MAYOR
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CITY OF STAMFORD
DEPARTMENT OF HEALTH
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ANDREW D. McBRIDE, M.D., M.P.H
DIRECTOR OF HEALTH AND MEDICAL ADVISOR
977-4396

April 3, 1992

Contact Person: Phyllis Erlandson, R.S., Stamford Health Department (203)977-4381

FOR IMMEDIATE RELEASE

The Lyme Borreliosis Foundation and the Stamford Health Department will hold the "Lyme Disease 1992 State of the Art Conference" at the Sheraton Hotel in Stamford Connecticut on Friday and Saturday, April 10 & 11. This will be the first Lyme disease conference of this scope in the United States. This conference will feature 55 experts on Lyme disease from 12 states and 3 European countries. Emphasis will include tracks for diagnosis and treatment; research advances; veterinary issues, tick vectors and prevention.

Lyme disease is a serious infection, and is on the increase with more than 8,000 cases reported last year. The number of reported cases of Lyme disease doubled over the previous year. It is estimated that thousands of cases go undetected or unreported. Lyme disease is difficult to diagnose and treat. Serious neurologic, arthritic and cardiac complications can ensue from this infection.

Willy Burgdorfer, Ph.D., M.D.(hon), Scientist Emeritus, Laboratory of Pathobiology, Rocky Mountain Laboratories, who first identified the causative agent of Lyme disease, will present the global perspective on Lyme disease. Lyme disease is found in temperate zones throughout the world. Dr. Burgdorfer will discuss the research activities under way on various continents.

Richard T. Marconi, Ph.D., NIAID Rocky Mountain Laboratories, Montana, will cover research which indicates that genetic variation within strains of the Lyme disease bacteria may contribute to the different clinical manifestations of Lyme disease experience in the U.S. compared to other parts of the world.

John F. Anderson, Ph.D., Director of the Connecticut Agricultural Experiment Station and a leading authority on Ixodes dammini (deer ticks or Lyme disease ticks), will discuss the spread of Lyme disease in wild animals and birds. Ixodes dammini have been found to feed on 31 species of mammals and about 50 species of birds. White-tailed deer and white-footed mice are important hosts for the Ixodes dammini.

Rance B. LeFebvre, Ph.D., College of Veterinary Medicine, University of California, Davis, will present research on the response and effectiveness of the Lyme disease vaccine for dogs.

Family physicians and local health departments are often the first called by citizens concerned with Lyme disease. In response to this need, the Stamford Health Department has established a Lyme Disease Program centered on public education and tick testing. Dr. Andrew D. McBride, Director of Health and Medical Advisor for the City of Stamford will be highlighting the progress achieved in this endeavor which emphasizes prevention in this highly endemic area. In 1991, 327 deer ticks were submitted by citizens to the Stamford Health Department and tested at the Connecticut Agricultural Experiment Station. Twenty percent of the ticks were infected with the bacteria that causes Lyme disease.

The general public is invited to attend a free Lyme disease program at 7:30 PM on Friday April 10 at the Sheraton Stamford Hotel. At that time the worlds leading authorities on Lyme disease will be available to answer questions. The best defense against Lyme disease is public awareness and knowledge.

TRACK C - PUBLIC HEALTH & VETERINARY ISSUES

8:00	**Epizootiology in the East: Vectors of Bb**	
	John F. Anderson, PhD	*Connecticut Agricultural Experiment Station*
8:30	**Epizootiology in the Far Western USA**	
	Robert Lane, PhD	*University of California, Berkley*
9:00	**Public Health Issues of Borreliosis in the Southwest: Lyme vs. Relapsing Fever, New Vectors**	
	Julie Rawlings, MPH	*Texas Department of Health*
9:30	**Epizootiology of Lyme Borreliosis in the Southeast**	
	Gary Mullen, PhD	*Auburn University, Alabama*
10:00	Break	
10:20	**Epizootiology of Lyme Borreliosis in the Midwest**	
	Dorothy Feir, PhD	*LBF / Hartz Fellowship St. Louis University*
10:50	**Environmental Risk Assesment & Control Strategies: I**	
	Edward Bosler, PhD	*New York State Department of Health*
11:30	**Environmental Risk Assesment & Control Strategies: II**	
	Kirby Stafford, PhD	*Connecticut Agricultural Experiment Station*
12:00	Lunch	
1:00	**Spirochete Vector Supression Utilizing Acaricides for Topical and Systemic Treatments of Wildlife**	
	John George, PhD	*United States Department of Agriculture*
1:30	**Equine Borreliosis**	
	Elizabeth Burgess, DVM, PhD	*University of Wisconsin Veterinary School of Medicine*
2:00	**Bovine Borreliosis**	
	Sandra Bushmich, MS, DVM	*University of Connecticut*
2:30	**Canine Borreliosis**	
	Steven Levy, DVM	*Durham Veterinary Hospital*
3:00	Break	
3:20	**Neuro-Borreliosis in Canines: Expanding the Clinical Case Definition**	
	Edward Schneider, PhD	*Veterinary Research Associates*
3:50	**Surveillance Using Canines**	
	Pete Teel, PhD	*Texas A&M*
4:20	**Development of a Subunit Vaccine**	
	Rance LeFebvre, PhD	*University of California, Davis*
4:50	**Vaccine Roundtable**	
	Julie Rawlings, MPH	*Texas Department of Health*

Sponsors: Stamford Department of Health
Lyme Borreliosis Foundation
Co-Sponsor: Stamford Hospital

Price: $120 - If paid in advance. $150 - If paid at the conference
Hotel: $79 for single or double occupancy. Includes breakfast.
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* Please identify yourself as a Lyme Disease Conference Attendee

LYME DISEASE
1992 STATE OF THE ART CONFERENCE:

PRIMARY CARE:
Diagnosis, Treatment, Patient Management

RESEARCH:
Microbiology, Immune Response, Pathogenesis, New Laboratory Diagnostics, Vaccine Development

PUBLIC HEALTH & VETERINARY:
Prevention, Control Measures, Regional Differences

THE MOST USEFUL & INSIGHTFUL LYME DISEASE CONFERENCE YOU WILL EVER ATTEND !

April 10 & 11, 1992

• Chair•
Andrew D. McBride, MD, MPH
Stamford Director of Health

• Co Chairs •
Claude F. Garon, PhD National Institute of Allergy & Infectious Diseases
James F. Katzel, MD Family Practitioner, Calif.
Julie Rawlings, MPH Texas Department of Health

55 International Landmark Presentations

Who Should Attend:
Physicians, Nurses, Health Departments, Health Educators, Veterinarians, Researchers, Risk Managers, Corporate Wellness Managers, Camp Directors, Insurance Administrators.

Physician CME's - 16 hours Category I
Veterinary CME's - 16 hours
Nursing CME's - 16 hours

AM

Friday, April 10, 1992

7:00 -8:30 Registration

PRIMARY CARE, RESEARCH, PUBLIC HEALTH & VETERINARY ISSUES

8:00 **Welcome**
The Honorable Stanley J. Esposito *Mayor, City of Stamford*

8:15 **Keynote: Lyme Disease - Facing the Issues** (tentative)
The Honorable Joseph I. Lieberman, JD *United States Senator*

8:45 **Lyme Borreliosis: The Global Perspective**
Willy Burgdorfer, PhD, MD (hon) *Discoverer of Bb*

9:20 **Financial Cost to Society of Lyme Borreliosis**
Irwin Vanderhoof, PhD, FSA, CLU *Society of Actuaries*
Stern School, New York University

9:50 Break

10:15 **Lyme Disease: New Education Techniques & Advocacy**
Thomas E. Forschner, MBA, CPA *Executive Director, LBF*

10:45 **Public Health Programs - Aggressive Prevention**
Andrew D. McBride, MD, MPH *Stamford Director of Health & Medical Advisor*

11:25 **Front Line Diagnosis & Treatment in a Known Endemic Area**
Joseph Burrascano, MD *Southampton Hospital, NIAID Antigen Study*

Noon Lunch

1:00 **Neurologic Manifestations in Children**
Dorothy M. Pietrucha, MD *CornelliNY, Jersey Shore Medical Center*

1:40 **Tissue Responses and Pathology**
Paul H. Duray, MD *Harvard- Brigham & Women's Hospital*

2:20 **Laboratory Diagnostics**
ELISA, IFA, Western Blot, Culturing
Louis A. Magnarelli, PhD *Connecticut Agricultural Experiment Station*

2:45 **Use of PCR for Molecular Diagnosis and Monitoring of *Bb***
David H. Persing, MD, PhD *Mayo Clinic & Mayo Foundation*

3:10 Break

3:30 **New Laboratory Diagnostic Tests on the Horizon**
Tom Schwann, PhD *NIAID, Rocky Mountain Laboratories*

New Discoveries about the Immune System's Response to *Bb*

4:00 • **Cellular Responses to Blebs Released by *Bb*** *LBF/Hartz Fellow*
William Whitmire, PhD *NIAID, Rocky Mountain Laboratories*

4:30 • **Escape Variants of *Bb*: Selection with Antibodies**
Ariadna Sadziene, MD *LBF/Hartz Fellow , University of Texas, San Antonio*

7:30 **Public Forum** - Moderator, Derrick DeSilva, MD *Raritan Bay Medical Ctr*
John F. Anderson, PhD *Ct. Agricultural Experiment Station*
Other scientific experts as available.

AM

Saturday, April 11, 1992

TRACK A - PRIMARY CARE DIAGNOSIS & TREATMENT

8:00 **Tick Borne Diseases & Their Presentations**
Michael Parry, MD *Infectious Disease Associates, Stamford, Ct.*
Columbia University School of Medicine

8:30 **Family Practice Diagnosis & Treatment in a Non-endemic Area**
Edwin Masters, MD *St. Francis Hospital, Missouri*

9:10 **Dermatologic Manifestations**
Rudolph Scrimenti, MD *Univ. of Wisconsin School of Medicine*
First doctor to document Lb acquired in the United States

9:40 **Ophthalmologic Manifestations of Lyme Disease**
Robert Lesser, MD *Yale University School of Medicine*

10:15 Break

10:40 **Role of the Infectious Disease Specialist in an Endemic Area**
Debra Adler-Klien, MD *Infectious Disease Associates, Stamford, Ct.*
Columbia University School of Medicine

11:15 **Lyme Borreliosis Rheumatologic Manifestations & Treatment**
Mori Schwartzberg, MD *Jersey Shore Medical Center*

11:50 **Rheumatologic Differential Diagnosis - Bb DNA in the Blood of 3 SLE Patients**
Paul Lavoie, MD *University of California, San Francisco*

12:30 Lunch

1:30 **Cardiac Involvement and Management**
Gerold Stanek, MD *Hygiene Inst. University Wein, Austria*

2:00 **Blood Culturing: Implications for Treatment & the Blood Supply**
Ross Ritter, PA *Physicians Assistant*

2:30 **Psychiatric Presentations of Lyme Borreliosis**
Brian Fallon, MD *Psychiatrist, New York & Connecticut*

3:00 Break

3:20 **Prophylatic Treatment Controversy & Recommendations**
Kenneth Liegner, MD *Internal & Critical Care Medicine, New York Medical College*

3:50 **LBF Medical Advisory Committee Diagnosis & Treatment Guidleines**
Andrew McBride, MD, MPH *Stamford Director of Health and Medical Advisor*

4:30 **Treatment Roundtable**
James H. Katzel, MD *Family Practitioner, California*

TRACK B - RESEARCH

8:00 **Adhesion to Host Cells by *Bb***
John Leong, MD, PhD *New England Medical Center*

8:35 **Lyme Borreliosis in C3H Mice & Implications for Pathogenesis**
Stephen W. Barthold, DVM, PhD *Yale University School of Medicine*

9:10 **Immune Responses in the Hamster**
Ron F. Schell, PhD *University of Wisconsin Medical School*

9:50 Break

10:10 **Canine as an Animal Model & Vaccine Experience**
Terri Wasmoen, PhD *Ft. Dodge Laboratories*

10:45 **Antigenic & Immunogenic Components of *Bb***
Antimicrobial Sensitivities
Russell C. Johnson, PhD *University of Minnesota School of Medicine*

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Noon Lunch

1:00 **Ribosomal RNA Genes for Diagnosis & Phylogeny**
Richard Marconi, PhD *NIAID, Rocky Mountain Laboratories*

1:35 **High Level Expression of Surface Proteins**
John Dunn, PhD *Brookhaven Laboratory*

2:05 **Chromosome Mapping and *Bb* Genetic Variations**
Isabelle Saint-Girons, PhD *Institut Pasteur, France*

2:40 Break

3:00 **Genetic Capacity & Ultrastructure**
Claude F. Garon, PhD *NIAID, Rocky Mountain Laboratories*

3:20 **Spirochetal Chaperonins**
Peter Hindersson, MD *University of Copenhagen, Denmark*

3:50 **Analysis of *Borrelia burgdorferi* Motility**
Nyles W. Charon, PhD *West Virginia University Medical Center*
Stuart Goldstein, PhD *University of Minnesota, Department of Biologicals*

4:20 **Surface Components of *Borrelia burgdorferi***
Justin Radolf, MD *University of Texas, Dallas*

LYME BORRELIOSIS - 1992 STATE OF THE ART CONFERENCE
55 LEADING INTERNATIONAL PRESENTATIONS

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1992 STATE OF THE ART CONFERENCE

