More reports from the 1998 LDF conference - page 24

Publication of the Lyme Disease Resource Center

the **Lyme Times**

NUMBER 23 *Education, Support, Advocacy, Research* **NOVEMBER-DECEMBER 1998**

New form will improve local reporting of tick-borne disease

by Cynthia McCormick

Lyme disease activists say the number of tick-borne diseases, particularly Lyme, are underreported on Cape Cod.

Now the Barnstable County Department of Health and the Environment has come up with a "user-friendly" reporting form it plans to make available to Cape and island doctors' offices by Feb 1.

"The goal is to have all the physicians reporting into Barnstable County from the Cape and islands," said John Coughlan, a member of the Barnstable County advisory task force on Lyme disease.

The form also will be made available to physicians in Dukes and

See **Tracking** *on page 14*

New test raises patients' hopes and scientists' doubts

by Garret Condon

A Ridgefield physician and his colleagues say they are developing a "gold standard" test for late-stage Lyme disease. Such a test would be a breakthrough for Lyme disease doctors and patients - but critics are doubtful.

Dr. Steven Phillips, a Lyme disease researcher and clinician, reports that he has grown the bacterium that causes Lyme disease from the blood of late-stage Lyme patients, all of whom were treated with antibiotics. This bacterium, *Borrelia burgdorferi*, has been extremely difficult to culture from blood, especially in late-stage cases.

In an article just published in the German journal **Infection**, Phillips and his associates report that they have developed a nutrient medium in which the Lyme-causing bacterium will grow. They contend that they successfully grew a mutated version of *Borrelia burgdorferi* in blood samples taken from patients with persistent Lyme - all of whom had received antibiotic therapy, which is the standard treatment for Lyme disease. Of 47 such patients, 43 were positive and none of 23 control patients without Lyme disease were positive.

In addition, only 9 percent of this

See **Scientists skeptical** *on page 16*

Lyme Disease Vaccine Wins FDA Approval

by Kristin Reed and Kristin Jensen

WASHINGTON — SmithKline Beecham's LYMErix vaccine for preventing Lyme disease has been cleared for sale by the U.S. Food and Drug Administration, offering the first defense against the tick-borne infection.

The agency cleared the vaccine for use in people between the ages of 15 and 70, who live or work in areas where infected ticks exist. The vaccine could generate annual sales of as much as $267 million by 2002,

See **Vaccine** *on page 16*

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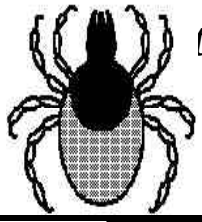

the
Lyme Times ©
Publication of the Lyme Disease Resource Center

In this issue...

Features

Letter from the Editor

Dear Readers,

This issue completes the publication cycle for 1998. We are grateful to several fine writers whose contributions grace these pages, as well as to several area newspapers whose publishers have generously allowed us to reprint their interesting and timely articles. It has been a fairly prolific season, with both the publication of Steven Phillips' revolutionary culture method as well as FDA approval of the vaccine and the subsequent SmithKline Beecham marketing campaign.

Meanwhile, back in the trenches, the battle continues, and it is time to honor the real soldiers. It is our pleasure to announce the recipient of the 1998 Lyme Disease Resource Center Distinguished Physician. This year the committee chose an old champion, someone who has been fighting the good fight almost since the beginning. See page 13 for details.

We thank patients who wrote eloquent nominations of their physicians, and with their permission, we will send those letters to the physicians with a personal letter of commendation from the LDRC. With all the complaints doctors hear, surely they appreciate an occasional pat on the back in the form of a laudatory letter.

In other news, the international Lyme disease conference is just a few months away. I am planning to make the trip to Germany and bring back as much information as possible to share with you. If any of you know you are going and would be willing to take notes and write reports, please let me know. There will be concurrent sessions and it would be good to be able to cover both tracks.

Again, please check your mailing label to see when your subscription expires. We depend on your donations for our operating expenses. We may get around to sending out renewal letters like a "real" magazine, but don't depend on it.

Recycle your old issues at your doctors' office or library, or ask them to subscribe. If you order videos, donate them after you have watched them. Your library may be interested, or even your local video store. Mine made me a gratis copy for the local library, while keeping the original for their own “free” shelf.

Remember to order extra issues of the Lyme Times well in advance for medical meetings and other special events. Prices are negotiable. Our chief mission is to educate, and if you can help us do that, so much the better.

Phyllis Mervine, Editor

The Lyme Disease Resource Center was founded in 1990 as a non-profit education and communications center for the public, for Lyme disease patients, for physicians, and other interested people. The goals of the LDRC are to educate the public about Lyme and other tick-borne diseases, including risk factors and prevention; to provide services for Lyme disease patients and their families and friends; to provide a forum for physicians and health care professionals for the exchange of ideas and information about symptoms, diagnosis, and treatment of Lyme disease; to be a communications center for individuals and groups who are working to help patients with Lyme disease; and to encourage Lyme disease research. The LDRC gratefully accepts tax-deductible contributions to assist its efforts.

the Lyme Times
November-December, 1998

Publisher

Lyme Disease Resource Center

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Editorial

Are we being led down the primrose path?

Two recent developments have the Lyme community in uproar: SmithKline Beecham's intense marketing campaign for its Lyme vaccine and publication by Phillips, Mattman et al of a novel lab method they claim is able to culture Lyme bacteria from patients with chronic disease. Both promise much, but are the promises real?

First, the vaccine. Obviously, after investing a great deal of money in developing its vaccine, SKB wants to reap its multimillion dollar reward by maximizing market share before the Connaught vaccine is released. Powerful ads have inundated the media; Lyme experts are addressing physicians around the country; patient groups are being courted with huge sums of money to use for Lyme education. And thousands of unsuspecting consumers are lining up to receive what they think is absolute protection against the tick-borne scourge, while physicians hastily educated by marketers intent on a profit will be eager to offer it to their patients.

But there are problems with the vaccine. Vaccinees clearly remain at risk for other dangerous tick-borne infections, and even some strains of *B. burgdorferi* that don't contain Osp A may not be killed. The vaccine's effectiveness was assessed by diagnostic criteria almost surely not sensitive enough to detect all cases of infection. There is even new evidence that an epitope of Osp A acts to stimulate immune system events that cause some autoimmune illnesses, prompting a **Science** editorial to express concern that the Osp A used in the vaccine may do this as well. There are already reports of several cases of latent, undiagnosed Lyme infection being reactivated after vaccination, with serious health consequences.

Second, the new culture method. If it works as claimed, the implications are truly revolutionary. But it involves a culture medium with unusual ingredients, and its rationale is based on the presence of stages of *B. burgdorferi* (L-forms) whose very existence challenges long-held scientific beliefs. No matter how much we want this new test to work, the political climate of Lyme disease testing, to say nothing of scientific method itself, dictates that it be validated in other laboratories before it can be accepted as the long-sought proof of active infection we need.

This may be a higher standard than most tests already in use have been subjected to. It is a higher standard than has been applied to the vaccine's safety and efficacy. But the controversies that surround interpretation of all current tests for Lyme disease underline the importance of objective replication and well thought-out studies comparing results of all available tests on a variety of patient and control populations.

A sure and safe vaccine to protect against Lyme disease, a test we can trust. How tempting to believe they've been found. Given these, science could focus on finding a cure.

But objectivity is hard to come by. Eagerness for solutions encourages too-ready acceptance of hurried science. Passionate preconceptions and vested interests readily bias research. And huge amounts of money are at stake.

We hope that patients and physicians will be cautious as well as hopeful. And that researchers will retain sufficient doubt, including self-doubt, to assess and continually reassess innovations with as much dispassion as being human allows.

Letters

We do not recommend any of the doctors or treatments which may be mentioned here by writers. You should discuss any treatment options with your physician. Signed letters of general interest may be printed.

Recognize the effects and try to accept them

Thank you for publishing my article on Lyme encephalopathy. I believe that over time, as we begin to recognize the various effects in the long course of chronic Lyme disease, we can better learn to cope with those organic brain dysfunctions that affect us; but only if we learn to recognize and respect them for what they are.

At one time, I wanted to crawl off into the woods and just let myself die. But then I realized that this was not a good thing to do for the children, grandchildren, friends , and my wife. This phenomenon was at the instinctual level: I was dying in fact at one time, from Ld, and my brain was signalling me to go ahead and do it. I had too much to live for. The thing that is important is that those who give this "feeling" time, are those who will not commit suicide or do take drastic actions.

We should respect our feelings, and learn to recognize them in context of a passing localized brain inflammation here or there. We should also learn to have the patience to let those inflammatory or nerve-death passages due to our disease to pass: and in a day or two or three, they usually do. That is my experience. We should ask ourselves sincerely, is this my usual self or is weird, out of the ordinary, strange. Many of us with usual habituations of feelings and thoughts have noticed aberrations following infection with Lyme.

And the neuropsychiatric question to be asked is did we have these problems before Ld or after we were infected. I feel that, for most, the change in our brain functioning is noticeable to us as victims. And our close friends/spouses/children may also feel the effects of this in our daily living.

But unless Ld is recognized as the causative factor in the observable behaviour changes that occur, our lives as we knew them change for towards the worse. First we must recognize the cause, Ld, and then we must learn to accept it and live with it: at least for a while for those who may be cured, and then also for the rest of our lives for those of us who have progressed in this particular infection beyond the point where any doctor in the world could possibly effect a cure.

In the mean time, we can hope for science and medicine to evlove towards our needs. Chronic disease is an unpopular subject today in the field of medicine: antibiotics most presume to be the "cure-all." But even in the early days of antibiotics, in the 1940's and 50's, another spirochetal disease, syphilis, was already defying us. So, hang in there everyone, and do not give up your hopes and wishes and desires! Better days do come now and again.

David Bartholomew
Allentown, Pennsylvania

David Bartholomew is the editor of LymeSig Newsletter and may be reached at 323 Chapel Avenue, Allentown, PA 18103-3457 or email at DRACUNSLAYER@prodigy.net.

Patient offers free educational program on Lyme

I have been receiving the Lyme Times for a few years . As soon as I get an issue I read it cover to cover. It is always welcome and informative.

Since I now have access to the internet and a decent working computer I would like to offer to help in any way I can. I would be glad to research articles or whatevever.

Also I would like to share some news. I often do free educational programs on Lyme disease to any group who is willing to listen. Since being diagnosised with Lyme 6 years ago I have been pounding on doctors doors trying to get them to recognize the disease and adequately treat it. I do feel I have made some progress, partly I believe because I'm an RN and partly because I won't take no for an answer.

The best news happened shortly after the news release about the FDA and the new Lyme vaccine. Representatives from Smith,Kline, Beecham contacted me after hearing about my program and have asked me to speak at area doctors' conferences about my experiences with Lyme and the need for them to recommend the vaccine to any patients that are at risk. Part of the problem they are facing is that many of our local MD's don't feel the Lyme is that big a problem here (upstate NY!!) I feel being able to talk to these MD's will be a giant step forward for the Lyme patients in our area. This is strictly volunteer so I'm not obligated to endorse any particular vaccine or company. My E-mail address is dawson@exotrope.net

Thanks again for the great magazine!

Nancy Dawson
Beaver Dams, New York

This is a wonderful idea for those who are able. The LDRC has a slide collection with script which may be purchased for those who wish to

make regular presentations. Contact the Editor for information.

If I have been treated for Lyme disease and still have symptoms, what about pregnancy?

I am a subscriber to the Lyme Times and I have been looking for information on pregnancy and Lyme disease/congenital Lyme. I am not able to find much information from literature or physicians. Do you have any articles or could you print a short article in perhaps the Letters column asking if any individuals that have any knowledge or experience with pregnancy and Lyme disease. I have been treated with antibiotics (so far one year on oral antibiotics and 10 weeks of IV) and still have several symptoms and was contemplating pregnancy.

Janet Goetz
San Jose, California

This is a tough question. There just isn't much information on pregancy and Lyme disease. Some studies which reported no adverse effects may have excluded data from stillbirths and miscarriages. You could contact the Lyme Disease Foundation to see if they have any information (860-525-2000). The Lyme Times hopes to do an in-depth article on this subject before too long.

Praise for Lyme Times 22

Excellent edition of Lyme Times! I read it from cover to cover. Jean Hubbard's review of babesiosis was the most thorough I have seen to date. Keep up the good work! Best regards,

Robert Bransfield, M.D.
Red Bank, New Jersey

We need better treatments for chronic Lyme

I've learned to cope with chronic Lyme, and do well enough to teach at a university level, as long as I take antibiotics. Hope being on antibiotics for life doesn't do in my liver and/or kidneys. Very strange about the antibiotics— they do not cure chronic Lyme; but they keep the symptoms low; an if one gets off of them for a few weeks, the symptoms return at a level to prevent anothing like a reasonable quality of life.

It would be nice if some medical researchers could figure out what the drugs are doing to "keep the bacteria dormant" if that's what's going on. Some researchers think that the bacteria "hide-out" inside of the body's cells (like viruses do) and don't cause symptoms in those locations — but neither can the antibiotics kill the bacteria within cells. But, somehow when the antibiotics are stopped, the bacteria sense the chemical changes in one's body, and come back out of the cells to cause symptoms again.

It is important to stop the antibiotics for at least a couple weeks about every 6 months, to permit one's liver and kidneys to clear out the toxins that develop as a result of metabolizing the antibiotics. Likewise, blood tests should be done every few months to provide indicators of liver and kidney functioning.

Most or all of the antibiotics used for Lyme disease have not been tested for their long-term potential as possible carcinogens. But, that is probably not a reason to stop taking Lyme antibiotics if they are helping. The neurological and cardiac symptoms of Lyme disease must also be considered as very serious health threats.

Lyme patients should continue to share with others whatever they have learned about coping with the disease. People with Lyme need to protect themselves from the thousands of doctors out there who don't know much of anything.

Doris Aaronson
New York University, New York

Psychiatrist sees rash of bizarre symptoms

I cannot ignore in my work an epidemic of bizarre neurological soft signs highlighted by acute increases in OCD, panic, rages, depression, and so on.

I am a 41-year veteran in the field of psychiatry and a life fellow of APA, and I have never seen anything like this before: Perhaps three dozen people of all ages in my practice have advanced multisystem symptoms of, among others, muscle, memory, and stomach distress, intermittent sinusitis, and neurological symptoms. These people, many of whom I have known for years, have gone from doctor to doctor in vain, seeking help before they finally decide they are hypochondriacs or have the "logical" emotional signs of specific stress. In the past, I might have agreed with them, but no longer.

The syndrome is all too familiar: irritability (impulsive hostility) with minimal provocation, bewildering short-term memory loss (immediate recall), transient numbness, a brief paralysis of a limb or limbs during the night, transient tremors, malaise, fatigue, GERD, lethargy, and sleep attacks. Unfortunately, each specialist sees one symptom relevant to his or her specialty and misses the big picture.

