lenge of reliably generating a tightly focused 130-megawatt proton beam—the most powerful ever created by a linear accelerator. The beam would smash into a tungsten target, producing neutrons and other particles that would be slowed in water and sprayed into a gas stream containing helium-3, which the neutrons would convert into tritium. Paul Lisowski, director of the Accelerator Production of Tritium program at Los Alamos, doesn't think the technical challenge is overwhelming: "What we're talking about is building up a system from parts that have already been tested." Counting the 1996 expenditure, DOE is now prepared to spend roughly $350 million for Los Alamos to build and test a lower energy prototype; a full-scale accelerator would cost in the vicinity of $2 billion and would probably be located at Savannah River, DOE officials say.

Reactor production of tritium is a more familiar technology: The current tritium stock was produced by bombarding lithium rods with neutrons in the cores of now-defunct reactors at Savannah River. At a total cost of about $250 million, the reactor studies will look at the safety of running a reactor with a full load of lithium bars and at regulatory issues. The actual cost of purchasing and converting a commercial reactor might be between $1 and $2 billion, say DOE sources.

O'Leary believes that the conversion or dual use of a fission reactor would have "the lowest incremental environmental impact," as the reactor would be operating anyway to produce electricity. Still, any reactor produces long-lived radioactive byproducts, and blurring the long-standing distinction between civilian and military plants raises questions "that would need to be resolved at the highest levels of government," says Jon Ventura, a legislative and public affairs specialist for defense programs at DOE. The accelerator, in contrast, would produce no long-lived waste and wouldn't suffer from the public fears surrounding fission reactors.

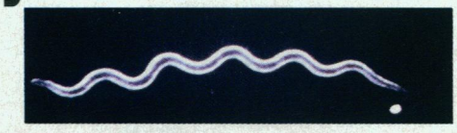
DOE has decided not to exploit what some scientists see as another strength of the accelerator option, however: the possibility of using it as the world's most intense source of neutron beams for probing materials and molecules. In times of thin funding, says Burton Richter, director of the Stanford Linear Accelerator Center, such dual use would yield "an accelerator for research built on military money."

O'Leary's announcement offers no encouragement to Richter and others who hoped to share the facility. But John Browne, director of the neutron-science center at Los Alamos National Laboratory, offers a small consolation prize. Even if the defense accelerator isn't open to basic researchers, future neutron sources for civilian research "will benefit from the R&D."

–James Glanz

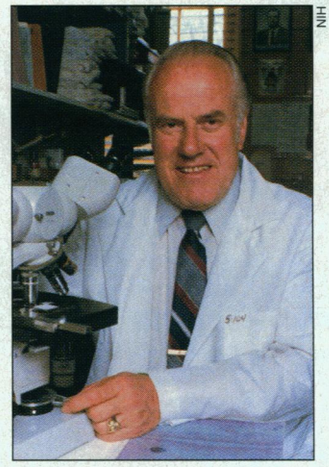
LYME DISEASE

NIH Gears Up to Test a Hotly Disputed Theory



CHARLES W. STRATTON/VISUALS UNLIMITED

The National Institutes of Health (NIH) is preparing to fund a $1-million-a-year study that it hopes will settle a dispute that has riven a segment of the medical community in the past few years. At issue: Is there a chronic form of Lyme disease that sometimes persists after conventional antibiotic treatment, inflicting a variety of symptoms such as muscle pain, fatigue, and memory loss on its victims? A group of physicians and patient advocates believes the answer is an emphatic "yes," and they have been agitating for the medical establishment to take them seriously. The upcoming NIH study means that their claims will finally be put to the test. But many Lyme disease researchers are skeptical of the need for this project.



NIH

Eponymous spirochete. Willy Burgdorfer and *B. burgdorferi*.

The very existence of the trial is testimony to the persistence of patient advocacy groups. They have lobbied Congress for many years to support research into chronic Lyme symptoms, promoting the need for long-term therapy. Their tactics have angered research leaders such as Allen Steere of Tufts University, who was the first to identify the U.S. Lyme syndrome in the 1970s. The multimillion-dollar trial that NIH is planning, he says, "would never have been funded" through the "normal mechanisms" of investigator-initiated research. But Greg Folkers, a spokesperson for the National Institute of Allergy and Infectious Diseases, says, "This trial has been under discussion for several years"—well before Congress recommended that NIH study new antibacterial strategies.

Steere, Alan Barbour—a microbiologist at the University of Texas, San Antonio—and other researchers believe that there's little evidence to support the notion that there is an epidemic of chronic infection by Lyme disease. Most so-called chronic cases, they believe, are not Lyme disease at all; NIH's study could be a waste of money. But advocate groups—particularly the Lyme Disease Foundation (LDF) of Hartford, Connecticut, which includes physicians who treat Lyme patients—argue that the disease is more elusive, more malignant, and more difficult to treat than academic scientists have acknowledged. They believe that the traditional treatment advocated by physicians at leading medical schools such as Yale, Tufts, and the University of Connecticut—2 to 4 weeks of oral antibiotics and, in rare cases when the central nervous system is infected, 4 weeks of intravenous antibiotics—is in many cases insufficient to wipe out the disease.

Joseph Burrascano Jr., a Long Island physician who specializes in treating Lyme disease and has served as board member of the LDF, argues that more aggressive therapy is often needed. He prescribes months-long courses of antibiotics for many of his Lyme patients, including intravenous therapy. Kenneth Liegner, a physician in Armonk, New York, has also written that clinicians should expect "a revolution in our conceptualization of this disease." Evidence is mounting, Liegner says, that "subsets of patients" with as-yet-unconfirmed immune system weaknesses do not benefit from routine therapy and may require "prolonged antibiotic treatment."

Patient activists have seized on these arguments and are pushing for studies which they believe will confirm a more radical attack on the disease than has been recommended by the establishment so far. One objective, says patient advocate Kenneth Fordyce, chair of the governor's Lyme disease advisory committee in New Jersey, is to get insurance companies to reimburse patients for antibiotic therapy that lasts longer than the standard 28 days.

Disagreement between the activists and the medical establishment erupted 3 years ago, when abstracts of a dozen papers submitted by clinicians to a Lyme disease conference were rejected by the program committee as lacking in scientific merit. The papers—most of which discussed chronic Lyme cases—were reinstated over the objections of several researchers after patient advocacy groups protested (*Science*, 5 June 1992, p. 1384).

After failing to convince the establish-

ment of its scientific views, LDF took a route that has been well trodden by AIDS and breast cancer activists: It mounted a lobbying campaign. NIH is now accepting proposals for a trial that will examine whether patients with long-lasting symptoms are truly infected with Lyme, and whether they benefit from prolonged antibiotic therapy.

Origins: Old Lyme. The tussle between the activists and the Lyme disease establishment stems in large part from inadequate diagnostic tests and limited understanding of how the culprit organism survives in humans. The symptoms of Lyme disease in the United States were first identified during the 1970s through Steere's studies of children in New England who were suffering from swollen knees and joints. Steere determined that the syndrome—which was heavily focused around Old Lyme, Connecticut—is a form of arthritis associated with bites from deer ticks and a strange, bulls-eye rash, erythema migrans. It soon became apparent that Lyme syndrome was similar to an infection that had been described in Europe in the 19th century. In 1982, biologist Willy Burgdorfer at NIH's Rocky Mountain lab in Montana nailed the infectious agent: a spiral-shaped bacterium (a spirochete) of the Borrelia family, mainly found in a small deer tick, *Ixodes scapularis*. In honor of the discoverer, the bacterium was named *Borrelia burgdorferi*.

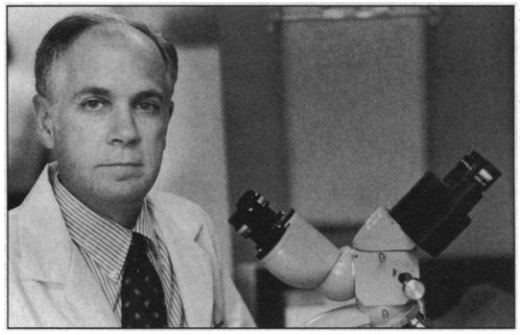
Today, Burgdorfer says that the Lyme organism and other spirochetes—slow-growing but potent organisms responsible for a variety of diseases including syphilis—deserve more attention from researchers. Syphilis, for example, "has been known for ages. ... But with all our advanced technology, we are not in a position to 100% prove that the manifestations shown by a patient are due to chronic spirochetosis [ongoing infection] or something else," such as late-appearing damage from an infection that may have stopped much earlier. The same uncertainties plague the diagnosis and treatment of Lyme disease, Burgdorfer says.

The weak understanding of the organism's biology is compounded by the lack of a good diagnostic test. Blood tests for human Lyme infection have been unreliable, often yielding false positives, and, some physicians say, many false negatives. It was only in October 1994, Barbour notes, that leaders of public health agencies from around the United States met in Michigan to establish common standards for testing and confirming the presence of Lyme infection.

