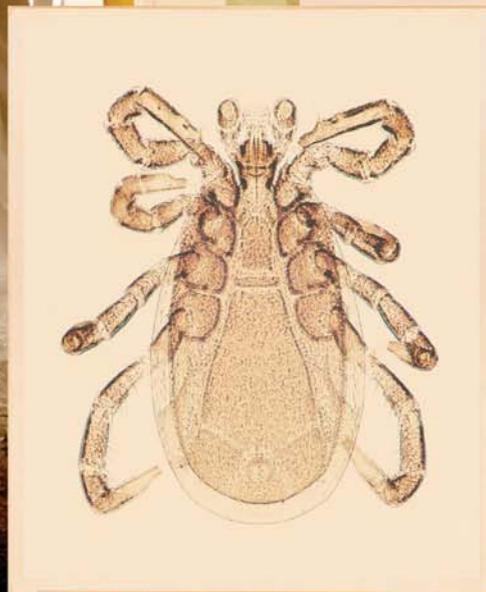


What We Don't Know About Lyme



When a mysterious and debilitating illness overtook her and her family, the author struggled to find some answers. What she discovered about Lyme disease — and how little is actually known or agreed upon by the medical experts — is something everyone who goes outdoors should learn.

ILLUSTRATIONS: CLIFF ALEANDRO

After we moved from the city to a wooded property in the suburban hamlet of Chappaqua, N.Y., in 1993, our family began to get sick. At first, the vague headaches, joint pains and bone weariness were so subtle they barely merited note. But as years passed, these symptoms intensified into frank signs of disease.

My arms and legs buzzed so palpably I felt like I was wired to a power grid. A relentless migraine became so intense I spent hours each day in a darkened room, in bed. My husband, Mark, an avid tennis player, began stumbling and bumping into walls. He was an award-winning journalist, but slowly he began struggling with memory and groping for words. Our youngest son, David, began to sleep — first, so long that he could not do his homework or see his friends; eventually, so much (15 or more hours a day) that he could not get to class.

Hardest hit was Jason, our oldest, who suffered fatigue and shooting pains starting at age 9, the year we moved to our little house in the woods. The doctors called these “growing pains” normal, but by February 2000, Jason, then 16, was essentially disabled. An honor student, he now had trouble reading even simple paragraphs. His joints and muscles hurt so much it was difficult for him to walk. And he couldn’t tolerate sound and light. On medical leave from high school, he spent his days in the tub in our darkened main-floor bathroom as hot water and steam eased his pain.

As his condition worsened, and as all sorts of lab tests came back negative, a raft of specialists at New York City’s top teaching hospitals suggested diagnoses ranging from migraine aura (migraine without the pain) to Fifth’s disease (caused by parvovirus). Each diagnosis elicited a treatment, but none of them worked.

“What about Lyme disease?” I asked from time to time, since we lived in an area where the infection was endemic; our backyard was a haven for deer, and Jason spent summers playing in a fort in the woods behind our house.

“There are too many symptoms here, and he’s way too sick for Lyme disease,” replied the pediatrician, who declined to even test for it. But with answers still eluding us, the pediatrician finally drew blood for a Western blot, a diagnostic test that matched antibodies produced by the patient against the proteins of the invading organism — in this case the bacterium known to cause Lyme.

When the labs came back, Jason had so many “bands” — with each band considered an antibody-protein match — that the result was off-the-charts positive. By the summer of that year, the rest of us had been diagnosed as well.

The news was a relief. With a solid diagnosis, we were told by doctors, we could get treated for this easily curable infection, and move on. We felt a flush of optimism, but it turned out that our struggle had just begun. I would spend the next nine years trying to make sense of our misdiagnoses and seeking effective treatment for my children.



Lyme 101

What I didn’t know about Lyme disease back then could have filled a book — one that, as a longtime science and medical journalist, I eventually wrote. My book, *Cure Unknown: Inside the Lyme Epidemic* (St. Martin’s Press, 2008), explores the complex science and disturbing political war over the illness. But a few facts can be served up straight: Lyme disease is caused by the spirochete *Borrelia burgdorferi*, a spiral-shaped bacterium, and is generally transmitted to people through the bite of a deer tick. The disease arrived in the Northeast United States, northwest California and the Great Lakes region in force in the 1970s, as the continent was being reforested and new suburban housing was increasingly built adjacent to woods. The spirochete lived in the blood of rodents and other small mammals inhabiting those woods. When ticks bit these mammals they became infected. When those same ticks bit human hosts, they transmitted Lyme disease to them.