I have learned to order tests for Lyme disease, ehrlichiosis, and babesiosis from a lab that does sensitive tests, and I am amazed to find so many positives. Sometimes the tests are positive but of low titer; however, regardless of titer, the patient does not recover until treated with the proper antimicroorganism agent for a sufficient length of time.

Is anyone else aware of the immensity of this problem?

Virginia T. Sherr, M.D.
Holland, Pennsylvania

July 3rd Letter to the Editor reprinted by permission from the of Psychiatric News, newsletter of the Psychiatry Association.

Patient appreciates the Lyme Times - but does she subscribe?

I have been reading your excellent Lyme Times for a year now. When I go to the Westchester Lyme Support Group, superbly run by Betty Gross, I pick up a copy. Nowhere else have I been able to find up-to-date information about Lyme disease. Thank you so much for your wonderful service to Lyme disease patients.

I am a grandmother and a ballet teacher who has had Lyme for two years. This year we discovered that my daughter and eight-year-old granddaughter have had Lyme for several years. We all have neurological damage.

Ruth Ann Brinker
St. Michaels, Maryland

This letter provides an opportunity to point out the obvious – without the support of our subscribers, we could not continue to provide our "wonderful service." Occasionally we do send bulk orders at a reduced price to community educators for special events such as medical meetings, but these low-cost or free issues are intended for newcomers, not for people who have had many chances to obtain their own subscriptions. We encourage everyone who enjoys the Lyme Times to subscribe with the knowledge that their contribution is helping others as well.

Subscribe to the Lyme Times. Use the handy envelope in the centerfold.

Beginners' Pages

How to prevent Lyme disease

by Teresa Royer MacKnight, D.O.

Whether you work in the woods or just play in the great outdoors, take time to be safe.

1. Avoid areas where ticks are likely to be found. This includes high grasses, wooded areas and areas with brush and debris. Ticks do not like hot, dry places such as a well-mowed backyard.

2. Ideally, one should wear light colored clothing with pants tucked into high socks. It's not that ticks don't like light colors (actually they don't have eyes), but the ticks are more easily spotted and more likely to be removed before they've attached.

3. Designate one or two pairs of socks and pants as your outdoor clothes, which you will then wear for yard work, hiking, gardening, etc. Spray these with a long lasting tick repellent, such as Duranon or Permanone (order by calling 800-749-8425). The repellents are made from chrysanthemums and contain a chemical called permethrin which is neurotoxic to ticks. The clothes are sprayed front and back and must dry for 24 hours prior to wearing. It's suggested that these clothes be removed when you come inside. One may also spray the underside of a picnic blanket or tent for added protection.

4. Repellents containing DEET may be applied to clothes and to skin to deter ticks. Showering the repellent off immediately after outdoor activity is a good idea and this may also wash off any not yet attached ticks. Use only products labeled safe for kids on young children.

5. Get in the habit of doing total body "tick Checks." Warm, hairy areas are common sites of attachment, but ticks have been known to attach anywhere. The nymphal ticks are the size of a pinhead and may sometimes be more easily felt than seen. Tick checks of children at bedtime are especially important, as there is an increased risk of disease transmission with a longer attachment. In the medical literature Lyme disease has been reported to have occurred after a tick attachment of only six hours.

- **Avoid tick-infested areas**
- **Wear proper clothing**
- **Spray with repellent**
- **Shower after outdoor activity**
- **Check your body and children for ticks**
- **Remove the tick properly**
- **Identify the tick**
- **Treat tick bites if in a highly endemic area**
- **Test biting ticks for Lyme**

6. If an attached tick is found, the goal is to remove it as soon as possible. Ideally, removal is done with fine point forceps, grabbing the tick close to the skin. Apply a steady backward pull. Take care not to squeeze its body or to apply chemicals or matches as this will only irritate the tick and may cause it to regurgitate into the wound. In the European literature recently they reported a decrease in transmission of Lyme when the tick head was cut out of the skin with a fine pointed

scalpel, applying no pressure to the body of the tick.

7. Learn to identify the ticks that transmit Lyme and other tick-borne infections: A) The deer tick whose scientific name is *Ixodes scapularis* on the east coast and *Ixodes pacificus* on the west coast, is solidly reddish brown with no white spots or markings;.B) The Lone Star tick, A*mblyomma americanum*, has a white spot on its back; C) The dog tick, *Dermacentor variabilis*, has white streaks of mottling on its back.

8. To treat or not to treat a tick bite, that is the big question. If a tick bite were to occur on Shelter Island, N.Y., where more than 90% of the ticks are infected with Lyme, noone would likely argue about the decision to treat with prophylactic antibiotics to prevent Lyme disease. However, depending on where you live the decision to treat is not so clear-cut. For example, according to the Maine Lyme disease project report of 4/97, "limited studies in Maine have shown that although in some sites (along the coast) over one-half of the adult ticks samples contained Lyme spirochetes, rates may vary considerably, even in adjacent areas." Ticks travel on pets and via bird migration, causing a dynamic situation with spreading from one area to another. Complicating the matter further is the fact that people travel and it may not be obvious by the time the attached tick is discovered, where it was acquired.

The Lyme Disease Foundation (1-800-886-LYME) recommends testing removed ticks for the presence of Lyme infection. For $49 ticks can be identified and tested by PCR for the Lyme organism. Place the tick(s) in a ziplock baggie with a moistened cottonball and send by regular mail to IGeneX Laboratory, 797 San Antonio Rd., Palo Alto, CA 94303 (1-800-832-3200). [*Other private and state laboratories perform tick testing. Call your public health agency for information. – Ed.*]

"The Rest of the Story"

The following points are notes from a lecture influenced by Diagnostic and Treatment Guidelines of Dr. Joseph Burrascano, Jr.

1. Lyme disease is endemic in New England [and other areas of the USA]. In addition, people travel, pets travel, ticks travel. Ticks do not know geographic boundaries.

2. Lyme disease is a clinical diagnosis. Spirochetal infection of multiple organ systems causes a wide range of symptoms. Familiarity with its varied presentations is key to recognizing this disease.

3. The CDC surveillance criteria were devised to track epidemiologic change and were not set up to be used s diagnostic criteria.

4. The CDC/ASTPHLD eliminated the reading of bands 31 and 34 from the Western blot analysis. These bands are so specific to *Borrelia burgdorferi* that they have been chosen for vaccine development. However, if your patient has not been vaccinated for Lyme and has positive 31 or 34, this is highly indicative of Bb exposure.

5. Lyme testing should be done at a lab specializing in tick-borne illnesses, such as IGeneX (1-800-832-3200) or BBI North American Labs (1-800-856-6254). The Western blot report should include the reading on all bands, especially 31 and 34 [and not simply say "positive" or "negative."]

6. Fewer than 50% of patients with Lyme disease recall a tick bite. In some studies this number is as low as 15% in culture-proven borreliosis.

7. Fewer than 50% of patients with Lyme disease recall a rash. An erythema migrans rash is pathognomonic of Lyme disease and requires no further verification prior to starting 4-6 weeks of antibiotic therapy.

8. The ELISA is unreliable and misses 40% of culture-proven Lyme (only 60% sensitivity) and is unacceptable as a preliminary diagnostic test.

9. In patients with culture proven Lyme, 20-30% remain seronegative on repeat Western blot testing. Additionally in seropositive patients, antibody titres decline over time, making indirect testing less helpful in diagnosing chronic Lyme disease.

10. A preponderance of evidence indicates that active ongoing spirochetal infection is the cause of persistent symptoms in chronic Lyme disease.

11. An uncomplicated cases of chronic Lyme disease requires an average of 6-12 months of high dose antibiotic therapy.

12. Many patients require treatment for 1-4 years, or until the patient is symptom free. Relapses occur and maintenance antibiotics may be required. There are no tests available to assure us that a patient is cured.

13. There are five subspecies of *Borrelia burgdorferi*, over 100 strains in the US, and 300 strains worldwide. This diversity is thought to contribute to Bb's antigenic variability and its changing antibiotic resistance.

14. Antibody titres for *Babesia microti*, human granulocytic and human monocytic ehrlichiosis should be considered. The presence of coinfection points to probably Lyme infection, and when left untreated increases morbidity and complicates the successful treatment of Lyme disease.

15. Lyme disease is the latest great imitator and should be considered in the differential diagnosis of MS, ALS, seizure and neurologic disease, as well as arthritis, CFS, Gulf war syndrome, ADHD, hypochondriasis, fibromyalgia, somatization disorder, and patients with various difficult-to-diagnose multisystem syndromes.

Dr. MacKnight practices medicine in Andover, Maine.

Patient stories

Ticked off: A Lyme disease patient fights for treatment

by Sharon Lerner

Michael Egan often feels like he has a bad, full-body sunburn. The sensation worsens throughout the day; by 6 p.m., it's so bad that the 55-year-old former artist usually just heads off to bed with sleeping pills. Egan also struggles against a constant, creeping befuddlement. Movies are confusing: "It's as if they're foreign," he says. Reading is difficult, too. And painting and drawing, which he once did professionally, are now out of the question. "That would be a completely frustrating and unrealistic goal," he says grimly. "I don't even think about it."

Egan suffers from an advanced case of Lyme disease, which can cause bizarre symptoms and even death if it progresses without treatment. Hard as it is, Egan's "half-life," as he calls it, is a huge improvement over the more tortured existence he led before he was diagnosed and treated. "Now I can clean myself, go to the post office, drive a car locally," he proudly reports.

In 1995 and 1996, Egan spent most of his time in a dark room wearing a blindfold and earplugs. Light, sound- even vibration- had become unbearable. His brain felt scrambled. He fell into inexplicable rages and frights that drove him to hide in his bathroom. He got lost in his own kitchen. And his eyes, ears, and skin hurt. Because of his pain and near-constant confusion, he couldn't walk. So, on the rare occasions he felt well enough to leave the room, he crawled.

During this period, Egan's partner, Chris Boslet, cared for him and ran the antiques business they co-own (the store recently hosted a book signing for Starr Ockenga, wife of Voice editor-in-chief Don Forst). It was only after two years of such severe disability and desperate visits to all sorts of doctors that the problem was identified as Lyme disease. (Earlier tests he had taken for the disease had been inaccurate. Like a considerable number of patients, Egan never developed- or, perhaps, never noticed- the "bull's-eye" rash that sometimes signals the disease.)

Blue Shield refused to pay for the IV treatment recommended by Egan's doctor.

While relieving the angst of having his condition misunderstood, the diagnosis brought no easy answers. The severity of chronic Lyme disease is questioned by some in the medical community, and even Lyme experts are not always successful in treating the disease in its advanced stages. Egan began seeing one such specialist, Kenneth Liegner, who started him on high doses of several oral antibiotics. Yet, even after six months, when his gradually increasing intake of pills reached the peak of what his body could tolerate, Egan was still miserable. That's when Liegner suggested he have antibiotics injected intravenously. (This method gets higher levels of antibiotics to the bloodstream by bypassing the sensitive digestive tract.)

Egan was eager to try the treatment, even though it meant being hooked up to an IV for two hours a day. But his insurance company, Blue Shield of Northeastern New York, was not eager to pay for it. In July 1997, Liegner sent a letter to the company requesting authorization for reimbursement for Egan's IV regimen. Without the treatment, Liegner wrote, "Mr. Egan is likely to remain very compromised, may remain unable to earn a living, and runs the risk of pursuing a course of progressive deterioration."

Unmoved, Blue Shield, which declined to comment for this article, denied his request in November. The company sent a letter saying it didn't have evidence that Egan's Lyme disease was severe enough to warrant the treatment. Egan then filed an appeal of that decision, which was again denied, this time, according to the company, because "the requested prolonged IV therapy is not a generally accepted therapy."

Meanwhile, Egan began treatment, paying the more than $200 it cost each day from his own pocket. He took out a second mortgage on his house. But he soon spent all the cash from his mortgage and maxed out all his credit cards.

His financial bind- and the urgings of his doctor, many of whose patients have faced similar insurance problems (several of them with the same company)- ultimately moved Egan to seek legal help. He signed up with a law firm, Gruen and Farrelly, which at first recommended a nonconfrontational legal strategy. Egan's doctor simply sent the insurance company documentation of Egan's condition and the improvement he was making with the new treatment. "We were hoping to gently coax the company into paying," says Egan.

But that tack failed and soon the company was leading in a cynical legal dance. Sometime this spring,

Blue Shield ceased paying for all of Egan's medical expenses, and his lawyers finally took steps to sue the company. Then Blue Shield resumed payment, and, hoping the matter was resolved, Egan's lawyers decided not to move forward with the suit. But once again Blue Shield stopped paying Egan's bills- and the company revived its court action, arguing that the case should be dismissed on the grounds that Egan's side took too long with its court proceedings. (The New York supreme court judge who heard the case, James Canfield, rebuked the company for this behavior and, as a slap on the wrist, ordered it to pay $100 to Egan.)

Canfield's preliminary decision in the case, which was delivered in late November, also requires the company to pay for Egan's treatment until the trial and to reimburse him for medical costs that could total some $60,000. Egan's lawyers are delighted, calling the ruling "a complete and total victory."

But so far, Egan hasn't gotten a check. And the insurance company has begun its appeal, which will draw out Egan's legal battle even further. Egan's other battles are also likely to go on indefinitely. He says his legal and medical bills have put him about $125,000 in the hole, a figure he says "goes up all the time, like the national debt."

Egan suspects he will never again be completely well. Though he's made dramatic strides in the past two years, he is still far from the healthy, active artist he once was. But he's come to appreciate the small things he can do. "I can look at picture books and read captions," says Egan, who also reads fiction now, though slowly. A good day involves a stretch of six pain-free hours and a few such activities to fill it. "I just have to keep myself occupied," says Egan, "and keep from going mad."

HMO Watch by Sharon Lerner, reprinted by permission from The Village Voice, December 16 - 22, 1998.

Lyme isn't overdiagnosed and overtreated for this family

by Jean and Charlie Brune

Our family of five has had Lyme for 3 1/2 years, treated for 1 1/2 years with antibiotics (one of us with IV rocephin for over 10 months). We still culture positive for Lyme, and four of us also culture positive for a "leptospira-like orgamism". This surprised our Lyme literate doctor (LLD) a bit, as this was usually found in people who work with livestock or in warmer climates with unsanitary water conditions.

We live in Indiana, and have thought all along that we were never bitten by ticks that we remember, but that our troubles started sometime after clearing rocks for several days by hand from our new property. There is a pond on the property, so we were constantly shooing away the geese as we all worked. Can geese carry leptospira?

