At the Drop of a Tick

By INGRID WICKELGREN

When European physicians came to New Haven, Conn., in 1983 to hear U.S. scientists tell the tale of woe experienced by a large cluster of people living on the East Coast, they recognized the story. It usually begins with a red dot on the skin, encircled by increasingly faint rings. Weeks to years later, the saga continues with episodes of chronic or acute arthritis, neurological problems ranging from a stiff neck to meningitis, and/or cardiac malfunctions. The disease has plagued Europeans for nearly 100 years, but before the U.S. epidemic, no one had linked the seemingly unrelated array of symptoms to a single cause. Not until 1982 did scientists identify the bacterial perpetrator, propelled by the bite of a tick.

There remains no surefire way of diagnosing Lyme disease, with its confusing array of symptoms. Physicians don't know how to treat Lyme-affected people who don't respond to antibiotic therapy. And scientists still do not understand how the invading bacterium causes the disease, how it affects so many organs or why the body's immune system doesn't combat it effectively.

But the most alarming new information concerns the Lyme-carrying tick army that both outnumbers and continues to outwit the scientific community. Evidence now suggests a booming increase in the population of the main Lyme-carrying tick, prevalent in the Northeast and upper Midwest, and its spread into new areas. And scientists are discovering just how deeply the tick's life is embedded in the ecosystem as they identify a variety of animal hosts on which it depends for food. These animals abet the tick's spread and make it harder for scientists to target. In addition, some scientists suggest humans may contract the disease even without a tick bite.

The story stars the microscopic *Borrelia burgdorferi,* a slender, spiral-shaped bacterium, known as a spirochete, that became famous for its devastating performance in Lyme, Conn., in the 1970s. Primarily spread by deer ticks, *B. burgdorferi* has infected humans in 43 states as well as in Europe, Asia and Australia. In the United States, only Alaska, Hawaii, Montana, New Mexico, Nebraska, Arizona and Wyoming still remain Lyme-free. "This is the [United States'] biggest insect-borne disease of the half-century," says entomologist Durland Fish of New York Medical College in Armonk.

Reported cases of Lyme have increased 10-fold in the United States over the last six years, says epidemiologist Theodore F. Tsai of the Centers for Disease Control's Division of Vector Borne Viral Diseases in Fort Collins, Colo. Last year, 5,000 cases joined the growing U.S. total that now hovers around 13,000. But experts agree that Lyme is both underreported and underdiagnosed. If it follows the pattern of many infectious diseases, Tsai says, the actual total probably numbers four times higher.

At present, 90 percent of the U.S. Lyme cases occur in eight states: California, Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island and Wisconsin. But the disease is spreading because the tick responsible for most of the U.S. cases is spreading. By systematically examining deer, Fish and his coworkers recently discovered the deer tick in Pennsylvania, Maryland, western Massachusetts, upstate New York and new areas of the Midwest.

The recent tick proliferation remains a mystery, but it probably has had something to do with the replacement of farmland by forests in the Northeast, Fish says. Forests support deer, which have been rapidly increasing in numbers since the turn of the century, and deer support ticks. "We know that deer are essential in maintaining large populations of [this] tick," Fish says.

The human side of the Lyme story in the United States began in the mid-1960s, when Polly Murray, a woman living in the town of Lyme, began to suffer periodic episodes of a flu-like illness, rashes, arthritis and neurological problems such as severe headaches and a stiff neck. When her children and others in the community began to suffer similar symptoms in the early 1970s, Murray began to wonder if the ailments had a common cause. With some of her family on crutches from the mysterious malady, Murray called the State Health Department and the Yale Rheumatology Clinic to report the problem.

But it was not until November 1975 that Yale rheumatologist Allen C. Steere launched the first survey for the disease and found an unusually high incidence (39 children and 12 adults) of what looked like juvenile rheumatoid arthritis in the

Female and (smaller) male I. dammini. *Adults, shown greatly enlarged here, are about the size of a sesame seed. Nymphs, shown as specks on a human palm, are so tiny that most people do not remember their bite.*

Rocky Mountain Labs, NIAID, NIH

Fish/Fran Heyl Assoc.

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A corps of Lyme-disease fighters meets its match in an army of arthropods

towns of Lyme, Old Lyme and East Haddam, Conn. In 1976, Steere and his colleagues named the disease. In 1977, they published the first report on it in ARTHRITIS AND RHEUMATISM (Vol.19, No.7). That same year, Andrew Spielman of the Harvard School of Public Health in Boston found that the tick responsible for spreading Lyme in the Northeast was a previously unidentified species and named it *Ixodes dammini.* Although *I. dammini* is the most abundant, widespread and frequently infected Lyme-carrying tick, a different species causes the disease in the West, another in the South and yet another among Europeans.