Pushing the disease to epidemic proportions, however, required something else: large mammals, like deer, are each able to provide nourishment for hundreds of large adult ticks, enabling them to reproduce en masse. As the deer population exploded across the forested regions of the country, the Lyme epidemic followed suit. Ultimately, infected ticks traversed the continental flyways on the backs of migrating birds, bringing Lyme to every state. Today, 12 to 40 percent of deer ticks are infected in the most endemic areas of the Northeast, and between 3 and 40 percent in endemic areas of the West Coast. With more than 200,000 CDC-acknowledged cases a year in the United States (the tip of the iceberg, many believe), Lyme has become one of country’s fastest-spreading diseases.

Slipping Through the Cracks

When diagnosed with a Lyme rash and treated early, most infected patients are easily cured. But this upbeat message has little meaning for those diagnosed late. Show up at the doctor without a rash, and diagnosing Lyme disease becomes an elaborate, labyrinthine affair.

The standard guidelines, published by the Infectious Diseases Society of America (IDSA), call for early diagnosis exclusively through the presence of that telltale rash — mistakenly thought of by many practitioners as a classic “bull’s-eye” shape. Yet the spreading red rash with areas of white clearing, called an *erythema migrans*, might not be round or oval — let alone a bull’s eye. (Jason’s rash, which I later recognized in a medical textbook, was dismissed by our medical group because it covered his torso in a swath.) According to some studies and estimates, fewer than 60 percent of Lyme patients ever exhibit or notice a rash of any sort. →

Those without this early sign may roam the diagnostic desert for years seeking answers. Yet, IDSA guidelines require that, to qualify for diagnosis, patients without the rash must present with one of a small group of quantifiable disease signs, from measurable nerve damage to grossly swollen knees. Though many experts say a significant percentage of Lyme patients experience only “symptoms” — headache, memory loss or fatigue — IDSA calls these problems just too vague to consider a diagnosis of Lyme. But, even with objective signs like swollen knees, patients must pass a series of tests before a diagnosis can be made.

And that’s the other part of the problem. Should the patient present those frank signs of disease and qualify for the test, the bar for passing is set perilously high for some. According to the peer-reviewed journal *Mayo Clinic Proceedings*, “The tests are prone to false-negative and false-positive results and can be misleading, especially early in the course of the disease. . . . Because serologic [blood] testing is not 100 percent sensitive or specific, some people with Lyme disease will not have confirmatory laboratory results.”

“I’ve been scraping Lyme patients off the sidewalk for years,” says Kenneth Liegner, MD, who practices in Armonk, N.Y., not far from where my family got sick. “By the time some of these people get to me, they are so disabled they can barely think or walk.”

Lyme on the Brain

Given the barriers to diagnosis, many patients slide ever deeper into illness, where disability can be profound. Lyme invades not just our skin and our joints, but our hearts, nervous systems and eyes. Lyme is commonly considered a knee disease, an impediment in tennis, but the Lyme spirochete, like the syphilis spirochete, also invades the brain.

Testing hundreds of such patients, New York University neuropsychologist Leo J. Shea III, PhD, found specific deficits in concentration, short-term memory and processing speed. Patients can be so impaired they have trouble driving around their neighborhoods and can no longer perform their jobs.

Psychiatrist Brian Fallon, MD, director of the Lyme and Tick Borne Diseases Research Center at Columbia University Medical Center, found that brain infection could trigger a host of psychiatric problems, ranging from bipolar disorder and depression to panic and obsessive-compulsive disorder (OCD).

Time and again, Fallon has seen Lyme disease “misdiagnosed as a primary psychiatric problem,” while the root issue — infection with the spirochete *B. burgdorferi* — was never addressed. This is especially damaging, he says, since a delay in treatment could turn an acute and easily curable infection into a chronic disease highly resistant to treatment.