We've been told by a New York doctor that it was possible we got the Lyme from goose urine entering small cuts on our hands as we worked. Could it be the same with the leptospira? Our LLD says Leptospira can also get in your tissues and organs like Lyme and cause many of the same symptoms.

Has anyone out there ever been diagnosed with Leptospira or know anything about it being a co-infection with Lyme? A couple of us also have Babesia.

By the way, all of us had negative ELISAs, one had four reactive Western Blot bands, one had five and one had six (that one was even CDC positive - can you believe it?). The three positive Western blots were negative on the Lyme Urine Antigen Test, while the two negative Western blots were LUAT positive.

To all of you who have been told your symptoms were due to things like overwork, atypical MS, stress paralysis, conversion reaction, typical teenage laziness, typical preschool rebellion, typical middle-child emotions, etc. etc., we sympathize with you. It is clear to us that, in our case, Lyme is not "overdiagnosed and overtreated"

The Brune family lives in Decatur, Indiana, where there is "no Lyme disease" (just ask the experts). Charlie, 40, owns a printing business, Jean, 39, is a vice-president of marketing for Formula Boats, Jason, 14, is an 8th grader, Ryan, 10, is a 4th grader, and Nathan, 6, goes to kindergarten.

Free brochures and tick cards may be ordered for educational purposes

Free cards with the pictures of Lyme-carrying ticks on them (enlarged and to scale), are available from:

Fort Dodge Animal Health 9401 Indian Creek Parkway, Suite 1500 Overland Park, KS 66225-5945 Attn: Lyme Disease Information

Pfizer Central Research offers an informative Lyme disease pamphlet with good illustrations. You can order 50 free pamphlets by calling 1-860-441-5544. Additional copies are 4 cents each.

Patient Support

Taking the "tough" approach wins treatment for child

by Rita Stanley, PhD.

I'm a support gal, so not much surprises me; have heard all kinds of stories and I have been fighting the medical establishment for years to get care for myself. Am used to that. But in the last 2 weeks, the absurdity between working to get treated for an easy case of Lyme vs having a case of acne hit home. My home. And it's not like I haven't heard this before, but when you experience it, WOW.

My ten-year-old daughter had a "beautiful" bull's eye rash on the back of her leg a couple weeks ago. I was amazed! It hit my kid and I was shocked (NO, not my kid; not after all the tick checks, etc. .....) - but I started her on 2 grams amoxycillin before I even headed for the pediatrician's and the fight I would have.

Now, I followed the guidelines I give to the people who consult me: take in Conn's '97, photos of rashes (if possible), Dr. Burrascano's expanded guidelines and tell the doctor the treatment you want. I did just that, and added who I was: group leader of NW for years, dealt with hundreds of cases and clinical documents, and that I knew how this should be treated in an aggressive manner for 6 weeks. In other words, I am no fool and know a lot. Don't mess with me.

Well, the doc quizzed me about reported cases, and said he bet I never saw a case of neurological Lyme result from only 2 weeks treatment of a rash. My kid, who listens to me all the time on the phone, said, "Wanna bet?" And I told him of a case I had just that morning.... Our attitude won and we got the meds. In addition, the pediatrician showed me his guidelines: "The Red Book." Very enlightening; it contains essentially Conn's '98; conservative treatment guidelines that are Steere derivatives. So know that your pediatrician has this in all likelihood and you have to "outdraw" with Conn's 97 (docs know this book well).

In contrast, yesterday I took in my son who has a mild case of acne. The doc said she'd put him on Minocin in open-ended fashion; how long a script did I want? That easy! How long - she said, oh even for 3 or so years!!!!!! I commented how easy it was to get antibiotics for zits and you had to bring out the storm-troopers for Lyme. No comment. The docs there don't "like" us anymore for driving the show. Tough; got what I want.

So, it takes an aggressive approach to get treated for Lyme at any stage of treatment, and with all the conservative guidelines out there, you have to push hard. Real hard. Or get a case of the zits....

Rita Stanley directs the NorthWest Lyme Disease Support Group in Portland, Oregon. She is also a director of the Lyme Alliance.

Campaign to Identify Potential Victims of HMO Drug Switching Policies

From a July 1 BW HealthWire

In response to an increasing number of calls from patients reporting problems associated with managed care's restrictive drug formularies, the International Patient Advocacy Association (IPAA) is launching a first-of-its-kind outreach effort to identify individuals who have been drug switched by their HMO.

IPAA believes the insurance industry's actions will prove damaging to health consumers, since there is no one drug which works for every patient. "Until drugs are considered to be equivalent, a patient should never be switched from one medication to another. The heart medications or insulin, suitable for one person could prove harmful — even lethal — to another. It is impossible for decision-makers at insurance companies to dictate the medical needs of all members. Individual doctors should be afforded that right and responsibility," Van Pelt concluded.

The International Patient Advocacy Association provides resources and support to individuals with chronic diseases. The IPAA brings patients together to network in person, by telephone, or by mail. On a pro bono basis, the association helps appeal when insurance companies deny access to treatment. The association also helps with employment law issues and other legal matters regarding medical records, patient confidentiality, database forms, etc. In addition, the IPAA provides a wide range of information on treatment options and other developments in the management of genetic disorders and other disease states.

IPAA may be contacted by calling 1-800-844-7823.

New Jersey LDA president gives state reps no slack over sick kids' problems in school

by Pat Smith

This is the text of a speech given by LDANJ president Pat Smith to a group of legislators in June, 1998, as part of an educational program. A video of the event is available (see next page)..

Education is the key to the future. I am sure everyone in this room agrees with that statement. Yet we have in this country today a whole segment of the population who are denied access to that key. They are the lepers of the 20th century-children with Lyme disease. I speak to you now not only as a mother but also as a former 12-year member and past president of a board of education. I travel across this state as an advocate trying to help our children get the education which they deserve and so desperately seek, yet are often denied. I have seen many problems associated with educating classified children, i.e., children with learning disabilities, but rarely have I seen the degree of ignorance, and outright callous indifference I have witnessed toward children with Lyme. Children with Lyme are behind the eight ball. They have no classic symptoms, the symptoms they do exhibit frequently have physical, psychiatric, and emotional components, and often go unrecognized as Lyme disease symptoms. Districts many times have difficulties fitting these children into the public school mode, first because school officials do not think Lyme is serious, and second, because they do not understand the accommodations necessary to educate these children. They do not know nor do they seem to care about the legal requirements pertaining to this education.

For example, the state of NJ requires under 18A that districts annually inservice teachers who instruct children with Lyme. This is rarely done. You, as federal legislators, have no control over New Jersey's failure to monitor district compliance with state laws, however, you certainly have jurisdiction in the federal arena. 504 is a federal statute which applies to all public schools who receive any federal aid. Children can be placed under 504 if they have a physical or mental impairment that substantially limits one or more major life activities (walking, learning, working), or have a record of having a substantial impairment, or are regarded as having an impairment. After listening tonight, there should be no doubt that Lyme students qualify for placement. Yet districts continually fail to place students in this category. Or they place students under 504 but do not make the proper accommodations for learning-shortened days, untimed tests, dropping unnecessay requirements, alternate testing methods, a modified home instruction program, and tailoring assignments.

School physicians who may never have seen the child contradict the child's personal physician and that child is not able to be classified or may not get the proper educational accommodations. Children are often misclassified or labeled as ADD, attention deficit disorder, when what they need is to be treated for the underlying disease causing their symptoms. Their symptoms fluctuate rapidly from month to month, day to day, hour to hour. No one believes they are really sick.

The emotional damage these children suffer is tremendous and it follows them throughout the most impressionable stages of their lives. To get out of bed is an accomplishment, to shower is a miracle. They have few or no friends, no regular school attendance, no sports or activities, and no self-esteem. Some contemplate suicide, unfortunately, some are successful.

Districts are easily able to fool parents into thinking they are doing all they can when in fact, they are doing nothing for the child. I have helped several children who were on the verge of graduation when the districts suddenly realized the children had not been getting the proper requirements. Instead of accepting responsibility for their failure to provide a thorough and efficient education, the districts tried to prevent the children from graduating. Fortunately, they were unsuccessful.

"I have witnessed outright emotional cruelty in meetings with school personnel when a child's plight is not believed and the parent is brutally questioned in an accusatory fashion."

Children who are exceptionally bright and have Lyme are often penalized and told they may not take honors courses, advanced placement, and other courses designed for gifted students. Why are we being penalized, they wonder, when our only crime seems to be having a disease we have no control over? Even the local chapters of the National Honor Society discriminate against these students, many with A averages and 1300+ SAT scores. In a country which prides itself in being progres-

sive and promoting human rights, we have blatant discrimination going on in our public schools.

I have witnessed outright emotional cruelty in meetings with school personnel when a child's plight is not believed and the parent is brutally questioned in an accusatory fashion. I have seen some of these same personnel look the other direction when an athlete is accused of a substance abuse problem or is failing and could potentially be removed from a school sports team.

What do our children with Lyme have to do to get help? To what depths must parents go to get that unalienable guaranteed right for their children, a public education? Facing loss of home, loss of job, public scorn, and inadequate medical care, these poor parents are unprepared to handle the task of securing an education for their children. They are already struggling to rescue their children from a disease whose tortures never end.

Ladies and gentlemen, I have been there. Like Dante in Dante's Inferno, I have been unwilingly dragged down into the bowels of Hell. There I have seen unspeakable devils, devils which no Spielberg movie can even begin to match, grip my child with an unrelenting hold. I begged and pleaded with a deaf universe to give me answers or at the very least, give me strength to carry on. I sought compassion from friends, from doctors, from educators. Sadly, I got very little, my child, less. When Lyme comes in the window, humanity goes out the door.

Help the children in this great country of ours. Help them obtain the key to a successful future: education. You have the power. You award school districts nationwide monies to educate children with special needs. It is up to you to ensure those needs are being met. If they are not, you must provide a more readily accessible avenue for parents to follow. You can ensure that doctors are properly educated about Lyme. You can ensure that monies are withheld if districts are discriminating against children with Lyme. You are to far away to do it personally, but you can require the states to enforce the provisions of 504 and other statutes which guarantee that our children should be treated as human beings, sick ones at that, ones who need and deserve an education like their non-sick peers automatically get.

You have all heard the saying about walking a mile in my shoes. Tonight I ask you to take my hand or the hands of those around you and we will take you on a journey that will forever be burned into your soul, like it is burned into ours and our children's. With your help, thousands of sick minds and bodies can become productive again, and new growth will cover the wounds. With your help, the scars will just become a fading symbol of a distant past, a nightmare we will never experience again. You have the power. You can provide the resources, you can provide the direction. You can make Lyme disease a priority, you can make it a memory. You can end the nightmare.

Video available

The Lyme Disease Association of New Jersey made a 2-hour video of their educational meeting for politicians, to help them understand the need for the LD research funding bill. On it, Drs Pietrucha and Fallon discuss neurologic LD in children, Drs Harris (IGeneX Laboratory) and Schutzer discuss testing; Drs. Liegner and Lionetti talk about other aspects of LD; and Pat Smith, President of the LDANJ and her now college-student daughter, who's had LD since childhoood, share the wisdom of their personal LD experiences. The video is aimed at laypeople, not medical people, so is easy to understand.

For a copy of the video, send $7.00 to NJLDA, PO Box 1438, Jackson, NJ 08527.

Announcing Lyme-Teens, an electronic mailinglist for teens and ex-teens

Teenagers suffering from Lyme disease are invited to subscribe to Lyme-Teens. To subscribe, send a completely blank Email message (no subject, no message body) to: Lyme-Teens-subscribe@onelist.com The address for posting messages will be revealed to you after you've placed your subscription.

Meg Hughes, Marta McCoy and Harry Dewey are list-moderators for Lyme-Teens.

Group in South Carolina wants to host conference

by Sue Fox

The Lyme Disease Network of SC is very interested in hosting a conference on Lyme disease. There is a growing awareness of Lyme in the South but there is still much work to be done. Are there any other groups in the region who would be interested in getting involved? We also are interested in guidance from others who have hosted conferences in the past. Call or email sclyme@aol.com.

Lyme Disease Resource Center honors Lyme Warrior Dr. Joseph Burrascano

Joseph J. Burrascano, Jr., M.D.

The 1998 Distinguished Physician Award, which recognizes a physician for clinical excellence, leadership, compassion, and dedication to the treatment of Lyme disease, has been awarded to Dr. Joseph J. Burrascano, Jr. of Southampton, New York.

Practicing medicine in the highly endemic eastern end of Long Island, Dr. Burrascano has treated Lyme patients since the mid-1980s. He was one of the first physicians to recognize the chronicity of Lyme disease and to design a treatment program to address the problem of constant relapses in patients treated with the recommended 10 to 14-day courses of antibiotics. He observed that many patients responded well to repeat courses of antibiotics and suspected that persistence of symptoms represented ongoing infection. A 1987 study confirmed his suspicions: 26 culture-positive patients who were treated with ceftriaxone IV for two weeks were culture negative at the immediate end of therapy but became culture-positive again within several weeks. This phenomenon has now been substantiated by other studies.

Dr. Burrascano has studied the effects of lengthened duration of treatment and established a direct relationship between duration and success, starting at 17% for one month of therapy and reaching a plateau at 67% at five months duration. He has participated in further studies of prolonged treatment, including one with the NIH utilizing the antigen detection method of Dorward and colleagues. *Borrelia burgdorferi* were recovered from body fluids of patients who had received months to years of antibiotic therapy.

"He has been on the front line for Lyme patients for years," says John Coughlan, president of the Cape Cod Lyme Disease Awareness Association and one of Dr. Burrascano's patients. "He's our Number One advocate. He has helped so many people, and he gets the worst of the worst, patients who have been to one doctor after another."

Coughlan has another reason to praise his doctor: Dr. Burrascano's trip to Massachusetts in 1996 "virtually woke up the entire Cape and islands when over 600 turned up for his lecture. It started to unravel the ignorance and the suppression of information that has been going on." Coughlan added they have run the tape of the lecture at least 1000 times on local cable stations.

Patients appreciate Dr. Burrascano's openness about having had Lyme disease himself. "It makes him a role model for success as a Lyme patient," says one patient, "and it's reassuring. It's scary to be a Lyme patient." Others appreciate his tone of quiet confidence, of "absolute thoughtfulness and concern." "You feel such trust," says another. "He never jokes about it." Another important quality is never giving up on a patient. "If one thing doesn't work, you try something else." And Dr. Burrascano has hired an insurance specialist to work as a mediator between patients and insurance companies, to help reduce the stress on sick patients. His understanding of the total Lyme situation is the ultimate in patient support.

Colleagues praise Dr. Burrascano for his courage in taking a stand and for being so persistent that his ideas are gaining acceptance. He has contributed to the medical literature and taken time to write up results and get them published. His Diagnostic and Treatment Guidelines were published in the 1997 Conn's Current Therapy and are widely distributed on the internet and to local public health departments and physicians' offices where they are serving as guides to clinical practice. One colleague stated: "He has done more singlehandedly on how to diagnose and treat than any other physician I can think of."

