Presentation **Sunday April 26, 1998**

Anthony Lionetti, M.D.
Lyme Disease Diagnostic Center
530 South Egg Harbor Road
Hammonton, NJ 08037

Early Localized Lyme Disease

Anthony Lionetti, M.D.

This is a general presentation of currently accepted medical practice of the clinical manifestations, laboratory evaluation, diagnosis and management of early localized human Lyme disease.

Notes:

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Dennis Parenti, M.D.
SmithKline Beecham Pharmaceuticals & Biologicals
1250 S. Collegeville Road
Collegeville, PA 19426

Erythema Migrans and Sero-epidemiologic Findings from SmithKline Beecham's Lyme Vaccine Trial

D. Parenti, D. Krause, SmithKline Beecham Biologicals and the Lyme Disease Vaccine Study Group, Collegeville PA

Erythema migrans (EM) is the most common presenting symptom of Lyme disease. Textbooks and early descriptions state that it accounts for 50-80% of the cases, although recently some authors claim that EM may be the presenting symptom in greater than 90% of cases. The EM rash has been classically described as a "bulls-eye" rash with central clearing occurring at the site of the tick bite. There are only a few authors who have described the morphologic findings, including atypical appearances, from large series of EM lesions.

SmithKline Beecham has recently concluded a double-blind, placebo-controlled trial of it's candidate vaccine, LYMErix (recombinant Lipoprotein OspA with adjuvant) for Lyme disease. In this study of over 10,900 volunteers, subjects who developed a rash were evaluated with photographs, skin biopsies for culture and PCR as well as acute and convalescent sera for Western Blot testing. Serological results were compared to baseline sera drawn at study start for evidence of seroconversion.

There were 142 laboratory confirmed cases of EM diagnosed during the study. Examples of typical EM as well as the most common and atypical appearances will be displayed. Data regarding the incidence of positive cultures and PCR will be discussed. In addition, epidemiologic data regarding baseline serologic findings will be presented.

Notes:

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Kenneth Liegner, M.D., P.C.
Internal & Critical Care Medicine
8 Barnard Road
Armonk, NY 10504

Lyme Borreliosis and Related Disorders

Kenneth Liegner, M.D., P.C.

Dissemination:

- Movement of the Lyme organism from the site of entry into the host to remote sites within the body
- May be hematogenous, via lymphatics, or by direct invasion along tissue planes
- Plasminogen activation may facilitate direct tissue plane invasion
- Minimum tissue to dissemination unclear but may be very early possibly within days of occurrence of erythema migrans
- Dissemination early following infection may set the stage for chronicity with constitutional and multi-system symptomatology and late organ system involvement
- Intracellularity has been demonstrated *in vitro* but not in human disease. If it occurs, this may help explain both chronicity and refractorisness to antibiotic therapy.

Diagnosis of Disseminated Lyme disease: Clinical Features

- CDC has always emphasized Lyme disease as a **clinical diagnosis**; lab data supportive only

- Spectrum of illness: expanding, and limits of clinical manifestations presently unknown: need for open mindedness in considering what may or may not be "Lyme disease"

- Correct diagnosis requires good understanding of Lyme disease and a good fund of basic medical knowledge is necessary considering the potentially broad differential diagnosis of Lyme disease with its many manifestations

- Detailed geographic history is crucial; consider that most human beings in the course of their lives have epidemiologic exposure risk for ticks:
  summer vacations/summer camp
  visits to shore or mountain areas
  residence in or visits to Lyme endemic areas vocational & avocational pursuits in tick infested areas

- Bear in mind a low inoculum of spirochetes may take months or years to attain a body burden of infection sufficient to case clinically evident symptomatology; we don't know the minimum infectious dose of borreliae sufficient to cause infection and clinical disease. Time from first manifest signs of illness to diagnosis also may entail many years during which direct and immune-mediated injury can occur.

- Constitutional complaints w/multi-system symptomatology although non-specific, actually rather characteristic. A tip off is these occur in previously essentially healthy individual:
  - fatigue
  - arthralgia & myalgia, often migratory
  - cervicalgia
  - recurring low grade fever
  - night or day sweats
  - recurring sore throat & swollen glands
  - paresthesisa
  - sleep disturbance
  - enthesitis
  - panic attacks
  - anxiety
  - cognitive difficulties
  - mood disturbance
  - a "sick" feeling, malaise
  - often cyclic with 4-6 week cycles
- Often look "well", may exhibit few physical findings. Sometimes a veritable "blizzard" of symptoms that threaten to overwhelm the physician, as it has overwhelmed that patient. Psychosomatic Yet multiple individuals proving to have disseminated Lyme disease report nearly identical phenomena, almost carbon copy.

- Occasionally isolated symptom or organ involvement and thus lacking the multi-system "flavor"

Organ systems:

- Central nervous system
  - Brain, brain stem, and spinal cord:
  - meningitis
  - meningoencephalitis
  - meningoencephalomyelitis
  - myelopathies
  - transverse myelitis
  - hemiparesis
  - paraparesis
  - spastic para- and tetraparesis
  - motor neuron disease
  - extrapyramidal syndromes/choreiform syndromes
  - "locked-in" state
  - coma
  - progressive leukoencephalopathies
  - multiple sclerosis-like syndromes
  - seizure disorders
  - cerebral atrophy
  - organic brain syndromes/dementia
  - encephalopathy;
  - neuropsychiatric syndromes: psychoses; OCD; depression: mania; bipolar disorders; other psych. syndromes.
  - Cranial nerve palsies involving any CN
    - multiple Cns may be involved
  - radiculoneuritides
  - sciatica-like syndromes
  - neurogenic bladder

- Peripheral nervous system:
  - peripheral neuropathies
  - motor/sensory/plexopathies

paresthesias/dysesthesia

- Autonomic nervous system dysfunction:
  - cardiogenic syncope and vasodepressor syncope
  - abdominal bloating and abnormal peristalsis

- Auditory & vestibular apparatus:
  - tinnitus
  - disturbances of balance
  - vertigo
  - hyperacusis
  - hearing loss

- Ocular: all levels, all structures of eye may be involved
  - conjunctivitis
  - keratitis
  - uveitis
  - optic neuritis
  - retinitis/retinal vasculitis
  - cataract formation
  - retrobulbar myositis
  - optic cortex cerebritis

- Musculoskeletal:
  - arthralgia
  - arthritis/synmovitis
  - myositis/myopathy
  - painful myalgia/fibromyalgia-like syndrome
  - muscle fasciculation
  - fasciitis
  - enthesitis

- Genitourinary:
  - neurogenic bladder
  - "interstitial cystitis"
  - renal damage/glomerulonephritis? (Reported in dogs, so far cases in humans have not been reported)

- Endocrine:
  - thyroiditis?
  - Effects on libido
  - central hypothalamic ?
  - orchitis
  - cyclic flare of symptoms temporally related to menstrual cycle in women.