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The most comprehensive review of the standard Lyme tests comes from Johns Hopkins University. Working with patients from Pennsylvania and Maryland, the Hopkins scientists studied state-of-the-art serology and DNA tests for Lyme and found serious flaws: Most tellingly, when the standard two-step method recommended by the CDC was used on patients with other laboratory evidence of Lyme disease, it was positive between 45 percent and 77 percent of the time. As for DNA tests, the Hopkins researchers reported these rarely pick up otherwise-confirmed Lyme disease at all.

It is made all the more complicated because there are hundreds of strains of the Lyme disease spirochete throughout the world, says Benjamin Luft, MD, chief of the Division of Infectious Diseases at the State University of New York at Stony Brook. Each strain has its own combination of proteins, evoking a variety of bands on diagnostic tests; some will match the pattern the CDC has approved for a positive on the Western blot (the second of two tests in the series), but others may not. Each Lyme strain evokes a unique antibody pattern and its own flavor of disease.

In short, Mayo Clinic researchers note, diagnosis should be clinical — based not on the tests but on the patient and the patient’s situation as a whole. With so many strains of Lyme disease and a unique immune system for each new patient, this only makes sense. Yet with Lyme disease so controversial, most primary-care doctors end up deferring to the tests, leaving those who fail them out in the cold.

The Treatment Controversy

Patients diagnosed in the earliest stage of the disease through a classic rash can usually look forward to full recovery after a monthlong regimen of the oral antibiotics doxycycline or amoxicillin. Those with neurological or arthritic symptoms may be offered intravenous ceftriaxone for a month or two. But experts like Luft and Liegner have found that some 20 percent of those infected for over a year before the start of treatment will fail these protocols and stay sick.

Without further options from the IDSA team, these late-diagnosed patients have sought help from controversial doctors known as Lyme-Literate MDs (LLMDs), who argue that longer courses, higher doses and multidrug antibiotic regimens provide a viable option for many of the “incurable” 20 percent. As ever more patients flock to LLMDs like Liegner, the controversy has mounted, with IDSA pitted against another, newer group: the International Lyme and Associated Diseases Society (ILADS). IDSA says the short-term treatment always stamps out infection and argues that overexposure to antibiotics can generate treatment-resistant bugs.

Competing guidelines from ILADS hold that patients already *have* a hard-to-treat infection (chronic, persistent Lyme disease) and that more aggressive treatment is thus warranted.

The debate has recently come closer to resolution with surprising research from veterinary scientist Stephen Barthold, DVM, PhD, who spent 25 years investigating Lyme disease at Yale before setting up shop as director of the Center for Comparative Medicine at the University of California at Davis. Barthold reports that if he allows the infection to remain untreated for months across a range of mammal species in the lab, he can always recover living spirochetes, generally sequestered in tissues that are rich in collagen. When laboratory mice infected with these spirochetes are treated with what should be effective doses of various antibiotics, the spirochetes cannot be cultured from tissues by conventional means, but they are alive and can be transmitted by ticks to other mice.

The finding resonates with what late-diagnosed patients report: If surviving spirochetes are so sluggish they cannot replicate, they may be impervious to antibiotics that work by targeting bacterial cells as they divide. The persisting spirochetes could be the presumptive source of the constitutional symptoms like pain and fatigue that often follow treatment; they may be provoking the production of symptom-causing cytokines (immune molecules), yet still be too low in number to cause the gross inflammation or provoke the antibody response that many mainstream experts call the *sine qua non* of the disease. Infection might be suppressed but not eradicated by treatment, as so many relapsing patients report.

Spurred by the findings, university-based researchers are attacking the infection on several fronts. Scientists like Luft and Barthold are actively testing antibiotics designed to purge these dormant, resistant spirochetes. Some researchers are trying to destroy them with nanotechnology and heat. And a California company called Viral Genetics, with research headed by M. Karen Newell, PhD, and aided by Nobel laureate Luc Montagnier, discoverer of the HIV virus, is trying to modulate the immune system so it can clean out infection on its own. Still others suggest that the low-level infection might be benign if the immune response could be contained.