Patients from around country and the world come to see Dr. Burrascano. Dr. Marylynn Barkeley says, "Any time I have had to refer a patient to him he never let them down. Patients became functional after going through his treatment." Patients have flown in from Germany, Sweden and other foreign countries to consult him.

Dr. Burrascano serves on the Board of Directors of the Lyme Disease Foundation and is on call as a speaker to conferences. He traveled to California to speak at the first Lyme Disease Resource Center conference in 1990, came again in 1994, and was on the program for the 1998 conference when a broken leg prevented his attendance.

The Lyme Disease Resource Center is proud to honor Dr. Burrascano for his years of service to the Lyme Disease Community. As John Coughlan says, "He's been there for all of us for a long time. He's the best."

Regional News

Tracking Lyme with new form

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Nantucket counties.

The old Centers for Disease Control form was outdated and contained a narrow definition of Lyme disease, which requires a bull's-eye rash or positive Western blot test, Coughlan said.

On the new form, doctors can check off Lyme even if it doesn't meet the CDC reporting criteria, but meets the physician's own diagnostic conditions.

Symptoms of Lyme, listed on the form, include the classic bull's-eye rash—which not everyone gets—arthritis-type pain, cardiac problems, fatigue, sweats, fever and chills.

Nantucket public health officials say 100 to 150 new cases of Lyme are reported each year on the island, while a few miles away on Cape Cod only 30 to 40 new cases are reported each year.

A state report last year said community hospitals in coastal Massachusetts did not report one-third of diagnosed Lyme disease cases to the state, but Coughlan said the figure is even higher.

"To say it's underreported is really a euphemism. What's being reported now is less than 1 percent of what's been going on here," he said.

Coughlan said that, based on the number of cases seen by an organization he heads, the Cape Cod Lyme Disease Awareness Association, and other local Lyme groups, there are as many as 3,000 Cape Codders suffering from Lymme.

But research by the Yale University Lyme Disease Clinic, published last March in the Annals of Internal Medicine, showed a different sort of problem in the hard-to-diagnose disease: Of the 209 patients in the study treated for Lyme, 60 percent were found by later blood tests not to have had the disease.

Researchers said fear of long-term debilitating effects may be pushing both doctors and patients to err on the side of treatment, although the antibiotic treatment causes side effects in more than half of the disease-free patients.

If Lyme isn't treated properly with antibiotics, it can get into the central nervous system, where it might cause lifelong neurological problems.

"Nobody wants to treat with antibiotics unnecessarily," Coughlan said. He said the 28-member county task force on Lyme also is doing tick "drags" and testing the ticks to see how many are infested with disease.

Getting a sense of where "hot spots" exist should help doctors better diagnose the disease in their patients, he said.

Coughlan's Lyme group also is planning to set up and educational seminar for doctors on behalf of the county task force.

From the January 5, 1999, Cape Cod Times. Reprinted by permission.

Babesiosis is a potentially deadly tick-borne disease

by Nelson Sigelman

While less well-known and recognizable than Lyme disease, babesiosis is a rare and sometimes fatal disease transmitted by the bite of a deer tick. The disease poses the greatest risk to the elderly, people without a spleen, and those with damaged immune systems, say health experts.

Unlike Lyme disease, which is caused by a bacterium, babesiosis is caused by a protozoan, a single cell complex organism that feeds on the body's red blood cells. Drugs similar to those used for malaria are often used for treatment. But in severe cases a total blood exchange may be needed.

There have been at least three confirmed cases of babesiosis diagnosed in the past four weeks on Martha's Vineyard, say medical sources. Two of those patients, both elderly, were airlifted to Boston area hospitals for specialized treatment. One, Francis "Sancy" Pachico, a former Island school administrator, later died of complications associated with the disease.

Dr. Dennis Hoak, an internist and specialist in infectious diseases at the Martha's Vineyard Hospital, cautions that there is no reason for people to be unduly alarmed. The number of recognized cases treated on the Island are few and far between, and he says that in many cases, people infected with the disease experience nothing more than flu-like symptoms.

Dr. Hoak recommends that anyone who has had a deer tick bite and is reasonably certain the tick has been in for 24 to 36 hours and then gets sick should "definitely see somebody." He adds that even in the case of Lyme disease, approximately 20 percent of cases have no signs of the telltale rash.

Janine Cory, an epidemiologist and health educator with the Massachusetts Department of Public Health, says there is every reason to believe that babesiosis is underdiagnosed and underreported. One reason that many cases may go unreported, she says, is that most people have only mild clinical symptoms, such as fever, chills, and fatigue, and don't require specific treatment.

Over the past 10 years, there have been more than 100 cases reported in the state, says Dr.Cory. In 1997 there were 21 cases reported, most in places where doctors are already familiar with tick-borne diseases, such as the Cape and islands.

Babesiosis, also called Nantucket fever, was first identified on Nantucket, says Dr. Sam R. Telford, a research scientist and tick specialist at the Harvard School of Public Health.

"Nantucket is the hottest place in the world for this infection," says Dr. Telford, who has conducted research on the island for more than a decade.

Dr. Telford says the first evidence of babesiosis in humans was in 1969 when an elderly woman on Nantucket became infected with a disease formerly only seen in mice. "It was a real medical oddity," he says. But when a subsequent case occurred in 1973 just down the road from the first case, the Centers for Disease Control, along with researchers from the Harvard School of Public Health, began an investigation of more than a dozen cases over the next few years. That research, says Dr. Telford, led to the identification of the deer tick which previously had not been found on Nantucket or Martha's Vineyard, but was on the Elizabeth Islands. It was also about that time, starting about 1975, says Dr.Telford, that people realized the deer tick was also found on eastern Long Island, coastal Connecticut, and was linked to Lyme arthritis. Dr. Telford says fortunately for humans, both babesiosis and ehrlichiosis (HGE), another lesser known tick-borne disease, are "about a fifth as common as Lyme disease."

The ticks most people find on the Vineyard are the adult dog, or wood, ticks. But it is the small deer tick that is responsible for infecting humans with most tick-borne illnesses.

Dr. Telford says there are normally about 20 cases of babesiosis and about a hundred cases of Lyme disease reported on Nantucket each year. But he says, "Frankly I don't see how people on the Vineyard ever get Lyme disease because the number of ticks that you find there are much, much less than what we see on Nantucket."

Dr.Telford suggests one reason is the habitat on Nantucket may be more conducive to the tick's life cycle. The tick begins life as an egg, which hatches into a larva the size of a pinhead and attaches itself to a mouse for a single blood meal. At this stage, the deer tick picks up the Lyme disease micro-organism, as well as other diseases such as babesiosis and HGE, from its host mouse. After feeding on the mouse, the deer tick then molts to the nymph stage, the size of a sesame seed, and waits in ambush for a larger mammal. Usually it is a deer, but sometimes it is a human who brushes by the waiting tick.

The deer tick is most dangerous in its nymphal stage, usually in May and June, when it is no larger than the period at the end of this sentence and may go undiscovered on a person long enough approximately 48 hours to infect them.

Over the summer the deer tick digests its blood meal and emerges as

an adult when it is again a threat to humans because it needs to feed in order to lay its approximately 2,000 eggs, but then it is more visible because of its size.

Dr. Telford says that while skunks and raccoons are responsible for the Island's large population of wood ticks, it is the deer and researchers are not quite sure why that provides a critical link in the life cycle of the deer tick. He says that for some reason adult deer ticks prefer to feed on deer as opposed to the numerous raccoons or skunks.

Dr. Telford says unequivocally that the deer population has a direct relationship to the amount of tick-borne disease in any community. Last winter Nantucket increased its shotgun season for deer from one to two weeks, primarily to reduce the public health threat from an ever-expanding deer herd. But Dr. Telford says the real impact will be felt by the next generation.

"It's a long-term process and Nantucket realizes that," says Dr. Telford. But he adds that a problem for all communities in New England in terms of the deer population is the restrictions on hunting that remove an effective means of managing the deer herd, particularly on private property.

"What I think will end up happening is if they don't allow hunting on their property, their property might become risky," says Dr. Telford.

People can protect themselves from ticks by avoiding areas of brush and grass and, when in those areas, wearing light-colored trousers tucked into one's socks. Spraying clothing with an insect repellent is also recommended. But most important is the tick check, particularly for children.

From the Martha's Vineyard Times Aug 7, 1998. Reprinted by permission.

Research

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Vaccine reduces risk for people who spend a lot of time outdoors

according to Merrill Lynch analysts.

``For people who spend a lot of time outdoors in areas where Lyme disease is common, this new vaccine may be a good option,'' said FDA commissioner Jane Henney.

LYMErix is aimed at preventing the bacterial infection behind Lyme disease, which can lead to arthritis, facial paralysis, fatigue, and sometimes severe symptoms afflicting the heart and nervous system.

Caught early, the condition can easily be treated with antibiotics. It's often hard to diagnose, however, and people at risk for Lyme disease need the option of a vaccine, SmithKline told the government panel that reviewed the vaccine.

Lyme disease was discovered in Lyme, Connecticut, in 1975. Typically transmitted by deer ticks, the disease has become common in rural and seaside areas of the U.S. in recent years —particularly in the Northeast. During the company's tests, LYMErix proved safe and effective in a massive U.S. study of almost 11,000 patients. The vaccine reduced the risk of contracting Lyme disease by 79 percent in the year after the third of three shots were administered, the company said. Its most frequent side effects include pain at the injection site, redness, swelling and in some cases flu-like symptoms, company representatives said.

Because it's hard to diagnose, estimates of the incidence of Lyme disease vary. Some experts say the actual incidence of the disease is as much as five to 10 times the 10,000 to 20,000 cases reported in the U.S. each year.

Like many other vaccines, SmithKline's is composed of a solution containing the lifeless outer-surface protein of the bacteria, a substance that prompts the body into an immune response. The company said it also plans to file for regulatory approval in other places where Lyme disease is a problem, including Europe.

Reprinted by permission of Bloomberg News

Scientists skeptical of new test

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group tested positive using the standard, first-line blood test, which is designed to find antibodies to the Lyme bacterium.

In Phillips' view, the study demonstrates that so-called post-Lyme syndrome - ongoing or recurrent illness in patients who have received the standard antibiotic regimen - is a misnomer. He doubts that post-Lyme is a separate illness as many Lyme researchers contend.

"It's just continued infection," he said. In addition, he said, the appearance of the bacterium in patients who tested negative for Lyme using standard blood tests underscores the inadequacy of these tests. His work could be the basis of future tests.

But other experts who have seen the article called it weak. They said that no conclusions could be drawn from the work until it is repeated elsewhere.

Richard Tilton is senior vice president and chief scientific officer of BBI Clincal Laboratories in New Britain, a major medical testing lab. He is also editor-in-chief of the

Journal of Clinical Microbiology. He said there are a number of inconsistencies and flaws in the study, including the way in which patients were selected and the lack of data from DNA testing.

The lack of DNA data makes the authors' claims difficult to interpret, according to Dr. Raymond Dattwyler, professor of medicine and director of the Lyme Disease Center at State University of New York at Stony Brook University Hospital and Medical Center on Long Island.

Although the text of the study says that the results were confirmed using DNA tests, there is no actual data on these tests in the article. Dattwyler notes that where there is bacteria, there is DNA.

Phillips said DNA testing was performed on some samples and was positive, but that across-the- board DNA testing was too costly for this study. He added that some of Tilton's criticisms are overly broad and unscientific.

Most Lyme disease cases are effectively cured using short-term antibiotics. The existence, extent and treatment of chronic or persistent Lyme is the source of great controversy among those who have–or believe they have–chronic Lyme. It also divides doctors. Many doctors feel that Lyme is over-diagnosed and point to recent studies supporting this view. Others see it exactly the other way around. The accuracy of current tests is one point of contention.

Dr. Kenneth Liegner of Armonk, N.Y., who believes in chronic Lyme infection, says that most physicians agree that better diagnostic tests would improve Lyme treatments and might encourage insurers and HMOs to broaden coverage for chronic Lyme. He said Phillips' technique would be a breakthrough if others can repeat it. Tilton, who has his doubts, agrees.

"If this can be repeated, it's absolutely remarkable," he said.

Lyme disease is the most common tick-borne infection in the country. More than 99,000 cases of Lyme disease have been reported to the federal Centers for Disease Control and Prevention since 1982. In Connecticut, 18,486 case have been reported since 1987, when the state first required cases be reported to the state health department.

This article appeared in the Jan. 5, 1999, Hartford Courant. Reprinted by permission.

L-forms may be bacterial self-defense mechanism

by Mary Lynch

Introduction: L-forms remain controversial. Not everyone even believes in them. Since they cannot be identified by any of the markers which characterize the cells from which they are allegedly derived, how do we know that they are actually the same organism? Since science has not yet answered that question, we still need to keep all the options open—for most diseases there is never just one test to use in all stages—the L-form culture may need to be added to the existing armamentarium.

When Dr. Preac-Mursic discussed L-forms of the Lyme bacteria in 1996, I was challenged to not only understand it, but explain it to other patients. Today we have a proposed culture test which is based on L-form research undertaken by Drs Phillips and Mattman. But what are L-forms, and why is this new test so remarkable?

We recognize bacteria by their shapes, sizes, structures and more. Bacteria have sturdy cell walls, lined by soft inner membranes. Lyme patients know that *Borrelia burgdorferi* (Bb) are spirochetes, which are characterized by their shape. They look like corkscrews, or an "S" that went out of control. But what if these same bacteria decided to remove their cell walls, would we recognize them?

Welcome to the world of L-form variants, where *Borrelia burgdorferi* no longer resemble spirochetes.

A hundred years ago an observant researcher found that bacteria can get bored with wearing the same outfit, so they change it. No one knows why, but sometimes that sturdy cell wall around bacteria will either partially or completely disappear and the live bacteria are left running around wearing nothing but their inner membrane. Bacteria that were rod-shaped become round, round bacteria may become comma shaped, whatever. If you're missing pieces of your cell wall you can end up looking pretty strange, but it's a good way to travel incognito! Some researchers speculate that this habit can come in handy for bacteria trying to live in an environment populated by hostile immune cells.

These cell wall deficient forms were called "L-forms" after the Lister Institute where they were discovered. Researchers have been quietly watching L-forms for a century, and while some scientists believe that all bacteria might make L-forms, only some have been confirmed. These include things like staph, strep, TB, salmonella, syphilis, and now of course, Bb.

