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Report to Congressional Requesters

June 2001

LYME DISEASE

HHS Programs and Resources

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Contents

Letter		1
Appendix I	**Background on Lyme Disease**	18
Appendix II	**Centers for Disease Control and Prevention**	22
Appendix III	**National Institutes of Health**	24
Appendix IV	**Recommendations Made to CDC and NIH Lyme Disease Programs**	26
Appendix V	**Comments From the Department of Health and Human Services**	30

Tables

Table 1: States With the Highest Rates of Lyme Disease 20
Table 2: Expert Recommendations for the CDC Lyme Disease Program, 1994 26
Table 3: Congressional Appropriation Committees' Recommendations Related to CDC Lyme Disease Activities 27
Table 4: Board of Scientific Counselors Recommendations for the NIAID Lyme Disease Program, 1998 27
Table 5: Advisory Panel Recommendations for NIAID's Clinical Studies on Chronic Lyme Disease 28
Table 6: Congressional Appropriation Committees' Recommendations Related to NIH Lyme Disease Activities 29

Figures

Figure 1: CDC Allocations for Lyme Disease, Fiscal Years 1991 Through 2000 11
Figure 2: CDC Allocations for Lyme Disease Relative to CDC's Overall Appropriations and Infectious Diseases Budget Authority (Inflation-Adjusted), Fiscal Years 1991 Through 2000 12
Figure 3: NIH Obligations for Lyme Disease, Fiscal Years 1991 Through 2000 14
Figure 4: NIH Obligations for Lyme Disease Relative to NIH Overall Appropriations (Inflation-Adjusted), Fiscal Years 1991 Through 2000 15

Abbreviations

CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
NCRR	National Center for Research Resources
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke

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Accountability * Integrity * Reliability

United States General Accounting Office
Washington, DC 20548

June 22, 2001

The Honorable Christopher J. Dodd
The Honorable Rick Santorum
United States Senate

The Honorable Virgil H. Goode, Jr.
The Honorable Joseph R. Pitts
The Honorable Christopher H. Smith
House of Representatives

Lyme disease is a systemic, tick-borne disease with varied manifestations, including abnormalities of the skin, joints, heart, and nervous system. According to data from the Centers for Disease Control and Prevention (CDC), Lyme disease is the most common illness transmitted by insects or other nonhuman organisms in the United States, accounting for 95 percent of all such reported illnesses. From 1991 through 1999, the annual number of reported cases of Lyme disease increased by 72 percent. Although Lyme disease has been reported in 49 states and the District of Columbia, 9 states, mainly in the eastern part of the country, account for 92 percent of the nationally reported cases.[1] Persons of all ages and both sexes are equally susceptible, although the highest attack rates are in children under 15 and in adults from age 45 to 65.

For over 10 years, two components of the Department of Health and Human Services (HHS)—CDC and the National Institutes of Health (NIH)—have conducted programs to study Lyme disease and educate the public and professionals about this disease.[2] Some practitioners, patients, patient organizations, and researchers in the Lyme disease community are concerned about the pace and direction of the research, including studies of chronic Lyme disease.[3] Given these concerns, you asked that we examine CDC and NIH research and education on Lyme disease. We

[1]These states are Connecticut, Delaware, Maryland, Massachusetts, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin.

[2]The Food and Drug Administration is also part of the federal response to Lyme disease, but it does not maintain an organized research and education program to combat Lyme disease in the same way that CDC and NIH do.

[3]Chronic Lyme disease is a condition of persisting symptoms in patients who have been treated for Lyme disease.

address these questions: (1) What activities have the CDC and NIH Lyme disease programs been engaged in, and to what extent have they initiated responses to the recommendations of outside experts and congressional appropriations committees? (2) What funds and other resources have CDC and NIH devoted to Lyme disease?

We focused our review on those agency components with significant Lyme disease research and education programs, CDC's Division of Vector-Borne Infectious Diseases and NIH's National Institute of Allergy and Infectious Diseases (NIAID). We reviewed program plans, grant lists, and financial documents for activities occurring from fiscal years 1991 through 2000. CDC and NIH research and education on Lyme disease were examined in light of the stated objectives of the programs, recommendations to initiate Lyme disease activities,[4] and program reviews made by independent experts, but were not judged for their scientific merit. In addition, we compared CDC allocations for Lyme disease with CDC's overall appropriations and budget authority for infectious diseases, adjusted for inflation.[5] We compared NIH obligations for Lyme disease with appropriations for NIH and NIAID, adjusted for inflation.[6] We also interviewed agency officials, patients, officials of patient organizations, and nonfederal researchers and reviewed minutes from agency meetings related to Lyme disease. We did not perform an audit allowing us to attest to the accuracy of the allocations and obligations data provided by the agencies. We conducted our work from June 2000 through May 2001 in accordance with generally accepted government auditing standards.

Results in Brief

Consistent with their respective missions, CDC and NIH have conducted an increasingly broad range of research and educational activities related to Lyme disease. CDC has instituted a system for the surveillance of Lyme disease, helped to standardize diagnostic testing, conducted and funded basic research on Lyme disease and on its prevention, and developed

[4]From House and Senate Appropriations Committees' explanations of the Departments of Labor, HHS, Education, and Related Agencies Appropriation Bills.

[5]Throughout this report, except where otherwise indicated, we have adjusted all dollar values for general inflation, using the Consumer Price Index for all items with fiscal year 2000 as the base.

[6]CDC and NIH were not able to provide us with directly comparable funding data for their Lyme disease programs. We report the data they were able to provide, allocation data for CDC and obligation data for NIH.

patient and practitioner educational materials. CDC has initiated most activities recommended by external reviewers and congressional appropriations committees regarding changes to its programs. For example, for fiscal year1994 the Senate Appropriations Committee recommended that CDC continue to develop a substantial pool of scientific expertise and support for Lyme disease, and in that year CDC funded a cooperative agreement with the American College of Physicians to educate physicians who treat Lyme disease. NIH has conducted and funded basic research on Lyme disease and on its etiology, diagnosis, treatment, and prevention. In addition, NIH research is addressing two topics of particular interest to patient advocates, chronic Lyme disease and the occurrence of other tick-borne infections in Lyme disease patients. NIH has also responded to most expert recommendations and congressional recommendations. For example, for fiscal year 1996 the Senate Appropriations Committee recommended that NIH expand its research on chronic Lyme disease, which the agency did in the same year by funding two new studies.