Tick Menagerie

Improved treatments for Lyme disease alone may not solve the problem. There are other infections inhabiting the ticks that spread Lyme, and they are factors as well. The malaria-like parasite *Babesia* infects our red blood cells and results in fever, exhaustion and drenching sweats. Babesiosis combined with Lyme disease can be especially protracted and difficult to treat. Tick-borne bacteria like *Anaplasma* and *Ehrlichia*, which live in human cells, are rife throughout regions where Lyme has reared its head. These organisms don't necessarily →



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respond to all common treatment for Lyme disease and may cause serious illness even when Lyme is not involved.

Added to this are other microbes as well; though still controversial, these, too, are now considered possible agents of the disease complex broadly referred to as “Lyme.” One of the most notable is the rod-shaped bacterium *Bartonella henselae*, known as a cause of “cat scratch” disease and commonly transmitted by cats. More recently, forms of bartonella have been discovered in abundance in deer ticks. Some doctors cite *Bartonella* as a culprit when symptoms are particularly neuropsychiatric, and when treatment for Lyme does not work.

Another tick-borne suspect, *Mycoplasma*, has been discovered in deer ticks in Connecticut and New Jersey. “This could be the missing link,” says Eva Sapi, PhD, associate professor of biology at the University of New Haven, who also hypothesizes that nematodes play a role in tick-borne disease. It would explain why some patients don’t get well when treated for Lyme disease alone. Other researchers have found *Tularemia*, often an agent of bioterrorism, in Lyme ticks.

formats, spewing a kaleidoscopic oeuvre of novel bacteria and viruses, some of them pathogens the world has never seen.

A New Lyme Science

I wish I had understood Lyme as an emerging infectious disease and political hot potato when my family first got sick. Exposed to the noxious debate, the naive patient sees two polarized factions and feels pressured to choose one. But interview the workbench researchers and you will find a complex, nuanced reality emerging from the science itself. Sadly, the vicious political fight over Lyme disease has dumbed down the dialogue and prevented the best science from being heard.

In 2009, the pace of scientific progress is great. Instead of testing for a mere 10 antibodies to a limited number of spirochetal proteins — the procedure still being used in most of today’s commercial labs — new diagnostics that Luft and his Stony Brook colleagues have developed will use proteomics (study of proteins) to tap 1,800 *B. burgdorferi* proteins found across the range of strains. “We want to test against the entire array of borrelia proteins in all their variability,” says Luft. “So if I look at a patient over time, over the course of their disease I can see whether new proteins, ones we’ve never noticed, might emerge.”

The work on strains could alter how we diagnose and treat the disease in the years to come, says Alan Barbour, director of the Pacific-Southwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases at the University of California Irvine and one of the world’s foremost spirochete experts. “If some strains are more likely than others to spread in the blood, and by that route to other tissues, then identification of the strain a person is infected with could help guide therapy,” Barbour explains. “Some strains may call for a longer course of antibiotics. The problem is isolating the microbe out of the patient to see what strain it is. This could be done by a Polymerase Chain Reaction (PCR) test of the blood or a skin biopsy, when there is a rash. Isolating the microbe is harder when the illness has been going on for longer than a few weeks, but any isolate of *Borrelia burgdorferi* from a patient would mean a diagnosis of Lyme disease.”

Also shedding light on treatment is genomics (the study of genes). The Luft team has recently found that Lyme spirochetes have genes for pumping out the first-line antibiotic doxycycline. This means that even as doxycycline enters the Lyme bacterium, it is being ejected, much like a sump pump might eject water from a basement floor. As a result, the dose might not climb high enough to kill the infection, and the patient won’t get well.

Based on this finding, Luft is now studying another drug — tigecycline, an intravenous antibiotic currently used for infections of the abdominal organs and skin. Its mechanism is much like that of doxycycline — except that its chemical structure inhibits the spirochetes’ “pump,” keeping the antibiotic from being ejected by the cells.

“We are just starting to understand the full range of infections that we might get. I don’t think we know half of the agents that are potentially transmissible by ticks.”

A host of other spirochetes, some not yet identified, complete the scene. Yale researchers found that 20 percent of the spirochetes thought to be *Borrelia burgdorferi* in the Northeast are really another species, a relapsing fever spirochete never seen in North America before. There’s a still-unidentified spirochete in Montana, this time transmitted by the wood tick. And then there’s the lonestar tick, which has recently spread from the South throughout the Midwest and up the East Coast, as far north as Maine. The lonestar carries an unidentified spirochete, the cause of a Lymelike disease that the CDC has recently recognized.