- Cardiac:
  - dysrhythmias
  - heart block
  - various types of extra-systoles
  - autonomic dysfunction: cardiogenic syncope, vasodepressor syncope
  - cardiomyopathy; congestive heart failure
  - myopericarditis

- Gastrointestinal:
  - bloating
  - GERD?

Irritable bowel/colitic presentations?
Myoenteric autonomic dysfunction?
Abdominal pain/cramping esp. in children
Lyme hepatitis
Lyme enterocolitis?

Differential diagnosis: multi-system involvement:

not too many things do this e.g. joint **and** neurologic involvement:

CTDs
syphilis
sarcoidosis
chronic viral infections (hepatitis/HIV/CMV/parvovirus)'
TB
brucellosis
relapsing fever
parasitic disease

- **Mimicking other multi-system and autoimmune diatheses:**

RA-like w/ ^ RF; often RF decrease with antibiotic RX

Lupus-like w/ ^ ANA, Anti-DS DNA AB; ^ c1Q I.C.s etc. seositis/pericarditis/thyroiditis/ etc. markers may diminish with ABx Rx

Mimicking the Chronic Fatigue Syndrome

Mimicking Idiopathic fibromyalgia

Disseminated Lyme disease: Laboratory Diagnosis

- Lyme ELISA and Western blot:

Over-emphasis on "false positive" ELISAs
Is Late Lyme/disseminated disease almost invariably seropositive?

- Seronegativity: Real or Bogus? Many of the culture proven cases of Lyme disease in the world literature occur with seronegative patients. Study in our practice specializing in Lyme disease in last quarter of 1996: 16% of patients had positive Elisas and positive Western blots whereas 21% of patients had dead negative Elisas and fully diagnostic IgG or IgM Western blots; many others had suspicious Wbs having less than 5/10 "CDC-specific" bands (Kochevar & Liegner). Always request reporting of ALL bands on a Lyme Western blot.

Useful laboratory tests:

- ESR
- C-Reactive Protein
- Lyme Elisa and Western blot to **two** GOOD laboratories
- always ask that ALL bands present be reported!
- CBC w. Diff
- Chemistry profile
- ANA
- FTA-ABS, if +, MHA-TP
- TFTs w TSH
- Angiotensin-1-converting enzyme
- Anticardiolipin antibodies

- Quantitative immunoglobulins (frequent polyclonal IgM elevation, occas IgG ^)

- Histologic demonstration by silver staining in biopsies or tissues removed at surgery; role for electron microscopy - (must be fixed in glutaraldehyde)

- Research Assays: role being explored
  PCR in any body fluid; tissue PCR
  LUAT (Lyme urine antigen test)
  Gundersen (borrelial immobilization) tes
  Lyme-specific immune complexes - Coyle/Schutzer
  Elisa-capture Osp A and Osp B antigen detection CSF

- Direct culture BSK-II (Barbour-Stoenner-Kelly media)

- CSF examination
  Paired Lyme Elisas and paired Western blot in serum and CSF
  Multiple sclerosis panel,
  Cytology
  Cell count & differential, glucose & protein
  VDRL
  CSF viral culture and if appropriate, viral titers
  PCR for detection of Bb-specific DNA
  If available, OspA and/or OspB antigen detection
  ample CSF so excess can be stored frozen (in a non-cycling freezer) indefinitely for possible future study.

Other useful adjunctive diagnostic studies:
MRI
Brain SPECT
Detailed neuropsychological testing
NCS/EMGs

Disseminated Lyme Disease: Approach to Treatment

- Cookbook approach inappropriate
- Duration of treatment should be based upon clinical response
- In most instances trial of **oral** RX is appropriate before resorting to intravenous antibiotic therapy. Since many patients with disseminated Lyme disease can be adequately treated with oral therapy.

- Careful periodic assessment of the patient by the physician is essential.

- Several months of treatment may be necessary to assess response to RX

- Full discussion of risk/benefits of treatment

- Careful periodic monitoring of the patient is necessary to detect any adverse consequences of antibiotic therapy CBC, chem, U/A usually monthly to quarterly depending on agent

- Attention to gut hygiene with acidophilus 2 hr. following oral antibiotic dosage

- Anticipate and try to deal early with any complications of Rx (e.g. *C. difficile* etc., yeast overgrowth)

- Oral antibiotic therapy: monotherapy:
  - tetracycline class
    - tetracycline (TCN) 500 T.I.D.
    - doxycycline (DCN) 100-200 mg Q 12 hr.
    - Minocycline (MNCN) 50-100 mg Q 12 hr.
  - amoxicillin .5-2 rams TID with or without probenicid
  - cefuroxime (Ceftin) 500-1000 mg Q 12 hr
  - azalide class
    - clarithromycin (Biaxin) 500-1000 mg. Q 12 hr
    - azithromycin (Zithromax) 250-500 mg. Q 12 hr

- Combined oral antibiotic therapy:
  - amoxicillin + TCN, DCN, or MNCN
  - amoxicillin + an azalide
  - cefuroxime + a TCN class or azalide class agent

- Intravenous Rx: monotherapy
  - ceftriaxone (Rocephin) 2 QD
  - cefotaxime (Claforan) 6 grams/day
  - imipenem/cilastatin (Primaxin) 250-1000 mg. Q 8 hr
  - doxycycline 100-200 mg. IV Q 12 hr
  - vancomycin 500-1000mg. IV Q 12 hr
  - azithromycin (Zithromax) 500mg IV QD
  - amipicillin 1-2 grams IV Q 6 hr
  - penicillin G 12-20 million units/day

Role of Empiric Diagnostic and Therapeutic Trial:

Important and legitimate role for empiric trial of treatment in **appropriate** clinical setting **after** detailed and thorough evaluation; may be appropriate even in the absence of any laboratory **proof** of diagnosis. Onus is on physician to have carefully excluded other identifiable and treatable conditions.