Over the past 10 years, allocations for Lyme disease have increased slightly at CDC, and obligations for Lyme disease have increased significantly at NIH. CDC allocations for Lyme disease research and education have increased 7 percent, from $6.9 million to $7.4 million in inflation-adjusted dollars, from fiscal years 1991 through 2000. Over the same period, the CDC infectious diseases budget authority rose from $48.5 million to $175.6 million, or 262 percent, in inflation-adjusted dollars. In spite of the slight increase for the entire period, CDC allocations for Lyme disease declined prior to fiscal year 1998, when the allocation rose considerably, to $8.3 million in inflation-adjusted dollars. Since then, allocations have again been declining. In contrast, the NIH increase in obligations for Lyme disease has been steady and relatively large, at 99 percent. NIH obligations for Lyme disease have increased almost every year, from $13.1 million in fiscal year 1991 to $26.0 million in fiscal year 2000 in inflation-adjusted dollars. By comparison, appropriations for NIAID rose from about $1.1 billion to about $1.8 billion, or 55 percent, in inflation-adjusted dollars over the same period. A portion of the increase in NIH's Lyme disease obligations results from a very large increase in obligations for research on chronic Lyme disease, which has grown, in inflation-adjusted dollars, from about $124,000 in fiscal year 1991 to $3.5 million in fiscal year 2000. NIAID funds the majority of Lyme disease activities at NIH, an average of 69 percent annually over the period reviewed, but several other institutes have also funded research on the disease.

We provided a draft of this report to HHS for review. HHS stated that it had no comments.

Background

Lyme disease was identified as a separate disease in 1977 because of a cluster of cases in children in Lyme, Connecticut, who were first thought to have juvenile rheumatoid arthritis. It was not until 1982, with the discovery of the causative bacterium, *Borrelia burgdorferi*, that Lyme disease could be defined by nonclinical observations. Carriers of *Borrelia burgdorferi* include the deer tick in the upper Midwest and Northeast and the western black-legged tick on the Pacific Coast, two areas where Lyme disease is considered to be endemic. Lyme disease symptoms generally appear 7 to 14 days after transmission, but this period may range from 3 to 30 days. Manifestations include musculoskeletal, nervous system, or cardiovascular irregularities that are not attributable to any other cause. However, some individuals may have no recognized illness or manifest only nonspecific symptoms, such as fever, headache, fatigue, and muscle pain. For more details on the definition of Lyme disease and on its diagnosis, prevalence, treatment, and prevention, see appendix I.

Federal Lyme disease research programs are administered by two agencies within HHS. CDC funds laboratory and field research, surveillance, and education. CDC's Lyme disease program, an effort of the National Center for Infectious Diseases, is housed at Fort Collins, Colorado, in the Division of Vector-Borne Infectious Diseases. NIH funds intra- and extramural basic and clinical research and promotes educational activities. NIH carries out its Lyme disease activities at several NIH institutes and centers, primarily NIAID, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Center for Research Resources (NCRR). NIAID conducts clinical research related to Lyme disease at the Clinical Studies Unit on the NIH campus in Bethesda, Maryland, and laboratory research at the Rocky Mountain Laboratories in Hamilton, Montana. For more information on the roles of CDC and NIH, see appendixes II and III, respectively.

The Lyme disease programs at both agencies have been reviewed by experts for their scientific merit. In 1994, CDC convened an ad hoc panel of outside experts to review its Lyme disease program. NIH's Board of Scientific Counselors, an advisory panel composed of nonfederal experts, periodically reviews NIH's intramural research programs, including those involving Lyme disease. This board reviewed NIH's Lyme disease program in 1993 and 1998. Also at NIH, the Advisory Panel on the Clinical Studies of

Chronic Lyme Disease, a panel composed of nonfederal researchers and patient advocates, provides guidance on Lyme disease-related clinical trials. It provided annual reviews beginning in 1996 and continuing through 1999.

CDC and NIH Programs Continue to Broaden Understanding of Lyme Disease

CDC and NIH have conducted a broad range of research and educational activities related to Lyme disease. CDC has instituted a surveillance system, helped to standardize diagnosis, and funded research on prevention and education, while initiating most recommendations made by expert review committees and related activities recommended in congressional appropriations committees' reports. NIH has funded research on the basic nature of Lyme disease and on its diagnosis, treatment, and prevention, and initiated most related expert and congressional recommendations.

CDC Lyme Disease Activities

CDC's Division of Vector-Borne Infectious Diseases has conducted a broad range of Lyme disease activities consistent with its program plans. In 1990, it developed a Lyme disease surveillance case definition,[7] approved by the Council of State and Territorial Epidemiologists for uniform national reporting of Lyme disease beginning in 1991. Using surveillance data, CDC conducted epidemiological and ecological studies of disease and tick distribution for many areas of the United States. CDC's research focused on those areas in which Lyme disease is highly endemic, but some activities were conducted in areas in which Lyme disease may be emerging. For example, CDC conducted research in the south central United States to investigate the emergence of a disease similar to Lyme disease. In addition, CDC has developed a national map showing risk of infection based on geographic area.

CDC's laboratories have conducted basic research on diagnostic test development. In 1994, CDC, along with a group composed of representatives of academic research laboratories, state and federal public health agencies and organizations, and manufacturers of diagnostic tests, developed a two-step approach to testing for Lyme disease that was more accurate than individually performed diagnostic tests available at the time.

[7]The CDC case definition is a set of criteria designed to identify individual cases of disease for surveillance purposes. This definition is not intended to guide patient diagnosis and treatment.

The two-step approach was developed to detect new cases of Lyme disease.[8] CDC, in collaboration with NIAID grantees and intramural scientists, is developing a single-step test that is intended to improve diagnostic accuracy.[9]

With regard to the prevention of Lyme disease, CDC

- has developed targeted ways of disseminating tick-killing pesticides, including feeding devices that apply the pesticides to deer and mice, which serve as tick hosts;
- has worked with community-based programs to educate high-risk communities on managing vegetation that can harbor ticks;
- initiated a cooperative research and development agreement with SmithKline Beecham[10] Animal Health and SmithKline Beecham Biologics to identify and characterize proteins of potential value in the development of products for immunological protection against Lyme disease and for new and improved diagnosis;
- monitors the Vaccine Adverse Events Reporting System, along with the Food and Drug Administration (FDA), to continually evaluate the Lyme disease vaccine's safety; and
- has developed written recommendations through its Advisory Committee on Immunization Practices for the administration of the Lyme disease vaccine.

To educate the medical and patient communities, CDC

- has funded activities by professional groups and associations to develop diagnosis and treatment recommendations for both physicians and nurses;
- maintains an informational Web site for patients and health professionals and provides the public with educational materials;
- has provided training and funds to state and local health departments to improve surveillance and educational activities, including sponsoring

[8]The Association of State and Territorial Public Health Laboratory Directors, CDC, and the Michigan Department of Health, *Proceedings of the Second National Conference on Serologic Diagnosis of Lyme Disease* (Washington, D.C.: ASTPHLD, 1994), p. 1.

[9]F.T. Liang, A.C. Steere, A.R. Marques, B.J.B. Johnson, J.N. Miller, and M.T. Philipp, "Sensitive and Specific Serodiagnosis of Lyme Disease by Enzyme-Linked Immunosorbent Assay with a Peptide Based on an Immunodominant Conserved Region of *Borrelia burgdorferi* VlsE," *Journal of Clinical Microbiology*, Vol. 37, No. 12 (1999): 3990-3996.

[10]SmithKline Beecham is now part of GlaxoSmithKline.

conferences and workgroup meetings in 1993, 1994, 1998, and 1999 to update the Lyme disease community and help guide the future of CDC Lyme disease programs; and

- has disseminated the results of its Lyme disease research in hundreds of articles in peer-reviewed journals.