Ixodes dammini has been found on 12 mammalian species and 18 bird species, according to Fish and entomologist John F. Anderson of the Connecticut Agricultural Experiment Station in New Haven. In the West, entomologist Robert S. Lane and his associates at the University of California, Berkeley, found 80 species of vertebrates hosting California's and Oregon's most important Lyme-carrying tick, *I. pacificus.* While engorging an animal's blood, the tick unknowingly may receive or donate a spirochete, but not all animals are susceptible to infection.

White-tailed deer are likely the primary host of the adult tick in the eastern United States. Ticks lay their eggs in the spring and the emerged larvae feed in late summer. The larvae remain quiet throughout the winter and develop into nymphs in the spring. The nymphs feed in May and June, just before the peak appearance of human infection in early July. Scientists believe tick larvae acquire the infection from white-footed mice and then transmit it to humans as nymphs. The adults, which feed any time from late fall to late spring, probably do not account for many human cases because they are large enough to be detected and removed before the spirochete is transmitted, Fish says.

I. dammini often eats its main larval meal on the foot of a white-footed mouse. At several Massachusetts sites, Spielman and his co-workers found that 80 to 90 percent of the larvae dropping off mice just after their early autumn feeding were infected with *B. burgdorferi,* says parasitologist Sam Telford, who works in Spielman's laboratory. "We've taken ticks off of all the other animals in these areas, [and although] many animals have ticks, few others produce infected ticks," Telford says.

Checking for adult *I. dammini* on various mammals living on Long Island, N.Y., Spielman found 93 percent of the ticks on deer and the remaining 7 percent on dogs and other animals. Deer provide all the nourishment for the adult tick and its typical brood of about 2,500 eggs. However, the deer don't seem to carry the spirochete. Spielman found that only about 1 percent of ticks dropping off the backs of deer were infected. This is no more than the tick's natural infection rate – the percentage of young that contract the spirochete from an infected parent – so it appears deer do not increase the proportion of infected ticks.

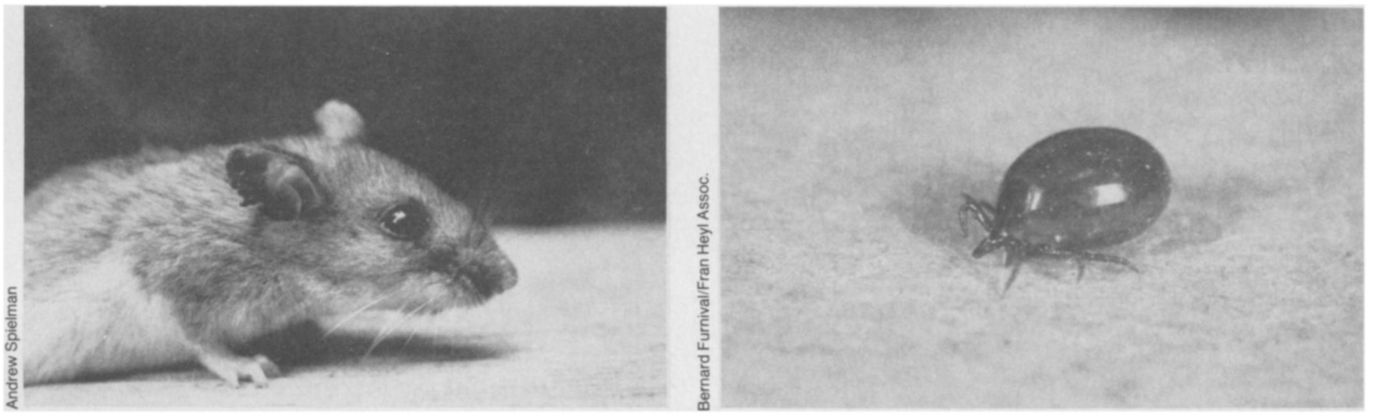
Ground-feeding birds also serve as important hosts of *I. dammini,* but how important is hard to determine because birds are hard to track, Fish says. Scientists do know that birds transport the tick long distances and so contribute to the spread of the disease. In addition, Anderson has shown that birds carry the spirochete and are able to infect ticks.

In the West, *I. pacificus* is most often found on lizards and the black-tailed jackrabbit, Lane says. Lizards aren't easily infected and so help dilute the prevalence of the disease, but jackrabbits can infect ticks. Probably because more lizards than jackrabbits live in the West, the infection rate of *I. pacificus* is low, Spielman says. Only 1 to 2 percent of *I. pacificus* are infected, compared with 30 to 60 percent of *I. dammini.* This difference in infection rates probably explains the lower incidence of the disease in the West, Lane says.