One problem with identifying L-forms is they resemble mycoplasma, which are bacteria that aren't supposed to have a cell wall in the first place. L-forms are bacteria that should have a cell wall, but don't. L-forms can be created artificially by polluting a bacteria's environment - change the pH, add annoying

bacterial neighbors that grate on their nerves, or oddly enough, add antibiotics. Scientist are particularly fond of using Penicillin G for this purpose and have done so for decades. Yes, antibiotics can cause Bb to create L-forms. More recently, a European team found that spinal fluid will have the same effect. If you think that sounds like trouble, then you won't be happy to hear that antibody and complement - key components of your immune system - are also culprits.

Dr. Mattman doesn't call them "stealth pathogens" for nothing. There are all too many theories about the deformed little creatures and not enough proven facts just yet. For example, bacteria might be replicating in ways we never realized. Some L-forms create colonies of cell wall-less spheres or tree-like formations and it appears that these colonies might be a bacterial maternity ward. Theories suggest that L-forms are part of the normal developmental life-cycle of bacteria, that they'll turn L-form whether you annoy them or not. We've known that some antibiotics kill Bb while the spirochetes are reproducing, but we believed this "fission" was the only way Bb propagated itself, which may not be the case at all.

While we would think that an outer cell wall would shield the bacteria within, there seems little question that Bb actually drops its cell wall as a defense mechanism in hostile environments. We have yet to know whether Bb's wall-deficient forms are dormant or still create disease. Even if dormant, can they wake up just like any other creature in hibernation? This is what Phillips' paper and others suggest.

Perhaps the most interesting and critical part of Preac-Mursic's work is that she documented an L-form magic trick called "reversion". Dr. Mattman elaborates on this trick in her book, "Stealth Pathogens." She explains that L-forms can re-develop their cell walls and return to their normal shape if you re-create the proper environment.

We know from recent work done in the US and Europe that Bb is reversion-capable. This fact may be a key to understanding relapses and/or chronicity in certain diseases including LD.

Preac-Mursic found that the longer Bb were exposed to Penicillin G, the more L-forms developed. Under favorable conditions, the more time passed after removal of the penicillin, the more L-forms reverted back to normal (and presumably back to creating havoc). This doesn't mean that all spirochetes, or even L-forms, survived antibiotic treatment. But if sufficient numbers remain alive they may keep the disease process going. We could have reversion going on in deep tissues or other sequestered areas like joints, eye fluid, the brain or inside cells. Here, both antibiotics and the immune system have difficulty gaining access via the blood stream.

Reversion plays a key role in the proposed new blood culture test, which provides the necessary environment for the re-growth of fragile L-forms back into spirochetes. No other LD test available today has the mechanism, or the sensitivity, to detect L-forms or permit their reversion. The bloodstream is a logical place to search for L-forms, where spirochetes are vulnerable to both the immune system and antibiotics. Hopefully a spinal fluid test won't be far behind.

Many questions remain. 1) are L-forms part of Bb's life cycle? 2) Are they dormant, or can they cause active disease? 3) Do they escape immune system detection and/or present a possible explanation for seronegative LD? 4) How sensitive are they to antibiotics? 5) Is treatment relapse caused by reversion? 6) If Bb converts to L-forms on contact with spinal fluid, does this explain why spinal taps are so often negative, particularly in late-stage or chronic LD? 7) Can any Lyme test be considered "gold standard" without the capacity for L-form detection? 8) Does the presence of L-forms explain why it appears that so (relatively) few bacteria in our bodies can create illness, and why those "S" shaped spirochetes are so hard to find? 9) Add your own questions here...there are too many to count!

Drs. Phillips, Mattman and their team have created the first proposed Lyme test which is based on L-formation. The test is a culture - the most important standard for proof of infection. The LD community hopes this test represents the beginning of a journey on the road to our long-sought and desperately needed gold standard test. The scientific path into the future seems clear. Follow the L-forms....they may have a lot to teach us about Lyme disease.

Special Report

the Lyme Times asks Dr. Phillips...

Dr. Phillips kindly agreed to an interview with the Lyme Times regarding his newly published research.

Lyme Times: In your Abstract you write "fluorescent antibody immuno-electron microscopy." Exactly what is this and who does it?

Steven Phillips: Unfortunately, there's a small typo. There should have been a comma between "fluorescent antibody" and "immuno-electron microscopy". They are two separate tests.

Fluorescent antibody was performed by Dr. Mattman and immuno-electron microscopy was performed by Dr. Hulinska. Fluorescent antibody testing is performed by exposing the organisms to a protein which specifically binds to them.

Continued on page 23

A Proposal for the Reliable Culture of *Borrelia burgdorferi* from Patients with Chronic Lyme Disease, Even from Those Previously Aggressively Treated

by S. E. Phillips, L. H. Mattman, D. Hulinska, H. Moayad

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Summary: Since culture of *Borrelia burgdorferi* from patients with chronic Lyme disease has been an extraordinarily rare event, clarification of the nature of the illness and proving its etiology as infectious have been difficult. A method for reliably and reproducibly culturing *B. burgdorferi* from the blood of patients with chronic Lyme disease was therefore sought by making a controlled blood culture trial studying 47 patients with chronic Lyme disease. All had relapsed after long-term oral and intravenous antibiotics. 23 patients with other chronic illness formed the control group. Positive cultures were confirmed by fluorescent antibody immuno-electron microscopy using monoclonal antibody directed against Osp A, and Osp A PCR. 43/47 patients (9l%) cultured positive. 23/23 controls (1OO%) cultured negative. Although persistent infection has been, to date, strongly suggested in chronic Lyme disease by positive PCR and antigen capture, there are major problems with these tests. This new method for culturing *B. burgdorferi* from patients with chronic Lyme disease certainly defines the nature of the illness and establishes that it is of chronic infectious etiology. This discovery should help to reestablish the gold standard in laboratory diagnosis of Lyme disease.

INTRODUCTION

Lyme disease is a multi-system illness caused by infection with *Borrelia burgdorferi.* Its manifestations can be myriad. This, coupled with problems in current serologic assays, leads to frequent misdiagnosis at all stages of the illness. Some investigators believe that Lyme borreliosis is overdiagnosed, while others maintain that it is underdiagnosed. To further confuse matters, a significant percentage of patients with Lyme disease relapse despite antibiotic therapy [1, 2].

Chronic Lyme disease is a controversial topic. Even after extended antibiotic treatment, persistent infection in chronic Lyme disease has been strongly suggested by the persistence of borrelial antigen, as demonstrated by polymerase chain reaction [3, 4]. However, these diagnostic tests are plagued by the absence of a gold standard. The gold standard for laboratory diagnosis in the field of infectious diseases has usually involved culturing the causative organism from the infected host. In the case of Lyme disease, attempts to do so have been disheartening.

The organism has seldom been cultured from cases of treated, late-stage disease, and if so, primarily from cerebrospinal or synovial fluid [5-8]. Culture of the organism from blood has been a rarity, with successful cultures primarily from cases of untreated, early disease [9, 10].

We set out to demonstrate a methodology by which we could reliably and reproducibly culture *B. burgdorferi* from the blood of patients with chronic Lyme disease even though they had had extended antibiotic therapy. If this were successful, it would also provide a unique opportunity to compare the serologic diagnostic criteria set forth by The Centers for Disease Control (CDC) in conjunction with The Association of State and Territorial Public Health Laboratory Directors (ASTPHLD) to what is potentially a gold standard diagnostic test.

PATIENTS AND METHODS

The study was a multi-center, controlled blood culture trial with an approximately 2:1 ratio of cases to controls. Patients were selected from private practices in areas both hyperendemic and non-endemic for Lyme disease. All cases had a diagnosis of Lyme disease and had failed or relapsed after extended oral and intravenous antibiotic therapy. The diagnosis of Lyme disease was made primarily on clinical grounds. Although almost all cases had serologic evidence suggestive of infection with *B. burgdorferi*, few had positive ELISAs and only a little over half met CDC serologic criteria for Western blot positivity. 4/47 (9%) were positive by Lyme ELISA. 3/47 (6%) were equivocal by ELISA. 26/47 (55%) were positive by CDC criteria for Lyme Western blot. Of these, 20/26 (77%) were IgM positive, 10/26 (38%) were IgG positive, and 4/26 (15%) were positive for both IgM and IgG.

To participate in the study, all patients had to have had at least 6 consecutive weeks of therapy with an intravenous third-generation cephalosporin and a subsequent relapse. Some patients had had as long as 6 months of intravenous therapy, with the mean being approximately 3 months. Controls resided in non-endemic areas and consisted of patients with chronic illnesses other than Lyme disease.

The following MPM medium was used for this study: To 1 l of Detroit tap water was added: proteose peptone 20g, beef infusion from 1,000g, dextrose 10g, sodium chloride 10g, dipotassium phosphate 4g, sodium thioglycollate lg, purified agar lg, bacto methylene blue .004g, sucrose l00g, soluble starch 5g. This was autoclaved for 15 min at 120 degrees C. For the medium to be used in tube or slide culture, it had to be refrigerated for 24 h before final preparation.

For the medium to be used in tubes, l0ml of medium were boiled to dissolve the agar just before use and the following was added to each tube: l ml separately autoclaved yeast extract from a 10% solution to give a final concentration of 1%, and 1 ml of sterile 10% $NaHCO_3$. Since yeast extract may contain heat-resistant

bacilli, it was separately autoclaved for 30 min at 124 degrees C and batch-tested for sterility. The inoculum was 0.l ml of blood in EDTA to 4 ml of medium in a slender screw-top tube. Incubation was at 30 degrees C under normal atmospheric conditions for a period of 1-3 weeks.

For the medium to be used in slide culture, it was sterilized in 30ml amounts in screw-top tubes. Just before use, the medium was boiled to melt the agar and when cool but not solidified, the following was added: 3ml of separately autoclaved 10% yeast extract and l0ml of sterile 10% NaHCO3. The broth was then poured aseptically into a sterile plastic Coplin jar. Slides were smeared with the patient's chosen body fluid. The slides had to be specialized so as not to require fixative. The smears were dried in an aseptic environment before being placed in the Coplin jar. Once they were inside, the lid was tightly closed and incubation was at 30 degrees C under normal atmospheric conditions for a period of 1-3 weeks.

For the medium to be used for blood agar plates, the broth medium was modified by adding a total of 16 g of agar. Sixty ml of sheep's blood was added as soon as the medium was removed from the autoclave, resulting in ."chocolate agar." At this point, separately autoclaved 10% yeast extract was added to give a final concentration of 1%. The medium was then poured into sterile plastic Petri dishes and stored under refrigeration for 24 h once solidified. The inoculum was 0.5ml of blood in EDTA with incubation at 30 degrees C under normal atmospheric conditions for a period of 1-3 weeks.

Two blood samples of 5 ml each were collected in EDTA lavender-top test tubes from each patient and control. From these, seven cultures were processed from each participant. All positive cultures were stained with acridine orange at pH 3.5-4.0 and then confirmed by our laboratory with affinity-adsorbed polyclonal fluorescent antibody to *B. burgdorferi* (02-97-91, Kirkegaard & Perry Laboratories, Gaithersburg, MD, USA).

Further confirmation of positive culture results was accomplished by electron microscopy, immuno-electron microscopy utilizing monoclonal antibody directed against Osp A (monoclonal antibody no. 181, courtesy of Prof. B. Luft. Stony Brook, NY, USA), and plasmid PCR with Osp A primer. The methods employed in these processes have been previously reported [11, 12].

RESULTS

Of the 47 patients with chronic Lyme disease, 43 (91%) cultured positive for *B. burgdorferi*. while 23/23 (100%) of the controls cultured negative. Many of the cultures were clearly spirochetes when examined under light microscopy (Figures 1-3). Immuno-electron microscopy and Osp A PCR confirmation provided additional confirmatory evidence as to the identity of the spirochetes (Figures 4-7). The slide cultures consistently demonstrated the fastest and most abundant yields. With this technique, placement in the Coplin jar allows for varying gradations of oxygen tension. Sometimes spirochetal growth can be seen after as little as 20 h appearing as a band near the upper end of the smear.

DISCUSSION

An attempt to culture *B. burgdorferi* from the blood of previously aggressively treated chronic Lyme disease patients seemed at first a monumental task. Before undertaking this effort, we therefore had to be as sure as possible that the organisms were indeed present in the blood of these patients.

As a first step, we scrutinized a report where *B. burgdorferi* had been cultured from the blood of patients with early untreated disease. From this group of patients it had been noted in follow-up that subsequent blood cultures became routinely negative after antibiotic therapy, despite 71% of the patients remaining symptomatic [9]. Three possibilities readily come to mind for the explanation of this paradox: either 1) the infection is cleared, but a post-infectious process continues, or 2) the organism is cleared from the blood rapidly but finds a pathogenic harbor elsewhere, or 3) the organism is maintained in the blood in an altered state which cannot be cultured on routine media. In response to the first possibility, the notion of a post-Lvme syndrome has countless flaws. A post-infectious syndrome could not explain the observation that patients with ."post-Lyme" or "post-Lyme fibromyalgia" responded to retreatment with antibiotics, only to relapse with its discontinuation [13-15]. With the advent of PCR, antigen capture, and the benefit of those rare successful culture experiments even in the face of prior "curative treatment" [3-8], the notion of "post-Lyme" should have been dismissed long ago. In response to the second possibility, given the common finding of circulating immune complexes with Lyme disease, we thought this unlikely [16]. Thus we were left with the third and most logical possibility. Specifically, we chose to pursue the organism in its cell wall-deficient state, i.e. L-forms, as previously reported [17].

Although L-forms will complex with fluorescent antibody to *B. burgdorferi*, only as they revert to classic parent forms can the typical spirochetal morphology be seen. There has been a considerable spectrum of cell wall deficiency demonstrated in our laboratory. *B. burgdorferi* may exist in various forms depending on its environment. In addition to the spirochetal form, we have demonstrated its growth both as amorphous L-forms and rounded giant L-bodies which have been previously described as cystic forms [11, 18]. As *B. burgdorferi* reverts from cell wall deficiency with the rebuilding of its cell wall, classic spirochetal forms can be seen. Most often, in our cultures, *B. burgdorferi* can be seen in varying stages of reversion, i.e. some L-dependent spirochetal forms within an L-form colony.

The L-form variants, osmotically fragile by nature, require precise conditions to grow in culture. Our medium and methodology are specifically designed for the fostering of cell wall-deficient organisms and their reversion to classic parent forms. In most instances, the methods must be followed precisely. Even small variations produce no growth. For example, 2% yeast extract instead of 1% is inhibitory, or if the yeast extract is autoclaved with the rest of the medium instead of separately, that too will be inhibitory. However, there is one aspect of *B. burgdorferi's* growth characteristics which we found to be remarkably non-fastidious. The organism can be easily grown throughout a wide range of pH, from 6.8-7.8. This explains the different ratios of

NaHCO3 used in the various types of culture mediums. We are still not sure about the optimal pH for culture. Future research will address that question more specifically.