CDC has been responsive to experts and Congress. It has initiated most Lyme disease-related activities recommended by expert reviewers. In 1994, three nonfederal reviewers evaluated CDC's Lyme disease program and made 16 recommendations. For a list of these recommendations, see appendix IV. We found evidence that CDC initiated activities consistent with most of these recommendations. For one recommendation, concerning the expansion of physician education in the South, we found no evidence, although the agency did state that it conducted collaborative research with physicians in that part of the country. CDC initiated work on all Lyme disease activities recommended in House and Senate Appropriations Committees' reports. From fiscal years 1991 through 1998, Congress made 12 such recommendations. (See app. IV.)

NIH Lyme Disease Programs

NIH has supported a broad range of research, promoted educational activities, and improved research capacity related to Lyme disease. Most Lyme disease activities were funded by NIAID, the lead institute for Lyme disease. This work has been consistent with NIAID's general goal for its Lyme disease program: to develop better means of diagnosing, treating, and preventing the disease.

Much of the Lyme disease work performed at NIAID's Rocky Mountain Laboratories and about 20 percent of NIAIDs Lyme disease grants to nonfederal researchers have been devoted to research on diagnostic methods. For example, it has developed a diagnostic test that can differentiate between those infected with Lyme disease and those who previously would have tested positive because they had been immunized with the Lyme disease vaccine. In addition, because ticks may carry more than one disease, NIH has supported research on the co-infection of Lyme disease patients with *Babesia* and *Ehrlichia*.[11] NIAMS has also supported research on diagnostics and has developed a DNA-based diagnostic test for *Borrelia burgdorferi*, the bacterium responsible for Lyme disease.

[11] *Babesia* are particular kinds of parasites, and *Ehrlichia* are particular kinds of bacteria. Both may cause disease and are carried by ticks associated with Lyme disease.

NIH has also supported research on the treatment of Lyme disease, with an emphasis on chronic Lyme disease. In 1996, NIAID scientists initiated research to identify the clinical characteristics of both acute and chronic Lyme disease. The same year, NIAID entered into a contract to determine the efficacy of antibiotic treatment of chronic Lyme disease. The treatment component of this study was terminated after a scheduled review at the end of fiscal year 2000 because of a finding of "no observed difference" in self-reported improvement between the treatment and the control groups.[12] In 2000, NINDS initiated funding for a study of the neurological effects and treatment of chronic Lyme disease.

With respect to prevention, NIH has funded research on

- the basic biology underlying the development of a vaccine for Lyme disease, later used by SmithKline Beecham to develop a Lyme disease vaccine;
- animal models for the development and testing of other potential Lyme disease vaccines;
- tick ecology and control; and
- the relationship between maternal Lyme disease and congenital abnormalities in newborns.

NIH has produced educational materials and worked with other groups to sponsor conferences and workshops. For example, NIAID

- produced a 1996 fact sheet for physicians titled, "Tick-Borne Diseases: An Overview for Physicians," and a 1998 pamphlet for patients titled, "Lyme Disease: The Facts, The Challenge";
- maintains a Web site that provides information on diagnosis and NIAID activities related to Lyme disease; and
- has disseminated its Lyme disease research through over 100 scientific articles published by its researchers.

[12]M.S. Klempner and others, "Two Controlled Trials of Antibiotic Treatment in Patients With Persistent Symptoms and a History of Lyme Disease," *The New England Journal of Medicine* (early release on June 12, 2001; final version to be published in the July 12, 2001, issue): http://www.nejm.org, accessed on June 12, 2001.

NIH has responded to expert recommendations and to those of Congress. NIH implemented all recommendations related to the NIAID Lyme disease program made by the Board of Scientific Counselors, NIH's external committee that reviews the intramural program. In 1996 and 1998, the reviewers evaluated the Lyme disease-directed efforts of Rocky Mountain Laboratories and the Clinical Studies Unit, and made six recommendations. For example, the reviewers recommended that the laboratories hire additional technical staff. NIH followed this recommendation and pursued activities consistent with all of the others. (For a list of the recommendations, see app. IV.)

NIH has also initiated activities consistent with most of the recommendations of the Advisory Panel on the Clinical Studies of Chronic Lyme Disease. In 1996 and 1999, this panel of outside experts and advocates provided 15 recommendations regarding the NIAID intramural and extramural clinical studies on chronic Lyme disease. (See app. IV.) For example, the panel recommended using standardized neuropsychological tests in the intramural work. NIH implemented this and most of the other recommendations. A recommendation that it did not implement was to establish an unblinded oversight committee to review the placebo group of the clinical study conducted at the New England Medical Center. NIH did not believe that such an approach was warranted because procedures already in place were adequate to safeguard the welfare of all enrolled in the study.

NIH pursued work on most Lyme disease activities recommended in House and Senate Appropriations Committees' reports, including, for example, one concerning the avoidance of research duplication. (See app. IV for a list of these recommendations.) From fiscal years 1991 through 1998, Congress made 11 recommendations to NIH regarding Lyme disease. NIH pursued work on nine of those recommendations. NIH did not fully address the other two recommendations. One of these was a recommendation by the Senate Appropriations Committee to establish a pediatric Lyme disease program at NIAID's Clinical Studies Unit at NIH's Bethesda, Maryland, hospital. According to NIH, because of the invasive nature of the diagnostic tests required as part of the study planned at that facility, it was determined that including pediatric patients would not be appropriate. The second recommendation that NIH did not fully address, also by the Senate Appropriations Committee, was to consider funding a center in the Midwest or Southwest to conduct clinical trials of treatments that would otherwise not be tested. NIH officials told us that they convened a workshop intended to develop information for physicians on the diagnosis of, and therapy for, Lyme disease and issued a request-for-

application for research on the diagnosis and treatment of Lyme disease. They also told us that, taken together, these efforts helped to build a base of knowledge and necessary critical mass so that, in the future, research centers might be a viable option.

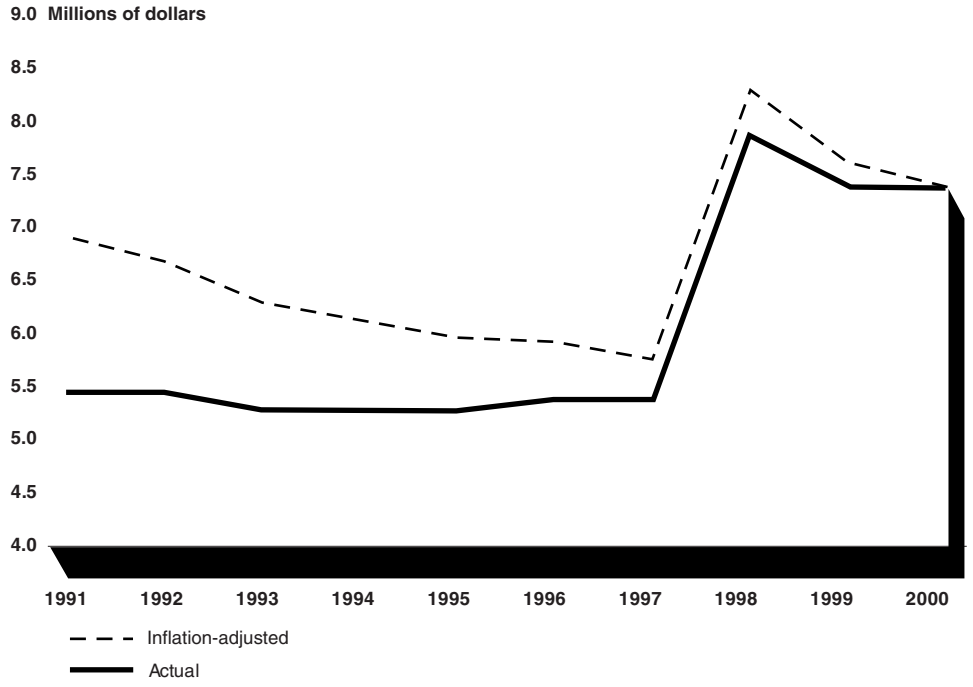
Funding for Lyme Disease Has Increased Slightly at CDC and Significantly at NIH