Monitoring of response to Rx:

- Meticulous clinical assessment
- Patient subjective report
- Physical examination
- Serial neuropsychological testing
- Serial Western blots
- Serial direct antigen detection methods, particularly at time of clinical relapse
- Serial MRIs, SPECTs, NCS/EMGs
- Serial CSF examinations if perturbed parameters present initially.

Notes:

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Robert Lesser, M.D.
Yale University
1201 West Main Street, Suite 100
Waterbury, CT 06708

Eye Findings in Lyme Disease

Robert L. Lesser, M.D.

1. Conjunctivitis
2. Keratitis
3. Uveitis
4. Optic Neuritis
5. Optic Atrophy
6. Pupillary Abnormalities

Notes:

Presentation **Sunday April 26, 1998**

Brian A. Fallon, M.D., M.P.H., M.Ed.
The NYS Psychiatric Institute
1 West 64th Street, Suite 1G
New York, NY 10023

Neuropsychiatric Aspects of Lyme Disease in Children and Adolescents

Brian A. Fallon, M.D., Felice Tager, Marian Rissenberg

Although Lyme disease in adults is known to be associated with cognitive and psychiatric problems, little research has been conducted on the neuropsychiatric aspects of Lyme disease in children and adolescents, even though the infection rates among children are high. Previous reports on children have found little evidence of neuropsychiatric sequelae, however these reports were conducted largely among children with recently diagnosed Lyme disease who presented with an erythema migrans rash, thereby precluding generalizations to the sample of young patients with chronic Lyme disease. In this talk, recent research results from our Lyme Disease Research Center and other sites will be reviewed.

In one ongoing study under the direction of Felice Tager, 20 children with Western-blot positive chronic Lyme disease were compared to 15 healthy control children age 9-17 on a battery of neuropsychological tests. The Lyme patients had significantly higher rates of psychopathology including feelings of incompetence, social withdrawal. anxiety/depression, trouble thinking, attention problems, and aggressive behavior. Cognitively, the Lyme patients had significantly higher rates of deficits in visual scanning and tracking, in verbal memory, and in the freedom from distractibility index of the WISC-III (a measure of attentional problems). On a continuous performance test, the Lyme children also had significantly worse performance.

These results, while preliminary, demonstrate that children and adolescents with chronic Lyme disease experience significant problems psychiatrically and cognitively. The impact of these problems on the child, family, and school will be addressed.

Notes:

Presentation Sunday April 26, 1998

Anthony Lionetti, M.D.
Lyme Disease Diagnostic Center
530 South Egg Harbor Road
Hammonton, NJ 08073

Clinical Characterization and Serological Data on 200 Patients PCR Positive For Lyme Disease

Anthony L. Lionetti, M.D.

OBJECTIVE: There have been few studies that have studied the serological response and clinical characterization in patients who have been proven to be infected with *Borrelia burgdorferi* by a direct detection technology. A retrospective analysis is presented of the serological and clinical data of 200 consecutive patients who tested positive for infection by *Borrelia burgdorferi sensu lato* utilizing a highly specific nested PCR of blood and/or urine from 1994-1998.

METHODS: A retrospective chart review was performed, extracting the data from the clinical notes and laboratory testing. Serological testing and PCR testing was performed by a single laboratory recognized for accuracy and reliability in Lyme disease testing by published peer reviewed laboratory proficiency testing. Other items registered included patient age, sex, residence, tick bite history, and duration of disease.

RESULTS: In this group of 200 consecutive patients primarily confirmed for infection with *Borrelia burdorferi sensu lato* by PCR, there was poor confirmation by IgG/IgM immunoblotting. In IgG there were 68% non reactive, 31% equivocal, and <1% reactive. In IgM there were 64% non reactive, 22% equivocal, and 14% reactive.

CONCLUSIONS: In this group of patients there was poor correlation between direct molecular genetic proof of infection with *Borrelia burgdorferi sensu lato* and Lyme IgG/IgM immunoblotting. Explanations for this lie in issues such as:

1. Duration of infection
2. The effects of previous treatment on the serological response
3. Antigen-antibody immune complexes which may prevent the availability of free antibody available for detection
4. Analysis of interpretative criteria for Lyme immunoblotting with evaluation of other algorithms for improving the sensitivity of this test.

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Edwin Masters, M.D.
Regional Primary Care, Inc.
69 Doctors Park
Cape Girardeau, MI 63703

Clinical Borreliosis in Missouri

Edwin Masters, M.D.

Examples of clinical erythema migrans in Missouri are presented along with other clinical presentations and examples of sequelae. Etiological and epidemiological theories are presented and discussed. This includes the hypothesis that just as there exists a clinical triad of *Ixodes scapularis* vectored borreliosis (Lyme disease), ehrlichiosis (HGE), and babesiosis *microti* in the Northeast, there may also exist in the South, including Missouri, a similar clinical triad vectored by lone star *(Ambylomma americanum)* ticks. Patients with signs and symptoms explained only by a borreliosis following lone star tick bites are presented. *Babesia* MO 1 has been identified in a Missouri patient and although vector studies have not been done, other *Babesia* are known to be carried by *Amblyomma* ticks.

Ehrlichiosis (HME) is known to be carried by lone star ticks in the South. Parallel evolutionary path in these two tick lines might explain what clinicians around the United States are seeing. Each of the three illnesses might have northern variants associated with *Ixodes scapularis* ticks and southern variants associated with lone star ticks. The clinical disease variants appear clinically similar, but have testing, microbiological, and culturing differences. Ehrlichiosis represents the prototype for this theory. Recent evidence of tick to tick (even different species) transmission of *Borrelia burgdorferi* while feeding on hosts and the isolation of *B. burgdorferi sensu lato* from a lone star tick feeding on a rabbit at one of my Missouri erythema migrans patient's farm are both consistent with this theory. More research is needed.