It should be noted from this study that currently accepted standards for serologic diagnosis seem to be inadequate. Only a small minority of participants in the study had positive Lyme ELISAs. Under the current recommendations for two-tier testing by the CDC/ ASTPHLD, 91% of the patients in the study would have been misdiagnosed as not having Lyme borreliosis.

It is hoped that our work will help to end a medical controversy which has been going on for far too long. This study proves that chronic Lyme disease is of chronic infectious etiology, and that even antibiotic treatment well in excess of current recommendations is not necessarily curative. Given the flaws in currently accepted serologic diagnostic criteria, it is likely that Lyme borreliosis is vastly underdiagnosed. May this research help to focus the scientific community on effective curative therapies for patients with chronic Lyme disease.

It should also be noted that, in addition to its utility in growing *B. burgdorferi*, the MPM medium may be useful for culturing a variety of other spirochetes from patients.

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Interview with Dr. Phillips, cont. from p. 18

This protein then glows when exposed to ultraviolet light, making the organisms readily visible.

Immuno-electron microscopy is a process comprised of two steps. First, the organisms are examined under electron microscopy to assure that the spirochetal morphology is consistent with borreliae. Then, the organisms are exposed to the monoclonal antibody (Mab). In this case the Mab is a protein which binds very specifically to Osp A (what the Lyme vaccine is based on). By examination with immuno-electron microscopy, it can be observed most definitively that the antibody is indeed binding to the organism. With light microscopy fluorescent antibody testing, there is always the risk that there is some excess fluorescent antibody which has not truly bound to the organism, thus producing a false positive result. There is no such risk of this with immuno-electron microscopy.

LT: Were the test and control samples blinded?

SP: No.

LT: Have any other labs tried to replicate your work thus far? If so, have any been successful? Who? Have any failed? If so, why do you think they failed?

SP: Aside from my present research partners, I haven't been in direct correspondence with any other researchers specifically in terms of helping them to reproduce our work. I would assume that some others must have tried to replicate it already without our knowledge or guidance. Given the fact that it took several years for us to get good results, and even to this day it's still very difficult, I don't expect anyone to be lucky right off the bat. However, I don't see any reason that it can't be reproduced with some teaching.

LT: Your Infection paper contains what looks like a recipe for MPM medium. Are you and your colleagues available to work with other laboratories that want to make the medium and verify your findings?

SP: I would be happy to work with others to reproduce our findings. Since I expect it may be difficult at first for others to reproduce our work, I think one of the easiest ways to corroborate our findings would be to receive blinded controlled samples for culture from outside sources.

LT: Is "beef infusion" really beef heart infusion or beef extract? From what suppliers were the medium ingredients obtained?

SP: These materials can be obtained from standard laboratory supply companies. Many of our materials were obtained from Difco.

LT: Are the values and units used for the quantities of medium constituents correct? How can 1000 g of a beef product be dissolved in 1 liter of water?

SP: The values are correct. The beef infusion is easily dissolved. It's not steak. Difco currently has premixed culture mediums which contain large amounts of beef infusion. These are marketed specifically for use with fastidious organisms.

LT: Your report notes that almost all the patients had "serologic evidence suggestive of *B. burgdorferi* infection." If 9% had positive ELISAs and 55% had positive Western blots (total 63%) is this what you mean by "almost all"? Or were you including the patients who did not meet the CDC criteria but who had some bands on WB?

SP: I was referring to patients who had multiple bands of WB, but didn't meet CDC criteria.

LT: Looking at the 45% (21 patients?) who did not have Western blots meeting CDC criteria, which Western blot bands did they typically demonstrate?

SP: Many demonstrated 41, 23, 31, 34, 58, and 83.

LT: The abstract indicates that a monoclonal anti-OspA antibody was used for fluorescent and immune electron microscopic analyses. The methods state that the fluorescent antibody reagent was a commercial polyclonal antibody. Which is correct?

SP: I refer to the typo (lack of a comma) as above. The Mab was used for immuno-electron microscopy and the commercial reagent for the FA.

LT: Do you have plans to verify the identity of the cultures by DNA testing? What other types of studies do you hope others will do to evaluate your method?

SP: As clearly written in the article, we have already performed verification of the cultures via DNA testing with Osp A PCR. Osp A PCR is widely recognized as one of the most specific means for positively identifying *B. burgdorferi*. In addition to this, after the article had gone to press we had also achieved further DNA confirmation of our culture technique using two different PCR primers. All told, we have demonstrated PCR positivity with 3 different PCR primers through 2 different third party research laboratories.

LT: Would your medium and procedure be likely to be useful in culturing the cystic forms seen by Brorson and Brorson in spinal fluid? In culturing cell-wall deficient forms from other body tissues?

SP: Absolutely. We have demonstrated cystic forms of *B. burgdorferi* over and over again. These forms look exactly like those demonstrated by Drs. Brorson and Brorson, as well as those demonstrated years ago by Dr. MacDonald, a man for whom I have great respect.

LT: Do you plan to conduct double-blind followup studies?

SP: Of course.

LT: Dr. Phillips, thank you for your time. The Lyme Times wishes you success with your work.

Conference Reports

Fascinating facts about *Borrelia burgdorferi* and other tick-borne diseases

Approximately 300 people attended the 11th Lyme Disease Foundation conference in New York City on April 25-26, 1998. A brisk pace was maintained for over 30 speakers who covered basic sciences, tick vectors and animal models, laboratory testing, diagnosis and treatment, and vaccines.

Keynote speaker **Willy Burgdorfer**, PhD, gave evidence of mosquito/spirochete associations and spoke about the possible role of mosquitoes as vectors of spirochetal diseases. The recent demonstration and isolation of spirochetes (including the Lyme disease agent, *Borrelia afzelii*) in and from *Aedes* and *Culex* mosquitoes in southern Moravia (Czech Republic) prompted Dr. Burgdorfer to review the literature on this association.

As early as 1904 there were reports of spirochetes in larval and adult mosquitoes. Yet there is no information as to the ability of these insects to transmit spirochetes by bite, with the exception of one report of transmission of *Borrelia anserina* by experimentally infected *Aedes aegypti.*

Studies by Magnarelli, Anderson, and Barbour published in 1986 and 1988 demonstrated spirochetes in field collected mosquitoes as follows: *Aedes canadensis* 1/13 (7.7%); *A. stimulans* 3/89 (3.3%); and *A. vexans* 1/14 (7.1%). In later study they found spirochetes in 11/113 *A. canadensis*; 2/21 *A. stimulans*, and 2/18 *A. triseriatus*.

In the Czech Republic, Halouska and colleagues published results of a study in 1993. Collecting mosquitoes in August and October and then again in March and April (i.e. early and late hibernation periods), the researchers found naturally infected mosquitoes and demonstrated that spirochetes could survive long hibernation periods within the insects (3.5-4.3% infection rates). In a second study (Halouska, Postic and Hubalek, 1998) they found 7% of total mosquitoes of many varieties tested positive, and that the percentage increased during hibernations (7.4% during early, 4.8% during late hibernation period). Similar experimental infection and transmission studies of the Lyme disease agent *Borrelia burgdorferi sensu stricto* in three species of mosquitoes (*Ae. aegypti, Ae. atropalpus, Ae. triseriatus*) showed the duration of spirochetal infections in the intestinal tracts of these insects to be ephemeral and not involve salivary gland tissues.

Borrelia burgdorferi (Bb), the causative organism of Lyme disease, has been observed in *A. vexans*, which may be involved in the maintenance of spirochetes in nature. Two isolates of Bb were obtained and identified as *B. garinii* and *B. afzelii*. There is no proof that they play a significant role in transmission of Bb to humans.

Studies are in progress to determine whether these spirochetes produce in their mosquito vectors systemic infections including the tissues of salivary glands from where they could be transmitted via saliva during feeding on animal hosts and possibly humans. One paper (Hart, 1966) reported erythema migrans associated with mosquito bites, but the victim may have had tick bites as well. More studies are in progress.

Basic sciences

Claire Fraser, PhD, Vice-President for Research at The Institute for Genomic Research in Rockville, MD, described the work on sequencing the Bb genome, which researchers hope will elucidate the mechanisms of disease. Fourteen genomial sequences have now been developed and more than 60 are under way. The genome program will enable scientists to design more sensitive tests, more effective treatments, and vaccines. The program is cost effective, costing only $200 per gene.

Pathogenic spirochetes tend to be large—up to 50mm—and require special staining techniques for visualization. Their rate of growth is slow, and they are sensitive to elevated temperatures. Most pathogenic spirochetes are microaerophilic, that is, they require a low level of oxygen to thrive. Pathogenic treponemes cannot be cultured on artificial media. They cause chronic symptoms and do not produce toxins. Unusual features are the linear and circular plasmids, which tend to be lost in serial cultures, leading also to loss of virulence.

An interesting requirement for Bb culture is the addition of acetylglucosamine to the medium. This is an ingredient of chitin, which makes up the exoskeleton of ticks.

For the genome study, the researchers chose Bb isolate B31 which has not been passaged in culture. The genome contains a linear chromosome and 21 linear and circular plasmids. It is a minimal genome, the chromosome containing only 853 genes encoding a basic set of proteins for DNA replication, transcription, translation, solute transport, and energy metabolism, which are, as Dr. Fraser said, “basic housekeeping genes.” Of the genes making up the coding sequences, 29% had no match in the database, suggesting that they are unique to Bb. Only 14% of the plasmid genes have been putatively identified. Of

these, 86% have no known biological function.

"Genes for which we know the biological role are very limited," stated Dr. Fraser. "Like *Mycoplasma genitalium*, the organism appears to lack biosynthetic capability, making it totally dependent on the host for survival."

Treponema pallidum (Tp) and Bb are closely related, sharing 50% of their genes. One half the genes in each are unique., and Bb does not share a single plasmid gene with Tp. Researchers speculate that the plasmid-encoded genes may play a role in antigenic variation or immune evasion. A description of the genome project may be found online at www.tigr.org.

Jon Skare, PhD, a microbiologist at Texas A&M Health Science Center, spoke on Identification and Characterization of Virulent Strain-Associated Outer Membrane Proteins of *Borrelia burgdorferi* (VSA). The goal of the research project was to identify and characterize VSA outer membrane proteins and to determine their role in pathogenesis and their efficacy as vaccine candidates.

The VSA outer membrane proteins mediate the initial host/ pathogen interaction. Bb encounters several challenges during its life cycle: temperature shift and innate immunity in both tick and mammal hosts. Schwan and Rosa reported that Bb is a host-adapted spirochete in which outer surface protein (osp) expression changed as the tick fed. In the unfed tick, ospA is expressed and ospC repressed. As the tick feeds, ospA is down-regulated and ospC is up-regulated. OspA is currently being used as the target of the Lyme disease vaccine.

The researchers hypothesized that antibodies within the immune rabbit serum would recognize VSA antigens. Using adsorption techniques, they created a reagent consisting of antibodies specific for VSA antigens. They were able to determine that decorin binding protein (Ddp) A and B and VSA repetitive antigen A (Vra) were expressed at high levels at 37 degrees C compared to cells grown at 23 or 32 degrees C, i.e. the temperature of a mammalian host. Because these antigens are expressed at high levels within mammalian hosts, they are logical targets for new vaccines to complement the current ospA vaccine.

Pathologist **Maria Picken**, MD, PhD, Loyola University Medical Center, reported on Lyme disease in the Midwest. Many housing developments are now being called conservation communities, with space reserved for wildlife. It amounts to houses being built in what are basically nature preserves, with attendant increased risk of acquiring Lyme disease.

Dorward's video showed living Bb penetrating lymphocytes and cloaking itself in lymphocytic membrane as it emerged.

During 1996-97, the researchers trapped small animals in forested areas in suburban Chicago and cultured them for Bb. They obtained ten isolates; in the case of 3 *Microtus pennsylvanicus*, isolates were obtained from both urinary bladder and ear snips. Forty percent of the ticks were culture positive. Pulsed-field gel electrophoresis analysis showed similarities and differences among the isolates. It is not known whether the isolates are pathogenic to humans. Another study is focussing on dual infections in ticks.

Chronic Lyme disease often causes fatigue, pain and neuropsychiatric symptoms. This research project of **Mark Cartwright**, PhD candidate at Boston University Medical Center, and colleagues postulated that the Lyme spirochetes reside in neurons, glial cells or endothelial cells that provide the nervous system with its blood supply, and focussed on identifying toxins of Bb that may affect neurophysiology.

Toxins target specific amino acids which are expressed by different types of cells. Cholera toxin targets agmantine, for example, which is expressed by eukaryotic cells. Peters and Benach discovered that Bb is toxic to rat neural cells. Using PCR, the researchers identified Bb genes that express proteins analogous to cholera, diphtheria, and pertussis toxins. The putative toxin genes are identical to several unidentified genes contained in the recently published complete DNA sequence of Bb. In the future the researchers will attempt to identify new Bb proteins which are conserved to known toxin sequences. It is hoped that this work will enable scientists to develop antibodies to Bb proteins and to explore their use as vaccines.

David Dorward, PhD, microbiologist at the NIH Rocky Mountain Laboratories in Montana, once again showed fascinating live videos of Bb in cultures with B lymphocytes, a type of human immune cell. Although his studies provide visual evidence of how Bb is able to cloak itself in lymphocytic membrane, Dorward emphasized that the proportion of Bb compared to immune cells in vitro is much lower in vivo. Implications of this study must be understood in that light, he said.

In the videos Bb spirochetes may be seen gently rotating with their tips touching the surface of lymphocytes. They appear to penetrate the lymphocyte and to re-emerge from the cell cloaked in membrane. Using a technique that labels the lymphocytic membrane with tiny gold particles, one can see that the membrane surrounding the re-emerging

spirochete is continuous with the lymphocytic membrane. If such interactions do indeed occur in vivo, this process could provide Bb with a camouflage which masks spirochetal antigens and protects it from antibody-mediated recognition and neutralization.

It appears that there is an optimal time period during which this mechanism is operative. One third of Bb coincubated with stained lymphocytes pick up the stain within the first 12 hours. The percentage then drops off. This corresponds to the generation cycle of Bb. Dorward said that the envelopes provide a cloak of host cell antigens which persists for 1-2 cell cycles. Researchers are still looking for evidence of this Bb/lymphocytic interaction in vivo.

Tick vectors and animal models

The Ixodes ticks which carry Lyme disease are one of about 839 species of ticks in the world. They are known to feed on more than 120 species, including over 30 large, medium, and small mammals and 60 species of birds, which are a natural means of distribution.