“We are just starting to understand the full range of infections that we might get,” says David H. Persing, MD, PhD, chief medical and technology officer for Cepheid, a California biotech firm and a world expert in molecular diagnostics. “I don’t think we know half of the agents that are potentially transmissible by ticks.”

Add to this the morphing quality of the various microbes implicated in these Lymelike diseases. Through constant shifting of plasmid DNA among the microbes, ticks facilitate a rapid form of evolution and drive the creation of novel strains and microbes, virtually nonstop. Indeed, in the universe of emerging infectious disease, the tick is the final frontier. The ultimate germ generator, it is the ideal wet lab for microorganisms to mix and remix in infinite

"It's a hundred times more active against the spirochete than doxycycline. Instead of just inhibiting the spirochetes, like doxy, it kills them dead," says Luft.

"We're at a critical point," he adds. "We have powerful new tools and a fundamental understanding of the biology of the *Borrelia*. We know every gene in that organism. We know all the variations of those genes. We know what's in the human genome. So, when someone gets sick, we've got to put this together, in context, and ask what's going on."

Indeed, work like this will explain why prognosis varies so widely from one patient to the next. With so many strains, so many co-infections and so many immune systems, Lyme — in the broad sense of the word — will never be one-size-fits-all.

"Some researchers have thrown down their gloves and retreated to their corners, leaving patients out in the cold," says Luft. "But despite what they say, the patients are still sick. It's a question of doing right by them — it's not a question of whether you might have to eat crow. We've got to go in and do the right experiments, and then we can look truth in the eye."

Last Dance With Lyme

My family has come a long way since our Lyme diagnoses almost a decade ago. We've left the Lymelands for safer ground — the concrete expanse of Brooklyn. I've been off antibiotics since 2004 and am back at a full-time job. Mark continues to relapse when he stops his antibiotic, but with it, he works his day job, plays tennis and seems fine. Jason has recovered. He graduated from Brown University in spring 2008 and leaves for film school in the fall.

But Lyme still clouds our lives because our younger son, David, was re-infected in Westchester County a couple of years back and remains ill.

In all my years of research, I never doubted that IDSA was right about early Lyme: Treat the rash and a cure would be guaranteed. So in the summer of 2007, when David called to tell me that friends in his college dorm had recognized a classic bull's-eye rash on his arm, I was actually relieved: For once, we'd caught it early. A month of antibiotics, I told myself, and David would be cured.

We took a 40-minute drive to Dr. Daniel Cameron's office in downtown Mount Kisco, N.Y., and his physician assistant easily diagnosed a bull's-eye-shaped *erythema* →

How to Protect Yourself Against Lyme disease

For those who live and work in Lyme endemic areas, a little protection goes a long way. You can enjoy nature, according to Pat Smith, president of the Lyme Disease Association, as long as you take some precautions:

- **WALK IN THE MIDDLE OF TRAILS.** Avoid sitting on logs or leaning on trees.
- **WEAR A HAT.** Tuck your hair in, if possible.
- **WEAR A LONG-SLEEVED SHIRT,** fitted at the waist.
- **WEAR BOOTS OR SHOES, NOT SANDALS.** No bare feet.
- **WEAR LONG PANTS** tucked into high socks, or duct tape around pant bottoms.
- **CONSIDER APPLYING DEET** for skin and permethrin for clothes (use your own best judgment in weighing exposure to these toxins against risk of tick bites).
- **WEAR WHITE** or light-colored clothing so ticks stand out.
- **CHECK YOURSELF AND YOUR CHILDREN** for ticks immediately after outdoor exposure. Repeat the tick check again, three days later. Remember that nymphal (adolescent) ticks can look like freckles. They are the size of poppy seeds.
- **IF YOU FIND AN ATTACHED TICK, REMOVE IT CAREFULLY** with tweezers placed as close to the skin as possible. Pull the tick upward with steady, even pressure, making sure that mouth parts are cleanly removed. Apply antiseptic and call a doctor. Save the tick in a sealed container with a moist cotton ball. Call your state health department to inquire about testing. (Ticks do fall off on their own eventually, so even if you don't see a tick, it is possible that you may have been exposed to disease.)
- **CONSULT YOUR DOCTOR** about treating the tick bite with oral antibiotics. Though the number of days required for this treatment remains controversial, new findings from CDC research suggest that the single dose of treatment generally recommended for this scenario may be inadequate and that a doxycycline sustained release protocol (19 days) the CDC is developing might be more effective.



migrans that was an archetype of the form. She prescribed a few weeks of amoxicillin and sent us home.

“When you get a rash so classic that everyone at college tells you it’s Lyme disease, it’s a beautiful thing,” Dan Cameron, now president of ILADS, said at the time.

But by spring 2008, David’s fatigue was so profound, his memory and focus so poor, that he had to drop his classes at Vassar College and come home. Back in New York, doctors discovered gross damage to David’s cranial nerves — irrefutable, IDSA-style proof of inflammatory disease and hardcore evidence of Lyme. Ordering more tests, Cameron found not just Lyme disease but a co-infection — babesiosis — known to complicate the picture and make Lyme harder to treat.

I completed work on my book about this mysterious

disease more than a year ago, but I know now that our journey is far from over. Our family, along with many others, continues to deal with the fallout at the frontlines of an epidemic, in that unforgiving land called Lyme. ●

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Web Resources

Infectious Diseases Society of America
www.idsociety.org

Lyme Disease Association
www.lymediseaseassociation.org

International Lyme and Associated Diseases Society
www.ilads.org



LYME DISEASE is never pleasant, but if you are exposed in endemic areas of the Northeast, the Midwest or the West Coast and develop the spreading red Lyme rash known as *erythema migrans*, the best person to consult is your family doctor. The classic Lyme disease rash is considered diagnostic for the disease in these areas, according to the standard guidelines from the Infectious Diseases Society of America (IDSA). Physicians following these widely accepted guidelines will not even have to order a blood test to make a bulletproof diagnosis. For most people without other complications, including other infections from the same tick bite, a month of treatment with oral antibiotics like doxycycline or amoxicillin should cure the disease.

Finding a doctor able to make the diagnosis and treat you adequately becomes far more challenging if you *do not* see or develop a rash, or if you live outside areas considered most endemic for the disease. Given the debate in the medical community over the classic signs and symptoms for Lyme, the inaccuracy of the tests, and the presence of complicating co-infections, patients in this circumstance can advance into later, harder-to-treat disease before they are ever diagnosed.

In this instance, it may be appropriate to consult a neurologist, rheumatologist or infectious disease doctor in your community for specialized but mainstream care. Following the IDSA guidelines, these physicians will treat these sicker patients with specialized antimicrobials aimed at co-infections, or with a month or two of intravenous Rocephin, which crosses the blood brain

barrier and better penetrates the joints, often resolving Lyme disease.

But about 20 percent of patients diagnosed with late-stage Lyme disease report that they fail even this more aggressive treatment; others report that their co-infections are missed. Still sick, they find themselves navigating the tortuous backroads of the Lyme wars. Those seeking clinical evaluation of the range of tick-borne infections or continued treatment for Lyme disease itself — as I did with my own family — may decide to cross the line, leaving the restrictions of the mainstream viewpoint for the alternative world of Lyme doctors, referred to by patients as Lyme-Literate Medical Doctors, or LLMDs. These physicians will test patients for a range of co-infections and treat Lyme disease longer, using antibiotics in combination (as is done with tuberculosis cases) for months and sometimes years.

Many patients report recovery on such protocols — but many do not, and for them, the search for treatment goes on. Some patients consult trained naturopaths, who help them boost their immune systems. One new trend used by neurologists at New York University and Yale involves treatment with IVIG (intravenous immunoglobulin), a blood product rich in immune molecules that can heal damaged nerves.

For reference to a doctor skilled in mainstream protocols, contact the Infectious Diseases Society of America. For reference to a doctor willing to treat tick-borne infection beyond the standard guidelines, contact the Lyme Disease Association or the International Lyme and Associated Diseases Society. (See Web Resources, above.)