme research will continue to focus on gaining a stronger understanding of what happens to people suffering from post-treatment Lyme-related symptoms. The CDC is funding a five-year study with New York Medical College looking at patients diagnosed with Lyme disease to find out what percentage wind up with post-Lyme disease symptoms after they finish antibiotic therapy and how those symptoms manifest themselves.

In the meantime, the ticks that transmit Lyme disease continue to spread, and the number of cases seems to be increasing. Much has been learned since the disease was first discovered almost 40 years ago, and it's now clear what causes the infection and how to treat it effectively. However, post-Lyme disease syndromes remain problematic. As Steere puts it: “There is still much more to learn.” ■

## DOSSIER

1. “Lyme Disease,” by Eugene Shapiro, *The New England Journal of Medicine*, May 2014. This paper walks readers through the diagnostic and prescriptive steps Shapiro takes in caring for a pregnant 32-year-old woman with a skin rash who had been bitten by a tick.
2. “Lyme Disease,” by Allen C. Steere, *The New England Journal of Medicine*, July 2001. This seminal review cited many times in medical literature covers how the spirochete is transmitted and goes about its business, as well as the various physical manifestations of its presence in a human host.
3. “Lyme borreliosis,” by Allen C. Steere, *Harrison’s Principles of Internal Medicine*, 18th Edition, Chapter 173, pp. 1401–1406. *Harrison’s Principles* is the most widely read book of its kind. Steere’s contribution covers guidelines for diagnosis and treatment and other essential information.

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