John Anderson, PhD, of the Connecticut Agricultural Experiment Station, described the feeding process of ticks. After latching onto a host and finding a biting site, they grasp the skin with tarsal claws and cut the skin with chelicerae, which are sharp, flexible cutting blades. The tick then inserts the hypostome and secretes a cement-like substance which holds the tick in place. The upper surface of the hypostome and lower surface of the chelicerae form a channel for sucking. The tick feeds in cycles: sucking may last 15-30 seconds followed by a 1 second interval of salivation. The saliva contains anticoagulants, an antiinflammatory substance, immunosuppressants, immunogens, and pathogens.

In Connecticut, *Ixodes scapulari* (formerly *dammini*) carry Lyme disease. The larvae hatch in mid-July through September, feed and drop off where they hibernate in leaf litter. The following spring they molt into nymphs, feed again, usually on a small mammal or bird, and drop off. They molt into adults. Adults become abundant in mid-October and feed on warm days throughout the winter and into mid-April, when they mate on a host. The female forms eggs which are laid wherever she drops off. Spirochetes ingested during any of the feeding cycles may survive the molt to the next stage, except that transovarial transmission is very rare.

Ehrlichia may surround themselves with a host-derived membrane which enables them to evade the host immune system.

According to Dr. Anderson, Connecticut residents may be bitten by *Amblyomma lonestarii* (lone star tick), *Rhipicephalus sanguineus* (brown dog tick), *Dermacentor variabilis* (American dog tick), *Ixodes scapularis* (black-legged tick), *I. cookei* and *I. dentatus*. Most cases of Lyme disease are diagnosed in July (the beginning of the nymphal tick season), with June and August running a close second. Dr. Anderson emphasized that the most important of all the preventive measures is self-inspection.

Evidence from human patients suggests that co-infection with several tick- borne pathogens may complicate the diagnosis and treatment of Lyme disease. **Edward Bosler**, PhD, reported on his studies of co-infection of mammals and ticks with Lyme disease (Bb), Babesiosis (*Babesia microti*, or Bm), and human granulocytic ehrlichiosis (HGE). He and his co-workers collected questing ticks and ticks feeding on animals in the wild from sites on Long Island, Connecticut, and other locations along the eastern seaboard from Massachusetts to South Carolina. They found significant rates of co-infection at one location: Bb (30%), Bm (53%), HGE (17%), Bb/Bm (30%), Bb/HGE (7%), Bm/HGE (13%), all (6.7%). Comparable figures for co-infection in nymphal ticks are: Bb (45%), Bm (10%), HGE (29%), Bb/Bm (7%), Bb/HGE (17%), Bm/HGE (9%), all (7%). Comparing levels detected on one mouse which was captured twice, one week apart, during the nymphal tick season, revealed a dramatic rise in all levels: Bb (25 to 67%), Bm (13 to 44%), HGE (25 to 78%), Bb/Bm (0 to 33%), Bb/HGE (13 to 56%), Bm/HGE (0to 44%), all (0 to 33%). Other sampling sites showed somewhat different rates of co-infection. One area had no co-infection but a 50% infection rate with Bb, 7.1% with Bm.

Ibulaimu Kakoma, DVM, PhD, reported on canine monocytic ehrlichiosis (CME). First described in Africa 60 years ago as a mild disease of dogs, it subsequently evolved into a fulminating infection typified by fever, pancytopenia, a hemorrhagic crisis, and a host of multisystemic metabolic and pathologic disturbances, including cardiovascular and CNS complications, thus making CME an imitator, next only to Lyme disease. It is found practically everwhere in the United States. Clincal observations include fever, sero- nasal and ocular discharge, anorexia, depression, loss of weight, elevated erythrocyte sedimentation rate, and pancytopenia (predominantly thrombocytopenia). There are several related etiologic agents: *E. canis, E. risticii, E. sennetsu,* and *E. equi*, but testing is not yet reliable. The organisms infect monocytes. After invasion they multiply within the cells, filling the entire cytoplasm, and are then released to infect other cells. They

may surround themselves with a host-derived membrane which enables them to evade the host immune system. Atypical presentations are putatively attributed to different strains of *E. canis* and/or *E. risticii.* The treatment of choice is tetracycline.

Lyme disease in dairy cattle was discussed by **Sandra Bushmich**, MS, DVM, a University of Connecticut professor and researcher. Lameness is the predominant symptom of infected cows, and resolves quickly with tetracycline, although most also recover naturally in 2-3 weeks without treatment. Cows do develop erythematous skin rashes. In an experiment with calves, all developed skin rashes at the site of injection with cultured Bb. All became seropositive. Bb were isolated from urine, kidney and bladder of one calf, and from the spleen and hock of another. Some uninfected calves which were housed indoors acquired infections from other calves.

Dolly the Cow came down with severe lameness. She tested positive for Lyme disease and was treated. She responded well, but then relapsed. She was treated again and improved, but she became severely lame again and was euthanized. Bb wsa found in synovial tissue, lymph node, baldder and uterus at necropsy.

UConn maintains its own cow herd, which has a high seropositivity rate. Cows with clinical disease were more likely to shed Bb in their urine, and this may be an important mode of transmission among cattle in the context of barnyard confinement, since urine may splash onto the skin and mucosa of other cows. Lyme disease is significant to dairy farmers because of the cost: veterinary care, drugs, and the necessity of throwing out milk while cows are being treated. Lameness is the second most common cause of culling.

Reinhard Straubinger, DVM, is continuing the work of Max Appell at Cornell University. He presenting findings of his studies on the use of corticosteroids in dogs infected with Bb. Steroids are an attractive treatment for Lyme symptoms, because they inhibit the production of protaglandins and leucotreines which cause inflammation and pain.

Four beagles were infected by tick challenge and were monitored for over 500 days for clinical signs of Lyme disease. Antibody titres were obtained biweekly, and monthly skin punch biopsies were cultured. At day 413 after infection, two dogs received oral treatment with Prednisolone for two weeks. The other two dogs received the same treatment starting on day 566, which was 15 days before tissues were cultured for the presence of Bb. One month after tick exposure, all four dogs showed infection as documented by seroconversion and by positive skin biopsy cultures. Clinical signs of acute lameness developed between 50 and 169 days after infection in three dogs, usually spontaneously remitting after five days. One dog did not become lame. Antibody titres reached a maximum within 90 days of infection and did not change for the duration of the experiment.

In human patients with subclinical disease, their Lyme disease may become fulminant after treatment with corticosteroids.

Besides weight gain, no adverse effects were observed during the course of the corticosteroid treatment. However, post-treatment, two dogs develped severe polyarthritis, which resolved without treatment after an additional week. At the end of the experiment, 25 tissues of each dog were cultured in BSK II medium. Dog 1, which received no corticosteroids, had 14 positive tissues, while dog 2 which had received corticosteroids three months earlier had only one positive tissue. Dogs 3 and 4, which received corticosteroid treatment shortly before testing, had 10 and 19 tissues positive, respectively. Treatment with corticosteroids seems to trigger subclinical Lyme disease in dogs, although antibody titres were not affected. The research suggests that in human patients with subclinical disease, their Lyme disease may become fulminant after treatment with corticosteroids. This is especially significant for physicians trying to recognize the disease, since there will be no erythema migrans to aid in the diagnosis. Lyme disease has proven difficult to diagnose and difficult to treat.

Laboratory Testing

(An in-depth report of the presentations on testing was published in the Lyme Times 21—Ed.) Pathologist **Paul Duray**, MD, NIH National Cancer Institute, described a new system for Borrelia in vitro cultivation. Most in vitro cultivation systems are unicell type cultures involving one cell lineage type or another. The new system utilized a fluid filled bioreactor called a Rotating Wall Vessel Bioreaactor (RWV), which was developed by NASA engineers to conduct experiments in space on living cells and tissue samples. Rotation and microgravity within the RWV support the life systems of cells and allow tissues to remain viable for extended periods of time. This enables researchers to conduct experiments on living tissues without the need for using animals.

Examples of human tissues that can be maintained in the RWV include spleen, lymph node, tonsil, salivary gland, skeletal muscle, synovium, lung, skin, and prostate tissue. For reasons unknown, the researchers have been unsuccessful with growing CNS and renal tissue.

They recently cocultured Bb with human tonsil, skin, and synovial tissue, and showed that the spirochetes preferentially invaded the rotating tissue samples, and grew in numbers in the tissue that far exceed those seen in similar tissue samples under conditions of natural infection. Tonsil tissue was a preferred site; the greatest concentration of Bb was found in collagen.

What can be cultured in cell-free media? Many types of bacteria and fungi, but no viruses or parasites, according to **Charles Pavia**, PhD, professor at NY Medical College. Potential problems with culture can be caused by mishandling, delay in processing, media inadequately prepared, contamination, or not enough sample. Culture of Bb from blood samples is notoriously low yield —often 5% or less. Pavia asked, "What if not enough blood were being collected from patients?" In this study of patients presenting with erythema migrans, the researchers took 3 3ml tubes of whole blood plus 3 ml tubes of serum and within 3 hours inoculated them into BSK medium in 70 ml flasks. This is a very large quantity compared to the usual practice. The flasks were incubated up to 12 weeks.

Of 31 patients, 8 (25.8%) had a positive whole blood or serum culture, including 3 of 6 (50%) of patients with multiple EM lesions compared to 2 of 25 (20%) with a single lesion. In a second experiment, 7 (27%) of 26 patients were culture-positive including 2 of 7 (28.5%) with multiple lesions and 5 of 19 (26%) with a single lesion. Serum aliquots were twice as likely as whole blood to yield positive results.

The researchers concluded that Bb can be recovered from peripheral blood in 25% of patients presenting with EM if sufficient volume is inoculated into culture media.

Diagnosis and treatment

Julie Rawlings, MPH, Texas Department of Health, described various tick-borne diseases. Signs and symptoms for these diseases may be similar, however treatments differ. Relapsing fever, transmitted by soft ticks of the species Ornithodoros, is caused by *Borrelia hermsii*. The incubation period is 5-9 days. Ten to 25% of patients develop severe CNS symptoms. Infection during pregnancy can trigger miscarriage. Lyme disease is caused by another Borrelia spirochete. Rocky Mountain spotted fever, ehrlichiosis, and tularemia are caused by small gram-negative coccobacilli. Rocky Mountain spotted fever is caused by a rickettsia carried by Dermacentor and Ixodes ticks. Abnormal liver function is a clue for diagnosis. In 1996, North Carolina reported 289 cases, highest in the nation. There are three genogroups of Ehrlichia, peculiar to different hosts. The causative organisms are carried by Amblyomma and Ixodes and the incubation period is 10 days. Tularemia, caused by *Francisella tularensis*, is carried by Dermacentor species ticks and *Amblyomma americanum*, as well as biting flies.

The spirochetes migrate to the interstitium of the heart to obtain acetylglucosamine, an element essential for their metabolism.

Babesiosis is caused by infection with a protozoa, *Babesia microti*, which is carried by Ixodes ticks. It can cause hemolytic anemia. Colorado tick fever, caused by a double-stranded RNA virus, has an incubation period of 3-5 days. **William Golde**, PhD, SUNY at Stony Brook, studied coinfections in human patients presenting with erythema migrans. Eighteen Long Island residents were enrolled and blood and skin biopsies obtained. Serum samples were assayed for antibody to *Borrelia burgdorferi, Babesia microti*, the agent of babesiosis, and the agent of HGE. Whole blood and biopsy samples were tested by PCR and culture.

Of the 18 patients, 16 agreed to biopsies, of which 81% were positive for Bb by culture. Acute serum was 39% positive by CDC criteria. Convalescent serum was 62.5% positive by CDC criteria. PCRs of biopsy specimens were 100% positive. Two patients were positive for HGE by PCR, considered by Dr. Golde a rather high rate of coinfection. The rate of infection with B. microti was low.

Richard Tilton, PhD, who works at BBI Clinical Laboratories, was involved in the early development of the ELISA tests for Lyme disease and a paper on HGE ELISA on which he collaborated is about to be published. The mainstay of antibody screening for both Babesia and Ehrlichia is an indirect fluorescent antibody test (IFA). If the situation is analogous to Lyme disease, confirmatory tests should be performed, according to Dr. Tilton. The usual procedure is to confirm reactive IFAs with a Western blot. Great care must be given to establishing breakpoints (cutoff levels), said Dr.Tilton. A breakpoint of less than 1:64 on the Igm IFA may reduce specificity. Standardization is needed.

In a study of 500 patients, 13 were positive for HGE by IFA IgG; 9 were positive for HME. Some were positive on both. 10/13 HGE reactive patients were confirmed by Western blot with the 42 kDa band, 1/9 HME reactive patients were confirmed with the 29 kDa band. 5/7 with coinfections were confirmed. Dr. Tilton concluded that the Western blot is useful for confirmation of HGE but not of HME.

Paul Duray returned to the podium to describe host and mammalian histopathology in borreliosis. Bb spirochetes have a very diagnostic

morphology. They tend to predilect to collagen, although few oranisms may be observed.

Skin conditions are caused by Lyme disease. Acrodermatitis chronica atrophicans (ACA) is more common in Europe than the USA. Lesions show a characteristic inflammatory infiltrate that fills up the dermis but does not cause vasculitis. Panniculitis is an inflammatory process in the fatty layer below the dermis, very similar to that which occurs in systemic lupus erythematosis (SLE). In scleroderma, collagen is deposited in a terse, thickened fashion, but not many spirochetes are seen. Diffuse fasciitis may occur. Benigna cutis is caused by lymphoid hyperplasia and proliferation of B and T lymphocytes. During early disease, the viscera may be affected and spirochetes may be relatively easy to find. In studies by the US Army, the spleens and livers of Westchester County (NY) deer were loaded with Bb, and the spleens of mice showed proliferation of immunoblasts. Mice also had myocarditis which looked just like human Lyme myocarditis. The spirochetes migrate to the collagen and can be seen lined up with the collagen fibers. Duray said that they go to get the acetylglucosamine, an element essential for their metabolism, in the interstitium of the heart.

Arthritis of Lyme disease shows a proliferation of capillary sprouts, or a pattern of large deposits of fiber. The central nervous system may show pleocytosis, which is many abnormal tumor-like plasma cells in the CSF. Bb are also found in the vitreous of the eye.

Lyme disease has been associated with lichen sclerosis, morphea, and granuloma annulari. It may cause cystitis, uveitis, hepatic triadilitis, and gastroenteritis.

How to diagnose and treat early Lyme disease was addressed by **Anthony Lionetti,** MD, Lyme Disease Diagnostic Center in New Jersey. Early manifestations may include musculoskeletal (myalgias, arthralgias), constitutional (fatigue, malaise, flu-like symptoms, headache), swollen lymph nodes, elevated liver function (mild), conjunctivitis, and erythema migrans. Headache is a sign of disseminated neurologic disease.