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Sam Donta, MD
Professor of Medicine
Boston University Medical Center
88 East Newton Street
Boston, MA 02118

Chronic Lyme Disease

Sam T. Donta, M.D.

Patients who develop persisting symptoms after an initial episode of Lyme disease are often referred to as having chronic Lyme disease or post-Lyme syndrome. There are numerous other patients who never recalled having a tick bite or a rash who also develop what appears to be the same clinical disease. Often, depending on the results of serologic testing, these patients are given the diagnosis of chronic fatigue syndrome or fibromyalgia. The etiology and pathophysiology of these multisymptom disorders remain to be delineated. The major symptoms in all of these "Lyme-like" diseases consist of fatigue, musculoskeletal pains, and neurocognitive dysfunction, and it is not readily possible to distinguish these diseases on clinical grounds alone. In the case of chronic Lyme disease, the organism or its DNA can be detected, albeit rarely, suggesting that there is a persistent, intracellular infection. The response to certain antibiotics also supports the idea that this is a persisting infection. Additional clinical and experimental evidence suggests that the reservoir is the nervous system, perhaps in the sensory ganglia, as well as in the temporal and frontal lobes of the brain The possibility that there are borrelial toxins that interfere with normal neurochemical function is an idea that is being further investigated.

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Adriana R Marques, M.D.
Head, Clinical Studies Unit
Laboratory of Clinical Investigation
National Institute of Allergy and Infectious Disease
National Institutes of Health
Bethesda, Maryland 20892

Update on the NIH Intramural Chronic Lyme Disease Study

Adriana Marques, M.D.

Lyme disease has become a highly controversial illness. The issue that has probably generated the most controversy today is the mechanism underlying persistent signs and symptoms of disease, despite the administration of what is currently considered to be adequate antibiotic therapy. Determining whether chronic Lyme disease is caused by persistent infection or is a post-infectious disorder is a fundamental issue. Finding the answer to this question for any individual patient will have an important bearing on his or her treatment, as our approach to the disease would be different depending on the underlying mechanism.

To try to answer some of these questions, we developed a new study in collaboration with scientists in National Institute of Allergy and Infectious Disease, in the National Institute of Neurological Disorders and Stroke (NINDS), in the National Institute on Deafness and Other Communication Disorders (NIDCD), in the National Institute of Mental Health (NIMH) and with leading Lyme disease specialists at outside institutions.

The objectives of this study include evaluation of diagnostic laboratory abnormalities and their correlation with the various syndromes; assessment of the extension of infection with *B. burgdorferi* and its consequences to patients; and the study of the role of immune-mediated and other pathogenic mechanisms in injury to the nervous system, including spirochete interactions with the immune system, auto-antibodies, cytokines, cellular immune responses, and immune complexes.

The study is now open for accrual and 29 patients have been enrolled to date. At this point, it is too early to draw conclusions from the analysis of the results of the multiple and extensive testing done in the enrolled patients, but is our hope that these initial studies involving very selected patients will provide new information about chronic Lyme disease, and suggest additional avenues for patient care and research.

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Sam Donta, M.D.
Professor of Medicine
Boston University Medical Center
88 East Newton Street
Boston, MA 02118

Macrolide Antibiotic Therapy of Chronic Lyme Disease

Sam T. Donta, M.D.

Evidence is accumulating that patients with chronic Lyme disease respond to certain antibiotic treatments. The organism responsible for the infection is sensitive to several antibiotics *in vitro*, but their clinical efficacy remains to be further evaluated. Further questions exist regarding the location of the organisms and their state of metabolism or reproduction. A leading hypothesis is that these organisms are in intracellular compartments, and our previous results with tetracycline support that hypothesis. In contrast, the efficacy of macrolide antibiotics, which have excellent in vitro activity against *B. burgdorferi* and excellent intracellular penetration, has been unreliable.

Because macrolide antibiotic activity is very restricted at an acid pH, it was postulated that the borrelia may reside in acidic intracellular vesicles and that the addition of a lysosomotropic agent would improve the clinical activity of macrolides in Lyme disease. Reported here are the results of studies of 235 patients with a clinical diagnosis of chronic Lyme disease using a combination of the lysosomotropic agent hydroxychloroquine and a macrolide antibiotic. All patients had a clinical picture compatible with chronic Lyme disease. Less than half recalled a tick bite or rash. The EIA was positive in only 27% of patients, and the Western Blot positive in 76%. Brain SPECT scans were positive in 73% of patients. Overall, 80% of patients had significant improvement or were cured; there were no obvious differences among the three macrolide antibiotics used. Compared to patients ill for less than 3 years, the onset of improvement was slower, and the failure rate higher in patients who had been ill for longer time periods. The encouraging results of these studies provide the basis for additional treatment options and controlled studies in patients with Lyme disease.

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Irwin T. Vanderhoof, Ph.D.
NYU Stern School of Business
18 Two Bridges Road
Towaco, NJ 07082

Lyme Disease - Cost to Society A Catalogue of Symptoms

Irwin T. Vanderhoof, FSA, Ph.D.

In the last year there has been discussion of the costs justification for early treatment of Lyme disease. Several arguments have been presented based only on the relative costs of early treatment for a large group vs. a course of antibiotics for those cases confirmed by tests or by clinical diagnosis. This short course of antibiotics is presumed to be effective in all cases.

Such calculations can only seem justified if the calculation ignores the extreme problems of those cases which do not respond to a short course of treatment administered well after infection has taken place.

This presentation is based upon data provided by the joint data base of the Lyme disease foundation and the Society of Actuaries. In "Lyme Disease: The Cost to Society (Contingencies, Jan.-Feb., 1993, pp. 42-48, Karen Vanderhoof-Forschner and Irwin T. Vanderhoof) information on these costs were detailed and an estimate of the total cost of Lyme disease to society at &1 Billion per year was developed. The current presentation is based upon the somewhat larger data base now available. It confirms and supports the earlier analysis and confirms the relation between these costs and the length of delay from time to infection and treatment. The costs for the 771 diagnosed cases in the data base totaled $52,000,000. This amount would justify a large number of early treatments. In addition a clear relationship is demonstrated between the dollar costs of the disease, treatment and lost income, and the delay in treatment of these cases.