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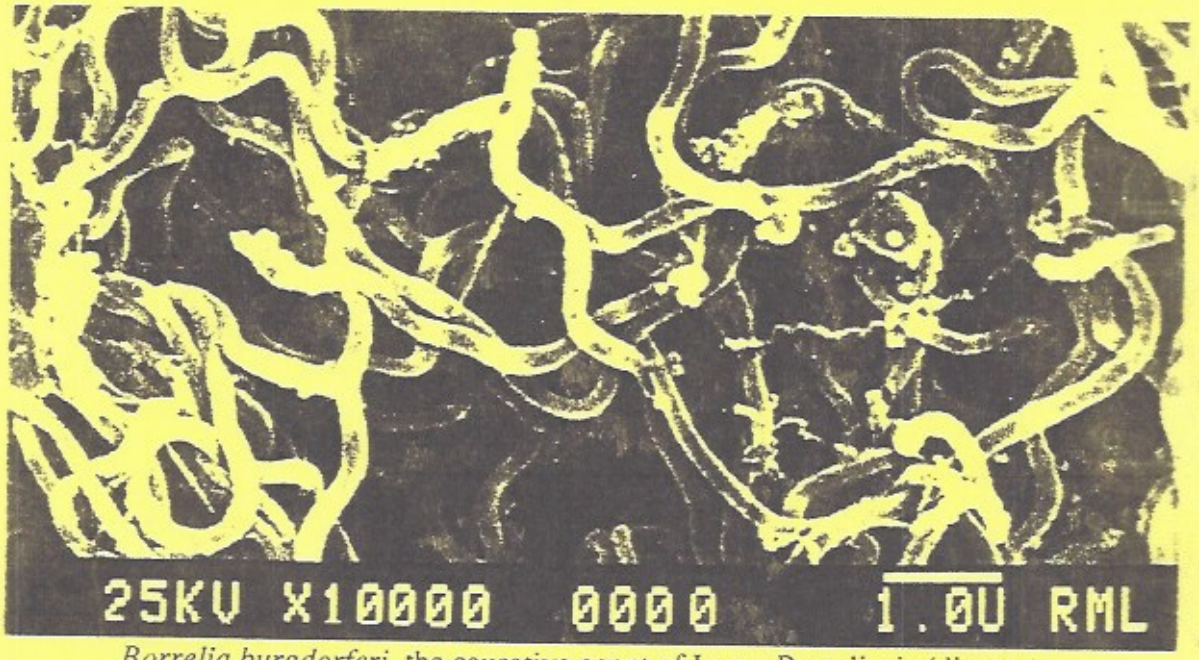
PRIMARY CARE
RESEARCH
PUBLIC HEALTH & VETERINARY ISSUES



Borrelia burgdorferi, the causative agent of Lyme Borreliosis (disease).

SPONSORED BY: THE LYME BORRELIOSIS FOUNDATION
THE STAMFORD DEPARTMENT OF HEALTH
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SPECIAL THANKS FOR THIS COMPENDIUM

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LYME DISEASE 1992 STATE OF THE ART CONFERENCE:

PRIMARY CARE: Diagnosis, Treatment, Patient Management
RESEARCH: Microbiology, Immune Response, Pathogenesis, New Laboratory Diagnostics, Vaccine Development
PUBLIC HEALTH & VETERINARY: Prevention, Control Measures, Regional Differences

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Sponsors: Lyme Borreliosis Foundation, Stamford Department of Health
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Louis A. Magnarelli, PhD *Connecticut Agricultural Experiment Station*

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4:30 • **Escape Variants of *Bb*: Selection with Antibodies**
Ariadna Sadziene, MD *LBF/Hartz Fellow, University of Texas, San Antonio*

6:00 **Reception - for attendees**

7:30 **Public Forum** - Moderator, Derrick DeSilva, MD *Raritan Bay Medical Ctr*
John F. Anderson, PhD *Ct. Agricultural Experiment Station*
Other scientific experts as available.

Physician CME's - 16 hours Category I, Veterinary CME's - 16 hours, Nursing CME's - 17 hours

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11:50 **Rheumatologic Differential Diagnosis - Bb DNA in the Blood of 3 SLE Patients**
Paul Lavoie, MD *University of California, San Francisco*

12:30 *Lunch*

1:30 **Treatment Options**
Bela Pal Bozsik, MD *National Institute of Hygiene, Budapest, Hungary*

2:00 **Blood Culturing: Implications for Treatment & the Blood Supply**
Ross Ritter, PA *Physicians Assistant*

2:30 **Psychiatric Presentations of Lyme Borreliosis**
Brian Fallon, MD *Psychiatrist, New York & Connecticut*

3:00 *Break*

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Kenneth Liegner, MD *Internal & Critical Care Medicine, New York Medical College*

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10:00 *Break*

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11:30 **Environmental Risk Assesment & Control Strategies: II**
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12:00 *Lunch*

1:00 **Spirochete Vector Supression Utilizing Acaricides for Topical and Systemic Treatments of Wildlife**
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1:30 **Equine Borreliosis**
Sandra Bushmich, MS, DVM *University of Connecticut*

2:00 **Bovine Borreliosis**
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Steven Levy, VMD *Durham Veterinary Hospital*

3:00 *Break*

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Edward Schneider, PhD *Veterinary Research Associates*

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4:20 **Development of a Subunit Vaccine**
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4:50 **Vaccine Roundtable**
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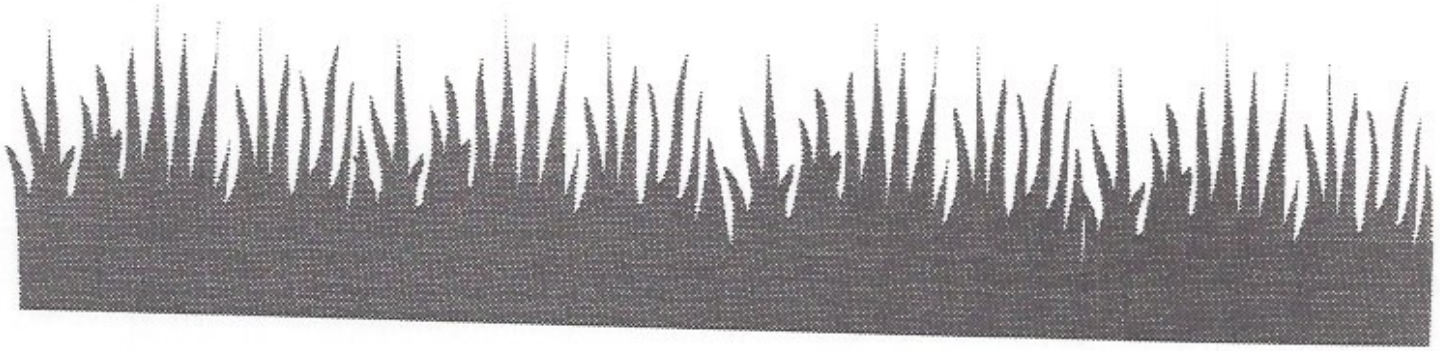
Lyme Disease 1992

State of the Art Conference
April 10 & 11



A PUBLIC FORUM will be held at 7:30 P.M., Friday, April 10, at which time over 50 of the world's leading authorities will be available. This session is FREE to the public, and questions will be addressed by experts in the field.

For more information, please call the
Stamford Health Department at (203) 977-4381.

Location: **Stamford Sheraton Hotel**
Stamford, Connecticut

Sponsors: **Lyme Borreliosis Foundation and the Stamford Health Department**

Chair: **Andrew D. McBride, MD, MPH**
Stamford Director of Health

Moderators: **John F. Anderson, PhD, Director**
The Connecticut Agricultural Experiment Station
Derrick DeSilva, MD, Raritan Bay Medical Center, Old Bridge Regional Hospital

Reprinted from the Archives of Dermatology
July 1970 Volume 102
Copyright 1970, American Medical Association

Dr. Scrimenti's publication predates Steele & Murray. He is the discoverer of the illness in 1969!

Erythema Chronicum Migrans

Rudolph J. Scrimenti, MD, Milwaukee

To my knowledge, this is the first case of erythema chronicum migrans in the United States. Eruption and radicular pain followed a wood tick bite. Treatment with benzathine penicillin G (Bicillin) was curative.

A MIGRATING erythema with systemic symptoms resulting from a tick bite is unusual in the United States. Our knowledge of this curious condition comes from European reports. This toxic, circinate skin eruption advances peripherally and is occasionally associated with neurological symptoms. The cause is uncertain. However, some believe it to be an infectious agent, perhaps a spirochete or rickettsia, possessing allergenic properties.[1,2] Ticks transmit the disease although other arthropods may be vectors.[3,4] It is not known whether the neurological manifestations are infectious, toxic, or allergic. The purpose of this communication is to reawaken interest in this obscure but classical condition, known for over half a century, which is now readily curable.[5]

Accepted for publication March 15, 1970.
From the Department of Dermatology, Marquette School of Medicine, Milwaukee.
Reprint requests to 5255 N Hollywood Ave, Milwaukee 53217 (Dr. Scrimenti).

Report of a Case

In January 1969 a 57-year-old physician had chronic erythema of the right side of the torso which was unresponsive to flurandrenolide (Cordran). A recent hospitalization failed to reveal any cause for his complaints of headache, malaise, and dull pain radiating over the right hip. Periodic, low-grade fever accompanied the progression of the skin eruption.

An annular area of edema and erythema was present, extending from the mid-chest to midback and encircling the right axilla and iliac crest. The dermatomes innervated by T-12 and L-1 were hyperesthetic. Above the iliac crest there was a tender, punctate area of redness and induration. The patient stated this was the site of a wood tick bite sustained three months previously while grouse hunting in north central Wisconsin (Medford). He recalled that after removing the tick from the skin, a nickel-sized welt appeared at the bite site. It slowly spread peripherally, cleared centrally, and culminated in the large circular area now present. A morbilliform eruption of the upper part of the torso appeared shortly after the bite, but vanished within one week while the patient took a combination antihistamine decongestant (chlorpheniramine maleate, phenylpropanolamine hydrochloride, and isopropamide iodide [Ornade]). It has not recurred.

This is the orginal discovery of "Lyme Disease"

Fig 1.—Low-power view of tick bite. Epidermis is unremarkable. Mixed leukocytic dermal infiltrate. No tick parts are identified. Bacteria not demonstrated (× 4).

Fig 2.—Higher-power magnification of tick bite. Lymphocytic and plasma cell periadnexal infiltrate is shown. Tissues about inflammation are slightly edematous (× 25).

The bite site was biopsied, and, surprisingly, all symptoms subsided for 24 hours only to return with increased intensity.

The histological changes showed a dermal leukocytic infiltrate arranged about the appendages. The tissues surrounding the infiltrate were slightly edematous. Foreign material was not seen. Spirochetes were not demonstrated with silver stains (Fig 1 and 2).

Lipoprotein electrophoresis showed a type IV pre-β hypertriglyceridemia. Electrocardiogram and roentgenogram of the chest were normal. Normal values were found for the following: complete blood cell count, differential cell count, serum electrolytes, carbon dioxide, fasting blood sugar, protein bound iodine, creatinine, blood urea nitrogen, bilirubin, cholesterol, lactic dehydrogenase isoenzymes, calcium, phosphorus, serum transaminase, total serum proteins, albumin, and the venereal disease research laboratory test for syphilis. The *Proteus* OX_{19} (serologic) test was negative.

Treatment consisted of the administration of 1.2 million units of benzathine penicillin G (Bicillin) intramuscularly. The patient became symptom-free within 48 hours. There has been no recurrence of symptoms for the past year.

Comment

Although specific organisms could not be incriminated, the patients' clinical course and response to therapy suggest that erythema chronicum migrans is a low-grade infection. Why it so rarely complicates so common an occurrence as arthropod bites remains an enigma. A search of the American literature failed to uncover a similar case in the United States.

References

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LYME BORRELIOSIS FOUNDATION, INC.

1992 UPDATE

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**Lyme Disease Patient*

Lyme Borreliosis (disease) is a chronic infectious disease that is spread primarily by the bite of an infected arthropod. Several types of ticks are proved vectors - Ixodes dammini ("deer" or "bear"), Ixodes scapularis ("black legged"), Ixodes pacificus ("western black legged") and Amblyomma americanum ("lone star"). Other biting, blood sucking insects may play a minor role in the transmission of this disease (eg. deer flies and fleas).

Common symptoms include skin, joint, heart and brain infections, yet every organ can be involved. Serious illness can lead to loss of vision, speech impairment, deafness, dementia, heart block, stroke, crippling joint disease, paralysis, miscarriage and rarely death.

The immune system response does not kill the bacteria. People can be reinfected anytime. There is no affordable, available test that directly detects the bacteria. Therefore, treatment modalities are uncertain. For some people there may be no cure, yet. No vaccine may be possible without a clear understanding of the spirochetes' microbiology. There are several variations of this bacterium. There is no easy, rational approach to elimination of the known vectors. The disease knows no geographic region nor socioeconomic class. People of dark skin are of particular risk since the common rash description refers to red discoloration on light tone skin. In the United States, people not fluent in English may be unaware of this disease.

The Lyme Borreliosis Foundation is the first & only nationwide organization dedicated to Lyme Borreliosis Education and Research. The LBF is the centralized focus of almost all activity and enjoys a high profile position in numerous areas.

In 1987, Karen and Thomas Forschner, along with a team of business, research, and lay-people, decided Lyme Borreliosis was seriously underestimated. This insidious infection was worthy of its own dedicated organization. Therefore, the Lyme Borreliosis Foundation, Inc. was established in March of 1988. The LBF had an enormous task of education ahead of it. Knowledge of this disease was limited to a few physicians and researchers. Lyme disease was incorrectly considered a Connecticut shoreline disease. Even medical professionals thought it had only one symptom - arthritis. Many incorrectly thought it was easily diagnosed by a blood test. Medical experts were announcing that people "cured themselves" and had no need for treatment. Worst yet, the spirochetal infection was considered to represent no threat to the unborn. And it was of little importance to the general public.

In several short years the relentless efforts of the LBF changed all of that.

By 1990 the LBF's extraordinary multi-year Public Education Campaign made the necessary global change. The disease was now recognized as a worldwide threat worthy of Congressional funding, Governmental research, Media attention, and Public involvement. The LBF has directly reached 210 million people in the U.S. and has worked with people across several continents. LBF Research is peer reviewed and coordinated with other research to avoid duplication of efforts.

By 1991, 46 states reported (many voluntarily) a total of approximately 30,000 cases. Based on standard epidemiologic data applying to a perfect world, there has been, conservatively, between 300,000 to 600,000 cases in the United States. Lyme disease is now mandatory reportable in every state. Lyme Borreliosis can be contracted across six continents.

Even today, many people mistakenly believe that this is a "newly discovered" infection...that it was "discovered" in 1975 in Lyme, Connecticut. Truth is, it has been around for over one hundred years. And, as time goes on, scientists continue to recognize new manifestations that formerly had been thought to be unrelated.

Lyme Disease Education & Research

The first medical documentation of this disease, involving one of the Lyme Disease skin manifestations (ACA), was made in 1883 by Dr. Buchwald in Germany. In 1899 the first case of ACA in the United States was published by Dr. Holder. In 1902 Dr. Afzeleus of Sweden, described a second skin manifestation (ECM); a key component of his paper was the relationship to the Ixodes tick. In the following years Europeans continued documenting newly identified symptoms of this disease (including skin and nervous system manifestations), ticks as the potential vector, spirochetes or rickettsia as the causative agent, as well as the use of antibiotics (penicillin) for treatment.

Researchers have proven that infected ticks have been in the United States since, at least, the early 1940's. The first medically documented case of U.S. acquired ECM was in 1969, in Wisconsin, by Rudolph Scrimenti, MD. Dr. Scrimenti, a dermatologist, reported this condition in a 57 year old physician who had developed "Erythema Chronicum Migrans" (the hallmark expanding lesion) after a tick bite during a hunting trip. This report, appearing in the AMA *Archives of Dermatology*, went unnoticed. In 1975 the arthritic component was identified because of investigations (Steere, Malawista, et. al.) into a statistically significant clustering of juvenile rheumatoid arthritis. The people involved named this arthritic condition "Lyme arthritis", after the Connecticut towns involved (Old Lyme, Hadlyme, and Lyme). In 1982, Dr. Willy Burgdorfer, NIH scientist emeritus, discovered the cause, a new type of Borrelia spirochete, which was named *Borrelia burgdorferi*, in his honor. The term Lyme Borreliosis was now accepted as the correct scientific name because it recognized the European contributions and the multi-systemic nature of this infection. Still, the evolving disease was considered extremely rare. It generated little interest, almost no funding, and virtually no public notice. Then the LBF was formed and you know the rest !

The Lyme Borreliosis Educational Campaign continues as our primary focus but equally exciting is the recent establishment of our Research programs. By 1992 the LBF has invested over $100,000 in granted scientific research. We continue our dedicated efforts to eliminate Lyme disease as a threat to people and pets.

CLINICAL MANIFESTATIONS

Symptoms vary greatly. One or more systems may be involved.

EARLY INFECTION (lasts days to about 4 weeks)

EM - Single Erythema Migrans per bite
Influenza-like illness with significant fatigue, arthralgias, myalgias, headache, or stiff neck
Conjunctivitis
Spleen tenderness

DISSEMINATED INFECTION (lasts weeks to months)

EM's - Single or Multiple Erythema Migrans
Lymphocytoma
Meningitis, cranial neuritis (eg. Bell's Palsy), radiculitis meningoradiculitis (Bannwarth's)
Heart block, myocarditis, vasculitis
Myositis
Arthritis, brief attacks
Ocular keratitis, uveitis, choroditis, exudative retinal detachments, pars planitis, diplopia, neuroretinitis, optic neuritis

CHRONIC BORRELIOSIS (lasts months to years)

ACA - Acrodermatitis Chronica Atrophicans
Profound fatigue
Chronic encephalomyelitis, demyelinating-like syndromes, axonal polyneuropathies, cognitive and behavioral changes
Arthritis, asymmetric, pauciarticular, intermittent or chronic
Optic Atrophy

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W. Burgdorfer

Lyme Borreliosis: Ten Years after Discovery of the Etiologic Agent, Borrelia burgdorferi

Summary: Since the recovery of its causative agent, *Borrelia burgdorferi*, in 1981, Lyme borreliosis has become the most prevalent tick-borne disease in the United States as well as in Europe. Its steadily increasing clinical spectrum now includes erythema migrans, acrodermatitis chronica atrophicans, lymphadenosis beniga cutis, arthritis, myocarditis, progressive meningoencephalitis, myositis, and various ocular and skin disorders. The true incidence of Lyme borreliosis in the world is unknown. In the United States, it has increased from 2,000 cases in 1987, to more than 8,000 in 1989. It occurs now in regions where the tick vectors, *Ixodes dammini* and *Ixodes pacificus*, are absent and where other species of ticks may be responsible for maintaining and distributing the spirochete. In Europe, Lyme borreliosis has been reported from 19 countries; its occurrence coincides with the distribution of the vector tick, *Ixodes ricinus* and possibly *Ixodes hexagonus*. Specific and dependable serological tests are still not available, but development of probes for specific antigens and the polymerase chain reaction appear promising in detecting ongoing infection and in identifying *B. burgdorferi* in ticks, animal, and human hosts. Brief reference is made to advances in the preparation of whole cell and genetically engineered vaccines.

Zusammenfassung: *Lyme-Borreliose: Zehn Jahre nach Entdeckung des ätiologischen Agens, Borrelia burgdorferi.* Die Lyme-Borreliose ist seit der Entdeckung des kausalen Erregers *Borrelia burgdorferi* im Jahre 1981 die häufigste durch Zecken übertragene Krankheit in den USA und in Europa geworden. Zu ihrem immer umfangreicher werdenden klinischen Spektrum gehören Erythema migrans, Acrodermatitis chronica atrophicans, Lymphadenosis benigna cutis, Arthritis, Myokarditis, progressive Meningoenzephalitis, Myositis und verschiedene andere Störungen, die die Augen und die Haut betreffen. Über die weltweite Inzidenz der Lyme-Borreliose gibt es keine Daten. In den USA haben die Fallzahlen von 2000 im Jahr 1987 auf mehr als 8000 im Jahr 1989 zugenommen. Die Lyme Borreliose tritt jetzt in Gegenden auf, in denen die Zeckenvektoren *Ixodes dammini* und *Ixodes pacificus* nicht vorkommen, wo aber andere Zeckenspezies für die Persistenz und weitere Verbreitung der Spirochete verantwortlich sein können. 19 europäische Länder haben Fälle von Lyme Borreliosis mitgeteilt, dabei korreliert das Vorkommen mit der Verbreitung der Zeckenvektoren *Ixodes ricinus* und möglicherweise auch *Ixodes hexagonus*. Immer noch fehlt es an spezifischen und zuverlässigen serologischen Tests. Vielversprechend erscheint die Entwicklung von spezifischen Antigenproben und der Polymerasekettenreaktion für den Nachweis einer bestehenden Infektion und die Identifizierung von *B. burgdorferi* in Wirten wie Zecken, Tieren und dem Menschen. Fortschritte in der Präparation von Gesamt-Zell-Vakzinen und gentechnologisch hergestellten Vakzinen werden kurz mitgeteilt.

Introduction

Almost ten years have passed since a survey for tick-borne rickettsiae on Long Island, New York, led to the discovery of a spirochete, in the midgut of the deer tick, *Ixodes dammini*, as the causative agent of Lyme disease [1]. Subsequently, similar, if not identical, spirochetes were demonstrated in the European sheep tick, *Ixodes ricinus*, as well as in the American western black-legged tick, *Ixodes pacificus* in California [2].

The discovery of these spirochetes as well as their successful cultivation in BSK II medium [3] rapidly led to their immunochemical and molecular characterization. Accordingly, they were shown to represent a new species of the genus *Borrelia* for which the name *Borrelia burgdorferi* was proposed [4].

Since the discovery and isolation of this spirochete were reported in the summer of 1982 [1], intensive investigations on both sides of the Atlantic have resulted in more than 2,500 publications on clinical, epidemiological, ecological, and bacteriological aspects of Lyme disease in the United States and of related disorders in Europe. Serologic studies strongly suggested that European erythema (chronicum) migrans and closely related disorders, such as tick-borne meningoradiculitis or Bannwarth's syndrome, acrodermatitis chronica atrophicans, and lymphocytoma benignum cutis, are caused by spirochetes similar to, if not identical with, *B. burgdorferi*. Indeed, spirochetes indistinguishable from it have been isolated from skin,

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blood, and cerebrospinal fluid of persons afflicted with these disorders. It may be recalled here that the disease affecting residents of Lyme, Connecticut, in the sixties and beginning seventies was first considered a heretofore unrecognized clinical entity; it was called Lyme arthritis because patients were affected by episodes of asymmetric swelling and pain in the large joints [5]. The term "Lyme arthritis" was changed to "Lyme disease" when the arthritis was recognized as only one expression of a rather complex multisystem disorder that may also affect the skin, heart, skeleton, muscle, and nervous system.

Enlargement of the Clinical Spectrum of Lyme Disease

The past ten years have shown a considerable broadening of the clinical spectrum of Lyme borreliosis, making it one of the most complex bacterial diseases ever known. Thus, transplacental transmission of *B. burgdorferi* has resulted in stillbirths or malformed fetuses. Although invasion of the placenta by spirochetes is well documented, malfunction and/or death of the fetus appear to be rare [6]. Of 19 pregnant women with Lyme disease reported in 1986, five had adverse outcomes, but in none of them could *B. burgdorferi* be implicated [7]. Similarly, in a more recent study in Old Lyme, Connecticut, six cases of Lyme borreliosis during pregnancy resulted in favorable outcomes in the offspring [8]. Two women had ECM, two had carditis, one suffered from persistent arthralgias, and one had a facial palsy and temporomandibular arthritis. In contrast, a culture-positive neonatal death was recently recorded in California; *B. burgdorferi* was grown from the frontal cortex, and spirochetes were found in silver-stained sections of brain and heart [9].

Lyme Myositis

Lyme myositis, the occurrence of pain and weakness in muscle groups during the course of *B. burgdorferi* infection, has recently been added to the clinical spectrum of this disease [10]. Distinguished from the effects of Lyme disease peripheral neuropathy, it may appear early after infection, or months, even years, later. Although so far spirochetes have not been cultivated from biopsy specimens of muscle, they have been demonstrated by silver staining in such specimens from several patients.

Carditis

Ever since the early description of Lyme disease, carditis in the form of transient disturbances in conduction and rhythm have been described in about 8% of patients. There has been increasing evidence that Lyme disease carditis may also be of long duration and may lead to permanent heart damage, such as cardiomegaly and pancarditis.

Demonstration of spirochetes in myocardial biopsy tissue from patients with fatal and nonfatal Lyme disease suggests cardiac abnormalities to be the result of local infections with *B. burgdorferi*. Of 81 patients with dil.. ed cardiomyopathy, 29.6% had antibodies to *B. burgdorferi* and had spirochetes in myocardial biopsy specimens. In at least one patient, a *B. burgdorferi*-like organism was isolated from such specimens [11, 12].

Encephalomyelitis

Among the more recently recognized manifestations of Lyme borreliosis is Borrelia encephalomyelitis or tertiary borreliosis – a syndrome that differs from the common and spontaneously resolving meningopolyneuritis (Bannwarth's syndrome) in its progressive nature, its invasion of the nervous system, and in the long lasting injurious effect especially if not treated effectively [13]. Numerous reports have now appeared of patients who several years after they had experienced ECM developed symptoms and evidence of chronic inflammation of the central nervous system; it is now well known that *B. burgdorferi* may cause a wide range of acute, chronic and progressive abnormalities mimicking a variety of other neurologic conditions, such as multiple sclerosis and amyotrophic lateral sclerosis. Apparently, the spirochete is capable of surviving in the central nervous system for years before producing evidence of clinical disease. Intrathecal antibody determinations are the most significant test for Lyme neuroborreliosis. Unfortunately, antibody is not always found in the cerebrospinal fluid, making the diagnosis of this disorder difficult. Subtle development of CNS symptoms, such as memory loss, somnolence, behavioral changes, and depression, following classic Lyme borreliosis, have become a controversial issue especially in the absence of intrathecal antibodies. Many physicians consider such symptoms epiphenomena, i.e. unrelated to Lyme borreliosis, and refuse treatment. On the other hand, a recent study of chronic neurologic manifestations of Lyme disease has shown that the most common form of central nervous system involvement is subacute encephalopathy affecting memory, mood and sleep, and sometimes also speech [14].

Ocular Manifestations

More recently, other reported neurologic manifestations of Lyme disease are those affecting the eye [15, 16]. Conjunctivitis, iritis, and uveitis occur early in the disease, where optic atrophy is seen in later stages. Other inflammatory eye disorders include interstitial keratitis, choroiditis, and episcleritis.

Skin Disorders

Of particular interest to today's discussion on the enlarging spectrum of Lyme borreliosis is the question of whether morphea (localized scleroderma) may be a manifestation of infection with *B. burgdorferi*. Detection of antibodies to it in nine of 21 (42.9%) morphea-affected patients in Switzerland led to the speculation of a spirochetal cause of this disorder [17]. Subsequent evaluation of 32 patients in

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the United States [18], and of 138 patients in Denmark [19], however, found no specific association between *B. burgdorferi* and morphea. In contrast to these findings are isolations of *B. burgdorferi*-like spirochetes in BSK II medium of skin biopsies of two morphea patients in Germany [20]. Both isolates unfortunately, were lost before they could be identified closer.

Status of Lyme Disease Diagnosis

With the discovery of *B. burgdorferi* as the causative agent of Lyme borreliosis, indirect immunofluorescence and the enzyme-linked immunosorbent assay (ELISA) were thought to provide effective and dependable laboratory tests for the diagnosis of this disease. It was soon realized, however, that both tests gave false negative results, particularly during the first weeks of infection. Moreover, they gave false positive results when healthy persons or patients suffering of other diseases, such as relapsing fever and syphilis, were evaluated. Also, results from different laboratories were highly variable. For example, one laboratory testing a given serum sample might report no reactivity whereas another testing the same serum by the same procedure might detect antibodies in significant titers [21].

Lack of standardized test reagents was considered the main reason for such discrepancies. It was also shown that continued *in vitro* culturing of the spirochetes, as is done in preparing test antigens, invariably leads to a loss of spirochetal plasmids believed to control the proteins antigenic for the human hosts [22]. In addition, it was found that the long persistence of *B. burgdorferi* in humans and other animal hosts is closely associated with the organism's ability to undergo antigenic variations in a way similar to that described for the North American relapsing fever borrelia, *Borrelia hermsii* [23]. Indeed, such rapid antigenic changes associated with *in vitro* as well as *in vivo* growth of *B. burgdorferi* should be taken into consideration when evaluating and interpreting data from serologic surveys and diagnostic tests. It may well be that spirochetes maintained in BSK II culture no longer have antigenic epitopes to react with specific antibodies in a patient's serum.

Use of Western blot (immunoblot) assays to determine the protein antigens to which patients are responding with antibody has led to the detection and characterization of several immunodominant proteins (OspA, 20 kDa, 39 kDa, 41 kDa, 60 kDa, 83 kDa). In the past few years, the genes encoding such proteins have been cloned and have been, or still are being, evaluated for their usefulness and specificity as recombinant antigens in detecting antibodies to the Lyme borreliosis spirochete [24–27].

The 39 kDa antigen, referred to as P39, was found to be species-specific and conserved among North American and European isolates of *B. burgdorferi* [28, 29]. P39 is distinct from previously described antigens and reacts with serum from Lyme disease patients. Mice infected with *B. burgdorferi* by tick bites produced anti-P39 antibodies not later than seven days, indicating that P39 is an effective immunogen and may serve as a reliable marker for active infection. No doubt standardized reagents prepared from recombinant immunodominant antigens, such as P39, will eventually provide the integral part for a specific and dependable diagnostic test.

The gradual involvement of the various organ systems (skin, cardiovascular, central nervous, muscle and skeleton) in a disease process that may last weeks, months, even years, suggests prolonged persistence of *B. burgdorferi* not only in body fluids but also in tissues. Thus, it would appear that the demonstration of spirochetes in histologic sections is a far more dependable diagnostic tool than serologic tests. Yet, most studies to visualize *B. burgdorferi* in biopsy tissues have shown that it is extremely rare; it has been demonstrated more abundantly in sections of skin lesions and in synovial tissues than elsewhere. Silver staining has been the method of choice for the detection of spirochetes in tissues even though the nonspecific uptake of silver by connective tissue fibers makes microscopic examination difficult and time consuming. Therefore, the detection of a single *B. burgdorferi* in the blood and/or tissues of patients has been the goal of molecular biologists at the Rocky Mountain Laboratories in Hamilton, Montana. They applied the polymerase chain reaction (PCR), which allows amplification of a target DNA sequence specific for the Lyme disease spirochete, and showed that this assay provides a specific, sensitive, and rapid means for identifying *B. burgdorferi* [30]. The technique was also used to detect *B. burgdorferi* in both live and desiccated ticks and to demonstrate spirochetal DNA in alcohol-preserved ticks in museums [31,32]. More recently, the PCR was applied to "typing" by differential primer activities a total of 31 *B. burgdorferi* isolates from North America, Europe, and Asia [33]. Accordingly, all North American isolates fall into a single reactivity group, whereas those from Europe fall into two groups, one of which is indistinguishable from the North American group. It was also speculated that these two groups may be reflected clinically in the arthritic versus neurologic spectra of Lyme borreliosis as seen in the United States and in Europe.

Immunization Against Lyme Disease

Successful active immunization with a whole-cell vaccine of inactivated *B. burgdorferi* against experimental infection in Syrian hamsters [34] has already led to the commercial development of a vaccine ("*Borrelia burgdorferi* Bacterin") conditionally licensed by the U.S. Department of Agriculture for vaccinating dogs. The vaccine is said to provide excellent protection, significantly reducing post-infection fever and preventing the arthritis-like limping seen in infected dogs. In the October 26 issue of Science [35], researchers from Yale University Medical School reported on the protection of mice against *B. burgdorferi* by immunizing them with the recombinant surface protein OspA. In immunocompetent mice (C_3H/HeJ), this protein was found to induce high levels of antibodies that protected them

Table 1: Mammalian and avian hosts from which *Borrelia burgdorferi* has been recovered.

American isolates	
White-footed mouse	*Peromyscus leucopus*
Meadow vole	*Microtus pennsylvanicus*
Eastern chipmunk	*Tamias striatus*
Woodland jumping mouse	*Nepaeozapus insignis*
Cottontail rabbit	*Sylvilagus floridanus*
Jackrabbit	*Lepus californicus*
Raccoon	*Procyon lotor*
Coyote	*Canis latrans*
Black bear	*Ursus americanus*
White-tailed deer	*Odocoileus virginianus*
Dog	*Canis familiaris*
Horse	*Equus caballus*
Cattle	*Bos taurus*
Bird (veery)	*Catharus fuscescens*
European isolates	
Long-tailed field mouse	*Apodemus sylvaticus*
Yellow-necked field mouse	*Apodemus flavicollis*
Bank vole	*Clethrionomys glareolus*

from challenge with infectious *B. burgdorferi*. German scientists using immunodeficient mice (skid) as their animal model, also claimed recombinant OspA as a candidate for a vaccine [36]. Thus, efforts are under way to establish the groundwork for a recombinant vaccine that eventually may become applicable for human use.

Tick/Host Relationship of Borrelia burgdorferi

The natural history of *B. burgdorferi* reviewed only recently [37] is as complex as the disease it causes. Once thought to be limited to the European continent, erythema (chronicum) migrans and related disorders are now known to occur also in North America, Asia, Japan, China, Australia, and Africa, where the spirochete is maintained and transmitted by ixodid ticks of the genus *Ixodes*, namely *I. dammini*, *I. pacificus*, and possibly also *I. scapularis* in the United States, *I. ricinus* in Europe, and *I. persulcatus* in Asian countries.

Although above cited ticks are recognized as the main vectors of *B. burgdorferi*, spirochetes identical with or resembling it have been detected in other species of ticks, including the American dog tick (*Dermacentor variabilis*), the lone star tick (*Amblyomma americanum*), the rabbit dermacentor (*Dermacentor parumapertus*), the rabbit tick (*Haemaphysalis leporispalustris*), the rabbit *Ixodes* (*I. dentatus*), the woodrat tick (*I. neotomae*), the brown dog tick (*Rhipicephalus sanguineus*), and the argasid tick, *Ornithodoros coriaceus*. Of these ticks, only *A. americanum* has so far been claimed a vector of *B. burgdorferi* in the northeastern state of New Jersey, in Missouri, and in Texas. Whether spirochetes isolated from these ticks are in fact *B. burgdorferi* or represent closely related organisms remains to be established.

The presence of *B. burgdorferi* in rabbit ticks (*Haemaphysalis leporispalustris, I. neotomae*, and *D. parumapertus*) and past or current spirochetal infections in black-tailed jack rabbits (*Lepus californicus californicus*) of northern California have long suggested that lagomorphs and their ticks are possibly involved in the ecology of the Lyme disease spirochete. More recently, spirochetes identified as *B. burgdorferi* were isolated from 71 of 168 *I. dentatus* – another tick parasitizing predominantly rabbits – taken off naturally infected cottontail rabbits (*Sylvilagus floridanus*) in New York [38].

Although rabbit ticks do not feed on humans, they may be involved in maintaining spirochetes and may be responsible for the occurrence of Lyme disease in areas free of the well established vectors.

In Europe, the sheep tick, *I. ricinus*, had been considered the only tick vector of *B. burgdorferi* until tick/spirochete surveys in Germany [39] revealed *B. burgdorferi*-like spirochetes in the hedgehog tick, *I. hexagonus*. This tick parasitizes primarily hedgehogs and mustelidae but is also known to attack cats, dogs, and occasionally humans. Its role as a vector of *B. burgdorferi* remains to be evaluated.

In southern Tirol, the finding of *B. burgdorferi* in the argasid tick, *Argas persicus*, associated with pigeons deserves our attention [40]. It suggests that certain avian species may also play a role in the ecology of this spirochete.

Isolations of *B. burgdorferi*, as seen in Table 1, have been made not only from human patients but also from at least 17 wild or domestic animals, including a bird.

Of special interest to us is the white-footed mouse, *Peromyscus leucopus* [37]. This rodent not only is the preferred host but also is the most important reservoir for infecting ticks with *B. burgdorferi*. Fed on by infected ticks or injected with spirochete-containing tick suspensions, this mouse has been shown to remain infectious throughout its life, producing in ticks infection rates up to 100%. In contrast, relatively low infection rates have been recorded so far for *I. scapularis* and *I. pacificus* in southeastern and western United States, respectively. This may be attributed to the fact that the immature stages of these ticks more commonly feed on lizards than on rodents. Only recently have lizards been shown to be non-susceptible to the Lyme disease agent [41]. In California, where *P. leucopus* does not occur, woodrats (*Neotoma* spp.) have been incriminated as possible reservoirs of *B. burgdorferi* (*Robert Lane*, personal communication).

Still, little information is available from Europe about the significance of animal hosts as sources for infecting *I. ricinus*. Tick/spirochete surveys in many countries have yielded infection rates as high as 66%; mice (*Apodemus* spp.) and voles (*Clethrionomys* spp.) are generally assumed to serve as the spirochetal reservoirs [42]. Certain species of ground-frequenting birds have also been found to be competent reservoirs for *B. burgdorferi*.

That spirochetal development is limited to the midgut in up to 95% of all established vectors of the *I. ricinus* complex, raises the question of the mode(s) by which *B. burgdorferi* is transmitted. Initially, it was speculated that transmission may occur as a result of regurgitation by ticks with midgut-limited infection. But early on, it was suggested

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that during the engorgement process, spirochetes may penetrate the gut wall and initiate mild systemic infections that include the tissues and ducts of the salivary glands. In saliva obtained experimentally, spirochetes could not be detected until three days after ticks became attached. Therfore. transmission is said to occur via saliva during the final stages of feeding. Whether regurgitation of spirochete-containing gut material is an additional mode of transmission is still under investigation.

Incidence and Distribution of Lyme Borreliosis

Because of variations in case definition and because Lyme borreliosis in most American states is not a reportable disease, accurate data on its prevalence in the United States are not available. From 1975 through 1979, a total of 512 cases were diagnosed in 14 predominately northeastern and midwestern states. In 1982, the year we reported the discovery of the Lyme disease spirochete, 491 cases came to the attention of the Centers of Disease Control. Since 1983 when 600 cases were recorded, the number has steadily increased to about 8,600 in 1989. Although the disease is now recognized in 43 states, 97% of cases come from the northeast, upper midwest, and Pacific Coast. The state of Missouri, with well over 100 cases reported in 1989, appears to be a new area where the disease is endemic. There, as pointed out above, the lone star tick, *A. americanum* is suspected to be responsible for maintaining and distributing *B. burgdorferi* or *B. burgdorferi*-like spirochetes. Thousands of Lyme disease cases have been reported also from Europe, where the disease now occurs in at least 19 countries.

Concluding Remarks

Few discoveries related to vector-borne diseases have evoked as much enthusiasm and interest among scientists and public health authorities as the 1981 detection of a spirochete in the midgut of *Ixodes* ticks that was identified as the long sought after causative agent of Lyme disease in the United States and of related disorders in Europe. Ability to isolate and maintain this microorganism, now known as *B. burgdorferi*, in the modified Kelly medium provided the material necessary not only for intensive bacteriological and molecular studies but also for developing diagnostic procedures and for the evaluation of antibiotic therapy. In addition, medical entomologists responded with enthusiasm and directed their research toward understanding how *B. burgdorferi* interacts with the ecological components of its natural history. After ten years of intensive investigations and more than 2,500 scientific publications. Lyme borreliosis is now recognized as the most prevalent tick-borne disease that every year affects thousands of people – children and adults alike. Indeed, in may regions where it is endemic, the disease has been considered second only to AIDS in public interest and concern. This is also reflected in the number of workshops and conferences held in the United States and in Europe. At the first symposium at Yale University in 1983, 150 participants and contributors were recorded. Two years later at the symposium in Vienna, Austria, there were 175 contributing authors alone, and at the third symposium in New York in 1987, 248 contributing authors and close to 400 participants registered. These numbers were surpassed last year in Stockholm, Sweden, where about 700 authors contributed to five workshops, 69 lectures, and 239 scientific posters.

In spite of the explosive growth in our knowledge of Lyme borreliosis and of its causative spirochete, many research problems dealt with during the past ten years remain unsolved and continue to challenge physicians, veterinarians, epidemiologists, entomologists, and molecular biologists. Among the many as yet unsolved problems are the pathogenesis of the infection with *B. burgdorferi*, particularly its ability to affect the central nervous system, the development of a specific and dependable laboratory diagnostic test with worldwide standardized reagents, the relation of *B. burgdorferi* to additional nonspecific tick vectors, the development of an effective recombinant vaccine, and problems not touched on in our discussion, such as therapy and prevention. The answers to these problems, I am convinced, will be the subjects of the next ten-year review.

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prevent a clinical rebound of inflammatory activity.

Congestive cardiac failure is usually controlled by bed rest and steroids. Occasionally diuretic therapy is necessary, and rarely careful digitalization is required.

Treatment of chorea, a self-limited feature, generally requires more than anti-inflammatory therapy. Most patients benefit significantly from quiet, nonstressful surroundings and administration of phenobarbital or diazepam (Valium) or other tranquilizer. The latter medications must be given on a trial-and-error basis, since patients vary considerably in their responsiveness to treatment and a single drug is not beneficial in all cases.

CHRONIC RHEUMATIC DISEASE

Individuals who have had an attack of ARF with or without cardiac disease or who are found to have chronic rheumatic heart disease (RHD) are at risk for recurrent attacks of ARF following streptococcal pharyngitis. Thus, they should receive *continuous* antistreptococcal prophylaxis to prevent recurrences of ARF. Three standard regimens are considered satisfactory for this purpose, in order of preference: (1) monthly intramuscular injection of 1.2 million units of benzathine penicillin (0.6 million units for those less than 60 pounds); (2) 500-mg tablets of sulfadiazine twice daily; and (3) 250 mg tablets of penicillin V twice daily.

The advantage of parenteral penicillin is that one does not depend upon daily patient compliance; however, the injections may be painful. Strict compliance with this regimen has been shown to result in healing of valvular heart disease (as reflected by disappearance of murmurs) in the majority of patients, in addition to prevention of recurrent attacks of ARF. The advantage of sulfadiazine over oral penicillin relates primarily to the induction of penicillin-resistant oral flora by the latter, which theoretically could predispose a patient to an episode of bacterial endocarditis due to a penicillin-resistant organism. Erythromycin has been suggested for the rare patient who is intolerant of both penicillin and sulfadiazine. A subject of considerable controversy is the optimum duration of rheumatic fever prophylaxis. Most investigators, including the American Heart Association, recommend lifelong prophylaxis for patients with RHD because the risk of recurrent ARF persists long beyond childhood, albeit in a diminished way. In patients without residual cardiac involvement, prophylaxis can probably be safely discontinued at age 21 if at least 5 years has elapsed from the last attack of ARF.

In addition to rheumatic fever prophylaxis, patients with RHD require subacute bacterial endocarditis (SBE) prophylaxis on an episodic basis related to dental or surgical procedures, or gastrointestinal or genitourinary tract instrumentation, as recommended by the American Heart Association.

out of date
But also addresses pregnancy

LYME DISEASE

(Lyme Borreliosis)

method of
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Lyme borreliosis is a recently described spirochetal infection caused by *Borrelia burgdorferi*. It is already recognized as the most common tick-borne infection in the United States. It is transmitted primarily by hard-shelled vegetation inhabiting ticks of the *Ixodes ricinus* complex. These include *Ixodes dammini* in northeastern United States, *Ixodes scapularis* in southeastern United States, and *Ixodes pacificus* in far western United States. This disease has been reported from 43 states, most European countries, Russia, China, northern and South Africa, and Australia. The nymphal stage occurs in spring and summer and accounts for most human attacks. The attachment is recognized in only 25 to 30% of patients, most likely because of the vector's tiny size.

CLINICAL DESCRIPTION

Although the infection often presents in a characteristic manner, many atypical presentations have been described in recent years, often leading to diagnostic confusion. It is a multisystem disorder affecting skin, joints, nervous system, and heart most commonly, but involvement of other systems has also been described. The key to diagnosis is the pathognomonic rash, erythema chronicum migrans. Unfortunately, it is often not present. The disease is described in stages, but considerable overlap between stages has been seen. Its pathogenesis appears to be predominantly immunologic.

Stage I: Early Manifestations

A few days to a month following a tick bite, the central erythematous papule becomes macular and expands gradually, at times to greater than 60 cm. Erythema chronicum migrans is typically flat, annular, with diffuse erythema early. Pain and pruritus are variable but usually not prominent. Central cyanosis leading to vesiculation may occur early. Late central clearing is common, leading to a ring pattern. Slow resolution typically occurs, but similar migrating an-

He also presented on Bb in the blood of 3 SLE patients - (Lupus)

nuli may occur elsewhere. The rash often does not occur and is especially infrequent in children. Constitutional symptoms, including fever, fatigue, malaise, myalgias, arthralgias, transient and migratory synovitis, tendinitis, bursitis, axial stiffness, pharyngitis, headaches, and lymphadenopathy, are common. Nonproductive cough, hepatosplenomegaly, hepatitis, orchitis, periorbital edema, conjunctivitis, iritis, and panophthalmitis are less common. Symptoms often wax and wane within an individual. They may remit within weeks, even without treatment, or persist for extended periods.

Stage II: Cardiac and Early Neurologic Manifestations

Onset is typically weeks to months following infection. This stage often appears prior to resolution of Stage I. Cardiac affliction affects about 10% of untreated subjects and often presents as syncope due to high-grade atrioventricular (AV) conduction disorders. Most commonly first-degree AV block is seen. It often resolves spontaneously or with therapy but may persist. Cardiomegaly, left ventricular dysfunction, pancarditis, and cardiac death have all been reported.

In untreated patients 20% develop neurologic injury. Cranial palsies, especially facial nerve, often symmetrical, are the most common presentations. Cranial nerves II, III, V, VI, VIII, IX, and XII have also been involved. The triad of cranial neuritis, meningitis, and radiculoneuritis (Garin-Bujadoux-Bannwarth syndrome) is commonly seen in Europe. Encephalitis, myelitis, ataxia, chorea, and mononeuritis multiplex may occur.

Borrelia lymphocytoma, a nodular cutaneous lesion often of the ear lobe, is recognized in Europe.

Stage III: Chronic Arthritis and Neurologic Manifestations

Typically, months to years following infection, inflammatory arthritis appears in 60% of untreated patients. It becomes chronic in 10%. The knees are most commonly affected, but any synovial joint may be affected. Symmetrical polyarthritis may be seen. The radiologic and pathologic findings are indistinguishable from rheumatoid arthritis. Panniculitis, myositis, and dermatomyositis have been described. Ulnar fibrous nodules clinically resembling rheumatoid nodules may be seen.

Acrodermatitis chronica atrophicans is often seen in Europe and has been seen in the United States. The inflammatory phase may resemble lymphedema or venous stasis while the atrophic stage can be confused with other cutaneous sclerosing disorders. Peripheral neuropathies with both axonal and myelin sheath injuries are often associated. Multifocal encephalitis, central nervous system (CNS) demyelination leading to multiple sclerosis presentations, psychoses, and dementia have been recognized.

PREGNANCY

Transplacental infection was recognized in 5 of 19 pregnancies reported in one study. Injuries there included fetal wastage, syndactyly, cortical blindness, prematurity, and neonatal rash. The organism has been cultured from fetal organs and from two neonatal deaths, one resulting from aortic thrombosis.

LABORATORY FINDINGS

Serology remains the mainstay of laboratory diagnosis. Unfortunately, the sensitivity of available tests is exceedingly low in early disease and is too often inadequate in late disease. Of the 19 mothers in the above quoted study on transplacental infection, 80% were falsely seronegative. Threshold for serodiagnosis has been set at three standard deviations (S.D.) above the control mean in some laboratories rather than the customary 2 S.D. This was done to reduce cross-reactivity with other spirochetal infections, but unfortunately, cross-reactivities with treponemal and other borrelia infections occur at and above that higher threshold. T cell stimulation studies support the concept of seronegative disease. T cell assays are not available commercially. Intradermal testing of delayed hypersensitivity may follow this in vitro assay. An antibody capture assay reporting only a 7% false negativity in late disease has recently been described. A urine antigen capture assay is under study. Direct culture of the organism is too often unsuccessful to be useful as a clinical assay. Elevation of serum IgM and transaminases as well as microhematuria is seen at times, especially in early disease. CSF assays often reveal only a mild pleocytosis and elevation of total protein. Lack of evidence for CNS in situ formation of borrelia antibodies should not exclude the diagnosis of neuroborreliosis. Conversely, malignant-appearing cells may be seen in the CSF leading to a misdiagnosis of CNS lymphoma. It is generally agreed that the diagnosis of Lyme borreliosis should be based on clinical factors and not excluded because of negative serology.

TREATMENT

General Considerations

Prevention remains the most important approach. Thorough covering by light-colored clothing whose openings are tightly closed offers the first line of defense. Careful tick checks should be done at the end of an outdoor day and more often if possible. Hairy and crural regions are special targets of the ticks. Gentle traction on the tick near its attachment is the best removal method.

Standard treatment for early disease (Stage I) has typically consisted of common oral antibiotics administered over a 2-week period. Penicillin V 500 mg, tetracycline 250 to 500 mg, or erythromycin 250 mg, all given four times a day, has been the usually recommended regimen. Recently, the adequacy of these as well as standard regimens for later stages has been questioned. This has been stimulated by numerous reports of

treatment failure or late relapses following all available forms of oral and parenteral treatment. According to a sizable European dermatologic study, 27% of early and 47% of late disease patients later developed extracutaneous signs and symptoms following standard treatment. The causes of these difficulties are likely manifold. Surely the very slow reproduction rate of this microbe in vitro (12 to 20 hours) and its suspected much slower reproduction rate when the microbe has become established in host parenchyma are probable contributors. Evidence for long asymptomatic intervals of many years is accumulating. This latency is reminiscent of lues.

B. burgdorferi is sensitive to common spirochetal antibiotics including the penicillins, tetracyclines, some cephalosporins, erythromycin, and chloramphenicol (Chloromycetin). Erythromycin's benefit in vivo is far less than its in vitro sensitivity would indicate. Rifampicin, sulfonamides, aminoglycosides, and quinolones appear to have no role in this infection.

Stage IA: Hematogenous

This is the earliest and usually asymptomatic stage when parenchymal infection has not yet occurred. It accompanies the tick bite and likely lasts for only a few days during which a low-grade spirochetemia exists. Treatment with the above noted standard oral agents may be adequate. The use of doxycycline at 2.5 to 3 mg per kg per day or amoxicillin at 25 to 30 mg per kg per day in divided doses for 2 weeks is preferred. Tetracycline should not be used in children under age 8 years. Erythromycin at 30 mg per kg per day in divided doses for 20 days may be used in penicillin-allergic children, although its efficacy is likely less than the agents it replaces.

Stage IB: Parenchymous

Experience with hamsters indicates that parenchyma is invaded within 7 days of experimental infection. Too often patients are seen initially weeks following spirochetal inoculation; therefore, the likelihood of parenchymous infection becomes high. Once systemic symptoms and signs are present, parenchymous infection likely exists. Antibiotics that cross the blood-brain barrier are then required. Doxycycline (Vibramycin) at 2.5 to 3 mg per kg per day or minocycline (Minocin) at 2 to 2.5 mg per kg per day or amoxicillin (Amoxil, Polymox) 1500 mg with probenecid (Benemid) 500 mg (in adults) three times a day appears to adequately penetrate CNS tissues and offer acceptable antibiotic effect. Children under age 8 should receive amoxicillin 60 mg per kg per day in divided doses. Those who are penicillin allergic may receive erythromycin at 30 mg per kg per day in divided doses, but its weaker effectiveness should be kept in mind. Studies of various oral third-generation cephalosporins and a new erythromycin class drug are in progress. These should be considered in this penicillin-allergic age group when they become available.

Persistent symptoms including fatigue, headaches, myalgias, and arthralgias have been noted in about half of all patients with this disease. These symptoms have been considered immunologically based by many. Molecular mimicry, where natural host proteins mimic spirochetal antigens, has been offered as one such mechanism promoting ongoing immune response. Longer antibiotic therapy has been beneficial to a number of these patients in uncontrolled observations suggesting that persistence of the infection in parenchymous sites may be the cause of these ongoing symptoms. Borreliae have been shown in deep tissues following 2 months of accepted oral antibiotic treatment. Such findings strongly support suspicion that parenchymal infection is probably not eradicable with short-term treatment. Treatment well beyond clearance of the last symptoms seems appropriate until controlled studies define optimal type and duration of therapy to achieve bacteriologic cure. To date there is no evidence of the spirochete's developing resistance to established antibiotics.

Stage II: Cardiac and Neurologic Treatment

This stage clearly implies parenchymous infection. It is also the stage of potentially dramatic and organ-threatening presentations. When cardiac signs are limited to mild PR interval prolongation, then the oral antibiotics and dosing mentioned for Stage IB parenchymous disease above should be applied. Duration of treatment should be at least 4 months, pending results of controlled studies. Nonsteroidal anti-inflammatory drugs (NSAID) such as high-dose aspirin (3 to 4 grams daily in adults) or equivalent should also be applied in the early weeks. Temporary restriction of physical activity may be appropriate.

In addition to minor conduction defects, this infection is known to cause major conduction defects (PR interval $\geq$ 0.3 seconds), which often present as syncope or as inflammation of any or all three layers of the heart (endocardium, myocardium, pericardium). Death may ensue. Hospitalization is often indicated, and temporary pacemaker placement may be required. In this setting of acute threat to vital organs, intravenous antibiotics appear to have their greatest applicability. High-dose penicillin, 20 million

units per day in divided doses, has been favored until recently. Ceftriaxone (Rocephin) 2 grams intravenously per day for 14 days now seems more appropriate based upon its superior tissue penetration and spirochetal sensitivity. It is also more easily administered in the home setting, allowing shorter hospital stays. Continued oral antibiotic treatment as previously described for Stage IB parenchymal infection should follow for at least 4 months or until resolution of symptoms, whichever is longer. NSAID treatment may be beneficial, but a rapidly tapering course of corticosteroids over 1 week is preferred for these life-threatening presentations. Prednisone starting at 1 mg per kg the first day is suggested.

Acute CNS presentations (meningitis, encephalitis, myelitis) typically require hospitalization. Intravenous ceftriaxone at 2 grams daily for 14 days has become favored for reasons mentioned above. In addition, its penetration of the blood-brain barrier is far superior to that of penicillin. Treatment with oral antibiotics as described for Stage IB parenchymal infection should follow for at least 4 months or until resolution of symptoms, whichever is longer. Less dramatic CNS presentations, e.g., headaches and memory difficulties, also are usually adequately treated by this oral regimen.

Peripheral nervous system afflictions should be treated according to the method suggested for Stage IB parenchymal infection. Duration should also be at least 4 months or until resolution of symptoms, whichever is longer. A rapidly tapering course of corticosteroids over 1 week, e.g., prednisone starting at 1 mg per kg the first day, may be additionally beneficial to patients presenting with recent onset (less than 2 weeks) cranial neuropathy, e.g., facial palsy or sudden deafness.

Stage III: Chronic Arthritis and Neurologic Disorders

A general consensus is arising among clinicians most familiar with this disorder that late disease is the most difficult to treat and refractoriness to various treatment modalities is often seen. Intravenous ceftriaxone 2 grams per day for 14 days has recently been favored in publications for this stage. Unfortunately, its long-term efficacy in practice falls below what has been published. It is conceivable that late disease represents the greatest adaptation of the microbe to its host environment. In turn, its reproduction rate may be far slower than its in vitro rate, leading to greater need for prolonged therapy as well as optimal antibiotic tissue penetration. Treatment of the kind outlined in Stage IB parenchymal disease is at times more efficacious than a short course of intravenous ceftriaxone. Unfortunately, symptomatic flares as a result of treatment are often seen. This likely represents tissue deposition of immune complexes formed as a result of antibiotic-induced release of antigen from its parenchymous sites. Interruption of treatment typically aborts the flares. A treatment approach that allows for ongoing clearance of immune complexes via scheduled interruption of treatment seems to be most efficacious when flares recur as a function of prolonged oral therapy. Using amoxicillin 1500 mg and probenecid 500 mg twice a day or even daily seems to offer the greatest comfort, especially in the case of chronic arthritis. Doxycycline or minocycline can similarly be interrupted by giving doses as described in Stage IB parenchymal disease on an every-other-day schedule. Treatment should be continued beyond clearance of symptoms or at least 4 months, whichever is longer.

In a 1981 report, hydroxychloroquine (Plaquenil) was shown be beneficial for chronic Lyme arthritis. It appears to improve the efficacy of prolonged oral antibiotic treatment in cases where antibiotics alone are insufficient. Standard dosing at 6 mg per kg per day is recommended along with the usual ophthalmologic precautions.

Pregnancy

Maternal treatment to prevent transplacental infection is not established. A standard, short course of oral penicillin given to the mother soon after appearance of erythema migrans did not prevent fetal infection and neonatal death in the only reported case of this circumstance. Two weeks of ceftriaxone 2 grams intravenously per day in early pregnancy and amoxicillin 1 gram three times a day for 6 weeks in late pregnancy have been protective to offspring in recent uncontrolled observations on eastern Long Island, N.Y. Six weeks of amoxicillin 500 mg four times a day given at various gestational times has resulted in no apparent fetal injuries in 12 pregnancies in Wisconsin.

The likelihood of placental infection is highest early in the disease when hematogenous spread is active. Very low-grade spirochetemia likely occurs in later stages and may continue for indefinite periods. Protection against this phenomenon should require lower serum antibiotic levels than those required for CNS penetration. Amoxicillin 500 mg orally four times a day should be adequate. Continuation throughout gestation would seem to offer the greatest protection, pending results of studies defining optimum treatment.

Maternal immunologic reaction to treatment of

the Jarisch-Herxheimer type could be acutely injurious to the fetus and could lead to fetal wastage, but this has not been reported.

ASYMPTOMATIC TICK BITE

As we learn more about the potential severity of late disease and the difficulties with effecting adequate treatment, consideration for treatment at the earliest time becomes rational. In the first days following a bite by an infected tick, potential for eradicating the infection is highest because the infection is presumed to be only hematogenous. In regions of high endemic tick infection, early treatment of asymptomatic tick bites by the method previously described for Stage IA hematogenous seems prudent. Serologic reactivity will likely not occur, but late disease should be prevented. In regions of low endemic infection, such prophylactic treatment offers no benefit statistically.

ROCKY MOUNTAIN SPOTTED FEVER

method of
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Rocky Mountain spotted fever (RMSF), an acute infectious disease, is the most prevalent and severe of the rickettsioses. The etiologic agent is *Rickettsia rickettsii*, an obligate intracellular parasite of several species of ticks and rodents and possibly of mammals. It is transmitted to man by the bite of the adult tick. A variety of ixodid (hard-shelled) ticks serve as both reservoir and vector for the disease. The western wood tick, *Dermacentor andersoni*, and the eastern dog tick, *D. variabilis*, are the principal vectors. RMSF of the United States is identical to Sao Paulo fever, Colombian spotted fever, fiebre maculosa, fiebre petequial, and the fiebre manchada of Mexico.

Despite its name, the disease is more common in the southern, southwestern, and eastern United States. Since 1960 the number of reported cases in the United States has increased steadily, and the increase has been particularly striking since 1970. The true incidence is likely higher than the reported incidence. Persons of all ages are susceptible to the disease, but most of the cases occur in children. There is a striking seasonal distribution, with most cases occurring during the spring and summer. This parallels both the activity of ticks and the behavior of individuals that brings them in contact with the ticks.

The incubation period in man is 2 to 12 days, with a mean of 7 days. Since about one-fourth of patients have no history of a tick bite or of the presence of ticks on the body, the absence of such a history should not prevent the physician from suspecting the disease.

The severity of the disease ranges from cases that are clinically quite mild to fulminant forms. In untreated patients the mortality rate ranges from 10 to 40%. Appropriate treatment has reduced this to between 5 and 10%. Prognosis is influenced by age and other factors, but the most important influence in successful treatment of the infection is early diagnosis and institution of therapy.

CLINICAL ASPECTS

The most prominent clinical features of RMSF are headache, fever, rash, and edema. However, many patients have nonspecific features such as nausea, vomiting, abdominal pain, diarrhea, arthralgia, myalgia, and neurologic manifestations. The onset of symptoms may be either abrupt or gradual. The neurologic manifestations, particularly when alterations in mental status and vomiting are present, may suggest a diagnosis of meningoencephalitis.

The rash of RMSF is the earliest dependable and most important diagnostic sign. It typically begins on the ankles and wrists and spreads centrally. In the early stages it is maculopapular but in many cases (more than half) assumes a petechial character. Some patients do not have a typical rash, and in others, the rash may not appear until later in the disease. Variability in the nature of the rash is common, and failure to recognize this may result in a delay in diagnosis, which can be catastrophic. When looked for, many patients show generalized nonpitting edema. Conjunctivitis, splenomegaly, and a variety of neurologic manifestations may occur.

RMSF may be confused clinically with other infectious diseases, including meningococcal infections, enteroviral infections, atypical measles, infectious mononucleosis, and others. The rash of drug eruptions may be confusing. A newly recognized rickettsial disease, ehrlichiosis, may clinically resemble RMSF. It is caused by *Ehrlichia canis*, an intraleukocytic parasite that infects a variety of wild and domestic animals, including dogs. The clinical findings are similar to those of RMSF, except that rash is usually absent.

RMSF cannot be clearly identified in the early stages on the basis of routine laboratory procedures. Urinalysis is usually normal, but specimens may contain traces of albumin and, sometimes, casts. Leukopenia, present in the first week, evolves into moderate leukocytosis in the second. There may be mild to moderate normochromic normocytic anemia, thrombocytopenia, and multiple coagulation disturbances, including hypofibrinogenemia and evidence of disseminated intravascular coagulation.

Serial determinations of serum proteins usually show a progressive decrease, particularly of the albumin fraction. Serum electrolyte measurements frequently demonstrate hyponatremia and hypochloremia. These abnormalities may be associated with increased aldosterone excretion.

Mild CSF mononuclear pleocytosis with slight elevation of the protein content is common. The leukocyte count almost never exceeds 300 per mm^3. The glucose concentration is normal.

Liver function abnormalities include decreased

LDF 9th Sci Conference 1992

ANTIBIOTIC SEEKING BEHAVIOR

What is this thing called antibiotic seeking behavior? Is it improper patient behavior or is it an aberration? Is it something to be laughed at? Is it another way that we as physicians label our patients, or is it something we might be able to learn from? Are the patients trying to tell us something, and are we listening carefully enough? I first heard the term antibiotic seeking behavior in 1990 in Stockholm, Sweden, at the Fourth International Conference on Lyme Borreliosis, in reference to patients constantly asking for antispirochetal antibiotics long after they had been "treated" for their Lyme borreliosis. At a later Lyme borreliosis conference in Lincoln, Nebraska, Dr. Edwin Masters questioned the behavior. He seemed perplexed that to his knowledge Lyme borreliosis was the only disease process in which patients continually ask for more antibiotics. In fact, patients would seek out physicians willing to prescribe antibiotics in repeated doses and for extended periods of time. We have long been familiar with patients coming to the office asking for narcotics and analgesics, either for pain relief or for some other secondary gain. The question in this situation is: What is the secondary gain in seeking out antibiotics? We may never understand the content of such activity, but the process of the behavior may help us to explain the strong link between Lyme borreliosis and family medicine.

Is there a link between Lyme borreliosis and family medicine? Dr. Gayle Stevens, one of the modern fathers of the specialty noted that family medicine protects the patient from the extravagances and the risks of too much medical care. Family practice also protects the subspecialist from having to do general medical practice in order to identify the patients who need their unique services. That is not to say that specialists are not important in Lyme borreliosis, but it is the generalist, the family physician and the other primary care providers, who should be the front line in dealing with Lyme borreliosis. The family doctor is most uniquely qualified to be that front line person in most of the serious maladies of our time including, AIDS, heart disease, cancers, aging problems, and certainly Lyme borreliosis.

This is not to imply that the specialist does not perform an important task. However, when the role of the family physician atrophies, the patient is entirely at the mercy of these "experts." And so as Dr. Stevens observed, neither the patient nor the subspecialist is safe from the other. No one knows the patient better than their own family doctor. As Dr. Masters notes, the family doc is the best one to tell if the patient is "real". Since the family doc has the benefit of knowing the patient and the family for many years, she/he knows the chronic complainers and the "crocks" in the family. With such familiarity, the family doc can quickly identify the patient with something new or with a subtle problem, often just by talking to the patient.

With all this information, we are lead by simple logic to the conclusion that most patients need what the family physicians have to offer most of the time. And when they need more, it can be obtained through the normal processes of consultation and referral. The family doctor should be the one in charge of the case; the one to gather the data, to be there for the patient phone calls, to listen carefully, and to bring all the referrals and extraneous information from the experts and the consultants into proper perspective. By doing this, the family doctor is the real expert on the dynamics and the needs of the family and should be the one to be called on first, especially in the context of Lyme borreliosis.

After all, who would better recognize a subtle mental chance or an abnormal mood shift sooner than the family physician?

The patient with this so called antibiotic seeking behavior comes to the office and says: "I need the doxycycline again doc," or what ever antibiotic that may have worked well in the past. In that situation will most specialists be able to deal with that sort of behavior? Can any physician listen to a patient and take them seriously when they tell the doctor that they need a "few more months" of antibiotics. The doctor immediately thinks to her/himself if there are other conditions where patients ask for more antimicrobial medicines. Patients with tuberculosis often use antibiotics for years, but at least in my experience, it has almost always been a struggle to make sure that the medicines were actually taken. So unsure about some patients, many T.B. clinics set up weekly injections for those non-compliers. Personally, when I am ill with a documented strep throat by culture, rarely do I use the full ten day course of penicillin. After five or six days, or when I feel well again, I usually stop the antibiotics. After all it is difficult to take pills four times a day for ten days. In fact, most people simply stop after felling better. And herein lies the key to the dilemma. They feel better!! Apparently the Lyme borreliosis patients also feel better while they are taking antibiotics. Otherwise why would they be seeking out antibiotics like addicts on the street seek out morphine or percodan or dilaudid. They are treating themselves because no one else is treating them. They feel better when they use the antibiotic, and they use the antibiotic because they need them.

What we notice as this aberrant behavior of seeking out antibiotics and of seeking out doctors to prescribe them, is really one more expression of the unfulfilled patient-doctor relationship. When the doctor says: " no, you've already been treated and further antibiotics will not be of value to you," the doctor slams the door shut. It was that door that leads to open discussion and mutual trust. To open the door and re-establish that trust takes only to <u>listen</u> to the patient. This quality of listening is not a quality unique to one specialty of medicine, no one has the corner on that market. But, that type of listening is taught and encouraged in the training of the family physician. Along with the psychiatrist, the family doctor is the expert on interpersonal relationships, listening and observing patients. The family doctor is able to walk that fine line between the science and the art of what we call modern medicine.

Possibly this antibiotic seeking behavior isn't such aberrant activity. Maybe it is the only way for the patient to cry out for help. Maybe it is the only way for the patient to convey to the doctor that something is very wrong. Maybe we need to listen a bit better.

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Sequestration of antibody to *Borrelia burgdorferi* in immune complexes in seronegative Lyme disease

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To find out whether apparent seronegativity in patients strongly suspected of having Lyme disease can be due to sequestration of antibodies in immune complexes, such complexes were isolated and tested for antibody to *Borrelia burgdorferi*. In a blinded analysis the antibody was detected in all 10 seronegative Lyme disease patients with erythema chronicum migrans (ECM), in none of 19 patients with other diseases, and in 4 of 12 seronegative patients who probably had Lyme disease but had no ECM. These findings were confirmed by western blot, which also showed that immune complex dissociation liberated mainly antibody reactive to the 41 kD antigen and sometimes antibody to an approximate 30 kD antigen. Complexed *B burgdorferi* antibody was also found in 21 of 22 (95%) of seropositive patients with active disease, 3 additional seronegative but cell mediated immune reactive patients, and 3 other seronegative patients who eventually became seropositive. Apparent *B burgdorferi* seronegativity in serum immune complexes may thus be due to sequestration of antibody in immune complexes.

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Introduction

Lyme disease, which is caused by the spirochaete, *Borrelia burgdorferi*,[1,2] may affect the musculoskeketal, cardiovascular, nervous, and cutaneous systems.[3] Seronegativity is an unexplained feature and is a major obstacle to diagnosis when the hallmark, erythema (chronicum) migrans (ECM), is not observed,[4,5] as happens in up to 50% of patients with Lyme disease. The main laboratory test for the disease, the detection of antibody to *B burgdorferi*, may also be negative in many instances.[4] A negative test despite clinical features of the disease may perhaps be due to sequestration of the antibody in complexed form, as can occur in diseases such as hepatitis B, multiple sclerosis (MS), systemic lupus erythematosus, and syphilis, in which immune complexes (IC) often contain the relevant antigen and antibody, even in the absence of the free component.[6-10] To examine this possibility we have isolated and analysed IC from seronegative Lyme disease patients.

Patients and methods

Patients

The seronegative group consisted of 22 symptomatic patients who had been negative for *B burgdorferi* antibody by commercial enzyme linked immunosorbent assay (ELISA) before entry into the study ("Lyme FAST", 3M Santa Clara, California, USA) (table 1). Patients came from Monmouth and Ocean Counties, New Jersey, an area endemic for Lyme disease. All samples were received

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in a blinded manner, and the clinical histories, including past occurrence of ECM, were unknown to those of us doing the experiments until completion of all tests. For this study, Lyme disease was taken as definite when there was a history of unequivocal ECM (n = 10), and as possible when symptoms suggestive of Lyme disease were not accompanied by a history of ECM (n = 12). Many of the symptoms listed in table I were transient and occurred some time during the course of the disease. All but 1 patient had been prescribed antibiotics by other physicians for a diagnosis other than Lyme disease; none received a currently recommended regimen[3] for Lyme disease. No patient had a history or evidence of immune deficiency.

Controls

The controls were 22 seropositive Lyme disease patients; 9 patients, matched for IC levels, with a variety of other diseases (asthma, urticaria, upper respiratory infection, polyradiculoneuropathy, allergy, multiple sclerosis, polymyositis, stroke); 10 seronegative patients from an endemic area with chronic fatigue as a prominent symptom; and seronegative healthy individuals, also from an endemic area. To further evaluate specific IC formation, additional unblinded samples were analysed from 3 cell mediated immune positive[11] individuals and from individuals with definite and possible Lyme disease.

Antibodies to B burgdorferi

Samples were retested by ELISA[11] for anti-*B burgdorferi* antibodies to confirm the pre-study tests indicating apparent seronegativity. The 96 flat-bottomed-well microtitre plates were coated with a sonicate of *B burgdorferi* (B31) (5 μg/ml). Serum was diluted 1/500. Optical density readings greater than 3 SD above the mean for a standard panel of 10 healthy controls without a history of *Borrelia* infection was taken as a positive result. These 10 controls came from an endemic area and were used in each ELISA run. This assay was also used to probe isolated serum IC (diluted 1/10) for *B burgdorferi* antibodies. In this case the control panel used to define the optical density cutoff (mean + 3 SD) consisted of isolated serum IC from 10 individuals without a history of *Borrelia* infection.

Immunoglobulin concentration

An ELISA was used to measure the Ig isotype contents of the serum samples and isolated IC as previously described.[10]

Rheumatoid factor (RF)

The presence of RF, which could potentially bind *Borrelia* reactive antibody, was screened for in all samples by latex agglutination ('Rheuma-Fac', ICL Scientific, Fountain Valley, California, USA).

Immune complex detection

ICs have different sizes and physicochemical properties so two different assays[12] were used—anti C3 and anti-C1q assays ('Raji' cell replacement EIA and CIC EIA, Cytotech, San Diego, California, USA).

Analysis of immune complexes

Polyethylene glycol precipitation (PEG), modified[13] from the method of Digeon et al,[14] was used to isolate and analyse IC. Briefly, 100 μl of the sample was added to an equal volume of 7% PEG in 0·1 mol/l sodium borate, pH 8·4, incubated overnight at 4°C, then centrifuged at 8320 *g* for 15 min. Pellets were washed twice with 3·5% PEG-borate and resuspended in 100 μl of 0·1 mol/l sodium borate, pH 10·2. This dissociates IC into its components, which can be analysed by ELISA and western blot for *Borrelia* antibody and antigen. The precipitate was also probed for IgG, and IgM and IgA in appropriate cases, and the optical densities read on the microELISA reader. The ELISA described above was used to probe for anti-*Borrelia* antibody in the dissociated serum IC preparations.

TABLE I—CHARACTERISTICS OF SERONEGATIVE PATIENTS

Feature	ECM positive (n = 10)	ECM negative (n = 12)
Mean (SD, range) age (years)	35·4 (22·2, 8–86)	38 (9·2, 23–52)
Sex (M/F)	3/7	7/5
Mean (SD range) time from onset of sample (mo)	25·8 (26·7, 1–81)	22·4 (28·8, 4–78)
Clinical manifestations during course of disease		
Minor CNS (headache, cognitive, mood)	10	12
Fatigue	10	12
Paraesthesias	7	7
Arthralgias	9	11
Arthritis	2	2
Myalgias	8	10
Palpitations, tight chest, without conduction defects	5	8
Flu-like onset	7	2
Laboratory findings		
Positive Lyme (free Ab) tests		
Pre-study ELISA	0	0
ELISA*	0	0
Rheumatoid factor*	2	1
Immune complex assays* (mean)		
Anti C3 (+ > 15)	3·3 μg Eq/ml	2·4 μg Eq/ml
C1q binding (+ > 4)	5.1 μg Eq/ml	6·1 μg Eq/ml

CNS = central nervous systems.
*Tests performed after entry into study.

To confirm the ELISA results western blots were done as previously described,[11,15-17] with relevant modifications. Sonicates of cultured B31 strain *B burgdorferi* were used as the antigenic source (25 μg/85 mm of membrane) and run on a preparative 10% sodium dodecyl sulphate-polyacrylamide gel (SDS-PAGE) with a 4% stacking gel electrophoresis ('Mighty Small II' system, Hoeffer, San Francisco, California, USA). The separated proteins and molecular weight standards were transferred to nitrocellulose membranes, which were developed in a 28 lane 'Miniblotter' (Immunetics, Cambridge, Massachusetts, USA) by previously reported methods.[11,17] A 1/100 dilution of serum, and 1/10 dilution of the IC preparation was addded to each lane as the source of the first antibody. To better compare bound to free antibody proportions, serum was also diluted to a concentration of IgG equivalent to that of the isolated IC and then used in the western blot. This would also serve to control for any possible concentration of immunoglobulin during PEG precipitation. Controls included known positive sera, conjugate alone, and known seronegative sera from patients with other diseases and matched for IC levels.

To probe for *Borrelia* antigens and further assess the specificity of the anti-*Borrelia* antibodies, dissociated PEG IC preparations

TABLE II—ANTI B. BURGDORFERI ANTIBODY IN IMMUNE COMPLEXES IN SERONEGATIVE PATIENTS AND SEROPOSITIVE ACTIVE LYME DISEASE CONTROLS

Group	IC with antibody to *B burgdorferi*	IC without antibody to *B burgdorferi*	p (compared with other diseases*)
Seronegative samples			
Definite LD: ECM + (n = 10)	10	0	5×10^{-6}
Possible LD: ECM − (n = 12)	4	8	$1{\cdot}6 \times 10^{-2}$
Seropositive Lyme disease (n = 22)	21	1	$< 10^{-6}$
Other diseases (n = 19)*	0	19	..

LD = Lyme disease.
*9 (matched for IC concentration) with asthma, urticaria, upper respiratory infection, polyradiculoneuropathy, allergy, multiple sclerosis, polymyositis, or stroke; 10 with chronic fatigue.

(undiluted, 1/10 dilutions) were run on the SDS-PAGE and then immunoblotted along with the *B burgdorferi* sonicates and molecular weight standards. Affinity purified human IgG with a very high anti-*Borrelia* antibody titre was used to probe for antigen; non-specific staining was evaluated by the use of IgG from a non-disease control as well as probing isolated IC from the controls.

Statistical analysis

Fisher's exact test was applied to results obtained from the study of *B burgdorferi* reactive antibody in the serum IC in these 22 seronegative patients suspected of having Lyme disease.

Results

*Free anti-*B burgdorferi *antibody in serum samples*

The "seronegative" status of all 22 putative seronegative samples was confirmed by the anti-*B burgdorferi* antibody ELISA (table). 21 of the 22 samples gave readings of < 1 SD above that of control panel, the other was between 1 and 2 SD above that for controls. Other samples were analysed in the same way, and the seronegative and seropositive status confirmed.

Immune complex levels

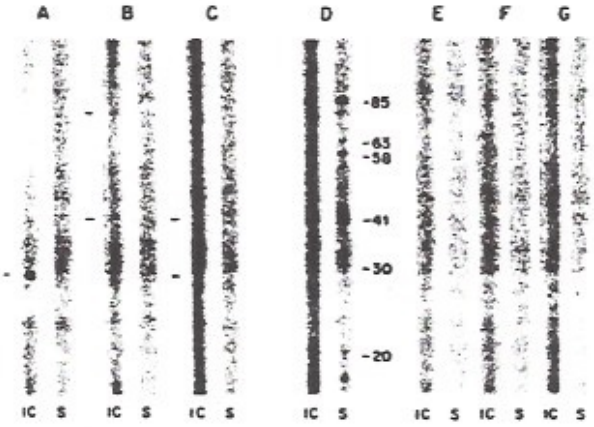
Although our primary intent was to examine the components of circulating IC in these patients, concentrations were measured so that controls could be matched for circulating IC concentrations. After decoding the samples, we found that IC levels were near normal in all groups when measured by the C1q and C'3 assays. There were no significant differences between the ECM-positive and ECM-negative groups with respect to the level of IC (table I). Specifically, among the seronegative patients, 5 of the 10 patients with ECM, and 9 of the 12 without ECM, had a low positive value in the C1q assay (above 4 μg Eq/ml); the mean concentrations were 5·1 and 6·1 μg Eq/ml, respectively. The anti-C3 IC concentrations did not rise above a positive threshold of 15 μg Eq/ml in either group—the mean values were 3·3 and 2·4 μg Eq/ml for the ECM-positive and the ECM-negative groups.

Rheumatoid factor (RF) in serum samples

Rheumatoid factor (RF), which can bind *Borrelia* reactive antibody, was rarely found.

*Anti-*B burgdorferi *antibody in isolated serum immune complexes*

Though serum IC concentrations were not raised, there was sufficient for analysis for complexed *B burgdorferi* antibody. All 10 ECM-positive seronegative Lyme disease patients had IC containing *B burgdorferi* reactive IgG antibody (table II). Included in this group was 1 patient who had not received antibiotic therapy. 4 of the 12 seronegative possible Lyme disease patients had complexed anti-*B burgdorferi* IgG antibody. 20 of 21 (95%) samples from symptomatic seropositive Lyme disease patients also had complexed IgG anti-*B burgdorferi* antibody. No complexed anti-*B burgdorferi* antibody was found in any of the 9 other disease controls, or any of the 10 seronegative chronic fatigue patients, or the 10 seronegative symptom-free healthy individuals from the endemic area. There was a significant association (Fisher's exact test, 1 degree of freedom, $p = 5 \times 10^{-8}$) between the detection of IC containing anti-*B burgdorferi* antibody and ECM-positive Lyme disease cases. The association was also significant for ECM-negative possible cases (table II).



Comparative western blots of IgG antibodies to *B burgdorferi* in immune complex dissociated preparations and serum samples in seronegative Lyme disease patients.

S = serum (diluted, see text); IC run undiluted. A, B, and C represent seronegative (determined by ELISA) Lyme disease patients with antibody *B burgdorferi* in the immune complex as determined by PEG-ELISA; A was ECM−, B and C were ECM+. D represents a known seropositive active Lyme disease patient. E, F, and G represent other disease controls. Not shown is conjugate run alone, which was negative. Approximate molecular weights in kilodaltons are indicated to the right of patient D. IC and serum samples from each patient were run in tandem. Not all patients were run on the same gel.

In these representative blots, IgG antibody liberated from the complex scans reacts with a polypeptide antigen of 41 kD (possibly the flagella) in most cases, as well as an approximate 30 kD one (possibly OspA- an outer surface protein) in some cases.

The western blots confirmed the appearance of *B burgdorferi* reactive antibody which had been sequestered and thus not detected before PEG-borate dissociation of the IC. IgG antibody liberated from the complex reacted with a polypeptide antigen of 41 kD (flagella antigen) in most cases, and with an approximately 30 kD antigen (probably OspA) in 2 of 10 cases. Dilution of serum samples to the equivalent concentration of IgG in the IC showed that the observed results were not due to possible concentration of IgG during PEG precipitation. In other experiments dissociated IC preparations showed heavier blot staining than even serum containing 10–100 times the equivalent IgG concentrations, thus further highlighting this liberation of complexed antibody. In analysis of free antibody a 41 kD band was clearly visible in the seropositive controls but absent or barely discernible in the seronegative Lyme disease patients and other controls.

Dissociated IC samples from 5 patients with complexed *Borrelia* antibody (2 ECM+ and 1 ECM− seronegative, 2 seropositive) were analysed by western blot analysis. Polyclonal affinity purified human IgG from a seropositive Lyme disease patient stained antigens, which co-migrated with antigens from the *B burgdorferi* sonicate, most visibly in the region of 43 kD and 38 kD. Polyclonal IgG from a healthy uninfected individual showed no reactivity. 5 control samples, matched for IC levels, were negative for such antigens when similarly probed.

Further support for sequestration of antibodies as a mechanism of seronegativity and IC formation as a feature even in seropositive Lyme disease patients is the finding of complexed anti *B burgdorferi* antibody in 3 seronegative

patients with positive T-cell-mediated immunity (CMI) to *Borrelia* and in 3 patients who eventually seroconverted on follow-up. Initially only complexed anti *B burgdorferi* antibody was found in all 3 seronegative patients; 2 later became seropositive and the third became borderline positive. One ECM-positive patient had complexed anti *B burgdorferi* IgM at 2 weeks, at which time treatment was started; and 2 weeks later the concentration of complexed antibody fell, but that of free, anti *B burgdorferi* IgM rose. In contrast to this rapid transition, in 1 patient in whom the diagnosis was not made and so remained untreated with antibiotics for a year, complexed IgG anti *B burgdorferi* antibody was detected in two samples a year apart; the patient seroconverted 8 months after therapy.

Discussion

Our data show that symptomatic seronegative or seropositive individuals with Lyme disease form circulating IC containing *B burgdorferi* reactive antibody, as determined by use of stringent criteria for the ELISA (>3 SD of the controls for a positive reading) and as confirmed by western blot. The specificity of the complexed antibody was also suggested in a preliminary fashion by western blot probes of the IC for *B burgdorferi* antigens.

Immune recognition of *B burgdorferi*, in the form of T cell reactivity to *B burgdorferi*, antigens, has been reported in 17 seronegative patients.[11] In 3 such patients, not part of the blinded aspect of the present study, we found complexed *B burgdorferi* antibody. Additional direct support for IC formation as a mechanism of apparent seronegativity in this disease is provided by the detection of *B burgdorferi* reactive IC in seropositive patients with active disease or in seronegative patients who later seroconverted. The absence of *B burgdorferi* reactive IC in patients with chronic fatigue, healthy symptom-free individuals, and other disease controls, all from an endemic area, indicates specificity of the IC.

Sequestration of antibody within IC occurred in all seronegative definite Lyme disease patients studied. However, these patients did not have raised levels of IC and did not show features of chronic IC disease such as those that occur in serum sickness or systemic lupus erythematosus. The near-normal levels in the patients with prolonged illness is consistent with reports[18-20] that in most patients raised C1q binding levels occurred at the start of the disease and returned to normal after 2 months. Complexes were also found in the serum of our seropositive patients.

Since early administration of antibiotics has been associated with apparent seronegativity in Lyme disease, we point out by way of observation that 3 of the patients in our study had not received antibiotics but were positive for specific IC. The other patients in the blinded part of the study had been treated with some antibiotic regimen but not any of those currently recommended for Lyme disease.[3] Though undefined mechanisms may contribute to seronegativity, in the present study, sequestration of antibody seems to be a sufficient explanation.

Western blot analysis revealed, in most cases, complexed anti-*B burgdorferi* antibody to a 41 kD antigen (probably corresponding to a flagella antigen), and in other cases to the 31 kD and higher molecular weight antigens. Antibodies to the 41 kD antigen may be found in some cases of non-Lyme disease.[11] In our study, such antibodies were absent or barely discernible in the free serum or IC of controls. In contrast these antibodies were present in the free serum of seropositive patients with Lyme disease and in the IC of seronegative patients with Lyme disease. Nevertheless, the possible occurrence of these antibodies in other diseases should be acknowledged and taken into account in interpreting positive findings.

Our study shows that, irrespective of the actual circulating concentration, the complexed antibody can be detected when simple techniques are used to isolate the complexes and dissociate antibody from its target antigen.[9] Complexed antibodies are likely to signify disease activity, whereas free antibodies alone do not necessarily do so.

The PEG-ELISA IC technique is simple and not time consuming and could be used as a diagnostic assay if the conventional ELISA is negative in suspected cases. In comparison the cell mediated lymphocyte stimulation assay is laborious and time consuming, and therefore only a few samples can be assayed per week. Selective use of diagnostic assays such as antibody or antigen analysis of IC components may be useful in establishing the diagnosis of Lyme disease in certain seronegative cases, as well as in variably positive cases, and in monitoring disease activity.

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Occurrence of Lyme Borreliosis in Hungary

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In Hungary there are certain facts on the basis of which we could postulate the occurrence of Lyme disease. The presence of ECM in our country has been proved decades long, although that wasn't included by *Schmid* in his recent study about world-wide distribution of Lyme-disease, In our country there is a well-organized program to vaccinate against tick-borne encephalomyelitis and set up the diagnosis. The disease is spread by the tick *I. ricinus*, which may be infected not exclusively by viruses, but by *B. burgdorferi* as well. During the treatment of tick-borne encephalomyelitis a group of patients could be recognized to be seronegative and curable with antibiotics among whom Lyme disease may occur even if not all these patients are affected.

In 1984, August–September four patients – two 8 year-old children and two adults – were hospitalized. Three of them were surely bitten by ticks in different forests of Transdanubia, one patient was bitten by mosquitos on the riverside of the Danube.

They all had ECM, which sometimes disappeared but shortly afterwards exacerbated at least twice on different parts of the skin. The children had regional lymphadenitis on the neck and one of them suffered from lymphocytic meningoencephalitis. Both children were completely cured. One got penicillin the other got steroids as well. The third patient a woman, allergic to penicillin, was given at the time of her first admission cotrimazol against ECM and general symptoms, and erythromycin twice at her repeated admissions for Lyme arthritis, ECM and measles-like eruptions, but only doxycyclin had cured her Lyme disease eventually. The fourth patient, a man, was treated with erythromycin, however during that time he developed several neurological symptoms of meningo-encephalomyelitis. These two cases told us that erythromycin was not an effective drug for Lyme disease. An intensive treatment with oxytetracycline intravenously and doxycycline after that for 6 weeks was given until he became well and a further fortnight, as well.

The presence of any causative agent among the lympho-histiocytes was searched for in the sedimented smear of his CSF obtained at the time of his admittance. After Giemsa's stain faded the acidic acridin-orange staining method of *Sciotto* and coworkers (Arch.Path. 83, *107*: 384–6) to detect *Borrelias* which emitted orange fluorescence against an apple-green fluorescence of the background. *Neisseria meningitidis* and *Haemophylus influenzae* in CSF's smears can be shown as controls. They emit a pale green fluorescence and not an orange one.

Summing up these facts the irregular orange fluorescent corpuscules may be considered as *B. burgdorferi* damaged by erythromycin. All the cultivations and different laboratory tests for diagnostic purposes were negative, except the FTA-ABS reaction

Preface

Gerold Stanek and Horst Lahrer
Vienna, October 1986

This book of proceedings contains the contributions to the Second International Symposium on Lyme Disease and Related Disorders which was held at the Hygiene Institute of the University of Vienna in September 1985. This symposium took place exactly 2 years after the first symposium on Lyme Disease which was organized by A. C. Steere who first described Lyme arthritis some 10 years ago and worked out the systemic character of the illness.

The Vienna Symposium opened a new horizon concerning the variety of clinical features of this disease, the routes of infection, the variable properties of the etiologic agent itself and gave a glimpse at the enormous frequency of cases and the wide geographical distribution of this infectious bacterial disease. Since the Vienna Symposium we have been using the more specific name Lyme borreliosis for the disease complex.

Vienna was an ideal place for this conference for several reasons.

First a historical one: some 70 years ago the Viennese physician Lipschutz described the now well known and frequent skin lesion erythema chronicum migrans. Then, another tick-borne disease, TBE, is present in this country and Vienna is a center of TBE-research. Formerly, stage 2 neurological manifestations of Lyme borreliosis were sometimes considered as seronegative arbovirus-infections.

Furthermore, Vienna is geographically well located between the North and South of Europe and the eastern and western parts of the northern hemisphere.

We were pleased for the attendance of representatives from a wide range of countries extending from Finland to Egypt and from the west coast of the USA to the Soviet Union.

We very much enjoyed the deep interest in all presentations as well as the friendliness and length of the discussions. The spirit of cooperation was always evident.

We hope that this book will help to inform the many scientists and physicians about the recent discoveries in this field and encourage many colleagues to contribute to the full understanding of Lyme borreliosis.

that meant some expected cross-reactions which could be detected as being between *Lyme spirochete* and *Treponema pallidum*. (Nichols). The pairs of sera were tested according to our modification to increase the sensitivity higher than usually. They gave a reaction with a borderline intensity, but high reactivity differing from that of the one we could see in syphilitic infections. The sera of three patients were lyophilized and sent for specific investigations to the CDC, USA. – *H. Russell* kindly carried them out and obtained one ELISA reactive and IFA borderline 1 : 128 result besides IFA reactions with 1 : 64 titers.

As we have no *B. burgdorferi* as antigen, we suppose that the diagnosis of Lyme disease may be set up according to the well-known antigenic relationship among the *Spirochetales*. The Biologically Aspecific Positivity we gained and syphilitic infection could be excluded. Both the history and clinical data failed to confirme any infection with other pathogenic spirochetes, which may cause cross-reaction among the FTA-ABS and Lyme diagnostic tests and the presence of any autoimmune disease.

Several serological tests fail to detect any viral, bacterial, parasitic or mycologic antigens. Summing up these facts I think reaction with *Lyme spirochete* antigen up to 1 : 128 serum dilution in relation to the patients' natural and clinical history and these patients' clinical process as well as their laboratory data may lead us to set up the diagnosis of Lyme disease.

As a working hypothesis we can assume that there is a clinico-pathological entity recently named "Lyme disease and related disorders" which calls us for a relevant terminus technicus. All the reactions as ECM, LCB, ACA, Bannwarth's syndrom, Lyme arthritis and *any further reaction to be found* have to be regarded as a response of the body against the causative agent *Borrelia burgdorferi*.

I, therefore, propose the name LYME BORRELIOSIS which commemorates the place where the first cases were detected and the persons who contributed to the recognition of this disease complex.

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COMBINED ANTIBIOTIC TREATMENT OF LYME BORRELIOSIS

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Monotherapeutic treatment was partially successful in the more than 400 patients who underwent a 3-year care.
In vitro experiments proved that combinations of antibiotics are 10 to 100 times more effective. One of antibiotics has to be capable of damaging the genetic material of the bacteria. The other one can be any antibiotic effective against B.burgd. Both of them must be able to penetrate into the intracellular and intrathecal space.
The clinical diagnosis, staging and the results of the treatment have been regularly checked in 251 patients with repeated passive hemagglutination investigation. The stored sera of the patients were determined with P-39 ELISA in a modification.
One of the antibiotics was fluroquinolon(which is ineffective in monotherapy): pefloxacin 3x400mg or ciprofloxacin 2x500mg per day. The other antibiotic was doxycycline 3x100mg or roxithromycine 2x200mg daily in per oral treatment. In parenteral treatment we used either doxycycline(Vibramycin) 2x200mg daily or ceftriaxon 2x2g daily. It was observed in these patients that average lifespan of B.burgdorferi is between 2 and 3 weeks. Therefore the patients were given antibiotics 30 days at least, occasionally for 6 weeks.
After the combined antibiotic treatment, 78,9% were healed, the clinical state of 15,1% improved; 2% no recovery, no data on 4%.

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