Dr Lionetti recommends using separate IgG and IgM tests. The combined ELISAs are weighted towards IgG and may miss early disease. Do not use ELISA or Western blots in the first two weeks, Lionetti said, however PCR may be useful during the period. The problem is that there are few Bb and PCR may be falsely negative.

Only 60-65% of the study volunteers who seroconverted displayed EMs, and the "bulls-eye" rash was not common. Most common were diffuse erythematous lesions, i.e. uniformly red areas.

SmithKline Beecham vaccine study

Treatment choices for early Lyme disease include doxycycline (100mg bid for 4 weeks), amoxicillin (500-1000mg tid for 4 weeks), cefuroxime axetil 500mg bid for 20 days), Zithromax (250-500mg qd for 4 weeks), clarithromycin (500-1000mg bid for 4 weeks). Dr. Lionetti plans to publish a paper on the use of ceftriaxone for 20 to 56 days in late stage Lyme disease, instead of the current standard 28 days. Treatment failures may occur.

What about prophylactic treatment of tick bites? Dr Lionetti said that in the cost-effectiveness study which concluded that prophylactic treatment was not desirable, only five patients accounted for over 50% of the cost of treating Lyme disease. They were not treated early and developed late stage Lyme disease which proved extremely expensive to treat. He believes that prophylaxis is both prudent and cost effective.

Interesting observations about serologic tests and rashes were obtained during **SmithKline Beecham**'s recently concluded a double-blind, placebo-controlled trial of its recombinant OspA vaccine for Lyme disease. In this multicenter study over 10,900 volunteers donated a baseline blood sample and received two doses of vaccine the first year and a third dose a year later. In the interval, which included two tick transmission seasons, they were monitored for signs of Lyme disease.

There were 142 laboratory confirmed cases of erythema migrans diagnosed during the study. Although some authors claim that EM may be the presenting symptom in up to 90% of cases, only 60-65% of the volunteers who seroconverted displayed this early symptom. And, while the bulls-eye rash may be classic, it was not common. Most common were diffuse erythematous lesions, i.e. uniformly red areas; different shapes of rash were seen, and some were vessicular. Results of serologic tests were not impressive, missing 30% of Lyme cases. Of 142 cases of EM, 105/135 (78%) were culture positive; 85/132 (64%) were PCR positive; 90/132 (64%) seroconverted. One third did not have positive blood tests. At baseline, 2.3% had positive IgG titres. There was a low rate (1.2%) of loss of IgG positivity; longstanding IgG antibodies develop in a minority.

There are many infectious causes of psychiatric disorders: bacterial, viral, and fungal. In 1920 a viral epidemic caused encephalitis lethargica, made children extremely sleepy, half of them developed conduct disorders, and some had to

be hopsitalized for being violently disruptive. Strep infections are now being investigated for their role in obsessive-compulsive disorder (OCD), attention-deficit disorder (ADD), depression, anxiety, and phobias. **Brian Fallon**, MD, spoke about neuropsychiatric aspects of Lyme disease in children and adolescents. Previous reports have concentrated on children with early disease and found little evidence of neuropsychiatric sequelae, however children with chronic disease have not been studied.

Recently a child in Connecticut presented with the totally abrupt onset of OCD and terrible tics. He was found to have anti-strep antibodies but also had Lyme disease. The child had B. burgdorferi in cerebrospinal fluid; he was treated with IV antibiotics. It was not clear whether he had both strep and Lyme disease or what caused the OCD and tics, but they resolved.

"I think a workup of children who develop new-onset psychiatric disorders needs to consider Lyme disease but also needs to consider strep infection," said Fallon.

Children present special problems. They tend not to report physical symptoms. One 16-year old adolescent said, "I'm too tired and too dumb to date." Children may suffer from mood changes; depression is common. Using a battery of neuropsychiatric tests, Fallon found significantly higher rates of psychopathology in 20 children age 9-17 with chronic Lyme, including feelings of incompetence, social withdrawal, anxiety, depression, trouble thinking, attention problems, and aggressive behavior. All reported fatigue; 94% reported mood swings. They all showed significant cognitive deficits. The children had seen an average of four doctors before being diagnosed. Fallon said that schools need to be flexible and creative in order to allow children suffering with these disabilities to succeed.

Dr. Lionetti reported on his retrospective study which correlated PCR positivity of 200 patients with serologic data. The blood and/or urine of all the patients was PCR positive. There was poor confirmation by IgG/IgM immunoblotting. In IgG there were 68% nonreactive, 31% equivocal, and <1% reactive. In IgM there were 64% nonreactive, 22% equivocal, and 14% reactive. Interpretative criteria for Lyme immunoblotting need to be evaluated in order to improve sensitivity.

The patient group had been diagnosed originally with rheumatoid arthritis, multiple sclerosis, chronic fatigue, and fibromyalgia. A fairly uniform pattern emerged on Western blots: bands at 41 and 83 kDa were more frequent, but otherwise no more than 12% showed up on any one band. Thirty percent were positive.

Treatment data indicated that 90% responded well to a 28-day course of IV, with 40% recurrence at one year. Ninety percent responded to a 56-day course of IV with a 10% relapse rate at one year. Ten percent had persistent disease despite aggressive treatment.

Lionetti emphasized that there is a great need for validated sensitive direct detection tests for active infection. He reminde the audience of Malawista's 1994 study (JInf Ds) which established an absolute correlation between positive and negative cultures and PCRs. He believes that the burden of proof rests on researchers who conduct clinical studies questioning the diagnosis of Lyme disease; they should utilize direct detection methods to prove that previously diagnosed patients do not have Lyme disease.

Eye findings were reported by **Robert Lesser**, MD, Yale University. "Eye findings of Lyme disease are not frequent," Lesser said, "but because it's a rare finding, it's important to establish that it's directly related to Lyme disease or whether it's coincidental."

In Steere's study, about 10% had conjunctivitis. Lesser said this will clear without treatment. Subconjunctival hemorrhages also occur. Keratitis, uni- or bilateral may occur; white opacities are distributed throughout the cornea. Topical steroids can be used if systemic antibiotics are given concurrently.

Lesser said that keratitis can be characteristic of Lyme disease.

"We see a kind of nummular keratitis, often it's bilateral, with irregular borders," he said. Bringing up a slide, he pointed out, "Slit-lamp examination shows white opacities distributed diffusely throughout the cornea in a patient who had been treated six months before. This was treated with topical steroids with resolution. Some opacities [are apparent] later on in the disease, and you can still see that some are peripheral."

In addition to the nummular keratitis, patients can also have interstitial keratitis, and there are a couple of reports of peripheral ulcerative keratitis. Lesser showed slides of a young girl who had history of Lyme disease with a dramatic titer. First she developed nummular keratitis then 10 months after onset had an interstitial type of keratitis. A diffuse inflammatory response in the cornea was evident. Another patient had inflammation within the eye and lesions between the iris and the lens.

Smith and Winward described inflammation within the vitreous in Lyme disease. Spirochetes have been cultured from the vitreous and iris. Duray's study with Syrian hamsters demonstrated that 20% of the eyes had spirochetes in the vitreous, and 55% had culture positive eyes on day 14. In one case of endophthalmitis, the patient lost his eye and spirochetes were found in the vitreous.

Lyme disease can cause optic neuritis; spirochetes directly invade the optic nerve. One patient with optic neuritis had accompanying systemic symptoms. Another had chronic cranial nerve paresis with optic neuropathy, fatigue, malaise,

depression and headache.

Pupillary abnormalities may be attributable to Lyme disease. One slide showed an irregular pupil shaped like a flower with large petals; another showed adhesions between the iris and lens.

Numerous inflammatory syndromes can be present an associated with Lyme disease.

· Granulomatous iritis, with adhesions between the iris and lens which are a sign of previous inflammation.

· Diffuse inflammation within the vitreous.

· "Snow balls" within the vitreous, described by Smith and Winward a few years ago.

· Pars planitis (an inflammation of the peripheral retina) is often so nonspecific that we can't see there's a direct association between it and Lyme disease, but it is probably one of the most typical findings.

"Some patients will have persistent vitritis or uveitis of unknown cause," Lesser stated. "Lyme disease would be one of the things in the differential diagnosis. One patient was seronegative, and they were able to demonstrate spirochetes in the vitreous. So sometimes it's appropriate to test the vitreous in a patient. Probably the most common thing I would think about in a patient with persistent vitritis of unknown etiology might be lymphoma, but Lyme disease is something to be aware of."

One patient who had opthalmitis lost his vision completely although he had been treated. Subsequently stains demonstrated spirochetes within the vitreous. Spirochetes have been isolated from the iris at least twice.

On one slide Lesser pointed to a small white spot; "That's actually a cotton wool spot, a sign of ischemic disease," he said. It is a nonspecific finding which can be seen in embolic disease or hypertension. However this particular spot coincided with onset of early Lyme disease, and it cleared with treatment, so at least there is a possible association, Lesser speculated.

Neuro-ophthalmologic manifestations of Lyme disease.

Some of the eye findings relate to neurologic disease.

· Abduction nerve weakness, classic 6th nerve palsy as sign of meningitis, with dramatic papilledema. This has been referred to occasionally as pseudotomor cerebri, an inappropriate term, as that is a strictly defined disease with strict criteria, with elevated intracranial pressure of unknown origin.

· Meningitis, manifesting primarily with headaches, somnolence and papilledema. For some reason, that's seen much more frequently in children than in adults.

· Isolated 6th nerve palsy is nowhere near as common as 7th nerve weakness. Abduction weakness is 6th nerve, in one patient it lasted about six months and resolved with IV treatment.

· Bilateral orbicularis weakness (eye-closing muscle) The patient was classed as bilateral 7th nerve paresis.

· Bell's. In endemic areas, perhaps 25% of patients who had "idiopathic Bell's palsy" may really have Lyme disease.

The optic nerve may be involved in numerous ways; optic neuritis, optic atrophy, neuroretinitis, and perioptic neuritis. A common cause of neuroretinitis is cat scratch fever (bartonella), but Lyme disease is in the differential diagnosis.

"When you see this picture of disc edema and neuroretinitis, and the macular star like that, the one thing you can tell patients is they are NOT at risk for MS, or demyelinating disease," Lesser said. "For some reason MS never presents with this picture; the picture is much more common with idiopathic or infectious cause."

Patients with optic neuritis all had associated systemic symptoms which strongly suggested some other disease like Lyme disease. In a patient who has routine optic neuritis, the risk of developing MS in 5 years is between 15% and 50%, and probably at 15 years is probably closer to 75%, at least for women, Lesser claimed.

Lesser presented a dramatic example of what Lyme disease can do. In the early 1980s, a 63-year old gentleman presented with an isolated 6th nerve palsy which did not clear, and then went on to develop other cranial neuropathies. In the late 1980s he developed optic neuropathy, infiltrative disease within the optic nerve. His visual field was dramatically restricted. The Lyme disease can directly invade the optic nerve. His MRI scan again showed diffuse enhancement in the periventricular region, which went along with diffuse neurologic Lyme disease.

Another case, this one a child whose MRI showed enhancement of 5th nerve, although there was no clinical 5th nerve dysfunction, and her symptoms were of the 7th nerve. She had a drooping lid and swollen periorbital area which got better after treatment. Several similar patients also responded to treatment.

Eye findings have been seen in some other spirochetal diseases: Lesser produced slides of classic syphilis with interstitial keratitis, significant uveitis with syphilis, including the posterior adhesions seen in Lyme disease. Retinal vasculitis is seen in syphilis but not known in Lyme disease. The spirochete can affect any part of the eye. Leptospirosis was shown with classic conjunctival effusion, and a leptospirosis patient with disc edema, inflammatory disease round the disc.

Lesser recommended that clear cut clinical correlations be observed before attirbuting eye symptoms to Lyme disease.

Continued on next page

The Vaccine

The vaccine, which has completed apparently successful trials and is scheduled for release this summer, has been hailed as the final solution to the problem. But is it? **Denise Foley**, PhD, assistant professor in the Department of Microbiology at Chapman University near Los Angeles, is doing research which suggests that the vaccine may not be all that it is cracked up to be. [*Foley's comments on the ospA vaccine were published in Lyme Times 21 – Ed.*]

The development of a human vaccine was a logical sequel to the dog vaccine which was released several years ago after pressure from the developer and from the public, and many veterinarians felt that FDA approval was premature, and still have questions about its efficacy. The vaccine went from trials to market without the rigorous review which would have been required for a human product. Pet owners demanded the vaccine because they had heard about Lyme disease, and many vets gave in to the pressure. Now it seems that the same pattern may be followed with the human vaccine.

Previous studies have reported that the protection afforded by a vaccine which targets OspA is incomplete. BJB Johnson reported on incomplete protection of hamsters (Vaccine 13, 1995). WT Golde reported on reactivity with specific epitopes of OspA (Infect Immun). Phillipp reported on the presence of Bb in tissues of vaccinated animals (Vaccine 15, 1997). OspA is not expressed in vertebrate hosts. Additional components may be needed for an effective vaccine.

Little attention has been paid to the question of asymptomatic (latent) Lyme disease. At present the conditions that trigger active infection are not known. In one experiment, 4/11 vaccinated animals became infected. Symptoms may not manifest, but spirochetes remaining sequestered in the tissues can later develop into full-blown disease.

Foley and her colleagues followed antibody titres in animals that had been inoculated three times. After the third dose, titres declined rapidly. She expressed concern that the OspA vaccine does not address the problem of OspA heterogeneity in Bb strains.

Calendar

12th International Scientific Conference on Lyme Disease and Other Spirochetal & Tick-Borne Disorders

April 9 & 10,1999
New York City

Deadline for submission of Poster Submissions - 2/25/99. For more information contact:

Lyme Disease Foundation,
One Financial Plaza,
Hartford, CT 06103
860-525-2000
fax: 860-525-TICK

Official hearing on Lyme disease

February 24, 1999, 10am
Legislative Office Building, Hartford, CT

Connecticut State Attorney General Richard Blumenthal will hold an official hearing on Lyme disease to discuss problems faced by patients regarding undertreatment, insurance denials, etc**.** Call Christopher Montes at 860 673-8759 or Jennifer Jaff at the Atty. General's office at 860 808-5358 for more information.

VIII International Conference on Lyme Borreliosis and other Emerging Tick-Borne Diseases

June 20-24, 1999
München Park Hilton
Munich, Germany

All correspondence and inquiries should be addressed to the Administrative Secretariat: Lyme '99, c/o AKM Congress Service, Clarastrasse 57, PO Box 6, CH-4005 Basel, Switzerland, Tel ++41 61 691 51 11, Fax ++41 61 691 81 89, Email akm@aluewin.ch.

Scientific Secretariat are PD Dr Bettina Wilske and Dr Volker Fingerle of Max von Pettenkofer Institut. Email: Bettina.Wilske@mvp-bak.med.uni-muenchen.de.

More on the International Conference in the next Lyme Times.

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