Data was available in the questionnaire concerning the outcome of pregnancies. This data had not been previously analyzed. 55 live births were reported by women diagnosed with Lyme disease. Also 19 miscarriages and 7 neonatal deaths were reported by this group. According to the Statistical Abstracts of the United States in 1992 7.4 fetal and 5.4 neonatal deaths were reported for each 1,000 live births. We would then have expected a total of one such early death for the 55 live births in our data base. The difference is statistically convincing. Lyme disease seems to be a significant risk factor for pregnancy. The separate pregnancy register of the Lyme disease foundation provides a similar result. Out of 732 entries there were 148 reported as abnormal births.

Because of the importance of early diagnosis an analysis was made of the symptoms in an attempt to establish their frequency for this group of intransigent cases. In an attempt to establish whether or not certain groups have the same sets of symptoms; the Hotelling T2 test was applied. This test makes comparisons using all the factors at once. If the symptoms constitute 55 weak indications of the disease then taken together they might become a stronger indicator. These tests showed that the symptoms for men and women were different, that those who had a tick bite and exhibited a rash and had positive tests had somewhat different symptoms from other diagnosed cases, and that cases from Minn. and Wis. had a somewhat different pattern from those in the rest of the country.

On the other hand cases reported from cooperating physicians were not different than all other cases. In addition, cases that responded to a follow up questionnaire on joint swelling did not differ from those not responding. This Hotelling test seems not to have been frequently used in medical studies. It has the advantage of being able to confirm that the results of one group can be justified in applying to differently selected group.

Finally this study details the pattern of symptoms that would be expected to mentioned to the attending physician. In addition to the significant symptoms the data indicate that over 4 of 7 designated systems of the body, on average, would be effected.

Notes:

LBF - LYME BORRELIOSIS (DISEASE) COST TO SOCIETY

The Lyme Borreliosis Foundation and the Society of Actuaries are conducting a survey to determine the impact of Lyme disease on society. Please complete this questionnaire as accurately as possible. Information obtained may help to reduce suffering from this disease. Your participation is appreciated. The questionnaire is for scientific purposes only. All names will be kept confidential. Mail this directly back to the LBF.
Lyme Borreliosis (disease) = "**LB**"

GENERAL INFORMATION ***Please print clearly***

Name: first_____ initial___ last_____
Address_____
City _____ State_____ Zip _____
Telephone: Home (_____)_____ work (_____)_____
male _____ female _____ married_____ single_ date of birth___/___/___
Occupation:_____
Where do you work? City_____ State/Province_____ Country_____
vacation/visit? City_____ State/Province_____ Country_____
Are you taking preventative measures against LB? No __ Yes __
How? Avoid tick infested areas__ Use repellents__ Do tick checks__ Apply insecticide on property___
Wear light colored clothes & tuck pants in socks__ No pets__ Other_____

Have you ever had a tick bite? Yes_____Date_____ No___
Did you get a rash after the tick bite? Yes _____Date_____ No___
Briefly describe the rash _____
If you are dark skinned what color was the rash?_____

Have you been diagnosed with LB? Yes___ No___*
Do you believe you have LB? Yes___ No___*
Where did you contract LB? City_____ State/Province_____ Country_____
How was this diagnosis made? (rank 1, 2, 3, with #1 being the main reason)
___Clinical symptoms (eg. rash, involvement of joints, heart, or brain)
___Test
___Combination (clinical symptoms + test)
How many positive tests have you had?
___ELISA test (blood) ___IFA test (blood) ___PCR (blood)
___Western Blot (blood) ___T Cell test (blood) ___Antigen (urine) test
___ Spinal Tap ___Other _____
How many negative tests have you had?
___ELISA test (blood) ___IFA test (blood) ___PCR (blood)
___Western Blot (blood) ___T Cell test (blood) ___Antigen (urine) test
___ Spinal Tap ___Other _____

How many doctors did you see before being diagnosed? _____
Which specialists did you see to obtain a diagnosis?
(enter the # per speciality, and a "**Y**" if you were told you had LB, a "**N**" if you were told you didn't)
___Family Practice ___Infectious Disease ___Dermatologist
___Pediatrician ___Internal Medicine ___OB/Gynecology
___Rheumatologist ___Neurologist ___Psychiatrist
___Ophthalmologist ___Cardiologist ___Immunologist
___Other _____

*** Those without LB are valuable controls and should complete this form, as best as possible.**

What specialty finally diagnosed you? _____

What specialities did you see **after** diagnosis, to determine the extent of damage?

1. _____ 2. _____ 3. _____

Were you treated for LB? Yes ____ No ____

What specialty treated you? _____

Indicate the medications you have taken for LB and how long you took them:

Medication	Treatment length - in days 1st time	2nd time	3rd time
Oral			
Penicillin	____	____	____
Amoxicillin	____	____	____
Probenecid	____	____	____
Doxycycline	____	____	____
Tetracycline	____	____	____
Ceftin	____	____	____
Suprax	____	____	____

Medication	Treatment length - in days 1st time	2nd time	3rd time
Intravenous			
Claforan	____	____	____
Penicillin	____	____	____
Rocephin	____	____	____
Other:			
_____	____	____	____

List the year that the following occurred:

Contracted LB_____ Diagnosed with LB_____ Treated _____ Cured_____

What did the **search** for a diagnosis cost?

Lost time from work/school _____days Lost income $_____

Medical bills (for everything that turned out to be LB related) $_____

How long after being infected were you diagnosed? _____ months

How long after being diagnosed were you treated? _____ week(s)

How long after being treated were you cured? _____ months

Are you symptom free? Yes___ No___

Do you have permanent damage? No___ Yes___ (type_____)

Were you hospitalized because of the **severity** of your symptoms? Yes___ No___

What did the total LB **treatment** & **follow-up** cost?