Funding related to Lyme disease has increased at both CDC and NIH from fiscal years 1991 through 2000. The CDC increase in allocations was about 7 percent during that period, from $6.9 million to $7.4 million in inflation-adjusted dollars. In spite of the slight increase for the entire period, the CDC allocations for Lyme disease declined prior to fiscal year 1998, when the allocation rose considerably, to $8.3 million in inflation-adjusted dollars. Since then, the allocations have again been declining. In contrast, the NIH increase in obligations has been steady and relatively large, at 99 percent. NIH obligations for Lyme disease have increased almost every year, from $13.1 million in fiscal year 1991 to $26.0 million in fiscal year 2000 in inflation-adjusted dollars.

CDC Lyme Disease Allocations Increased in 1998, but Declined in All Other Years

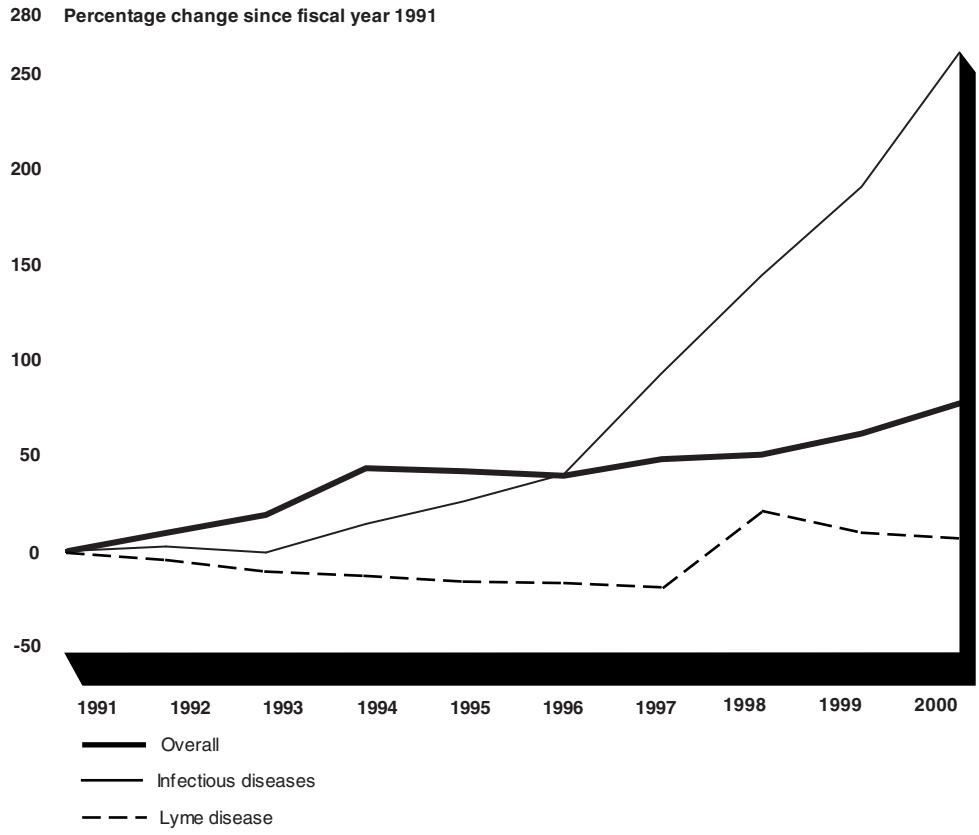
Total CDC allocations for Lyme disease programs increased during the period reviewed in spite of a downward trend in all years but one. Allocations, in inflation-adjusted dollars, decreased from $6.9 million in fiscal year 1991 to $5.8 million in fiscal year 1997, increased in fiscal year 1998 to $8.3 million, and have since declined to $7.4 million. (See fig. 1.) CDC's allocations for Lyme disease have grown much more slowly than CDC's budget authority for infectious diseases. This budget authority rose from $48.5 million to $175.6 million in inflation-adjusted dollars over the same period. The increase in allocations for Lyme disease in 1998 coincided with an increase in the CDC infectious diseases budget authority. During the period reviewed, Lyme disease allocations increased by 7 percent, while CDC appropriations and infectious diseases budget authority increased by 77 percent and 262 percent, respectively. (See fig. 2.)

Figure 1: CDC Allocations for Lyme Disease, Fiscal Years 1991 Through 2000



Source: CDC.

Figure 2: CDC Allocations for Lyme Disease Relative to CDC's Overall Appropriations and Infectious Diseases Budget Authority (Inflation-Adjusted), Fiscal Years 1991 Through 2000



Source: CDC.

The large increase in Lyme disease allocations in fiscal year 1998 was used to expand grant funding. From fiscal years 1991 through 1997, CDC reported that grants accounted for 58 percent of Lyme disease funding for the Division of Vector-Borne Infectious Diseases, while program operations accounted for 42 percent. However, after the fiscal year 1998 Lyme disease allocations increase, program operations funding remained relatively flat and grant funding increased from $2.8 million to $5.1 million in inflation-adjusted dollars. In fiscal years 1999 and 2000, grants have accounted for 69 percent of Division of Vector-Borne Infectious Diseases Lyme disease allocations. Over 80 percent of this grant funding has been used for cooperative agreements with universities and public health laboratories, with the remainder going to foundations and other kinds of organizations. The most commonly funded cooperative agreements have