Scientists do not know how to control the expanding tick population. Eliminating white-tailed deer from the entire Northeast, "which is essentially what you have to do to control the tick," is neither possible nor desirable, Fish says. And even if such a devastating feat were accomplished, ticks might find another suitable host.

Chemical sprays don't seem to work either. The main stumbling block is not the chemicals themselves, but finding clever ways to get them to the tick. One problem is that foliage gets in the way, says research scientist Terry L. Schulze of the New Jersey Department of Health in Mercerville. Attempts in 1985 to spray two 2½-acre sites in central New Jersey with general-use insecticides in the

The white-footed mouse (left) frequently harbors Lyme-disease bacteria and can infect tick larvae that feed on its blood. A well-fed larva appears in the photograph on the right.



Andrew Spielman

Bernard Furnival/Fran Heyl Assoc.

winter, when trees are bare, did diminish the following spring's tick population. But by fall, researchers found ticks as prevalent as ever, suggesting the insecticides did not reach the inactive subadult ticks, Schulze says.

Although treating the same area the next year would rid it of last year's nymphs, now adults, migrating bands of nymphal ticks would reinfest the area. Thus, only widespread spraying can effectively eliminate ticks, but such action could cause serious environmental damage. Existing chemical sprays kill not just ticks but all insects and spiders. "The notion to go out and [indiscriminately] spray forests for the tick is absolutely insane," Fish says.

Another way to eliminate the tick nymph is through its primary host, the white-footed mouse. A newly marketed product called Daminex, which consists of insecticide-treated cotton balls encased in biodegradable paper tubes, contacts and kills ticks when mice use the cotton for nesting material. Although experiments so far show the product works without harming the mice, ongoing tests need to verify this. Furthermore, although Daminex may prove useful in residential areas and some parks, placing its tubes at the required 10-meter intervals on a large scale would cost an impractical amount. Fish estimates that distributing Daminex throughout Westchester County, N.Y., probably would cost

Tick-tock: Still no shot

Could a vaccine protect against Lyme disease? Researchers say the answer remains elusive — in part because the Lyme-causing bacterium, *Borrelia burgdorferi,* fails to elicit a very strong immune response in humans. But some remain optimistic about the possibility of developing a vaccine against Lyme-transmitting ticks.

Compared with other blood-sucking arthropods such as mosquitoes, ticks remain on their hosts a long time, often days or even weeks. During this time they secrete several chemicals to aid in feeding. Scientists have already made a few experimental vaccines, some targeted against these chemicals and others against cells in the tick's gut. A tick feeding on a vaccinated person's blood would consume anti-tick antibodies that would interfere with the critter's ability to feed — in some cases killing the tick outright by destroying its intestinal lining.

Surveys suggest a low probability of Lyme transmission within the first few hours of tick attachment; the odds of infection approach 50 percent at about 48 hours. Researchers hope a purified dose of the right tick proteins, combined with a chemical that amplifies the host's immune response, might add up to a vaccine that would interrupt a tick's blood meal before disease transmission occurs.

"How does that ugly bag of skin called a tick manage your immune system? That's really the question," says Glen R. Needham, a self-described "biotick-nologist" and professor of acarology at Ohio State University in Columbus. Critical to the tick-host interaction, he and others say, is tick saliva: a cocktail of chemicals including anticoagulants, digestive enzymes and an "attachment cement" that keeps the tick securely anchored to its host during its long feeding time. Tick saliva helps a tick resist human defenses, but it also provides a target for an anti-tick attack.

"We're beginning to open the door to understanding just what is in tick spit," says Needham. But it hasn't been easy.

Needham and his co-workers have dissected nearly 3,000 salivary glands from the mouths of *Amblyomma americanum* — a relative of *B. burgdorferi* known as the Lone Star tick, which may itself transmit the disease in some areas. He and others have used recombinant DNA technology to purify and mass-produce chemical extracts from salivary glands in the search for an ingredient that might serve as a vaccine. The work has led to the discovery of several tick-spit proteins, common to a number of tick species, that elicit an antibody response when injected into test animals.

In some experiments, for example, researchers have immunized rabbits with an inoculum of partially purified tick cement protein. These rabbits show partial resistance to subsequent onslaughts by ticks, with the ticks falling off the rabbits sooner than usual and consuming only two-thirds the normal amount of blood.

Taking a different approach, John Sauer of Oklahoma State University in Stillwater foresees the possibility of developing a vaccine that would block the pathways involved in tick salivary secretion. Tiny nerves trigger chemical receptors on tick salivary glands via a calcium-dependent reaction. If, upon first biting its host, a tick were to get a mouthful of antibodies against some part of this chemical cascade, saliva production might not occur. Since Lyme and other diseases are transmitted in tick saliva — and because saliva secretion is critical to a tick's ability to maintain proper fluid balance while feeding — the chances of disease transmission would be greatly reduced in a dry-mouthed tick, Sauer says.

In what some researchers consider the most encouraging tick vaccine results so far, David Kemp and his colleagues at the CSIRO Division of Tropical Animal Production in Queensland, Australia, have developed a vaccine against the cattle tick *Boophilus microplus.* Starting with the digestive tracts of 50,000 ticks, they managed to get 0.18 milligram of a purified tick gut protein. An Australian biotechnology company sequenced the protein and synthesized a nearly identical substance as an antibody-triggering vaccine. Ticks suffer lethal damage to their midgut linings after feeding on a host's antibody-laden blood. Field tests showed a 91 percent reduction in the number of ticks on vaccinated animals, Kemp says.

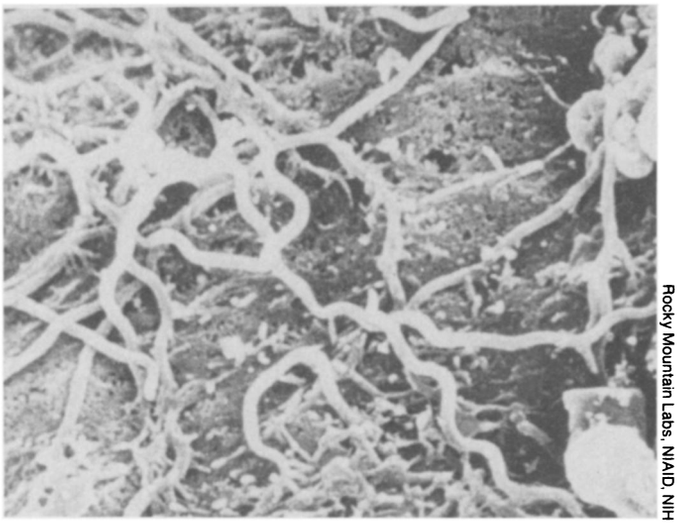
Despite these and other encouraging trials — none of which has been applied to humans — some scientists question whether standard vaccination approaches will ever outwit the wily tick. For 50 years, the scientific literature has been dotted with reports of animals sporadically acquiring natural immunity to ticks, they note. Yet the blood-sucking critters persist and the incidence of tick-borne disease continues to increase.

Indeed, says Jose M.C. Ribeiro of the Harvard School of Public Health in Boston, the real challenge is in understanding what the tick does to render its host's normal immune responses ineffective. The solution to many tick-borne diseases, he suggests, may lie not in boosting the host's immune response, but in blocking the tick's natural anti-immune defenses.

"Vaccine development has assumed that the absence of effective immunity is due to [host] immune incompetence," he says. "But this neglects the defensive mechanisms the tick can have *against* these responses."

Ribeiro injects ticks with pilocarpine — a naturally occurring chemical that makes them drool the way people do when walking past a cookout — and has analyzed the resulting tick spittle. He finds that tick spit can block the formation of anaphylatoxin and bradykinin — two potent components of the human immune response — and can prevent a process called complement binding, another host immune reaction that is usually lethal to a foreign invader.

If ticks are especially adept at doing end-runs around host defenses, he warns, they may quickly evolve new defenses to bypass whatever added immunity scientists develop in their current vaccine efforts. — *R. Weiss*



Rocky Mountain Labs, NIAID, NIH

This electron micrograph shows tick tissue infected with the spiral-shaped bacteria that cause Lyme disease.

several million dollars.

State health departments focus most of their efforts on educational campaigns. Although important, knowledge of the disease won't always prevent it. Even if some people *are* willing to lower their risk by donning long pants and several layers of clothing in August, such attire does not provide an infallible shield against tick bites, Fish says. Furthermore, the idea that a person can expect to prevent Lyme by removing a tick in time is a myth, he says. The tick nymph, responsible for 90 percent of human cases of Lyme, is about the size of a pinhead, so fewer than half of Lyme victims even remember being bitten, he says.

Scientists hope someday to find in the tick's life cycle a weak link, an as-yet-unidentified stage at which ticks might be particularly vulnerable to biological control. However, researchers don't yet know enough about the tick or what limits its numbers in nature to devise a control strategy. "Unless we are able to do the research to determine the reason behind this tick explosion, we will not have a long-range solution to the problem," Fish says.

In the short term, he says, the best strategy is to identify areas where people are being exposed. Half the Lyme cases originate in people's backyards and a large number in parks. Although Fish does not recommend widespread use of destructive or expensive tick-elimination techniques, he says treating local high-risk areas with insecticides, Daminex, a bulldozer or fire may be warranted.

Even if the tick population were significantly diminished, humans could still be at risk for the disease. New evidence suggests animals may transmit the spirochete to each other without a tick to intervene. After finding that an infected mouse could transmit Lyme to a cagemate, Elizabeth Burgess of the University of Wisconsin's School of Veterinary Medicine in Madison isolated the spirochete in mouse urine. Then, by feeding mice lab-cultured spirochetes, Burgess and her co-workers produced sick mice that were able to infect ticks and other animals, thus demonstrating that the disease can be transmitted through the mouth. These findings were published in 1986 in the AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGEINE (Vol.35, p.359). Burgess also found that dogs, horses and cattle can contract the infection when, as is common, they ingest infected urine from another of the same species.

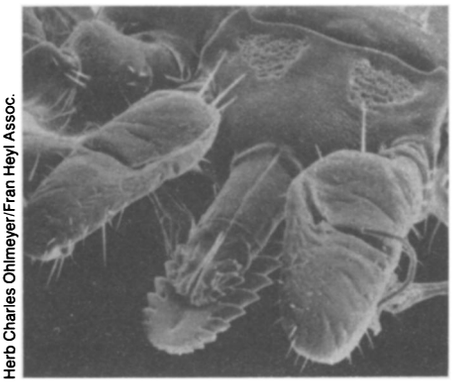
Although no direct evidence exists of nontick transmission in humans, the animal data suggest certain animals may threaten people who live or work with them. Mice that enter houses and urinate in food or drinking water could pose a hazard, as could cows that regularly soak dairy farmers and veterinarians with urine, Burgess says.

In both cows and horses, Burgess found *B. burgdorferi* can cross the placenta from a mother to her young. Young horses that contracted the pathogenic organism died soon after birth. Infected baby cows were aborted, born sick or born normal. In one case, doctors found the spirochete in the breast milk of a woman who contracted Lyme in the eighth month of pregnancy, according to physician Joseph Burrascano of South Hampton (N.Y.) Hospital.

Fish, however, says there is no evidence of any of the approximately 1,500 cases reported last year in Westchester County being caused by anything but a tick bite. He notes that the telltale Lyme rash almost always occurs in June and July. "If there were other modes [of transmission] we would be seeing cases all year long," he says. "I don't know what's going on in Wisconsin, but [nontick transmission] is not happening here."

Whether or not nontick transmission poses a threat, people are still at risk if they come in contact with the tick's animal hosts. Physicians have found a correlation between Lyme disease and pet ownership, and in a letter to the Jan. 19 NEW ENGLAND JOURNAL OF MEDICINE, Fish and entomology graduate student Kathleen L. Curran at Ohio State University in Columbus report collecting one adult and four nymphal ticks from two cats over a four-day period. "These small [nymphal] ticks," they write, "can pose a serious health threat if cats are frequently allowed outside in areas in which Lyme disease is endemic." Dogs and horses also carry ticks and often contract Lyme. Spielman, however, calls the risk of picking up ticks from pets insignificant compared with that from lawns and woods. Since a nymph feeds only once in its life, he argues, a pet-carried tick would not reattach to a human unless it had failed to feed successfully on the animal.

Electron micrograph of a tick's mouth parts. The long, tube-like organ draws the blood and the bone underneath punctures and attaches to the skin. The outer flaps, called pelps, cover the mouth parts.



Herb Charles Ohlmeyer/Fran Heyl Assoc.

The lack of knowledge puts a heavy burden on potential victims to watch for signs and take precautions. The primary way to control the transmission of Lyme disease at present is through human behavior.

Avoiding high-risk areas would help, though state agencies are unlikely to have such information. For now, Schulze says, people just have to walk the site and look for ticks. Spielman suggests watching for deer. To be safe, people walking the woods or parks in Lyme-affected areas should cover themselves with light-colored clothing and insect repellent, and inspect for ticks frequently, Fish says.

But behavioral methods are not tick-proof, and there is a need for backup support that only science can provide. Studies of the tick's life may yet reveal a fatal flaw in the creature's seemingly invincible survival techniques. After all, Fish says, "life can't be that easy for a tick." □