

## **Program Announcements (PA'S)**

### **CLINICAL AND EPIDEMIOLOGICAL RESEARCH ON LYME DISEASE**

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

#### **I. PURPOSE**

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invites applications for grants to conduct clinical and epidemiological research on Lyme disease (Lyme borreliosis).

#### **II. BACKGROUND**

Lyme disease is a spirochetal disease, usually transmitted by the bite of a tick, most often by a nymphal *Ixodes dammini*, when they are prevalent in the Spring. It has become the most common tick-borne illness in the United States. In 1988, about 5,000 new cases of Lyme disease were reported to the Center for Disease Control by 43 states. While this represents a considerable increase over the 2,800 cases reported by 35 states in 1986, the true incidence of new cases is probably several times larger due to considerable underreporting.

Lyme disease was initially called Lyme arthritis when it was first described in the United States in 1976. Soon it was recognized that the condition has both early and late manifestations that involve the skin and the joints, as well as the nervous and cardiovascular systems. It has now been recognized that one or another of the components of the illness has been observed in Europe over the last century.

The first manifestation of Lyme disease is an erythematous skin rash that expands from the site of the tick bite. This lesion, manifested by central clearing and presenting a target-like appearance, is called erythema migrans (formerly erythema chronicum migrans). It is often associated with a flu-like syndrome. Subsequently, a variety of acute and/or chronic signs and symptoms may appear involving the skin and the musculoskeletal, cardiovascular and nervous systems. The responsible spirochete, *Borrelia burgdorferi*, discovered in 1981, has been identified in most tissues and organs of infected hosts.

The clinical picture of Lyme disease, as with other spirochetal diseases, seem to have early, middle and late stages. Lyme disease appears to be responsive to treatment with antibiotics, such as penicillin, erythromycin and the tetracyclines, especially when given early in the course of the illness. Whether or not early antibiotic treatment prevents progression to the late stages of Lyme disease is unclear.

The case definition of Lyme disease has been a problem for both clinicians and epidemiologists studying this condition. The diagnosis of Lyme disease is usually made following the observation of erythema migrans subsequent to a tick bite in an endemic area. In non-endemic areas, supporting serologic evidence (presence of elevated antibody titers to *B. burgdorferi*) is sought. The sero-diagnosis of Lyme disease is currently fraught with difficulties. There are high percentages of false-negative and false-positive results. Detectable sero-conversion does not appear to occur until several weeks after the infecting tick bite; not all individuals develop detectable antibodies or typical illness. Some people appear to be particularly susceptible to developing the late manifestations of Lyme disease. It has been suggested that immunogenetic determinants may play a role in the development of the persistent arthritis associated with Lyme disease. There is also evidence of overdiagnosis of Lyme disease, especially in endemic areas.

### III. RESEARCH OBJECTIVES AND SCOPE

There are many research opportunities to address clinical and epidemiological questions surrounding Lyme disease. The goal of this Program Announcement is to encourage research proposals that address the following questions and other avenues of appropriate investigation.

- o What are the early and late manifestations of Lyme disease with respect to cutaneous, rheumatic, neurologic, and cardiac complications
- o Are other organ systems involved
- o Are there discrete stages of Lyme disease
- o What are the optimal classification criteria for Lyme disease for: a) clinical research; and b) epidemiologic investigations
- o What are the prevalence and incidence rates: a) across the United States; and b) around the world
- o Is Lyme disease spreading or just being increasingly recognized

o Does Lyme disease vary geographically? If so, what are the reasons for the variation? Are there different seasonal patterns in various climates

o What are the risk factors for Lyme disease: a) age b) sex c) race d) occupational factors e) recreational factors f) others

#### IV. MECHANISMS OF SUPPORT AND REVIEW PROCEDURE

Applications considered appropriate responses to this Program Announcement are the traditional research project grant (R01, R29), the Small Business Innovation Research grant (R43) and the postdoctoral fellowship (F32). The specific application forms and kits required in applying for these grants and fellowships are available in the business or grants and contracts offices of most academic and research institutions or may be obtained from:

Office of Grants Inquiries  
Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 449  
Bethesda, Maryland 20892  
Telephone: (301) 496-7441

Applications in response to this announcement will be reviewed in competition with other applications and in accordance with the usual National Institutes of Health (NIH) peer review procedures. The initial review for scientific and technical merit will be made by an appropriate review group of the Division of Research Grants, NIH. Funding decisions will be based upon relative scientific merit, program relevance, and the availability of appropriated funds.

#### V. APPLICATION PROCEDURE

Applications will be accepted in accordance with the usual receipt dates for the the different funding mechanisms mentioned in Section IV above. On the first (face) page, item 2 of the application, the word "Yes" should be checked and the phrase "CLINICAL AND EPIDEMIOLOGICAL RESEARCH ON LYME DISEASE" should be typed in the space provided.

The original and six copies of the application should be sent or delivered to:

Application Receipt Office  
Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
Bethesda, Maryland 20892\*\*

## VI. STAFF CONTACT

Investigators with specific questions are encouraged to contact:

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