Lost time from work/school _____days Lost income $_____

Medical bills (for everything that turned out to be LB related) $_____

Have you incurred **non-cash** losses due to Lyme disease? No____ Yes____

Lost job____ Lost school time____ Divorce____ Mental anguish____

Was your case of LB reported to the state? Yes ___(enter yr) No___ Don't know__

How many other family members have had Lyme disease? _____

Have any members of your family died from Lyme disease? Yes____ No____

Relationship to you _____ Was an autopsy performed? Yes ___ No ____

Did the death certificate list LB? Yes ____ No____

(If possible, complete a questionnaire in their name & write "deceased" after the last name)

Have you had pets? Yes ____ No ____

Have your pets been diagnosed with LB? Yes ____ No ____

What pets have had LB? (enter #) Dog_____Cat_____Horse_____Other_____

What did their treatment cost? $_____

Are any of the pets deceased due to LB complications? Yes ___(enter #) No ____

If you have other serious health problems, please list them: eg. cancer, MS, etc.

The following is a list of some of the different systems affected by Lyme disease, indicate the frequency and severity of the symptoms you experienced. Use the following scale: ***(circle as appropriate)***

0=Never 1=rarely 2=sometimes 3=frequently 4=constant

	Frequency	Severity	Still Have Problems?
GENERAL			
Profound exhaustion	...0 1 2 3 4	...0 1 2 3 4	Y N
Recurring fevers or sweats	...0 1 2 3 4	...0 1 2 3 4	Y N
Unusual weight changes	...0 1 2 3 4	...0 1 2 3 4	Y N
HEART & LUNGS			
Irregular beats, palpitations	...0 1 2 3 4	...0 1 2 3 4	Y N
Heart block/myocarditis	...0 1 2 3 4	...0 1 2 3 4	Y N
Heart attack	...0 1 2 3 4	...0 1 2 3 4	Y N
Chest pains, shortness of breath	...0 1 2 3 4	...0 1 2 3 4	Y N
LB pneumonia	...0 1 2 3 4	...0 1 2 3 4	Y N
Was a pacemaker installed? Yes___ No___			
MUSCULOSKELETAL			
Jaw/chewing pain, TMJ-like	...0 1 2 3 4	...0 1 2 3 4	Y N
Neck & back pain	...0 1 2 3 4	...0 1 2 3 4	Y N
Joint pain: arm & shoulder	...0 1 2 3 4	...0 1 2 3 4	Y N
hands & wrists	...0 1 2 3 4	...0 1 2 3 4	Y N
hips & knees	...0 1 2 3 4	...0 1 2 3 4	Y N
ankles & feet	...0 1 2 3 4	...0 1 2 3 4	Y N
Muscle pain/cramps	...0 1 2 3 4	...0 1 2 3 4	Y N
Loss of muscle tone	...0 1 2 3 4	...0 1 2 3 4	Y N
EYE & EAR			
Vision changes, corrected by glasses	...0 1 2 3 4	...0 1 2 3 4	Y N
not corrected by glasses	...0 1 2 3 4	...0 1 2 3 4	Y N
Reduced vision/blindness	...0 1 2 3 4	...0 1 2 3 4	Y N
Retinal damage/optic atrophy	...0 1 2 3 4	...0 1 2 3 4	Y N
Red eye, conjunctivitis	...0 1 2 3 4	...0 1 2 3 4	Y N
"Spots" before the eyes	...0 1 2 3 4	...0 1 2 3 4	Y N
Uveitis (inflammation inside the eye)	...0 1 2 3 4	...0 1 2 3 4	Y N
Eye pain	...0 1 2 3 4	...0 1 2 3 4	Y N
Double vision	...0 1 2 3 4	...0 1 2 3 4	Y N
Wandering "lazy" eye	...0 1 2 3 4	...0 1 2 3 4	Y N
Drooping eyelid	...0 1 2 3 4	...0 1 2 3 4	Y N
Light sensitivity	...0 1 2 3 4	...0 1 2 3 4	Y N
Ringing in ears/deafness	...0 1 2 3 4	...0 1 2 3 4	Y N

PREGNANCY Mark as indicated. We will contact you later to obtain more information.

Outcome: live birth___ miscarriage___ death at birth___ death shortly after birth___

Were you diagnosed during pregnancy? _____ Treated?_____

Child's birth date __/__/__ age___ Is the child's development normal?_____

Mother's problems: Difficult pregnancy___ LB tests during pregnancy___ Mother worse after birth___

Child's problems:

Rash at birth___ Premature___ Heart defect____ Vomiting___

Abnormal head size___ Facial weakness/palsy___ Low muscle tone___ Cross eyes___
Delayed speech___ Eating problems___ Delayed motor skills (eg. hands or body)___
Newborn's placenta checked___ Newborn tested for LB___How?_____ Spirochetes found?___

0=Never 1=rarely 2=sometimes 3=frequently 4=constant

NEUROLOGICAL	Frequency	Severity	Still Have?	
Weakness/paralysis of arms or legs	0 1 2 3 4	0 1 2 3 4	Y	N
Loss of reflexes of arms or legs	0 1 2 3 4	0 1 2 3 4	Y	N
Radiating abnormal sensations in arms or legs	0 1 2 3 4	0 1 2 3 4	Y	N
Meningitis	0 1 2 3 4	0 1 2 3 4	Y	N
Extreme headache(s)/stiff neck	0 1 2 3 4	0 1 2 3 4	Y	N
Changes in sense of smell	0 1 2 3 4	0 1 2 3 4	Y	N
Difficulty with chewing	0 1 2 3 4	0 1 2 3 4	Y	N
Bell's Palsy (facial droop)	0 1 2 3 4	0 1 2 3 4	Y	N
Dizziness/fainting	0 1 2 3 4	0 1 2 3 4	Y	N
Changes in sense of taste	0 1 2 3 4	0 1 2 3 4	Y	N
Difficulty swallowing	0 1 2 3 4	0 1 2 3 4	Y	N
Difficulty in speech/hoarseness	0 1 2 3 4	0 1 2 3 4	Y	N
Drooping shoulders or inability to turn head	0 1 2 3 4	0 1 2 3 4	Y	N
Paralysis of tongue/thick speech	0 1 2 3 4	0 1 2 3 4	Y	N
Seizures or abnormal EEG/brain waves	0 1 2 3 4	0 1 2 3 4	Y	N
Behavioral changes (depression, changes in personality)	0 1 2 3 4	0 1 2 3 4	Y	N
Cognitive changes (difficulty with memory, confusion)	0 1 2 3 4	0 1 2 3 4	Y	N
Changes in sleep patterns	0 1 2 3 4	0 1 2 3 4	Y	N
Stroke	0 1 2 3 4	0 1 2 3 4	Y	N
GASTROINTESTINAL				
Nausea/vomiting	0 1 2 3 4	0 1 2 3 4	Y	N
Diarrhea	0 1 2 3 4	0 1 2 3 4	Y	N
SKIN				
Initial rash, Single EM*	0 1 2 3 4	0 1 2 3 4	Y	N
Initial rash, Multiple EM*	0 1 2 3 4	0 1 2 3 4	Y	N
Recurring rashes, EM*	0 1 2 3 4	0 1 2 3 4	Y	N
Benign nodules** eg. earlobe, breast, face	0 1 2 3 4	0 1 2 3 4	Y	N
Discoloration/abnormal skin of hands, feet, or ankles***	0 1 2 3 4	0 1 2 3 4	Y	N