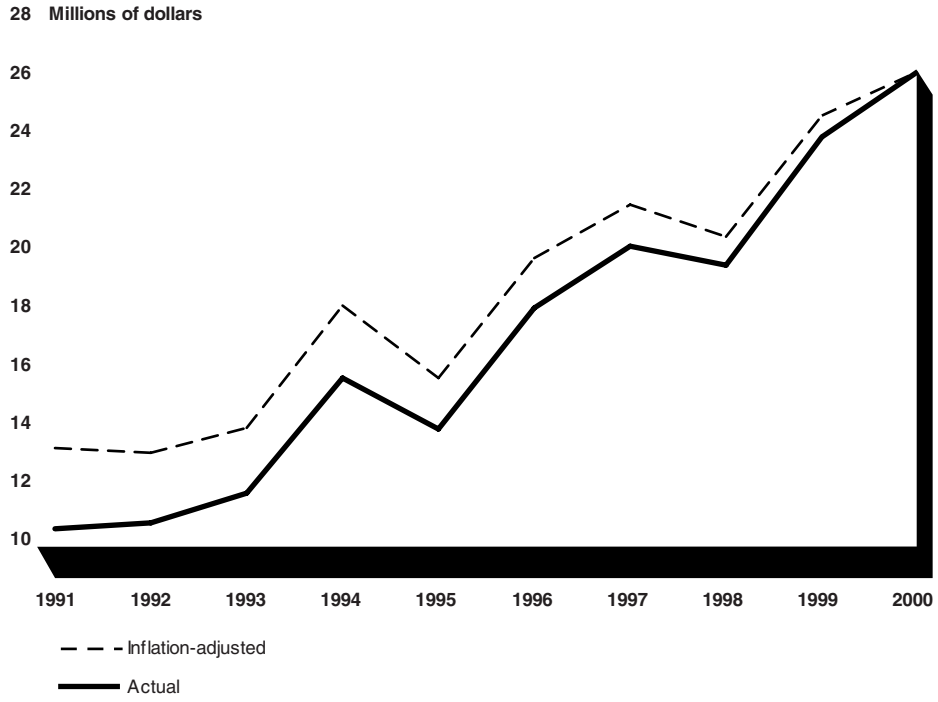
been related to research on the diagnosis and on the origination and development of the disease or have involved activities related to surveillance, diagnosis, prevention, and education.

In 2000, the Division of Vector-Borne Infectious Diseases had 24 full-time employees working on Lyme disease activities. Fourteen of those employees devoted 100 percent of their time to Lyme disease activities, and 10 employees spent from 10 to 90 percent of their time on Lyme disease.

NIH Lyme Disease Obligations Increased Significantly Over the Past Decade

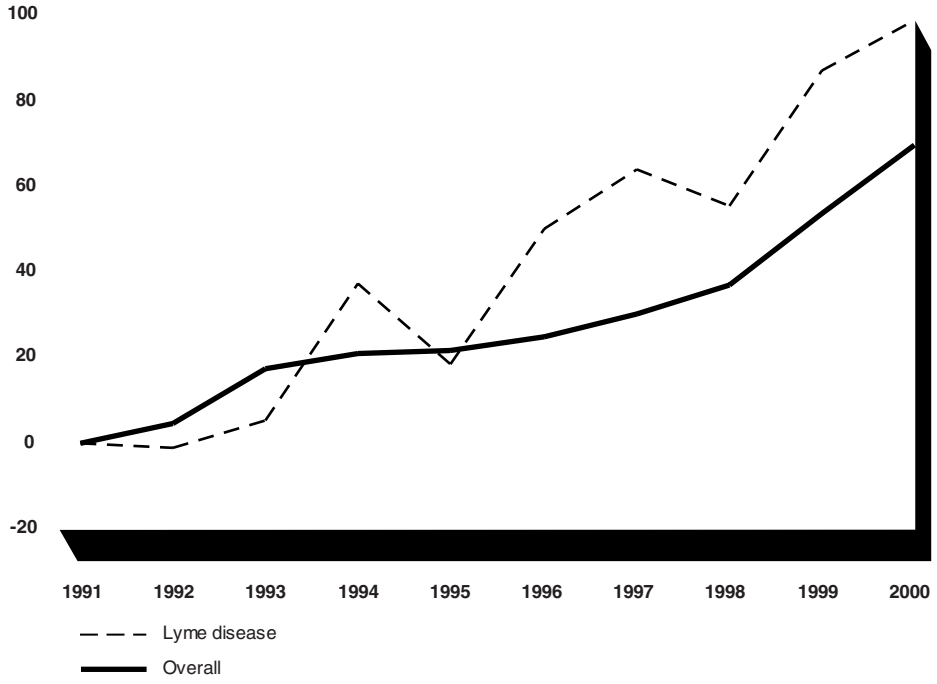
Total NIH obligations for Lyme disease activities in inflation-adjusted dollars increased from $13.1 million in fiscal year 1991 to $26.0 million in fiscal year 2000. (See fig. 3.) NIH Lyme disease obligations rose at a faster rate than overall NIH appropriations; NIH Lyme disease obligations rose 99 percent, while total appropriations for NIH rose 70 percent over the same period. (See fig. 4.) The majority of Lyme disease activities are funded by NIAID, but several other institutes have also funded Lyme disease research. During the period reviewed, NIAID Lyme disease obligations also rose at a faster rate than overall appropriations for NIAID. NIAID obligations for Lyme disease increased from $8.4 million to $18.2 million, or 116 percent, while overall appropriations for NIAID increased from about $1.1 billion to $1.8 billion over the decade, or 55 percent, in inflation-adjusted dollars. A portion of the increase in Lyme disease funding is related to an increase in the funding of chronic Lyme disease research, which has risen, in inflation-adjusted dollars, from $124,000 in fiscal year 1991 to $3.5 million in fiscal year 2000.

Figure 3: NIH Obligations for Lyme Disease, Fiscal Years 1991 Through 2000



Source: NIH.

Figure 4: NIH Obligations for Lyme Disease Relative to NIH Overall Appropriations (Inflation-Adjusted), Fiscal Years 1991 Through 2000



Source: NIH.

The majority of NIH Lyme disease obligations were used to fund extramural grants and contracts, which primarily support scientists within universities, medical schools, hospitals, and research institutions. From fiscal years 1991 through 2000, NIH spent 15.3 percent of its Lyme disease budget on intramural research activities and the rest on extramural activities. However, in fiscal years 1999 and 2000, NIH reported increases in intramural funding to 23.4 percent and 26.0 percent of the Lyme disease budget, respectively. Much of these increases can be attributed to two new activities: a large intramural study on the diagnosis and treatment of human uveitis, an eye infection that can be a complication of Lyme disease, at the National Eye Institute in fiscal year 1999, and an increase in NIAID intramural research on Lyme disease in fiscal years 1999 and 2000.

NIAID, NIAMS, and NCRR are the three NIH components to have funded Lyme disease-related activities every year from fiscal years 1991 through 2000. During the past 10 years, NIAID has provided an average of 69

percent of the total NIH Lyme disease obligations; however, total NIAID Lyme disease obligations increased in relation to the Lyme disease obligations of other institutes and centers. As NIAID Lyme disease obligations increased, NIAMS and NCRR Lyme disease obligations remained at around 20 percent and 5 percent of NIH Lyme disease obligations, respectively, and other institutes began funding small numbers of grants (fewer than five per year) partially related to Lyme disease.

Out of its overall obligations for Lyme disease, NIH increased obligations for grants related to chronic Lyme disease and post-Lyme disease syndrome[13] during the period reviewed. NIAMS awarded grants on chronic Lyme disease throughout the period reviewed. In fiscal year 1994, NIAID reported chronic Lyme disease grants totaling $745,692, increasing to $3.4 million in inflation-adjusted dollars in fiscal year 1999. The majority of this increase can be attributed to the NIAID clinical trials on chronic Lyme disease that started in fiscal year 1996. NIAID chronic Lyme disease obligations decreased to $1.5 million in inflation-adjusted dollars in fiscal year 2000. However, NINDS initiated a $1.2 million clinical trial on chronic Lyme disease in fiscal year 2000.