Because it was hard to diagnose cases with certainty, it was also hard to sort out the effects of different therapies. The confusion has been increased by the widening spectrum of symptoms attributed to Lyme infection. Initially, Steere focused on clear-cut indicators—the rash and swollen joints. But subtler effects have now been added to the list, including injury to the eyes, the heart, the nervous system, and the brain.

A polarized community. As the list of possible ill effects grew, so did the number of patients who felt they were suffering from Lyme disease. Their ranks stood at fewer than 1000 in 1982, but, according to the Centers for Disease Control and Prevention, rose to more than 13,000 in 1994. To Steere, the increase is a sign that Lyme disease "has become an overdiagnosed and overtreated illness." To back up this contention, Steere conducted a study, published in the *Journal of the American Medical Association* in 1993, in which he reported that 57% of 788 cases referred to the clinic as Lyme disease patients by other physicians were not infected with *Borrelia*.

Many other academics—such as Durland Fish and Eugene Shapiro of Yale—agree with Steere that clinical practice has gone overboard. They believe many physicians are classifying vaguely defined illnesses as Lyme disease and selecting antibiotic therapy as the most convenient solution, particularly for prolonged and ill-defined ailments, such as diffuse pain (fibromyalgia) and fatigue. One of the major problems in this field, says Shapiro, "is not Lyme disease itself but the misdiagnosis of Lyme disease and anxiety about Lyme disease."



BRADFORD F. HERZOG

Skeptic. Allen Steere believes Lyme disease is "an overdiagnosed and overtreated illness."

At the other pole are physicians who think Steere and his medical school colleagues ignore the subtlety and persistence of *B. burgdorferi*. Burrascano, in a 1993 Senate hearing, denounced the "conspiracy ... of university-based" scientists who he said were using their clout to promote the "outdated" idea that "Lyme is a simple, rare illness that is ... easily cured by 30 days or less of antibiotics." Burrascano points out that the Lyme bacterium is difficult to detect in the blood after the initial infection even if it has been left untreated. The aggressive treaters of Lyme disease have long argued that the spirochete hides within cells, deep in joints and connective tissue, in the eyes, and in the relative isolation of the cerebrospinal nerve system. These locations are inaccessible to routine antibiotic therapy, they argue, and long-term infections require the use of intravenous, potent antibiotics over many months.

Somewhere in the middle of the Lyme battleground are physicians like neurologist Patricia Coyle, a clinician at the Health Sciences Center of the State University of New York, Stony Brook, who see merit in Burrascano's arguments but doubt that many patients are afflicted with chronic infections. Coyle, who works in a special clinic at Stony Brook that sees 1600 Lyme patients a year, says key questions about Lyme infection remain unanswered.

First, Coyle asks: "Does the spirochete go into the cells or not? We don't know." However, she says in vitro studies suggest that it does, and that it may escape antibiotics that way. Second, Coyle would like to know to what extent and how often the spirochete penetrates the central nervous system. Also, she would like to confirm which antibiotics are best at attacking it there. Third, she would like to learn whether the organism enters a quiescent period after infection. While scientists have been exploring these issues in laboratory studies, Coyle argues that it is important and "very practical" to carry out a large clinical trial, because it's risky in dealing with infections to extrapolate from bench to bedside.

These are just the kinds of questions that NIH's clinical trial will address. The aim is to recruit patients who have previously been diagnosed and given routine therapy for Lyme disease, but whose symptoms persist. They will be carefully screened to fit criteria—as yet undefined—of confirmed Lyme patients. And they will be assigned blindly to one of several treatment regimens, including a placebo group, to be followed for several years, probably at more than one center. "One of the big unanswered questions," says John LaMontagne of the National Institute of Allergy and Infectious Diseases, "is whether or not *Borrelia* produces some sort of permanent neurologic damage that cannot be reversed with antibiotic therapy."

Researchers such as Barbour and Steere are concerned that the trial—if not well designed—could end up an expensive disappointment. But Barbour agrees it may serve a useful purpose. The debate among clinicians about what causes long-term symptoms and how to cure them "needs to be settled," he says. "People are spending millions of dollars on antibiotics," hoping to be rid of all kinds of symptoms. Adds Burgdorfer: "Once we have the answers to these questions, all the other stuff ... the politics ... the quarreling among the scientists, will disappear." In a community so split, that may be a forlorn hope.

–Eliot Marshall