* **E**rythema **M**igrans= enlarging discoloration with central clearing. Red on light skin, bruised looking on darker skin.
Lymphocytoma=benign tumor-like lumps ***Acrodermatitis **Chronica **A**trophicans

Place postage here

The Lyme Borreliosis Foundation

LYME DISEASE FOUNDATION

1 Financial Plaza, Hartford, CT 06103

Dear Lyme Patient:

Thank-you for participating in the "Cost to Society" study regarding Lyme Disease. The information is proving very valuable, especially to the medical community. We are refining our study information and are asking you to answer several additional questions.

Please complete this form and return it to us at the address listed above. We have enclosed a self addressed stamped envelope for your convenience.

Sincerely yours,

Karen Forschner

•YOUR NAME _____ PHONE _____

ADDRESS _____ FAX _____

CITY _____ STATE _____ ZIP _____

- Which **one** organ system caused your worst problem? brain__ joints__ heart__ skin__ muscle__
- Which University did you go to for: (skip this area if none)

Diagnosis _____ Doctor _____ Diagnosis _____ Doctor _____

Treatment _____ Doctor _____ Treatment _____ Doctor _____

- Indicate the frequency & severity of your LD symptoms. Circle your choices.

Frequency scale: 0=never 1=rarely 2=sometimes 3=frequency 4=constant.

Severity scaleof swelling: 0=never 1=slight 2=1/3 over normal 3= 2/3 over normal 4=more than 2/3 over normal size.

ITEM	PROBLEM	FREQUENCY	SEVERITY	JOINTS	STILL HAVE PROBLEMS?
Elbow (s)	Swelling	0 1 2 3 4	0 1 2 3 4	(1) left (2) right	(1) YES (2) NO
	Pain	0 1 2 3 4	0 1 2 3 4	(1) left (2) right	(1) YES (2) NO
Wrist (s)	Swelling	0 1 2 3 4	0 1 2 3 4	(1) left (2) right	(1) YES (2) NO
	Pain	0 1 2 3 4	0 1 2 3 4	(1) left (2) right	(1) YES (2) NO
Hip (s)	Swelling	0 1 2 3 4	0 1 2 3 4	(1) left (2) right	(1) YES (2) NO
	Pain	0 1 2 3 4	0 1 2 3 4	(1) left (2) right	(1) YES (2) NO
Ankle(s)	Swelling	0 1 2 3 4	0 1 2 3 4	(1) left (2) right	(1) YES (2) NO
	Pain	0 1 2 3 4	0 1 2 3 4	(1) left (2) right	(1) YES (2) NO
Knee (s)	Swelling	0 1 2 3 4	0 1 2 3 4	(1) left (2) right	(1) YES (2) NO
	Pain	0 1 2 3 4	0 1 2 3 4	(1) left (2) right	(1) YES (2) NO
Finger (s)	Swelling	0 1 2 3 4	0 1 2 3 4	(1) left hand(2) right hand	(1) YES (2) NO
	Pain	0 1 2 3 4	0 1 2 3 4	(1) left hand(2) right hand	(1) YES (2) NO

- ARE YOU LYME DISEASE SYMPTOM-FREE? (1) YES (2) NO
- DID YOUR INSURANCE CARRIER PAY ITS OBLIGATIONS? (1) YES (2) NO
- LIST YOUR INSURANCE COMPANY'S NAME _____
- TREATMENT

Date(s)	Antibiotic Code (see below)	(1)Oral (2)IV	# of days?	Did your symptoms improve?	Did you relapse?
1.				(1) Yes (2) No	(1) Yes (2) No
2.				(1) Yes (2) No	(1) Yes (2) No
3.				(1) Yes (2) No	(1) Yes (2) No
4.				(1) Yes (2) No	(1) Yes (2) No
5.				(1) Yes (2) No	(1) Yes (2) No
6.				(1) Yes (2) No	(1) Yes (2) No
7.				(1) Yes (2) No	(1) Yes (2) No
8.				(1) Yes (2) No	(1) Yes (2) No
9.				(1) Yes (2) No	(1) Yes (2) No
10.				(1) Yes (2) No	(1) Yes (2) No

Antibiotic Codes (For antibiotics not listed here write-in name)

A= amoxicillin
B=Biaxin
C=Ceftin
CL=Claforin/cefotaxime
D=doxycycline (Doryx)
P= penicillin
PR=probenecid
R=Rocephin/ceftriaxome
S=Suprax
M=Minocycline
Z= Zithromax (azithromycine)

Presentation **Sunday April 26, 1998**

Denise M. Foley, Ph.D.
Assistant Professor
Chapman University
Orange, CA

Potential Limitations of the OspA Vaccine for Humans Based Upon Experimental Studies in Animals

Denise M. Foley, Ph.D., Chapman University, Orange, CA and James N. Miller, Ph.D., UCLA, Los Angeles, CA.