The number of NIH staff working on Lyme disease grew during the period observed. The majority of NIH staff working on Lyme disease are in NIAID. NIAID's Rocky Mountain Laboratories funds three Lyme disease researchers, and NIAID's Clinical Studies Unit has one clinical researcher, plus staff. Both laboratories have added staff during the period observed. In addition, NIAID has funded a Program Officer for Lyme disease since 1993, to stimulate and oversee grants related to Lyme disease. NINDS, NIAMS, and the National Eye Institute report that they have one or two researchers who spend less than 5 percent of their time on Lyme disease. These researchers are in addition to the extramural researchers working on Lyme disease with NIH funding.

[13]Post-Lyme disease syndrome refers to the presence of symptoms, generally associated with chronic Lyme disease, in patients who have been treated for *Borrelia burgdorferi* infection. Some investigators prefer to use this term because it implies nothing about the existence or absence of infection, in contrast to "chronic Lyme disease," which suggests persisting infection.

Agency Comments

We provided a draft of this report to the Department of Health and Human Services for review. The department stated that it had no comments. HHS' response is reprinted in appendix V. HHS also provided technical comments, which we incorporated where appropriate.

We will send copies of this report to the Secretary of Health and Human Services, the Director of the Centers for Disease Control and Prevention, the Acting Director of the National Institutes of Health, and others who are interested. If you have any questions or would like additional information, please call me at (202) 512-7119. Marcia Crosse, Donald Keller, William Hadley, and Roseanne Price made major contributions to this report.

Janet Heinrich
Director, Health Care—Public Health Issues

Appendix I: Background on Lyme Disease

The initial stage of Lyme disease is usually marked by one or more of the following: fatigue, chills and fever, headache, muscle and joint pain, swollen lymph nodes, and a characteristic skin rash called erythema migrans. Late manifestations, possibly occurring weeks, months, or years after infection, include arthritis, nervous system abnormalities, and heart rhythm irregularities, but for some patients arthritis or nervous system abnormalities are the first and only signs. The infection is triggered by the bite of certain kinds of ticks.

Ticks become infected with the bacterium *Borrelia burgdorferi* while feeding on an infected animal, particularly the white-footed mouse in the Northeast. It is estimated that by adulthood from 10 and 50 percent of ticks in endemic areas carry the disease. Ticks are most likely to transmit *Borrelia burgdorferi* while they are in the nymphal stage. Nymphs feed during the spring and summer months, when people are most active, and the nymphs' small size typically allows them to go unnoticed and gives them ample time to feed and transmit the bacterium, a process that may take 2 or more days.

Case Definition and Diagnosis

According to the Centers for Disease Control and Prevention's (CDC) surveillance case definition, a person must meet either of two criteria to be considered a "confirmed case" of Lyme disease. One criterion is to have the characteristic rash. The second is to have (1) at least one late manifestation of Lyme disease from a list of signs and (2) laboratory confirmation of infection by *Borrelia burgdorferi*, using recommended tests.

It is not always easy to diagnose Lyme disease. The only definite confirmation of Lyme disease is the identification of *Borrelia burgdorferi* from a cultured sample. Although specimens can be biopsied, the procedure is invasive and requires a specific growth medium and observation period, making it impractical for most clinicians. In part because of these disadvantages, the CDC-organized Second National Conference on the Serologic Diagnosis of Lyme Disease, in 1995, recommended a two-step approach for the laboratory confirmation of Lyme disease. It consists of a sensitive Enzyme-Linked Immunosorbent Assay or indirect fluorescent-antibody test followed by a more specific Western Blot test. These tests measure the body's immune response, but they do not directly detect the bacterium. As a result, vaccination, antibiotic use, co-infection, residual antibodies, and duration since the tick bite all can affect the accuracy of the tests. Even among those patients with a history of tick bite, the characteristic rash, and other characteristic

symptoms, only about 30 percent are positive in the first weeks of infection using the CDC-recommended two-step approach. For that reason, CDC recommends that diagnostic tests be used as a confirmation only when Lyme disease is already suspected.

Estimates of Prevalence

Reported cases of Lyme disease currently account for more than 95 percent of all reported vector-borne[1] illness in the United States. Public health departments, clinicians, and laboratories have reported over 122,651 cases since 1990. Significant risk of infection with *Borrelia burgdorferi* is found in only a select number of states.[2] (See table 1.) Estimates of prevalence may be inaccurate for two reasons. First, although it is required, physicians may not report all cases of Lyme disease to CDC. Second, patients with abnormal Lyme disease symptoms may not be diagnosed as having Lyme disease. As a result, current diagnosis and reporting practices may account for only 36 percent of the actual cases.[3] However, some research has shown that Lyme disease may be overdiagnosed in highly endemic areas.[4]

[1]A vector is an organism, such as an insect, that transmits a pathogen, such as a bacterium.

[2]Only Montana reported no cases from 1990 through 1999.

[3]G.L. Campbell, C.L. Fritz, D. Fish, J. Nowakowski, R.B. Nadelman, and G.P. Wormser, "Estimation of the Incidence of Lyme Disease," *American Journal of Epidemiology*, Vol. 148, No. 10 (1998): 1018-26.

[4]A.C. Steer, E. Taylor, G.L. McHugh, and E. Logigian, "The Overdiagnosis of Lyme Disease," *Journal of the American Medical Association*, Vol. 269, No. 14 (1993): 1812-6.

Table 1: States With the Highest Rates of Lyme Disease

	Reported cases (1990-99)	1999 rate[a]
Connecticut	20,634	98.0
Rhode Island	3,917	55.1
New York	40,762	24.2
Pennsylvania	17,072	23.2
Delaware	1,177	22.2
New Jersey	14,762	21.1
Maryland	4,177	17.4
Massachusetts	3,287	12.7
Wisconsin	4,488	9.3
Total U.S. cases and average U.S. rate	122,651	6.0

[a]Rate per 100,000 residents.

Source: CDC *Morbidity and Mortality Weekly Report.*

Treatment

In the guidelines of the Infectious Diseases Society of America, treatment of Lyme disease ranges from 14 to 21 days of oral antibiotics for early disease without complications to a 2- to 4-week course of intravenous antibiotics, repeated once if necessary, for late-stage Lyme disease with particular manifestations. An untreated or inadequately treated infection can progress to late-stage complications.

Prevention

There are several different methods to protect against Lyme disease. CDC recommends that people active in endemic areas limit their exposure to tick-infested areas, spray their clothing with insect repellents, tuck in clothing, and make frequent skin checks. In addition, community prevention projects have addressed Lyme disease through reducing tick habitats and developing environmentally friendly methods of pesticide application. CDC does not recommend antibiotic treatment for a tick bite to prevent infection if there are no accompanying symptoms.

In December 1998, the Food and Drug Administration (FDA) approved an application to license a vaccine for Lyme disease. The vaccine requires a series of three injections to achieve the maximum preventive effect. Results from a clinical trial conducted by the manufacturer suggest that the vaccine is 50 percent effective after two doses and 78 percent effective after three doses. FDA has approved the vaccine for patients between 15 and 70 years of age, and clinical trials for children younger than 15 have

begun. CDC's Advisory Committee on Immunization Practices recommends that only individuals who are at risk in endemic areas be vaccinated. In addition, it advises physicians not to administer the vaccine to persons with a history of treatment-resistant Lyme arthritis. The duration of immunity conferred by the vaccine is not known at this time, nor are safety and efficacy beyond the manufacturer's 20-month clinical trial. The vaccine's manufacturer has begun postmarketing trials to answer those questions, and other pharmaceutical companies are developing second-generation Lyme disease vaccines.

Appendix II: Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention's (CDC) Lyme disease program, an effort of the National Center for Infectious Diseases, conducts surveillance, diagnostic research, and education. The program is housed at Fort Collins, Colorado, in the Division of Vector-Borne Infectious Diseases' Bacterial Zoonoses Branch. The branch has four sections responsible for Lyme disease activities: Epidemiology, Molecular Biology, Diagnostic Reference Laboratory, and Lyme Disease Vector.

CDC provides Lyme disease funding to state and local health departments, universities, and nonprofit foundations. CDC has conducted Lyme disease activities with state public health departments, academic medical centers, advocacy groups, the Food and Drug Administration (FDA), the Department of Agriculture, the National Park Service, the National Aeronautics and Space Administration, and the Council of State and Territorial Epidemiologists. In addition, CDC has entered into cooperative research and development agreements with pharmaceutical and diagnostic test manufacturers.

Specifically, the mission of CDC's Lyme disease program is to

- develop and maintain national surveillance for Lyme disease;
- perform epidemiological studies, and provide epidemiological assistance for local and state health departments and to national and local agencies;
- conduct laboratory and field research for improving diagnosis, understanding the origin and development of the disease, and developing strategies to prevent and control Lyme disease and other related tick-borne diseases;
- provide consultation, education, and training for the public and health professionals; and
- serve as a national and international Lyme disease reference and research center.

In addition to the Lyme disease program, CDC maintains two other activities that relate to Lyme disease, the Vaccine Adverse Events Reporting System and the Advisory Committee on Immunization Practices. CDC and the FDA developed and implemented the Vaccine Adverse Events Reporting System in 1988 to track adverse events associated with vaccines. Patients, practitioners, and manufacturers are encouraged to report clinically significant adverse events that may be associated with vaccinations. An independent contractor, funded by CDC, is responsible for distributing and collecting forms for reporting adverse events and maintaining the database. CDC and FDA monitor the data to detect patterns in the type and severity of adverse events associated with

vaccines. This information enables CDC to direct financial and technical assistance to public sector vaccine programs as needed.

The Advisory Committee on Immunization Practices, a committee of external experts, provides advice and guidance about immunization to the Secretary of Health and Human Services, the Assistant Secretary for Health, and the Director of CDC. The committee develops written recommendations, subject to the approval of the Director of CDC, for the routine administration of new vaccines to pediatric and adult populations, along with schedules regarding the appropriate periodicity, dosage, and contraindications applicable to the vaccines. The committee also reviews and reports regularly on existing immunization practices and recommends improvements in national immunization efforts.

Appendix III: National Institutes of Health

The National Institutes of Health's (NIH) Lyme disease program seeks to better understand the etiology of the disease and to develop better means of diagnosing, treating, and preventing it. NIH institutes and centers with funding related to Lyme disease include the National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Neurological Disorders and Stroke, National Eye Institute, National Institute of Child Health and Human Development, Fogarty International Center, National Institute on Aging, National Institute of Mental Health, and National Center for Research Resources. NIH designated NIAID as the lead institute for Lyme disease research in 1992. The NIH Lyme Disease Coordinating Committee, which has met annually since 1992, was created to facilitate the coordination of NIH's varied Lyme disease-related efforts.

NIAID conducts clinical research related to Lyme disease at the Clinical Studies Unit on the NIH campus in Bethesda, Maryland, and laboratory research at the Rocky Mountain Laboratories in Hamilton, Montana. The Board of Scientific Counselors, an advisory panel composed of nonfederal experts, periodically reviews NIH's intramural research programs. In addition, NIH provides funding for Lyme disease through extramural grants and contracts to universities, medical schools, and research laboratories. The National Advisory Allergy and Infectious Diseases Council oversees NIAID's extramural program. The council performs grant review, provides policy advice to NIAID, reviews NIAID programs, and develops program announcements and recommendations for proposals. The Advisory Panel on the Clinical Studies of Chronic Lyme Disease, a panel composed of nonfederal researchers and advocates involved with issues related to Lyme disease, provides guidance throughout each intramural and extramural clinical trial.

Clinical Studies Unit

The Clinical Studies Unit began a clinical trial in 1996 to better understand the natural history of chronic Lyme disease and possible causes for persisting symptoms. The trial seeks a comprehensive clinical, microbiological, and immunological assessment of patients who have suspected chronic Lyme disease despite previous therapy with intravenous antibiotics. The investigators are enrolling patients and a variety of control groups in an effort to better understand the origin and development of chronic symptoms and to study further immunologic aspects of Lyme disease.

Rocky Mountain Laboratories

Research at NIAID's Rocky Mountain Laboratories is focused on the molecular changes that *Borrelia burgdorferi* undergoes as it is transmitted from the tick. One laboratory seeks to understand variations in the proteins and genes of the organism. A second laboratory seeks to understand the roles of specific genes and develop the basic genetic tools necessary to manipulate *Borrelia burgdorferi* at the genetic level. A third laboratory seeks to understand the changes and adaptations of the bacterium as it is transmitted during tick feeding.

Extramural Clinical Trials

NIAID has also funded clinical trials on the treatment of chronic and late-stage Lyme disease at the State University of New York at Stony Brook and the New England Medical Center. The study at Stony Brook examines how well antibiotics work in reducing fatigue symptoms in patients with post-Lyme disease syndrome. For this study, the data have been collected and are being analyzed. The New England Medical Center study examined the safety and efficacy of two antibiotics for the treatment of patients with suspected chronic Lyme disease who may or may not test positive for Lyme disease on diagnostic tests.[1] In November 2000, a Data Safety and Monitoring Board, an independent monitoring group of doctors and researchers, unanimously recommended that NIAID terminate the treatment component of the study. This was suggested because a planned interim analysis showed no statistically significant difference between the placebo and the treatment groups, and NIAID agreed. NIAID has extended the contract for 1.5 years, with additional funding, so that the investigators can continue to follow the study's patients to monitor their health status and to obtain additional information that, in the future, could help to determine the underlying cause of chronic Lyme disease.

[1]M.S. Klempner and others, "Two Controlled Trials of Antibiotic Treatment in Patients With Persistent Symptoms and a History of Lyme Disease," *The New England Journal of Medicine* (early release on June 12, 2001; final version to be published in the July 12, 2001, issue): http://www.nejm.org, accessed on June 12, 2001.

Appendix IV: Recommendations Made to CDC and NIH Lyme Disease Programs

The following tables provide expert recommendations and congressional appropriations committees' recommendations made to the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) Lyme disease programs.

Table 2: Expert Recommendations for the CDC Lyme Disease Program, 1994

Identify "risk factors" and accompanying clinical features that may allow better discrimination of *Borrelia burgdorferi* infection from Lyme-like illness.
Give moderate to high priority to the investigation of illnesses clinically similar to Lyme disease in the southeastern United States, including Texas and Missouri.
Conduct more active and cost effective surveillance in areas at the edges of known endemic communities.
Charge most "users" for the laboratory services and reagents that are provided by the Division of Vector-Borne Infectious Diseases.
Evaluate new tests selectively, with special emphasis on new types of technologies or on antigens or other spirochete components not previously investigated.
Expand cooperative agreements with scientists from the southern United States to gather information and educate physicians.
Redirect studies pertaining to the ecology of Lyme disease to areas with a potential for Lyme disease expansion.
Increase personnel, especially at the technical level.
Define program priorities more clearly.
Reduce in scope and duration some ongoing basic research projects (e.g., animal models and tick vectorial capability).
Make further efforts to completely report cases of Lyme disease.
Refine the case definition through improved accuracy of diagnosis, making use of two-step testing with standardized reagents.
Intensify and evaluate present control measures.
Test new prevention strategies, including vaccines and control of ticks and wildlife, and make decisions about their effectiveness.
Focus laboratory research more sharply on areas germane to the control efforts.
Continue proficiency testing of commercial diagnostic test products.

Source: CDC.

Table 3: Congressional Appropriations Committees' Recommendations Related to CDC Lyme Disease Activities

Recommendation	Year recommended
Concentrate on states with the highest reported cases of Lyme disease.	1998
Use a portion of resources to address the infrastructure of state and federal health laboratories.	1997
Expand surveillance efforts to improve the detection and response to emerging pathogens.[a]	1996
Continue to develop a substantial pool of scientific expertise and support.	1994
Use funds for programs within the United States.	1993
Reconvene outside panel of experts, including a representative from Lyme Disease Foundation, to review the case reporting definition.	1993
Work with NIH Rocky Mountain Laboratories to ensure no duplication in research.	1993
Conduct further trials to determine the effectiveness of repellents and other personal protective measures in reducing the risk of acquiring Lyme disease.	1992
Review the surveillance case definition after the 1991 Lyme disease transmission season, and adjust accordingly.	1992
Disperse funds as follows: 50 percent toward grants: 75 percent of the grants shall be made to areas with more than 250 reported Lyme disease cases in fiscal year 1990, and 25 percent of the grants must go toward public education (with a preference to nationwide education).	1991
Appoint a committee to develop a comprehensive definition that addresses the issue of the growing population with the classic Lyme disease symptoms and negative blood tests.	1991
Make a report to the Senate Committee on Appropriations in January 1991 regarding CDC's new comprehensive definition.	1991

[a]Emerging pathogens include Lyme disease.

Sources: House and Senate Appropriations Committees' reports.

Table 4: Board of Scientific Counselors Recommendations for the National Institute of Allergy and Infectious Diseases (NIAID) Lyme Disease Program, 1998

Clinical Studies Unit
Make research more hypothesis-driven and less descriptive.
Rocky Mountain Laboratories' Laboratory of Microbial Structure and Function
Hire additional technical support.
Hire another tenure track entomologist.
Hire another vector biologist.
Rocky Mountain Laboratories' Rocky Mountain Microscopy Branch
Remove the Facultative Intracellular Bacteria Unit from the branch.
Purchase a new transmission electron microscope.

Source: NIAID.

Table 5: Advisory Panel Recommendations for NIAID's Clinical Studies on Chronic Lyme Disease

Recommendation	Year recommended
Clinical studies at the New England Medical Center	
Lengthen the study.	1999
Open at least one additional recruitment site, preferably in an endemic area such as New York or Pennsylvania.	1999
Assess the feasibility of accessing data on positive blood tests from centralized public health laboratories.	1999
Make every effort to gain the support of advocacy groups.	1999
Hold meetings between investigators and community-based Lyme disease physicians, who could serve as consultants.	1999
Establish an unblinded oversight committee to review the placebo group.	1999
Incorporate a test for the detection of antigens in urine.	1996
Use standardized neuropsychological tests to monitor research patients.	1996
Only accept patients diagnosed with Lyme disease up to 4 years prior to entry into study.	1996
Require previous documentation of acute Lyme disease by a physician.	1996
Use audiology competency testing during the neuropsychological evaluation.	1996
Clinical studies at the NIH Clinical Studies Unit	
Discuss the possibility of posttreatment infection with patients.	1996
Obtain four lumbar punctures from patients.	1996
Use standardized neuropsychological tests to monitor research patients.	1996
Incorporate a test for the detection of antigens in urine.	1996

Source: NIH.

Table 6: Congressional Appropriations Committees' Recommendations Related to NIH Lyme Disease Activities

Recommendation	Year recommended
NIAID should expand its research on chronic Lyme disease and make a report during the 1997 budget hearings.	1996
NIAID should expand resources devoted to investigating the etiology of chronic Lyme disease and its appropriate treatment.	1994, 1995
NIAID should investigate, in a systematic fashion, whether chronic Lyme disease is an infectious or postinfectious disorder and report prior to the 1995 hearings on how this will be accomplished.	1994
NIH should expand Lyme disease research.	1993
NIH should establish NIAID as the lead institute for Lyme disease research.	1993
NIH should establish a pediatric Lyme disease program in the Clinical Studies Unit at the Bethesda, Maryland, hospital with experiments devoted to chronically infected children.	1993
NIAID should designate one full-time position for coordinating Lyme disease extramural efforts.	1993
NIH should continue to give high priority to Lyme disease.	1992
NIH should consider funding a center in the Midwest or Southwest to conduct clinical trials of treatment modalities that would otherwise not be tested.	1991
NIAID and the National Institute of Arthritis and Musculoskeletal and Skin Diseases are directed to jointly establish and fund an education program that teaches Americans how to prevent Lyme disease and what to do when stricken by it.	1991

Sources: House and Senate Appropriations Committees' reports.

Appendix V: Comments From the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES Office of Inspector General

Washington, D.C. 20201

JUN - 1 2001

Ms. Janet Heinrich
Director, Health Care--Public
Health Issues
United States General
Accounting Office
Washington, D.C. 20548

Dear Ms. Heinrich:

The Department has carefully reviewed your draft report entitled, "Lyme Disease: HHS Programs and Resources" and has no comments at this time.

The Department provided extensive technical comments directly to your staff.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,

Michael Mangano

Michael F. Mangano
Acting Inspector General

The Office of Inspector General (OIG) is transmitting the Department's response to this draft report in our capacity as the Department's designated focal point and coordinator for General Accounting Office reports. The OIG has not conducted an independent assessment of these comments and therefore expresses no opinion on them.

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