The apparent success achieved in human trials in the United States with recombinant OspA lipoprotein vaccine has now been reported. However, several studies in animals, including those emanating from our laboratory, have revealed potential limitations that may be associated with its use. In this presentation, we will review published animal studies which demonstrate several of these limitations. Issues to be discussed include 1) the relationship of OspA heterogeneity among North American isolates and lack of expression in vertebrates as it relates to potential infection after vaccination, 2) potential low level infection (latency) and/or an altered disease state following exposure leading to misdiagnosis and subsequent disseminated disease among some vaccines following exposure.

Notes:

Presentation **Sunday April 26, 1998**

Dennis Parenti, M.D.
SmithKline Beecham Pharmaceuticals & Biologicals
1250 South Collegeville Road
Collegeville, PA 19426

The Safety and Protective Efficacy of an Adjuvanted Lyme Disease Vaccine

D.L. Parenti, C. Buscarino and D.S. Krause. SmithKline Beecham (SB) Pharmaceuticals & Biologicals, Collegeville, PA, and the Lyme Disease Vaccine Study Group.

A safe and efficacious vaccine against Lyme Disease (LD) is needed due to the progressive increasing incidence and geographical spread as well as the inadequacy of personal protection measures. A vaccine must also protect against asymptomatic infection as well as clinical disease. We conducted a double-blind, phase III vaccine efficacy (VE) study for the prevention of LD, in 31 centers, in LD endemic areas.

Approximately 11,000 volunteers (ages 15-70) received LYMErix^{TM} (30 mcg lipoprotein OspA, adjuvanted vaccine), or placebo (1:1) on a 0,1,12 month schedule. Subjects were followed for 2 LD seasons. Sera were drawn on all subjects at baseline, months 12 and 20 for Western blot testing to detect asymptomatic infection. Subjects with suspected LD provided biopsy specimens for culture and PCR, acute and convalescent sera and other appropriate lab specimens to detect infection.

After 3 doses, there were 13 laboratory confirmed cases of LD in the vaccinees [Attack rate (AR) = 0.27] and 61 in the placebo group (AR = 1.28, P: 0.001), yielding a vaccine efficacy (VE) of 79% (95% CI: 61-88). Partial protection was already achieved after 2 vaccine doses (VE 50%; 95% CI: 14-70; P = 0.01). VE was also high for asymptomatic infection (83% after 2 doses, P = 0.008; and 100% after 3 doses; P < 0.001). In vaccinees between 15-65 years, following 3 doses, the protective efficacy of the vaccine against laboratory-confirmed *B. burgdorferi* and asymptomatic infection was 90% (95% CI: 78-95; P = 0.001). Solicited local and general reactions were common, but most were considered "mild" to "moderate" by the subjects and were limited in duration. There were no unusual pattern(s) of adverse events.

SB's LYMErix^{TM} has an acceptable reactogenicity profile and is efficacious for prevention of laboratory confirmed clinical LD as well as asymptomatic infection.

Notes:

Presentation **Sunday April 26, 1998**

Bob Huebner, Ph.D.
Pasteur Merieux Connaught
P.O. Box 187
Swiftwater, PA 18370

Strategies for a Vaccine Against European Borrelia

Robert C. Huebner, Ph.D.

Lyme disease is the most prevalent tick-borne disease in the US and an important tick-borne disease in Europe. The completion of successful clinical trials with an OspA-based formulation in the US begs the question as to how this success could be translated to a European Lyme disease vaccine. Several factors must be critically considered when formulating strategies for development of a European Lyme vaccine. In Europe, *Borrelia burgdorferi*, the *Borrelia* associated with Lyme disease in the US, and two additional genospecies of *Borrelia*, *Borrelia afzelii* and *Borrelia garinii*, cause Lyme disease. The symptoms associated with *Borrelia garinii* or *Borrelia afzelii* infection suggest case definitions used for clinical trials in the US will need to be revised. Reports from European investigators describe *Borrelia* isolates that either poorly express or don't express OspA, the antigen used in US formulations. European isolates of *Borrelia* show more variation in their OspA genes and those of other vaccine candidates. The impact of these factors on the development of a European Lyme vaccine strategy will be discussed.

Notes:

Presentation **Sunday April 26, 1998**

David R. Cassatt, Ph.D.
MedImmune, Inc.
35 West Watkins Mill Road
Gaithersburg, MD 20878

Borrelia burgdorferi Decorin-Binding Protein A (DbpA) as a Second Generation Lyme Disease Vaccine Candidate

David R. Cassatt, Nita K. Patel, William C. Roberts, Nancy D. Ulbrandt and Mark S. Hanson.
MedImmune, Inc., Gaithersburg, MD

The binding of *Borrelia burgdorferi* to the collagen-associated extracellular matrix proteoglycan decorin has been found to be mediated by two lipoproteins, decorin-binding proteins A+B (DbpA, DbpB). In contrast with OspA, antibodies to these proteins can be found in chronically infected mice inoculated with low doses of *Borrelia*. As reported in *Infection and Immunity* (Vol. 66, No. 5, in press) we have found that active immunization with one of these proteins, DbpA, can completely protect mice against homologous challenge and partially protect mice against heterologous challenge with *Borrelia*. Anti-DbpA serum had cross-strain borreliacidal activity in vitro and in vivo.

We examined the post-infection potency of anti-DbpA serum to determine whether we could prevent infection of mice after the *Borrelia* were adapted to the host environment and found that passive administration of anti-DbpA, but not anti-OspA, sera could clear Borrelia up to four days after infection, further suggesting that DbpA, but not OspA, was expressed in host-adapted spirochetes. To obtain direct evidence of *in vivo* DbpA expression, we have isolated *Borrelia* from blood of infected mice and have performed immunofluorescence and antibody growth inhibition assays on these *in vivo*- adapted *Borrelia*. We report that antiserum raised against recombinant DbpA bound the isolated *Borrelia* and that *Borrelia* incubated with this antiserum was unable to subsequently form colonies in soft agar plate culture. Antiserum raised against OspA did not bind these isolated *Borrelia* nor did it inhibit colony formation after incubation. Furthermore, immunization of mice with DbpA, but not OspA, prevented infection from blood-borne *Borrelia*. These studies demonstrate the possibility of targeting *in vivo* expressed Borrelial antigens such as DbpA.

Notes: