

the Lyme Times

NUMBER 25

Education, Support, Advocacy, Research

APRIL-JUNE 1999

New British Lyme Disease Foundation

by Marc C. Gabriel

As Lyme disease and other tick borne illnesses are identified and described outside the United States, new charities and foundations are being established to support disease education and research.

The British Lyme Disease Foundation is a new organization which is currently striving to provide the latest available information to patients and doctors alike. Their long term goal is to fund research into the disease, its proper diagnosis and ultimately to finding a cure to chronic Lyme which will be of global benefit.

Lyme disease is officially recognized and reportable to health authorities in the UK, but little information is available.

“We know Lyme has been active

See **British Lyme** on page 19

Vaccine promoters gear up for Spring nymphal tick season

Lyme vaccine manufacturer SmithKline Beecham has recently completed a study which shows that their vaccine, LYMERix, is effective when three doses are given over a two-month schedule, according to a report given by Dr. Dennis L. Parenti said at the annual meeting of the Infectious Diseases Society of America. LYMERix was approved by the FDA based on a 12-month dosing schedule, but two-month scheduling will provide greater flexibility and convenience.

In the original clinical trial, which involved nearly 11,000 people, three doses of LYMERix given over a 12-month period had 76% efficacy in

preventing definite Lyme disease that year and 100% efficacy in preventing asymptomatic infection (N. Engl. J. Med. 339[4]:209-15, 1998), based on conservative diagnostic standards. The results led an FDA advisory panel last spring somewhat reluctantly to recommend approval of the vaccine.

Vaccine promoters expect that annual boosters will be necessary, preferably in April so that maximum protection is in effect at the time of maximum risk - the Spring nymphal tick season. Patients require very high antibody titers for LYMERix to be protective, and antibody titers

See **Vaccine** on page 13

Ticks carrying Lyme found in State Parks in Malibu

Ticks that tested positive for Lyme disease have been found in Tapia Park and adjacent Malibu Creek State Park, Los Angeles County health officials reported last week [end of March].

The first confirmed Lyme disease-bearing tick in the county was found last year in Topanga State Park, part of the Santa Monica Mountains National Recreation Area.

“We found 37 male and 28 female ticks in that area, and they were divided into seven pools of eight to ten,” said Dr. Roshan Reporter of the Los Angeles Department of Health Services acute communicable disease control unit. “Two of the pools were positive for Lyme disease.”

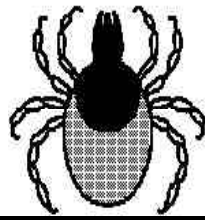
The ticks were found in low

See **Infected ticks** on page 13

Inside...

Dr. Allen Steere lecture with commentary by Jean Hubbard.
Page 34

NUMBER 25
APRIL - JUNE
1999



the

Lyme Times

©

Publication of the Lyme Disease Resource Center

In this issue...

Letter from the Editor

- 3 Editorial
- 4 Letters
- 5 Beginners Pages
- 8 Patient Story
- 10 Patient Support
- 18 National News
- 20 Regional News
- 28 Conference Reports
- 37 Subscription form
- 38 Order form
- 40 Calendar

Features

- 6 Interview with Dr. Kenneth Liegner, Lyme expert from New York
- 11 The Jarisch-Herxheimer Reaction, by James Katzel, MD
- 12 Lyme disease may cause psychiatric symptoms, by V. Sherr, MD
- 14 Vaccine position paper, LymeNet Editors
- 22 Massachusetts campaign to secure new reporting form, by John Coughlan

Dear Readers,

June is turning out to be an exciting month. I had just about "put this issue to bed," when several late-breaking stories arrived and demanded to be included. Therefore, you will find at least two urgent requests for action: Massachusetts residents, and indeed any Lyme patient who can relate to what is happening in that state, need to write to Governor Cellucci to complain about Public Health Department inaction and foot-dragging in the matter of Lyme disease reporting. The Lyme Times (#23) has already reported on the new reporting form thoughtfully and carefully designed under the leadership of John Coughlan, State Coordinator of the Massachusetts Lyme Disease Coalition. The Public Health Department has chosen, once again, to use their outdated form. Read the story, get out your pen and paper, and write to the Governor. Even a short note will help. Remember, your tax dollars pay their salaries.

The other urgent request concerns a class action lawsuit which is being financed by Susan Draddy of Westport, Connecticut. Ms. Draddy, who is president and CEO of her own company, has Lyme disease and is angry about how she and others have been treated by their insurance companies. She has engaged a lawfirm to represent herself and others who have had their Lyme

treatment limited by their insurance companies. Read the story and make a call if appropriate.

Recently, Lyme patients were responsible for instigating hearings with the Connecticut Attorney General. The meeting led to the introduction of legislation requiring insurance companies to pay for whatever care the doctor orders. The legislative session will be over by the time you receive this, but calls and letters to Connecticut legislators are still in order. The original patient-friendly bill was scrapped.

Lyme patients aren't the only people whose lives are too busy to get involved - the world is full of people like that. But we can't expect someone else to do our work for us. Some will contribute a lot; others will contribute a little. But everyone should contribute something. I hope you are excited, as I am, by these new developments and feel inspired to do your part.

One last word about this issue of the Lyme Times. We tried to focus on vaccine issues in more depth. We think it is important for you to understand that the effect of the vaccine on people with active or latent Lyme infection is not known.

Phyllis Mervine, Editor

The Lyme Disease Resource Center was founded in 1990 as a nonprofit 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

April-June, 1999

Publisher

Lyme Disease Resource Center

the Lyme Times Staff

Editor: *Phyllis Mervine*Associate Editor: *Jean Hubbard*Contributors: *Marc Gabriel, Harold Smith, Brian Carroll, Lynn Lane, James Katzel, Virginia Sherr, John Coughlan, Dorothy K., Rae Record, Bruce Fletcher, Carolyn Cramoy, Peter Rohleder*

The Lyme Times (Library of Congress card no.92-595999) is published four times a year by the Lyme Disease Resource Center PO Box 1423 Ukiah CA 95482

Ukiah CA 95482

Address correspondence to:

Phyllis Mervine, Editor

the Lyme Times

PO Box 1423

Ukiah CA 95482

or email at <pcm@pacific.net>

Individual subscription rates 1 year (4 issues): domestic \$25; Canada & Mexico \$35; Foreign \$40. Institutional/Library rates \$50. US funds only, please. Send check to: LDRC

PO Box 707

Weaverville CA 96093

Send address changes to:

Nancy Brown

PO Box 707

Weaverville CA 96093

or email LDRCsec@snowcrest.net

Include both old and new addresses, including zip code.

The articles in the Lyme Times are not intended as medical advice regarding the treatment of any symptoms or disease. Medical advice of your personal physician should be obtained before pursuing any course of treatment. The Lyme Times makes no express or implied warranties as to the efficacy or safety of any treatment in its articles or letters and disclaims all liability for any use of any such treatment. Opinions expressed in articles are those of the authors alone and are not necessarily those of the Editor or the LDRC.

Republication of any portion of the Lyme Times without written permission is prohibited. Please contact the Editor if you wish to duplicate articles.

To submit articles, please send electronic files on disk to the Editor or via Internet to <pcm@pacific.net>. Original articles are preferred. Published articles become the property of the Lyme Disease Resource Center.

© Copyright 1999 Lyme Disease Resource Center.

Guest Editorial

Monkey see, monkey do?

by Harold Smith, MD

Recently a study of the efficacy of the OspA vaccine in monkeys was reported in the journal, **Vaccine**. The researchers found that, after vaccination, monkeys bitten by ticks still became infected. That the infection was found in skin and disseminated to many other tissues was confirmed by histochemical staining and PCR analysis. At autopsy the vaccinated monkeys demonstrated infection by *Borrelia burgdorferi*. The authors found fewer borrelia and less inflammation in the vaccinated animals compared to controls but the numbers by PCR were not significantly different between the two groups.

Another finding was the failure of all vaccinated animals to seroconvert by Western Blot testing. (in fact, no bands were found). And although there was some skin inflammation, it was minimal in the vaccinated animals. What do these findings suggest?

One hypothesis suggested by the authors is that there really was no significant infection because the animals did not form antibodies detectable by Western Blotting and because there was little inflammation in tissues on microscopic study. Another hypothesis they put forward is that there was infection but that the borrelia were a strain which escaped agglutination in the tick midgut and were not very pathogenic. They hypothesized that in time these "weak" borrelia would be cleared from the disseminated tissue sites.

On the contrary, it may be that these borrelia escaped detection and antibody formation simply because there were not enough borrelia injected into the skin to stimulate a good immune response. A negative Western Blot in this situation may

represent dangerous immune evasion. After all, the skin is our natural vaccination site. Likewise, is there little inflammation at microscopic study because there is little infection, or is it because without antibody formation and microbe tagging for killing there is no inducement of inflammatory response? The authors did not suggest this possibility.

The absence of inflammation and antibody formation despite direct evidence of spirochetal presence is also found in the bad outcomes of congenital borreliosis. These fetuses may be infected (without skin inoculation) in the first trimester when the immune recognizing system has yet to develop. Yet the fetal outcome is disastrous (T. Gardner in "Infectious Diseases of the Fetus and Neonatal Infant").

The best case scenario for the vaccinated monkeys is that some borrelia did disseminate but that they would be recognized by the immune system and cleared over time. The worst case scenario is that the monkeys did not form good immunity to any of the other borrelial antigens except OspA, since there was little skin inoculation. Borrelia spread directly via blood to all tissues. Over time this disseminated infection would cause serious illness, although more slowly than in control animals.

For the human considering vaccination, the study raises questions about the dangers and efficacy of vaccination. The monkey model of borreliosis is faithful to human infection. It is possible that after vaccination borrelia will still become disseminated into tissues. It is possible that, like the monkeys, some vaccinated victims will not form Western Blot bands except for the OspA. Thus they will be infected but

Continued on next page

not detected. If there is no reliable direct testing available, these victims, over several years, may be misdiagnosed as MS, JRA, ALS, SLE, Fibromyalgia and chronic fatigue, or one of the other idiopathic diseases which share features with borreliosis. As a result, it will appear that borreliosis has been defeated by the vaccine, while other idiopathic diseases begin to rise in numbers.

The patient considering vaccination needs to ask these questions when consulting with the doctor administering the vaccines. When we study the history of borreliosis and man, borrelia has been a more formidable foe than at first appearances. Vaccination is not the easy answer.

his or her (the doctor's) own inability to diagnose or treat a disease. The red flags started flying for me when Chapter 8 got to psychosomatic considerations and hypochondriasis. I think many Lyme victims have, in their quest for a diagnosis, been told it was all in their heads. "Lymies" in this area do not go to Johns Hopkins for treatment and they warn off people who ask them for help finding a doctor. It was disheartening to me to learn that I couldn't count on help from Hopkins, a well-known medical facility only an hour and a half from me.

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.

Patient runs into Catch 22 - Lyme isn't covered, but symptoms are Lyme

Just read my first copy of the Lyme Times. Wonderful work you're doing.

The CDC position paper on the vaccine is full of incorrect data, blood tests included. This continual assumption by governmental agencies does continue to influence the courts of our land in respect to positive diagnosis of tick disease based solely on blood test results.

Coincidentally, we just received an unfavorable decision from a Federal Judge denying me social security disability (reimbursement of my 29 years of paying into the system) so-called "insurance." This, after an appeal of a year ago, and a year before that. The rendered decision was because, "prior to Dec. 31, 1995, the claimant did not have positive blood test for Lyme,... which also is not deemed by Federal Laws to be a disease covered under "totally disabling diseases." Unbelievable.

He totally dismissed all physical history and diagnoses from 1988 to 1995, and all positive blood results for Lyme, babesiosis, and ehrlichiosis from 1996 to date. He stated the fibromyalgia and chronic fatigue are

covered diseases, but decided that those two chronic disorders must have been misdiagnosed, and really were Lyme (so weren't covered either).

Aside from this personal defeat with the system, I was saddened to see how much a Federal Judge relied on positive blood tests, and again wished the CDC had drafted a better document.

**Melanie Smith
Glenmoore, Pennsylvania**

Sounds like it's time to contact your elected representatives. This egregious distortion of diagnostic standards should not be allowed to stand unchallenged.

Doctors avoid responsibility by blaming patients

Could I comment on Alan Barbour's Lyme book? I don't personally like his approach or attitude and I've heard similar comments in a support group. His is the establishment view at Johns Hopkins, which is apparently a fine institution in other fields but has a bad reputation among Lyme victims.

You know there's trouble when a doctor starts blaming the patient for

Thanks so much for the work you are doing. If it hadn't been for people like you and the support group and a couple of very good books in the local library, I'd be in much worse shape.

**Name withheld by request
Frederick, Maryland**

Lyme patient with ALS dies

Tim contracted Lyme while sitting in the grass with his buddy watching an auto race in Lime Rock, Connecticut, approximately six years ago. Both Tim and his friend were bitten by ticks. Tim's companion sought treatment immediately, and has been symptom free ever since. Tim delayed treatment, although a year later he was examined by a specialist in New York and was told he had Lyme. Tim declined treatment. He developed ALS-like symptoms, eventually contacting me on the internet. After he moved to the West Coast, I referred Tim to another doctor who also tested him serologically, diagnosed him clinically, and began treatment. Unfortunately Tim continued to decline in health and eventually had to relocate back to New York from Los Angeles for financial reasons. At the high point of Tim's production work in the entertainment business, he was extremely successful. Tim explored all avenues of treatment both

traditional and non-traditional (HBO, homeopathy).

To my great sadness, I just heard of Tim's passing. My husband and I will not forget the pleasurable afternoon we spent with Tim when he lived in Los Angeles, on the

canals of Venice Beach. Today I am keeping a box of Kleenex by my desk at work. I have to cry over a dear friend whom so many kind people tried to help.

Barbara Barsocchini
Malibu, California

Webb Terrace, Hull Street, Silver Hill, or Adanti Drive that have already contracted Lyme disease. This illness should not be taken lightly. It can affect the skin, heart, joints and the nervous system with symptoms that range from mild to very severe. Also, if Lyme disease is not diagnosed and treated early it can become chronic. Don't become the next victim!

Please read the enclosed "prevention tips" and accompanying brochure and you will be in a great position to safeguard your family again this year. If you have any other questions regarding Lyme disease, feel free to give me a call.

Have a healthy and safe spring and summertime.

Best Regards,

Brian

P.S. Pets can also get Lyme disease. Keep them safe too!

Beginners' Pages

A friendly reminder from a local Lyme patient

by **Brian Carroll**

Mr. Carroll composes an annual letter for his neighbors in Wilton, Connecticut.

Dear Neighbors:

It's that time of the year once again. The Lyme disease carrying ticks are already on the move in our neighborhood. The numbers for 1998 were just tallied and as I had predicted in last year's letter, it wasn't a good year. During 1998, Connecticut had a total of 3,435 reported cases of Lyme disease which met the CDC's surveillance criteria - the highest annual total ever reported in the state. The 1998 incidence of Lyme disease in Connecticut also reached a new record high of 105:100,000. Unfortunately, the best estimates are that these reported cases only account for 10% of actual cases. Putting this into perspective, it means there were approximately 35,000 new cases of Lyme in our state just last year and that for every 100 residents of Connecticut, one contracted the illness. This is a big deal.

What should we do? Well, it doesn't mean that we have to shut ourselves inside the house or give up any of our favorite outdoor activities - it simply means we should learn what measures can be taken that will decrease our chances of acquiring the illness. Prevention, and recognition

of the early Lyme disease symptoms are the most important keys.

You may recall from the flyer that I distributed last year that there have been a number of people, including myself, who live on either

Tips For Avoiding Lyme Disease

- **Stay Away:** when possible, avoid tick-infested areas, especially deep grass or moist wooded areas. Try not to sit on the ground or grass near such areas.
- **Dress Wisely:** wear light-colored clothes which helps you to see ticks more easily on your clothing.
- **Cover Up:** wear a long-sleeved shirt and long pants outdoors. Tuck shirt into pants and pants into socks and wear a hat or cap.
- **Spray Away:** tick repellents are useful, though controversial. Most contain DEET which can be sensitive to some people, especially children. Permethrin-based repellents such as Permanone can be a safe and effective alternative. Spray repellents on your clothing, never directly on the skin.
- **Do a Tick Check:** conduct frequent tick checks, inspecting clothing and all exposed skin. Shower and shampoo your hair after being outdoors.
- **Practice Pet Care:** carefully check pets for ticks, especially around their ears, neck and head.
- **Outsmart Lyme:** be mindful of heightened incidence of ticks in your area, especially during, but not limited to, March through November.
- **Tick Removal:** If you find a tick embedded in your skin, place a fine-pointed (blunt, not sharp-nosed) tweezer as close to the skin as possible and gently pull the tick straight out. When tweezers are not available, use gloves or at the very least, a tissue. NEVER use bare hands to remove a tick because infected juices can be absorbed into

Continued on next page

the skin through cuts that you may not even be able to see. Once removal is completed, thoroughly clean the bite site with an antiseptic such as alcohol.

Do not kill the tick - put it in a dry vial or jar (air-tight is OK) with a moist blade of grass and take it to a reliable lab for analysis. NEVER use

heat (e.g. lighters, matches) or any chemicals or solvents (e.g. vaseline, lighter fluid, nail polish) in an effort to coax the tick out. This may cause the tick to regurgitate the contents of its gut, including the bacteria into the host. Also, do not squeeze the main body of the tick since this also may inject the contents of the gut into the host.

as possible and avoid crushing it. Gently pull it out with tweezers. Then there's the question of whether it should be treated prophylactically with antibiotics. That's very controversial. One side says not to because the risk is so low that it's not justifiable. They say if you have a tick attachment, then observe. The only problem is, what if you don't develop a rash? What if a portion of those people did have disease transmission but it takes months or years to become manifest?

Q: What is your opinion of the new vaccine?

A: I think the work they are doing is interesting. I think the jury is still out, even though it was approved for use. I'm sort of reserving judgment. I'm not convinced of its safety or efficacy.

Q: How does Lyme work in the body?

A: It's a spirochetal bacteria. It has a very complicated life cycle. It may not be just a spirochete always; it may be able to change its form depending on the conditions it encounters and, for example, adopt cyst-like forms. There is now evidence that it can adopt an 'intracellular location' meaning that it can be inside the cells where it is protected from the action of certain antibiotics and protected from our immune fighting capability. Contrary to popular opinion, this may be a much more difficult infection to deal with than people thought.

Q: What are the long-term symptoms and long-term health implications if this is not caught?

A: Medical science is in the process of discovering that. We are still in a phase of relative ignorance. There can be many varied and long-term consequences of what I am quite convinced is a chronic infection. The debate is this: Is it due to active, ongoing infection or is it something different? Some physicians think that if a patient remains ill after being treated, he or she must

Expert emphasizes complexities and uncertainties of Lyme

Q & A for the Month of May reprinted from the online AmericasDoctor.com website. Dr. Kenneth Liegner is an internist with a specialty in critical care medicine. He runs a private practice in Armonk, New York.

Q: What are the regions most affected by Lyme disease and during what months are we most likely to be infected?

A: If you live in an endemic area it's very difficult to avoid getting infected. The most well-known endemic is the Northeast, New Jersey, lower Hudson Valley, Coastal Connecticut, New England, and the mid-Atlantic states. But I think there is a lot more of this disease in other areas that are not billed as being hotbeds. In the Northeast, the key months for infection are from April through September and October. The nymphs are out in April, May and June, and they are thought to be the most important in disease transmission because they are small and hard to see. The larvae hatch from the eggs in July and August, and those are not thought to be highly infected. The adults, which are infected at a rate of 50 percent, are most active in the fall.

Q: What is the best way people can protect themselves?

A: The best way is not to go into tick habitat. But on the other hand, you can't really live that way unless you want to remain a city dweller and never venture out of paved areas.

You can use barrier methods such as tucking your pants into socks. You can spray your clothing with a permethrin spray, which is a natural insecticide. That has been used by the Army and has been found to be a pretty effective barrier. Of course, if you're out, check yourself. If you do find them, try to remove them as soon as possible. Early tick removal is thought to help minimize the risk of transmission.

Q: What are the immediate symptoms?

A: The classic symptom is a bulls-eye rash. But studies are showing that a lot of people develop rashes that are in no way classic. They come in a wide variety of shapes and sizes and colors. You can have a rash without any other symptoms. You can have a rash with malaise, fever, headache, stiff neck, and joint pain. Or you could have those symptoms without the rash. Studies show at least 20 to 50 percent of people who contract Lyme disease do not have a rash.

Q: What is the best course of action?

A: If you have a definite tick attachment, remove the tick as soon

have a post-infectious syndrome or some kind of lingering reverberations of the immune system (for which it is wrong to treat with antibiotics).

Q: What are the long-term symptoms?

A: Neurologic illness is the most worrying and most difficult to deal with. There is a wide range of symptoms, but some people will develop thinking difficulties. It can be mild or very profound, to the point where people cannot function. They have to go on disability and give up their jobs. It takes people who were very high functioning and destroys their lives. Public health officials should be examining these effects — looking at statistical trends and incidences of neurological illnesses like multiple sclerosis, motor neuron disease, and dementia in patients who have had Lyme disease.

Q: Given that antibiotic treatment is so problematic, how should people be treated?

A: As unsatisfactory as it is, it still remains the mainstay of treatment. Some physicians think the normal course of action is a couple of weeks of antibiotics and the patients are sent on their way. Many of those people suffer and deteriorate. Every patient needs to have an in-depth evaluation with a careful history and physical exam, thorough testing of blood and urine, and maybe joint or spinal fluid. If there is evidence of neurological involvement, we'll do a neurologic evaluation.

Q: How well do we — the public and physicians — understand this disease?

A: I'm mindful of how much we don't know. I have many patients who, due to ignorance of physicians, go on quite an odyssey to get a diagnosis. Lyme is poorly understood. Unless you have studied it in depth, all you have is a soundbite concept — tick bite, rash, swollen knee. Lyme disease is much more than that. Although we have areas of hotspots, Lyme disease has been

reported in most of the states at this point. But some physicians will not even consider the possibility that their patient has it. It leads to delay in diagnosis and in treatment. It's a myth that patients with late Lyme disease invariably test positive, so the sickest patients are not getting treated.

Q: What is the success rate of treatment?

A: It has been the rare patient who does not respond at all to treatment. On the other hand, there are a lot of patients whose condition will improve but they don't get totally well. And when you stop treatment, sooner or later they go down hill again. Some patients you can treat, but not cure.

Q: What can these people do? How do they live their lives?

A: The majority of patients can live decent and manageable lives. But the majority of physicians and academicians do not believe it's a chronic infection. Even if the patient is sick and comes back with ongoing complaints, they are often met with a stonewall. The doctors will insist they are cured.

Q: How many people have Lyme disease?

A: My best guess is at least a couple of million. Using strict criteria from the Centers for Disease Control and Prevention, there have been about 100,000 total cases reported since the epidemic began. But the CDC acknowledges that for every one case, there is another 10 or 20 cases that do not get reported. That's got to be one or two million people who have the illness, whether they know it or not.

Q: A final word?

A: It is critically important to accept the idea that this is a chronic infection. If you don't, there is no incentive to develop better methods of treatment. We could have better treatments today, but nobody is working on it. As long as you live in a fantasy world you're not going to do the research that is needed to deal with the situation.

If you have any questions about your health or your child's health, visit our Medical Library or click on Ask-a-Doc for a one-on-one, live chat with an America's Doctor. We're here 24 hours a day with free, confidential answers to all your health questions.

Some tick removers work better than others

From "Tick Tools" by R. Stuart (from BackPacker magazine, May 1997.)

The Pro Tick Remedy: This nickel-plated steel tool resembles a skinny military dog tag with a precision V-shaped notch in one end. The notch captures and securely holds the tick - even a small one- for safe removal. A clinical study performed at Ohio State University reported, "The Pro Tick Remedy had the highest success over other tools in removing most of the tick's cement secretions intact, while causing the least damage to the

tick." Since it lacks sharp points, the Pro Tick is safe for use on squirming pets, children, and hard-to-see areas of your own body. This handy tool fits on any key chain or zipper. Pro Tick Remedy, SCS Ltd., P.O. Box 573, Stony Point, NY 10980; 1-800-749-8425 (\$3.00). This company also sells the best acaracides (tick-killing sprays).

Uncle Bill's Silver Gripper: This one wasn't mentioned in the Ohio

Patient story

Vaccine study volunteer has severe adverse reaction to experimental vaccine

by Lynn Lane

State study, but the clinicians did report that “fine forceps have traditionally been the tool of choice for mechanical removal of ticks.” With that in mind, you couldn’t do much better than Silver Grippers. The short shaft and wide surface for finger placement provide easier control than conventional tweezers. The sharp, precision points may make this tool inappropriate for use on wiggling children and pets, though. A convenient holster allows you to safely carry these in a pack pocket or on a key chain. Because they’re useful for more than just removing ticks, Silver Grippers should be in any backpacker’s first aid kit. Uncle Bill’s Silver Gripper, El Mar Inc., 43 Cody St., West Hartford, CT 06110; 1-860-953-2527 (\$5.25)

The Tick Nipper/Tick Plier: The Tick Nipper resembles a set of plastic wire cutters with a 20X- magnifying lens built into the uniquely shaped handle for closer inspection of the culprit. The Ohio State study suggested that unskilled users might be safer with these than with conventional tweezers or forceps. Unfortunately, the Nipper, like ordinary eyebrow tweezers, severed the mouthparts on a few ticks when used improperly, according to the Ohio State report. If the directions are followed carefully, however, this can usually be avoided. Because the tool lacks sharp edges, it’s safe to use on children and pets. Tick Nipper/Tick Plier, Sawyer Products, P.O. Box 188, Safety Harbor, FL 34695; 1-800-940-4464 (\$5.99)

The Tick Scoop: Resembling a kitchen measuring spoon with a V-shaped slot in the bowl’s edge, the Tick Scoop may be suitable for those uncomfortable with finer instruments. It’s easy to use on adult ticks, and is safe for children and pets. Tick Scoop, Sawyer Products, P.O. Box 188, Safety Harbor, FL 34695; 1-800-940-4464 (\$2.99).

I am writing to you in hopes of disclosing to the public the definite possibility of severe adverse reactions to the Lyme vaccine. My husband and I are living examples of what can happen to any person living in an endemic area.

Totally unaware that we had a long history of Lyme or “Lyme-like” symptoms, we volunteered to participate in the SmithKline Beecham Lyme vaccine trial study. I was forty-one years old.

We live on Cape Cod, Massachusetts, in a wooded area and have many animals. My sister and her daughter had been quite ill with Lyme (they live on Cape Cod, too) and my husband and I were interested in the study. Originally, we were supposed to receive \$350 for participating, but once signed up, that proposal was withdrawn. We figured, “Oh, what the heck, it’s for a good cause.”

We had blood drawn, and by Western blot testing were told we were all set to receive shots. Our first inoculation was March, 1995. The second inoculation (first booster) was in April, 1995. At the time I was seeing a chiropractor for neck and back pain. He noticed a decline in my physical well-being after receiving the vaccine. I thought it had nothing to do with the vaccine, even though it was a double-blinded study [*i.e. she didn't know if she had received the real vaccine or not - Ed.*]. The chiropractor did not agree. He was concerned.

On July 4th, after a busy day playing volleyball and walking two miles or more to and from the

fireworks, I went to bed pain-free and no injuries, only to wake the next morning with an extremely swollen left knee that I could not walk on. That was the beginning. At this time, I naively did not suspect that my knee problem had anything to do with the vaccine. I just plugged along - what else could I do as the mother of three children ages 15, 12 and 5? I attributed it to growing older. However, after the third inoculation (second booster), which I received March, 1996, within two days I became very, very ill. Having suffered PMS all my adult life, I thought maybe this was the reason - but something was different this time. Something was terribly wrong with me. I decided that maybe the chiropractor was right, so began my research on the subject of Lyme disease and its many symptoms. With every piece of literature I read -- books, cases, testing, causes, cures, controversy -- I became increasingly concerned. So many symptoms were just like mine. I contacted the study doctor who had administered the inoculations and he agreed that I should come in for an evaluation.

Waiting for the study doctor while my four-year-old played, I went over and over in my head just what symptoms and concerns I would tell him about -- rashes on my face and body, severe pain, anxiety, nausea, chronic fatigue, numbness and tingling of extremities, buzzing in my head, brain fog. I expected to be given more blood tests and discuss reasons that would explain my symptoms. But the study doctor quickly looked me over and dismissed me by saying, “You just have

PMS and have also been scratching yourself - you don't have Lyme disease." I left the office in tears. I normally don't worry about things, but now I was worried.

I then chose to order my own Western blot through the chiropractor. On the advice of a representative at the Lyme Care Center in New Jersey, the results were sent to an infectious disease doctor at Boston University Medical Center. The BUMC doctor called me and said I did indeed have Lyme disease, and that I had it for quite some time. He also told me that the vaccine alone could not have given me this test result. He informed the study doctor. I in turn sent a letter to the study doctor requesting treatment as well as withdrawing from the study because I was so ill. The study doctor would not treat me and refused to help me find out what my blood tests showed prior to inoculation. He wanted me to stay in the study until October, 1995 so I could find out what was really wrong with me. I said, "But I'm sick now - that's six months away!"

The BUMC doctor was willing to put me on oral antibiotics preceding an appointment with him in June. The orals were continued until September, 1996, at which time, on the advice of a legal representative recommended by the Lyme Care Center, I decided to attempt an appointment with Allen Steere, MD, the principle investigator in the SKB Lyme vaccine study. The attorney was hoping Dr. Steere might "come clean," so to speak. Dr. Steere diagnosed fibromyalgia, handed me a brochure with information about fibromyalgia, and said, "Good luck." After the X-rays and being stuck with needles, I knew I had gotten nowhere.

Driving was extremely difficult for me, and it had taken so much from me to drive 1 1/2 hours to Boston. I had to stop twice for fear of passing out. I was light-sensitive, prone to migraines, had to tolerate

severe migrating pains down my left leg as well as my hips, ribs, shoulders and both arms. I also had intermittent diarrhea, inability to speak correctly or recall what I said or did a few seconds before. Every single thing in my life became excruciatingly difficult, if not impossible. I felt useless, and to top it off, my research into Lyme disease led to the discovery that all three of my children as well as my husband also had Lyme disease. We are all being treated by the doctor at BU Medical Center. To be sick and have to take care of a sick family and try to deal with the mounting bills because of the loss of income is the most draining experience of my life.

My husband began his treatment -- thankfully, his symptoms were not as severe as mine. It was October, 1996. He was eager to learn whether he had received the vaccine or the placebo in the Lyme trials. In December, he finally went in to see the doctor connected with the study. The doctor would not tell him if he received the vaccine or the placebo, and said, "If you want to find that out, go get a lawyer."

Through our attorney, we did get SKB to admit that I had received the vaccine, not the placebo, but SKB claimed not to be quite sure if my husband had received the vaccine or placebo.

I was on oral antibiotics for one year, with some improvement, until March 1997. We then tried IV long-line catheter to my heart for four months, changing medications once after the first two months. My twelve year old was also on IV for three months at the same time. Stress was high because I could do so little. The pain became unbearable, and I was sure that I would die. I actually wrote a living will.

In July, 1997, I did come close to dying -- my liver functions went into the thousands. (the norm is 0-31). I couldn't eat, sleep or drink without vomiting. My temperature stayed at 103 degrees, give or take a point or

two. I was in constant pain. Every exhale in my breathing was a moan. One night, I awoke with my body shaking uncontrollably. I couldn't talk for fear I would bite off my tongue. My husband scooped up our youngest and managed somehow to get me in the car to take me to the hospital. We were petrified that I was dying.

I went home after the tremors subsided. The pain continued, and I refused to infuse again. The IV line was pulled. In December, 1997, I had to have my gallbladder removed. I lost over 30 pounds and endured much pain and suffering.

I feel I will never be as well as I was before being inoculated. Thank goodness the doctor at BU Medical Center was willing to help me and did not deny my symptoms as did the doctors connected with the SKB vaccine study. My major concern is for the thousands of other people who do not know that there are definite risk factors in taking the Lyme vaccine. Please be sure to be well-informed before you make a decision. To this day we still do not know with what we were inoculated, or how much we received.

In late January, 1998, I received a letter from my attorney stating that there were fundamental flaws in the pre-trial testimonies of his key expert witnesses which proved to be fatal to my case. No more lawyer. So much for compensation. I haven't been able to work for over a year because of my involvement in the Lyme vaccine study. These doctors and the pharmaceutical companies are going to make millions of dollars on the vaccine, and I can't even get a lawyer decent enough to represent me. Is everything all about money regardless of the consequences in human suffering? I have until March, 1999 to file my case, but FOREVER I will be scarred for volunteering to participate in this study.

The FDA approved the SKB vaccine for sale to the public in December, 1998.

Patient Support

Support groups continue to cater to needy patients

A new Lyme disease support group is starting on Long Island, New York. They will meet the first Weds. of every month at 7:30PM at St. Charles Hospital in Port Jefferson.

Organizer Bob Levine writes,

"I am hoping to use this group to distribute information on Lyme, (the real story), as well as offering support to others afflicted with this nightmare. I am ultimately interested in organizing a group with specific political goals to address the many problems with Lyme disease."

He may be contacted at: Phone: 516-434-7697 Office, 516-473-4389 Home; E-mail: omicron@erols.com.

Pat writes: "Still trying to get a support group started in Fishkill, New York, for people in South Dutchess Co. I'm told the demand is great but the first meeting in December had only one staunch supporter of the leader—me."

Meetings are held the second Thursday of each month at Trinity Episcopal Church, Fishkill on the corner of Route 9 and Route 52 (Main St.) The parking lot is on the north side of 9 next to Taco Bell. The entrance door is right on parking lot. All are welcome.

Mississippi now has a newly formed support group. Contact information is:

Lyme Disease Support Group of Mississippi c/o Linda K. Beasley
1540 Adams Lake Rd. Utica, MS
39175, tel. 601.885.2064.

They have not yet determined the location and times for their monthly meeting but plan to in the next few weeks.

The Morris Area Lyme Disease Support Group meets the 3rd

Tuesday of the month-(except December) in the Parish House of the Presbyterian Church- 65 South Street, Morristown, NJ. from 7-9 p.m. Facilitator and contact person for the meeting is Mrs. Elsie Anderson, tel. 609-409-0923. Parking is available and all are welcome.

Tennessee patient advocate Bonnie Huntsinger wrote:

"First of all, I wanted to tell you that our wonderful SG leader, Norma Engelhardt, teaches science at the TN School for the Blind. Her whole family of 4 all have Lyme. She is about 45 yrs. old. Talk about an ACTIVIST... Norma was a missionary over in Zaire at the very site of the Eblola outbreak hospital as it was being built. She caught malaria in Africa five years before contracting Lyme in Tennessee once back in the USA. She also helps run a support group for women in prison to help them make the transition from prison life back to "normal life". That program is called "DESCISIONS". I tell you, if we had

Only dogs get Lyme in Arkansas

Cindy Goode knew the variety of her symptoms meant Lyme disease, but a doctor she consulted thought otherwise.

The physician told the 29-year-old Conway pharmacist, "We have Lyme disease in Arkansas, but only dogs get it."

"Then should I see a veterinarian?" she shot back.

There was no reply.

From an article in the Log Cabin Democrat

more like her, we could whip this political monster we battle with."

"Norma's group, the Lyme Disease Network Of Middle Tennessee meets on the first Thursdays at 7pm of only certain months. The main four SG leaders and all who want to come may meet every first Thursday, but must first confirm with one of the four "leaders" if they are coming. (We stay in touch constantly on local LD cases and sometimes will meet at a home instead of our regular church hall.)

"We started meeting in 1992 and at one time had as many as 30+ come to meetings. Now we are lucky to have 8-10 show up. Everyone claims they feel too sick to come. So, recently, the four main leaders decided to publically stop meeting every month, in hopes of using the time in between to do more mail-outs, advertise and encourage better attendance."

Norma Englehardt may be reached by email at Aheart@usit.net.

Send news about your support group to the Editor.

Two Lyme organizations announce new websites

Steve Nostrum, Founder of the Lyme Borrelia Out-Reach Foundation has a new web site. Steve has been helping people with Lyme since 1987. Steve is also the columnist in the America On Lyme newsletter "Steve's Corner."

The website can be accessed by typing into your browser: <http://www.angelfire.com/ny/lymedisease/fdn.html>.

The Lyme Disease Association of New Jersey has a new website at <http://come.to/ldanj>.

The Jarisch-Herxheimer Reaction

by James H. Katzel, M.D

From "Lyme Disease 1991-patient /physician perspective"

Dorland's Illustrated medical Dictionary says this about the Jarisch- Herxheimer Reaction: "An increase in syphilitic symptoms after administration of antisyphilitic drugs." Although it is an illustrated dictionary, there is no illustration next to the words. I wonder what they would put next to such a definition. I suppose if they were to illustrate the Jarisch-Herxheimer Reaction, they would have to put a patient with syphilis or, more recently, a Lyme borreliosis patient standing in fright with extremities extended and large circles radiating from his eyes. We're talking about one terrible feeling person.

From back in the 1960s, Professor Harvey described the Herxheimer Reaction as an acute febrile reaction which may develop after treatment of late syphilis has begun. But Professor Harvey felt that this was a rare phenomena and such reactions were more common in patients with paresis, and he felt that they might be associated with a transient increase in agitation and confusion as well as with fever and convulsions. His suggestion was that small doses of adrenal corticosteroids such as 20 mg. prednisone per day usually prevent or ameliorate the Herxheimer Reaction.

Events similar to this Herxheimer type Reaction have been described in other disease states. I recently attended a medical conference where an experienced middle-aged man physician/pathologist described "crashing" and episodes of death after one dose of IV penicillin for children with meningococemia. Whether the death of these children was due to acute, fulminating Waterhouse-Friderichsen syndrome

or whether the deaths were due to a Herxheimer-type Reaction to one dose of penicillin is still unclear. The description of these events, which happened 40-50 years ago, is still vivid in the memories of these physicians. At times they were reluctant (but knew they had no choice) in giving the penicillin to these sick children who they knew would die if not treated and who might die from another cause with treatment.

The Herxheimer-type Reaction is somewhat different in Lyme. Because Lyme is caused by a spirochete, much of what we learn and think about Lyme borreliosis comes from our experience with syphilis. In the early stages of killing the Lyme spirochete (*Borrelia burgdorferi*) with antibiotics this Herxheimer-type Reaction can be found if looked for. Apparently it comes at different times. With I.V. antibiotics it may be noted within days of treatment; with oral antibiotics it may be noted within days to weeks of treatment. When these antibiotics begin to

destroy the Lyme spirochete, a toxin is given off causing either direct reactions or indirect actions through stimulation of the immune system. The symptoms can vary from systemic reactions such as a low blood pressure, fever, chills and hives, to more specific symptoms such as increase in joint pain, headaches, rash or in general, a reversal or worsening of the Lyme symptom complex.

Jarisch-Herxheimer Reaction should be watched for when treating Lyme borreliosis patients, and the patient should be adequately warned about this phenomenon. Mistaking the Herxheimer reaction for an allergic reaction to antibiotics or serum sickness or some other catastrophe might lead to prematurely stopping the antibiotics on the part of the physician or non-compliance in taking the medications on the part of the patient. When starting antibiotics, one expects to feel better, not worse. But if warned that there may be a period where symptoms recur or flare up during this reaction, better compliance can be expected. Herxheimer reactions are at least ten times more common than true allergic reactions to antibiotics.

Steroids are not recommended at this time for Herxheimer Reaction in Lyme patients. The best treatment is knowledge of the process so that panic attacks, anxiety and worry do not occur. Benadryl, which is an antihistamine, can be used to lessen the symptoms, and sometimes changing the dose and/or timing of the antibiotics is needed to make the reaction less symptomatic.

So next time you start antibiotics, ask your physician whether or not you should expect a Herxheimer Reaction to occur. It may be a learning experience for both of you, I'm not aware of any deaths from Herxheimer Reaction in treating Lyme borreliosis. So give me a Herxheimer Reaction over an allergic reaction any time.

Tick Cards

If you want to get nifty cards with the pictures of Lyme carrying ticks on them (enlarged and to scale), you can write away and get 100 free (yes!) from:

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

I use them for educational purposes.

Rita Stanley, NW Lyme Disease Support Network

Lyme disease may cause psychiatric symptoms

by Virginia T. Sherr, MD

Oprah Winfrey featured a television program on July 29, 1998 relating to the epidemic of cryptic diseases, frequently misdiagnosed by physicians today. One articulate patient recounted his history of rages, involuntary commitments to mental hospitals, and the destruction of life quality, until he was diagnosed correctly by a "Lyme Literate Psychiatrist" - the only one of many specialist doctors finally able to recognize the mental symptoms of that tick-borne disease. Proper ongoing antibiotic treatment of the disease brought him back to normal mental health. What is a "Lyme Literate Psychiatrist (LLP)?" An LLP is a psychiatrist who recognizes mental-emotional sequelae of Lyme Disease and its equally nefarious companions - babesiosis and ehrlichiosis. The "literate doctor" listens for evidence of personality change, a remarkable irritability, usually unacknowledged by the patient, but which is often demonstrated by a hostile attitude on the preliminary phone call and during the interview.

Conversely, prominent symptoms may include defiant irritability, with a Parkinson-like lack of expression; there may have been sudden panic attacks, total insomnia, psychotic paranoia, an upsurge of OCD, changes in cognition, memory impairments — especially recent recall, lethargy, clumsiness, depression, mood swings, impulsive hostile outbursts, distractibility, urgent rapid speech approaching mania in some, and/or verbal abusiveness in usually reasonable people. Many recognizable syndromes in the DSM-IV can be imitated by Lyme.

Mental-emotional symptoms usually are intermittent and accompanied by physical symptoms, such

as neurological pains, itchiness, numbness or skin tingling, muscular pains, sinusitis, rashes, TMJ and other joint pains which the patient may not reveal unless opened-ended questions in regard to system after system are posed to the individual.

The spirochete which causes Lyme, the several rickettsial-like organisms which cause ehrlichiosis, and protozoa which causes babesiosis, all may be carried in the same tick bite and may be found in the central nervous system within days of infection and, very much like the Lyme prototype spirochete, syphilis, if the diseases are not treated in a very timely fashion, they may cause multi-system infection which can imitate many other illnesses.

These diseases are very difficult for the body's own defenses to combat. They are also very difficult to diagnose by lab tests. The usual blood tests by conventional labs are frequently falsely negative and by and large are useless. The Lyme ELISA has recently been proven to have a fifty-five percent error rate in the average laboratory. Testing needs to be done in a research-oriented, sensitive lab. I prefer the IGeneX reference laboratory in Palo Alto, California, or BBI in Boston, Massachusetts. I routinely order two Western Blots (IGG and IGM), two ehrlichiosis (HME and HGE), babesiosis, and the ANA panel for symptomatic persons.

I personally walk the path of the Lyme/babesiosis/ehrlichiosis patient. I was bitten repeatedly in the 1980s and early 1990s by the nymph forms of the vector, but my rashes went undiagnosed for years and a disabling illness struck. At last a combination of oral antibiotics and

Mepron is providing real relief in my case. The infections had resulted in a severely painful muscle syndrome, utter weakness, diurnal crises of hyperesthesia pain and sweating, "soft" but disabling neurological symptoms and cardiac arrhythmias. Initially, IV antibiotics saved my life and my psyche. Unlike many infected children, I, as a physician, was able to describe my confusing, bizarre symptoms to a family doctor who recognized the syndrome. I consider myself very fortunate.

Patients being treated with the appropriate antibiotics initially tend to feel far worse for some time due to Herxheimer reactions. Then they gradually feel better and better. Their neurological and psychological symptoms slowly abate. The patient with notable neurological impairments, for example unequal pupils, major memory loss, dementia or paresis — should receive a full work-up, including a SPECT scan with sensitive evaluation for evidence of vasculitis, CNS ischemia, or demyelination.

I recommend that every hyper-irritable, confused, chip-on-the-shoulder, fatigued and/or depressed person with any physical complaints who consults a physician should be tested in a sensitive lab for tick-borne diseases and that a "Lyme Literate Psychiatrist" is the ideal professional to shepherd them as they go through the complex treatment process. In addition to antibiotics, these patients often need psychotropic medications before, during, and sometimes after the treatment for tick-borne diseases. In most cases the hopelessness of "depressed" patients clears up when they find out the cause of their misery and then stop being seen by others and themselves as hypochondriacs.

Until a July 16, 1998 article in the New England Journal of Medicine, describing the epidemic reality of low grade symptomatic babesiosis in the general public during the past and current era, most specialists in

infectious diseases discounted the importance of babesiosis in their patients, and some still do. Some also refuse to treat symptomatic patients who have babesiosis or Lyme Disease with low positive titers.

In the early years of this century, another related spirochete, syphilis, "The Great Masquerader," presented a confusing picture to the medical world. Psychiatrists were the ones who learned how best to diagnose,

treat, and manage this body/mind destroyer. Lyme Disease and its co-infection agents, "great masqueraders of the 1990s," deserve no less than our total attention.

Dr. Scherr practices medicine in Holland, Pennsylvania.

Letter to the Editor reprinted from Pennsylvania Psychiatrist, (Oct. 98) by the kind permission of the Pennsylvania Psychiatric Society

recommends that only people at high risk for acquiring Lyme disease be vaccinated. They say that even in endemic areas, it will be more cost effective to use generic antimicrobials to treat early-stage Lyme disease than to prevent the disease through vaccination. It may be safer, too.

An article in Skin & Allergy News 30(1):10,11, 1999, was used in preparing this report..

Vaccine has its dark side from page 1

appear to fall to suboptimal levels less than a year after the third injection.

But the possibility of vaccine-induced autoimmune arthritis in a genetically susceptible patient subset "remains a theoretic concern of mine, particularly when one is potentially boosting people multiple times," commented Dr. Allen Steere, lead investigator of the vaccine study and professor of medicine at Tufts University in Boston. There may be other side-effects as well.

Theory became reality for Tom Vogler's sixty-year old mother-in-law, who has rheumatoid arthritis. She received the LYMERix vaccine and two weeks later she woke up with the left side of her body paralyzed.

"By the time she got to the hospital, she could only move her head and her right hand," said Vogler. "MRI and CAT-scan are both negative for a stroke. Right now the doctors are talking about transverse myelitis affecting the spinal cord. Her doctor, who administered the LYMERix, is convinced this is a reaction to the vaccine."

Vogler knows a nurse at the same New Jersey hospital who told a similar story: another patient, who had also recently had this vaccine, was admitted two days after his

mother-in-law with near-total paralysis.

People who experience health problems after receiving the Lyme vaccine should use the Vaccine Adverse Event Reporting System (VAERS) of the U.S. Food and Drug Administration (FDA). If enough people have an adverse effect and report it, the vaccine could be pulled from the market. The VAERS form may be found on the FDA website at <http://www.fda.gov/cber/vaers/vaers.htm>, or call the FDA number listed in the Government section of your local phone book.

In a letter to the Philadelphia Inquirer (May 8, 1999) Dr. David J. Chang, professor of medicine at University of Pennsylvania reminds readers that "preventing tick bites and prompt removal of attached ticks should continue even if one receives the vaccine. [Furthermore], the efficacy of the vaccine does not extend to other diseases transmitted by deer ticks. Nor is it likely to be as protective against Lyme disease encountered in other parts of the world. And even if the vaccine is given, there should be no complacency among those vaccinated that they will be fully immune from Lyme disease or other tick-borne infections."

At present, the Centers for Disease Control and Prevention

Infected ticks found in Malibu

from page 1

brush and grass along several trails of the 7,000-acre Malibu Creek State Park and the nearly mile-long Tapia Spur Trail, which leads into a Malibu Creek campground.

Only the western black-legged tick is believed to carry Lyme disease, can be treated with antibiotics, although not always successfully. Symptoms may include a spreading or "bull's-eye" rash around the bite, fever and body aches that if untreated, may develop into long-term illness with complication such as arthritis, irregular heart beat or neurological symptoms.

Those hiking in local areas surrounded by brush are cautioned to regularly conduct tick checks.

California Public Health officials have historically minimized the risk of acquiring Lyme disease in the state, although the vector tick has been found in all but two counties. Studies in some of the northern coastal counties have proven that the risk of contracting Lyme disease in those areas may be as great as the risk in certain parts of the northeast, which is touted as a high risk area.

From The Malibu Times, April 8, 1999.

Lyme disease vaccine discussion and position paper: January, 1999

by the LymeNet Editors

This paper is available on the LymeNet website at www.lymenet.org. Reprinted by the kind permission of the editors.

Introduction

Over the last decade, public health officials have adopted a multifaceted strategy in attempting to contain the global Lyme disease threat. Prominent among the strategies employed has been a strong vaccine development effort. Just as the polio vaccine was the first step in virtually eliminating that disease from the American public health landscape decades ago, immunoprophylaxis against Lyme disease could, in theory, reduce the incidence of new Lyme cases dramatically, thus sparing countless individuals from the chronic form of the disease.

At a hearing convened on May 26, 1998, a vaccine review committee assembled by the U.S. Food and Drug Administration (FDA) recommended approval for a vaccine formulation developed by SmithKline Beecham Pharmaceuticals. Final FDA approval was issued on December 21, 1998. It will be marketed under the product name LYMERix. A second pharmaceutical company, Pasteur Mérieux Connaught, has also conducted Phase III trials and will likely be seeking FDA approval for their own vaccine (known as ImuLyme) shortly. Although the approval of a Lyme disease vaccine would obviously be welcome news, the recommendation for approval did not come easily and was accompanied by several important caveats. According to Dr. Patricia Ferrieri of the University of Minnesota, who chaired the FDA committee, "It's rare that a vaccine be voted on with such ambivalence and a stack of

provisos."

The Lyme Disease Network has received numerous requests from individuals seeking information and guidance on the issues posed by the new vaccines. We don't feel it is appropriate for us to make a specific recommendation as to whether or not individuals should opt for receiving the vaccine — that is a decision to be made by the potential vaccine recipient in consultation with his or her physician. In response to the volume of requests, however, we offer the following discussion of the Lyme disease vaccine effort and a short review of selected issues that were raised by the FDA review committee.

Background

Lyme disease is a multisystemic illness caused by the spirochetal bacterium *Borrelia burgdorferi* sensu lato. The organism is usually transmitted to humans by the bite of an infected ixodid tick. The commonest early manifestation of Lyme disease is the skin rash erythema migrans, sometimes accompanied by non-specific flu-like symptoms, such as sore throat, fever, headache and adenopathy. About 20 percent of patients develop frank neurological signs within the first few weeks of infection, including cranial neuritis, radiculitis and meningitis. Cardiac abnormalities can also occur early in the illness, the most common of which is atrioventricular block, sometimes requiring the insertion of a pacemaker.

Later disease manifestations

include arthritis, usually of the large joints, and a variety of neuropsychiatric syndromes, often involving disturbances of cognition, mood and sleep. Chronic neurological manifestations include disorders of sensation related to spinal nerve involvement, and, less commonly, demyelinating multiple sclerosis-type syndromes, often accompanied by white matter changes on brain MRI scans.

Patients with Lyme disease who are treated with antibiotics early in the course of their illness tend to do well, but treatment of the later manifestations is often less effective. Some retrospective studies have indicated that as many as one-third of Lyme disease patients continue to have persistent signs and/or symptoms after treatment for the disorder [1] [2]. The potential of Lyme disease to cause chronic morbidity has been one of the major motivating factors in the vaccine development effort.

The road to a vaccine

Both SmithKline and Connaught use Outer Surface Protein A (OspA) of *B. burgdorferi* as the stimulating antigen for their preparations. (The SmithKline formulation uses an adjuvant, while the Connaught formulation does not.) While OspA is prominently expressed by *B. burgdorferi* in ticks, its production appears to be down-regulated by the microbe when its tick vector feeds on mammalian hosts. The early antibody response to OspA in humans is weak and fleeting, if it occurs at all.

Several years ago, when scientists first began testing OspA vaccine preparations in mice, they made a startling discovery. The vaccine worked, but its mechanism of efficacy was highly unusual. Instead of priming the rodents' immune systems to recognize OspA and react quickly after challenge by *B. burgdorferi*, the researchers discovered that anti-OspA antibodies in the mouse sera were traveling into the tick's midgut and killing the Lyme spirochetes there, before they were even transmitted to the mice [3]. The prominent expres-

sion of OspA by *B. burgdorferi* in ticks was a vital component of this process.

OspA appears to be a good vaccine candidate for other reasons as well. Compared to OspB, OspC and OspD, it exhibits the least variability between strains of *B. burgdorferi* [4] [5]. Studies advanced by researchers and the vaccine manufacturers on recombinant OspA vaccines in animal models suggest antibody production against this protein is broadly protective against *B. burgdorferi* strains commonly found in the northeastern United States [6] [7] [8]. Another study has indicated that the vaccine was effective against *B. burgdorferi* strains from a more diverse range of geographic locales [9]. The SmithKline Beecham recombinant vaccine employs the OspA sequence of *B. burgdorferi* sensu strictu strain ZS7, which has been shown to be effective in the mouse model [10].

SmithKline Beecham started with small Phase I studies to evaluate safety and efficacy of their vaccine in 350 healthy adults. They then proceeded to Phase II efficacy and dosing trials in 353 adults with no previous exposure to *B. burgdorferi* [11]. Finally, a large scale, multicenter, double-blind, randomized, placebo-controlled Phase III study was initiated to evaluate the vaccine in a larger population. Almost 11,000 subjects received vaccine or placebo at enrollment and 1 and 12 months later, for a total of three doses. Subjects were followed for two years and outcomes were characterized as “definite Lyme disease,” “possible Lyme disease” and “asymptomatic infection” (seroconversion without symptoms). Short-term and long-term adverse events were also recorded. The study results were published in the *New England Journal of Medicine* on July 23, 1998 [12].

Results and discussion

1) Issues of Efficacy

According to the authors of the

study report, 22 subjects in the vaccine group and 43 subjects in the placebo group contracted definite Lyme disease during the first year, for a 49 percent vaccine efficacy rate. During the second year (after the final vaccine dose), 16 vaccine recipients and 66 placebo recipients contracted definite Lyme disease, for a vaccine efficacy rate of 76 percent.

It should be pointed out that the diagnostic criteria used in the study were extremely strict. Seroconversion was required for all post-erythema migrans “definite Lyme disease” cases (only a handful of these were diagnosed in the study), and cases of erythema migrans were not counted as definite unless accompanied by

In the absence of serological confirmation, it is likely that some true LD cases were bumped into the “possible Lyme” category, and were thus excluded from the final analysis.

culture positivity, seroconversion or PCR positivity. Even with these restrictions, the overwhelming majority (97%) of “definite Lyme disease” diagnoses in both the vaccine and placebo populations were cases of erythema migrans.

It could be argued that the over-reliance on serology may have led to the underdiagnosis of true Lyme disease cases in both the EM population and among subjects with possible later manifestations of Lyme disease. As one committee member remarked during the meeting, “I think the sponsors’ data would support that even in culture-proven cases, not everybody seroconverts. So that the serological data cannot be

used as a gold standard. And the fact that someone has EM and doesn’t seroconvert doesn’t mean that it is not a *B. burgdorferi* infection” [13]. Still, especially in non-EM cases, it is difficult to conceive of a reliable alternative diagnostic algorithm that the authors could have employed. But it should be noted that in the absence of serological confirmation, it is likely that some true LD cases were bumped into the “possible Lyme” category, and were thus excluded from the final analysis.

The higher efficacy rate during the second year of the study was apparently a function of much higher anti-OspA IgG antibody titers in vaccinated individuals after the final vaccine dose, at 12 months, as compared with their titers a year earlier, after only two doses. It appears that LYMERix is unusual in the vaccine world in that it takes a full year, at least under the proposed dosing schedule, to build optimal immunity. Furthermore, antibody titers dropped quite rapidly in study subjects even after the third injection; by the end of the second year the mean antibody titer level among vaccinated individuals had declined to the levels of a year earlier. These findings suggest that additional boosters will be necessary to maintain antibody levels sufficient to neutralize the spirochete during tick feeding. Unfortunately, the threshold antibody level that confers protection against *B. burgdorferi* infection has yet to be determined.

Even assuming that this protective level can be identified, how safe are repeated doses of the OspA formulation? There are virtually no data on the long term outcomes of additional boosters after two years. (SmithKline Beecham is presently studying a small cohort of patients who have received one or two additional boosters; at the time of the FDA committee meeting, SKB representatives were “not aware of any unusual events in these people who have received four or five doses” [14].) At present, the indication filed

with the FDA calls for three doses, on the 0-1-12 schedule. If the manufacturer pursues an indication for approval of additional boosters, additional requests will have to be filed. But at this point, researchers don't know the protective antibody level, they don't know how many boosters will be required, they don't know whether they are safe, and there is no FDA blessing for any subsequent vaccine dose. These unknowns are a potential cause for concern.

It is also theoretically possible that the vaccine may change the clinical picture of infection, making vaccine failures difficult to detect. One well documented case study in the literature describes this phenomenon [15]. According to the authors, "Physicians may eventually be faced with possible vaccine failures, and the presentation of Lyme disease may be modified in patients who are infected after vaccination. Partial protection gained from the OspA vaccine may be associated with the absence of erythema migrans, which would mask the infection at its earliest, most treatable stage."

Still, there is little doubt that this is generally an effective vaccine, at least over the time period studied. Yes, we wish that its performance in the first year was better. But if researchers can find a way to safely maintain high OspA antibody titers among vaccinees over the long term, it will be a major first step toward a dramatic reduction in the number of future Lyme disease cases.

2) Issues of Safety

Most vaccines have mild side effects. According to the FDA, "No prescription drug or biological product, such as a vaccine, is completely free from side effects. Vaccines protect many people from dangerous illnesses, but vaccines, like drugs, can cause side effects, a small percentage of which may be serious. The FDA continually monitors reports to determine whether any vaccine or vaccine lot

has a higher than expected rate of events. About 85% of vaccine adverse event reports concern relatively minor events, such as ordinary fevers or redness and swelling at the injection site" [16]

According to the SmithKline Beecham investigators, significantly more vaccine than placebo recipients in the LYMERix study had reactions typically associated with vaccination - local soreness and swelling at the injection site, or systemic symptoms such as fever, chills and myalgias.

In theory, the vaccine itself could cause symptoms in a genetically vulnerable population.

Most of these were mild to moderate in severity. After thirty days, no significant differences in type (or frequency) of symptoms were recorded between the two groups.

More importantly, the investigators reported no statistical difference in adverse events between patients who were seropositive at the time of enrollment versus those who were not, nor were differences observed among patients with a self-reported history of Lyme disease versus those without such a history.

Nevertheless, members of the vaccine review committee expressed considerable concern about the safety of the OspA vaccine in individuals with a previous history of Lyme disease. One specific subset of patients, those with the HLA-DR4 genetic marker, may be at increased risk for adverse events from the vaccine. Past research has shown that patients with this marker are more likely to develop chronic arthritis as a result of *B. burgdorferi* infection than are patients without it. A likely

mechanism for this chronicity is that HLA-DR4-positive patients apparently develop an untoward T-cell response to human proteins that resemble those of *B. burgdorferi*.

Recently, scientists have identified a specific candidate human protein, known as LFA-1, that may be the target of this autoimmune response [17]. Unfortunately, the *B. burgdorferi* antigen that seems to be triggering this response is found on OspA — the stimulating antigen of the vaccine preparation. Thus, in theory, the vaccine itself could cause symptoms in a genetically vulnerable population. The number of patients in the vaccine study population with the HLA-DR4 allele and a history of Lyme disease was too small to draw conclusions from, but it was noteworthy to the vaccine review committee that two of them developed arthritis and paresthesias after vaccination.

The committee also expressed reservations about the long term safety of the vaccine in the population at large. "My substantive concerns here are the longer-term issues," said Thomas Fleming, a biostatistician at the University of Washington and a consultant to the FDA. "It remains a concern whether the vaccine could be eliciting or inducing chronic sequelae over an interval of time that would not have been detected within the period of follow-up." [18] Ultimately, the committee recommended active surveillance to assess the vaccine's long term safety, along with the establishment of a vaccine registry to keep track of any potential complications that could develop in the future.

Conclusions

It is clear that further study is needed to determine the optimal dosing schedule for the vaccine, and to confirm its safety over the long term. For now, potential vaccine recipients will have to balance the vaccine's proven benefits against its more nebulous safety picture. It is not an easy calculation to make, even for the experts. As one vaccine review

committee member stated after the meeting, "We have a vaccine that I'm comfortable with, but it's not something I would push tomorrow."

References

1. Asch ES, Lyme disease: an infectious and postinfectious syndrome. *J Rheumatol* 1994 Mar;21(3):454-61
2. Shadick NA, The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. *Ann Intern Med* 1994 Oct 15;121(8):560-7
3. Fikrig E, Elimination of *B. burgdorferi* from vector ticks feeding on OspA-immunized mice. *Proc Natl Acad Sci U S A* 1992 Jun 15;89(12):5418-21
4. Sadziene A, Experimental immunization against Lyme borreliosis with recombinant Osp proteins: an overview. *Infection* 1996 Mar-Apr;24(2):195-202
5. Probert WS, Immunization with outer surface protein (Osp) A, but not OspC, provides cross-protection of mice challenged with North American isolates of *B. burgdorferi*. *J Infect Dis* 1997 Feb;175(2):400-5
6. Telford SR 3rd, Efficacy of human Lyme disease vaccine formulations in a mouse model. *J Infect Dis* 1995 May;171(5):1368-70
7. Luke CJ, An OspA-based DNA vaccine protects mice against infection with *B. burgdorferi*. *J Infect Dis* 1997 Jan;175(1):91-7
8. Chang YF, Recombinant OspA protects dogs against infection and disease caused by *B. burgdorferi*. *Infect Immun* 1995 Sep;63(9):3543-9
9. Fikrig E, Vaccination against Lyme disease caused by diverse *B. burgdorferi*. *J Exp Med* 1995 Jan 1;181(1):215-21
10. Simon MM, Recombinant outer surface protein a from *B. burgdorferi* induces antibodies protective against spirochetal infection in mice. *J Infect Dis* 1991 Jul;164(1):123-32
11. Meurice F, Specific issues in the design and implementation of an efficacy trial for a Lyme disease vaccine. *Clin Infect Dis* 1997 Jul;25 Suppl 1:S71-5
12. Steere AC, Vaccination against Lyme disease with recombinant *B. burgdorferi* outer-surface lipoprotein A with adjuvant. *N Engl J Med* 1998 Jul 23;339(4):209-15
13. US Food and Drug Administration, Center for Biologics and Research, Vaccines and Related Biological Products Advisory Committee Meeting, Tuesday, May 26, 1998. Transcript page 279, line 16.
14. US Food and Drug Administration, Center for Biologics and Research, Vaccines and Related Biological Products Advisory Committee Meeting, Tuesday, May 26, 1998. Transcript page 212, line 9.
15. Zhang YQ, *B. burgdorferi* enzyme-linked immunosorbent assay for discrimination of OspA vaccination from spirochete infection. *J Clin Microbiol* 1997 Jan;35(1):233-8
16. Vaccine Adverse Event Reporting System (VAERS) as published on the FDA's Center for Biologics Evaluation and Research web site.
17. Gross DM, Identification of LFA-1 as a candidate autoantigen in treatment-resistant Lyme arthritis. *Science* 1998 Jul 31;281(5377):703-6
18. Marwick C, Guarded endorsement for Lyme disease vaccine. *JAMA* 1998 Jun 24;279(24):1937-8

New vaccine ready for Phase 1 human clinical trials

Rx Technologies, Inc. has developed a new Lyme disease vaccine ready for Phase I human clinical trials. The patented vaccine provided 100% protection in three animal species including primates. All challenge studies were performed with strains of *B. burgdorferi* different from those utilized in preparing the vaccine.

The vaccine is non-recombinant and multi-antigenic; derived from *Borrelia burgdorferi*. It provides both humoral and cell mediated immunity and achieves complete protection with heterologous strains. It does not require adjuvants. No adverse reactions to the vaccine have been observed.

Study summaries

Canine Study: A challenge study supported by the National Institutes of Health was performed at a University-based School of Veterinary Medicine. Conditions of the study were comparable to those required by the USDA for approval of a canine vaccine. All dogs receiving the RxT vaccine were protected from both tick and needle challenge. The study is ongoing to determine longevity of protection.

Primate Study: In preparation for human clinical trials, a primate study was performed at the National Institutes of Health on rhesus monkeys. All of the inoculated

animals resisted challenge with live *B. burgdorferi*. No adverse reactions to the vaccine were observed; inflammatory responses and arthropathies, noted with other Lyme vaccines, were completely absent. Histopathological examination of major organs showed no pathology of any kind. No trace of *Borrelia* was detectable by PCR. Based on the absence of tissue pathology in joint or cardiac tissue, it was concluded that the vaccine does not induce any autoimmune response or side effects.

Hamster Study: A hamster model showing arthritic effects using other vaccine formulations showed no such pathology with the RxT formulation.

Mouse Study: Several experiments have shown complete protection in mice using the RxT vaccine. Animals produced both humoral and cellular responses and each was independently protective. Protection was long-lived, extending for up to one year, approximately half the life span of the mouse. The mice showed no evidence of splenomegaly, arthritis, inflammation or other adverse reactions.

Guinea Pig Study: A complete toxicity study was performed in guinea pigs immunized with the RxT vaccine. Animals showed no abnormalities either in blood chemistry or tissue histology.

The estimated size of the human Lyme vaccine market is \$1 billion.

National News

LDF launches "March to Victory" campaign

The Lyme Disease Foundation is launching a "March to Victory" campaign with a generous challenge grant from SmithKline Beecham. A full-page ad in the Wall Street Journal and USA Today commits SKB to unlimited matching of donations to the LDF through the end of the year 2000.

Patient reaction to the announcement was generally positive. Some hailed the program as an opportunity to bolster LDF research and education programs. A few voiced concern about the alliance between the patient advocacy organization and the giant pharmaceutical company. The vaccine has been associated with adverse events, especially in people

who had latent Lyme disease or a genetic predisposition to arthritis.

"I am sending a contribution to the LDF today," said patient advocate Carolyn Cramoy of Wilton, Connecticut. "If we all get behind this campaign, maybe we can offset the fund-raising campaign that the American Lyme Disease Foundation is doing through the mail. Everytime you get an ALDF letter, send a donation to the LDF."

The ALDF is known to patient groups as promoting the view that Lyme disease is overdiagnosed and overtreated. ALDF is also generously funded by SKB.

The "March to Victory" cam-

paign will raise funds for research on prevention, detection and treatment of Lyme disease, as well as education programs.

Founded in 1988, the LDF got its start from a personal tragedy when Tom and Karen Forschner's handicapped son was diagnosed with the disease. They established the nonprofit organization so that no other family would have to suffer the lack of awareness and scientific ignorance they experienced.

"I didn't know how truly devastating Lyme disease could be, until it cost us our son's life," said Ms. Vanderhoof-Forschner. She has also written a book, "Everything You Need to Know About Lyme Disease."

Over the years, the LDF has evolved into a successful organization for the dissemination of information to the public and liaison with the research community. For its efforts, the LDF has received awards, including one from the National

Advertisement

Outspoken, opinionated, intelligent - and angry.... Yale alumnus Douglas Dodge talks back in

LYMETRUTH

Now Available

**The first eighteen issues of www.lymetruth.org
(March 1998 through May 1999)**

130 spiral-bound pages include Forward, Table of Contents, and Index. Order by email to dodge@lymetruth.org or postcard to 45 Long Hill Farm, Guilford, CT 06437. There is no charge.*

Readers say:

"Thank you for giving me hope."

"Keep up the good work. I'm behind you all the way!"

"I'm sure your work has saved many lives already."

"You're single-handedly keeping Yale in check."

"I admire your willingness to call it like it is."

**Any person, support group, or organization may copy, distribute, and/or sell the entire collection or individual issues or articles. LYMETRUTH assumes that any profit after expenses will be used for further good works.*

Institutes of Health. Among its many educational activities, the LDF has created award-winning TV programs and other material for children, adults and businesses. It conducts medically accredited scientific conferences, funds research and publishes the peer-reviewed scientific **Journal of Spirochetal and Tick-borne Diseases**.

Working with Congress, the LDF was responsible for designating May as national Lyme Awareness Month. Its support group training and referral programs help patients and their families.

In the March to Victory campaign, the LDF is traveling the country conducting educational programs in communities from coast to coast. Their web page (www.Lyme.org) lists the areas they are scheduled to visit.

To make a contribution to the "March to Victory" campaign or for more information, contact the LDF, One Financial Plaza, Hartford, CT 06103. For brochures, please include a SASE (\$1 helps defray the cost) or visit the LDF website.

"This is an opportunity for the Lyme community to get some research done independent of the political considerations in Washington/Bethesda," said Lyme patient Ruth Genne'-Bacon. "Let's all get behind this action - not only this month of May which is Lyme Awareness month - but throughout the year."

The Lyme Quilt Page

Patient stories are still being added to The Lyme Quilt. If you would like yours entered, please email your story to: LYMECHAT@aol.com with a copy to PSpatches@aol.com. The Quilt may be accessed at <http://www.angelfire.com/ny2/James/>.

Lyme Alliance petition to be sent to Washington

Over 15,000 signatures have been collected for the Lyme Alliance petition so far, with more coming in every day, according to Lyme Alliance newsletter coeditor Sharon Smith. At the end of May the petitions will be delivered to Vice President Al Gore, along with a letter outlining the reasons for the petition. Copies of the letter to VP Gore will be sent to all Cabinet members, and an e-mail copy will be sent to all legislators. Lyme Alliance also plans to contact national news services and major television news shows and stations to try to get some media coverage. Letters from leading professionals and advocates in the Lyme community supporting the petition demands will accompany the package.

"It is our hope that the petitions and letters will help bring attention to the victims of Lyme disease," said Smith. "We don't expect this campaign to suddenly bring about dramatic changes, but it will help

keep Lyme disease out there. We're making dents. Each dent brings us closer to recognition and changes-but we have to continually keep making those dents any way we can. Every time they say, 'No Lyme disease problem here,' we need to counteract it by saying, 'Oh, yes there is!'"

The petition emphasizes the chronic and persistent nature of Lyme disease, and demands that physicians treating Lyme patients not be harassed; that insurance companies not be permitted to deny payment for treatment; that appropriate treatment be determined by the patient's physician; and that research be better funded.

According to Smith, the Lyme Alliance provides a way to join Lyme advocates together so they have the power of numbers. "The Lyme Alliance wasn't formed to do for you," she says, "but to give you a way to do for yourself. We can't do it without lots of people."

British Lyme patients face same problems as Americans

from page 1

for at least 100 years in the UK from results of tests on ticks in the natural history museum," notes Mark Greenfield, founder of the BLDF. "However, I still hear reports of doctors saying there is no Lyme disease in Britain, or there is no Lyme outside the New Forest. "

Greenfield believes the British Lyme situation is similar to where the US was ten years ago.

"Although we use the usual tests, there would seem to be a high

probability that if blood tests come back negative there is little consideration of whether the clinical symptoms fit," he observed. "While it is of course very important to rule out all other possibilities, I suspect we could learn much from studying the American situation over the last decade.

"We do not have all the facts about the disease and as such it cannot be stressed enough that accurate clinical diagnosis is vital in

cases of vague blood results,” Greenfield adds.

For more information on the British Lyme Disease Foundation, contact:

Mark J Greenfield
PO Box 331
East Grinstead, West Sussex
England, RH19 1YT
spud@wadhurst.demon.co.uk

<http://www.wadhurst.demon.co.uk/lyme/index.htm>

“All contributions will go towards research and provision of information,” said Greenfield. “We do not pay salaries or expenses to any staff.”

Reprinted by permission from LymeNet newsletter

Infectious Disease.

The paper -- written by Dr. David Walker of the University of Texas, a researcher who is renowned for his work on Rocky Mountain spotted fever -- described a new tick-borne disease in the South called human ehrlichiosis. The disease was characterized by a high fever and berrylike clusters within white blood cells called monocytes.

When Bakken saw the photograph, something clicked.

“It was a mirror image of what we'd seen under the microscope,” Bakken said.

But it couldn't be. All the cases described in the chapter were found in patients who lived in the South and who had been bitten by the Lone Star tick, which doesn't exist in Northern Wisconsin.

Bakken called Walker anyway and described what he'd seen inside his patient's white blood cells. The Texas researcher was skeptical, but agreed to look at a blood sample.

A few days later, Walker called back with surprising news. The elderly Wisconsin man had had ehrlichiosis.

“The only drug he didn't get was tetracycline,” Bakken said, “and that's the only drug that works on ehrlichiosis.”

A month later, Bakken and colleague Dr. Linda Van Etta had another chance to test that prescription and their hypothesis.

An 18-year-old Laotian man came to St. Mary's Medical Center with a high fever and flulike symptoms. But inside his white blood cells were the same mysterious berrylike clumps.

When doctors gave him tetracycline, the young man's 104-degree fever dropped to normal overnight.

It was a victory. But the illness still didn't make sense. How could these two men, who claimed to have never visited the South, have had the

Regional News

Mysterious illness prompts Duluth doctor's groundbreaking research

by Kendra Rosencrans, *News-Tribune staff writer*

Sometimes the flu isn't the flu, but something surprisingly different.

In the case of Dr. Johan Bakken of the Duluth Clinic, a mysterious flulike illness in an elderly Wisconsin man led him to the discovery of a previously unknown tick-borne disease that may be as common in residents of Northwestern Wisconsin as Lyme disease.

Thanks to Bakken's research, doctors now have diagnosed more than 450 cases of human granulocytic ehrlichiosis in Wisconsin, New York and six European countries.

For this original, groundbreaking research over the past nine years, Bakken was recognized in 1997 for a lifetime of outstanding achievement by the Infectious Disease Society of America. Last year, the 53-year-old infectious disease specialist was honored with the St. Mary's/Duluth Clinic Foundation's first lifetime achievement award.

Bakken says it's a story of serendipity, a case of being in the right place at the right time.

“There's more under the sun than

we can fathom,” Bakken said. “It takes an individual with curiosity and guts and a willingness to follow the mystery wherever it leads.”

The story starts in June 1990, when a previously healthy 80-year-old man from Trego was admitted to St. Mary's Medical Center in Duluth with confusion, a high fever and a possible blood infection.

To Bakken and his colleagues, it looked like a severe case of the flu, combined with some sort of bacterial infection. Although doctors bombarded the man with antibiotics, he died after three days.

“It was very disconcerting,” Bakken said. “We didn't know why he died.”

It wasn't the flu. And the only clue to the man's mysterious illness were some inexplicable clumps inside his white blood cells -- berrylike clusters that just didn't belong there.

A week later, Bakken opened his mail and found a chapter supplement to the bible of infectious disease -- Mandel's Principles and Practices of

same illness?

As an infectious disease specialist, Bakken is half doctor and half sleuth. Part of the challenge in treating people with infectious illnesses is discovering how they got sick. What did they eat? Who were they with? Where did they travel?

It's a guiding principle Bakken, who grew up in Norway, first learned from Dr. Ivar Helle, an infectious disease specialist at University Hospital in Oslo.

"The most important thing is not where a patient hurts, but where he has been," Bakken said, paraphrasing his mentor.

The high fever, the berrylike clumps and the response to tetracycline all pointed to ehrlichiosis. So

Bakken packed up some more blood samples and sent them to the Walker's lab at the University of Texas.

A new disease

The samples landed in the hands of Dr. Stephen Dumler, a researcher from the University of Maryland. He'd arrived in Galveston just weeks before to study Rocky Mountain spotted fever with Walker, but was reassigned to a project on ehrlichiosis.

Dumler was puzzled as to why a doctor from a clinic in Duluth, Minn., would be worried about ehrlichiosis. The kind of tick thought to transmit ehrlichiosis to humans just didn't exist in northern Minnesota and Wisconsin.

Curious, he looked at Bakken's blood samples.

"Within five minutes I was convinced it was something completely different from the human ehrlichiosis we had already identified," Dumler said.

The difference was in the white blood cells. The Southern version of the disease infected white blood cells called monocytes. But Bakken's patient samples showed infectious particles in a different type of white blood cell called a granulocyte.

To his surprise, Bakken's samples showed that the "bacteria were living inside a vacuole, just like ehrlichia," Dumler said.

It was an intriguing finding, but the researchers needed much more proof to put a name on the organism or claim a new disease.

It would be best, Dumler told Bakken, if researchers could map the mystery organism's DNA using a new technique called polymerase chain reaction. But they would need fresh blood samples to do it.

Patients, clues

By 1993, Bakken had seen six more patients with the suspicious illness -- from Esko and Aitkin, Minn., and Gordon, Barnes, Cable, and Hayward, Wis. The first patient died, but the subsequent five patients recovered when treated with tetracycline.

Bakken faithfully sent fresh tissue and blood samples to Walker and Dumler in Texas, but all their tests to match the Duluth bacteria with the Southern version came back with the same answer: Negative.

All Dumler could tell Bakken was that the bacteria looked like ehrlichia, but they couldn't prove it.

In the three years since his first patient, Bakken had been searching the research literature to see if anyone had described what he was seeing.

This search brought him to

Minnesota doctor gets low marks for Lyme disease

While Lyme patients give physician-researcher Johan Bakken credit for his role in recognizing HGE as a cause of tick-borne illness in Minnesota, they don't think much of his stand on Lyme disease. They say he considers HGE a much more serious disease, and likes to state, "Lyme disease has never killed anyone!"

According to Lyme activist Tom Grier, president of the Lyme Disease Coalition of Minnesota, Bakken has told many people on the phone that they probably don't have Lyme disease if they have been treated for two weeks with doxycycline, despite continuing symptoms. This is the treatment recommended by the Duluth Clinic, where Bakken works, to cure both diseases.

But HGE is confined to the bloodstream, while Lyme can hide deep in body tissues, making it more difficult to cure.

"So now patients with relapsing

Lyme symptoms are showing up a year later and being told they no longer have a physical disorder but a psychological disorder, and are denied treatment," Grier said.

Antibody titers for HGE can routinely hit 1:10,000 and cases at 1:80,000 have been reported, yet studies done in northern Wisconsin used a very low cutoff for determining active disease.

In Lyme, titers above 1:1024 are rare, yet that is the cutoff point for Lyme disease at Mayo Clinic.

"So why the low titer cut off for HGE?" asks Grier. "Well, it showed that 15% of Wisconsinites were potentially exposed. The incidence of actual disease is about 80/100,000 or about 0.08%, a far cry from 15%."

This alarming statistic was useful in garnering funding support for ehrlichiosis research. But it also meant that a diagnosis of ehrlichiosis would limit a patient who also had Lyme disease to two weeks of treatment.

ehrlichia species that caused illness in animals. The two ehrlichia that matched the best were *Ehrlichia equi* and *Ehrlichia phagocytophila*, which caused big problems in horses and sheep, but were not known to cause disease in humans.

Still, there were helpful clues.

“We learned that the agent that transmitted the bacteria to sheep in Scandinavia and England was the European equivalent of the deer tick,” Bakken said.

It was an important connection. Deer ticks are prevalent in North-western Wisconsin and are known to transmit Lyme disease, another bacterial infection, to humans.

Dumler was curious to see if he'd have better luck getting Bakken's samples to react to the animal versions of the disease. So he flooded some infected sheep cells with serum from Bakken's patients.

If the antibodies produced by the humans attached themselves to the infected sheep cells, which were tagged with a fluorescent substance, the combination would shine when placed under indirect fluorescent light.

And it would prove that the bacteria infecting Bakken's patients was indeed ehrlichia.

“It lit up like a Christmas tree,” Bakken said.

Findings, questions

In the five years since that breakthrough, Bakken and Dumler have mapped the new bacteria's genetic code and have learned much about their new disease.

Like Lyme disease, human granulocytic ehrlichiosis (HGE) is transmitted by the deer tick. The bacterium, which belongs to the family Rickettsiaceae, also uses the whitetail deer and the white-footed mouse as hosts in nature.

HGE appears to be as common among residents of Northwestern Wisconsin as Lyme disease. As many

as 15 percent of people living in that region have been infected by HGE, according to research by Bakken.

Although some people have died, HGE “is probably a less severe illness than we previously thought,” Bakken said. “In most cases, the illness is mild or not even recognized.”

Questions remain about HGE, its

transmission and its effect on the human body, in particular its influence on the immune system. Once recognized, HGE can be cured with a common and readily available antibiotic. That's why Bakken hopes this research will lead to a simple diagnostic test for area clinics and possibly a vaccine.

Reprinted with permission of the Duluth News-Tribune, Jan. 31, 1999.

Massachusetts patients being asked to write the Governor

by John Coughlan

URGENT!

LYME PATIENTS EVERYWHERE: MASSACHUSETTS NEEDS YOUR HELP!!

Please contact Governor Cellucci as soon as you possibly can! EMAIL, FAX or Mail !!

Email: goffice@state.ma.us FAX: (617) 727-9725 Mail: His Excellency Argeo Paul Cellucci State House, Room #360, Boston, MA 02133

URGE THE GOVERNOR'S OFFICE TO HOLD AN EXECUTIVE OVERSIGHT HEARING IN AN OPEN FORUM WHERE THE UNRESOLVED LYME DISEASE ISSUES CAN BE DISCUSSED IN AN OPEN, FAIR AND THOROUGH MANNER (see attached letter to Governor Cellucci).

The Massachusetts Department of Public Health (MDPH) doesn't take Lyme disease seriously. That needs to change. We have been working to create a comprehensive, user-friendly Lyme Disease Reporting Form with the MDPH for more than one-and-a-half years. Our goal is to create an effective Lyme disease reporting method that will include ALL Lyme cases within Massachusetts. This includes all cases that meet the CDC definition and those (the majority) that are physician-diagnosed. However, the MDPH doesn't

recognize the serious ramifications of some of their recent decisions and the potential adverse effect on every person who lives or works in Massachusetts.

In our effort to provide the best possible information in the preparation of a Lyme disease physician reporting form, we sought out the expertise of physicians who have much experience in the diagnosis and treatment of Lyme disease. We put together a survey of their opinions. How was it received by the MDPH? It was IGNORED. “It was delivered too late! We can discuss it next year”, they said. Oh really?? The survey was hand-delivered April 16th and their FLAWED forms were mailed out more than a month later to 12,000 physicians in Massachusetts. Unfortunately, they were unwilling to delay this flawed mailing temporarily until an oversight meeting could be arranged.

The response, “we can discuss that next year” is far from adequate for many reasons. First, they said the same thing LAST YEAR (summer of '98). Second and more importantly, a lot of people and their families will be infected over the next year — and the ramifications can have lifelong effects. Unfortunately, many of our public officials, sealed in the offices of the Massachusetts Department of

Public Health, appear not to have sufficient concern for the plight of the citizens and families of our state that have been (or will be in the future!) personally devastated by the effects of Lyme Disease. If any of THEIR spouses or children had Lyme disease, I am sure it would be easier to get their cooperation.

We ask that the issues raised in the "Physicians' Survey" be considered openly, fairly and thoroughly along with the physician reporting forms just distributed by the MDPH.

Please help us convince them to take Lyme disease seriously. Make your voice heard — help us prevent countless more tragic Lyme stories by making the MDPH and the Governor ACCOUNTABLE to the general public and the Lyme community here in Massachusetts. Demand that they hold an EXECUTIVE OVERSIGHT HEARING of the MDPH through the Governor's Office. Or will they turn their backs on every person living or working in Massachusetts? Connecticut has the support of many legislators, their Department of Public Health, their State Attorney General - Why don't we?

1. Please read below.
2. Then, contact the Governor!

In whatever communication you have with the Governor's office, be respectful, be firm, be fair, be levelheaded and INSIST that the Governor hold an EXECUTIVE OVERSIGHT HEARING of the MDPH regarding Lyme Disease reporting here in Massachusetts as soon as possible.

THANKS FOR ALL YOUR SUPPORT !!

John Coughlan is the State Coordinator of the Massachusetts Lyme Disease Coalition. He may be reached by email at molalor@capecod.net, by mail at the address on the letter (next column), or by phone 508-563-7033.

Patient group chastises Public Health Department

Massachusetts Lyme Disease Coalition
P.O. Box 1916
Mashpee, MA 02649
May 18, 1999

His Excellency Argeo Paul Cellucci
State House Room 360
Boston, MA 02133

Dear Governor Cellucci,

We are writing this letter to you due to our concern for the vulnerability of the general public to Lyme disease. More specifically, our concern centers around the Massachusetts Department of Public Health's disregard for the years of experience and insights of top Lyme physicians and the potential risk to the public if several issues are not adequately addressed on the Lyme disease Physician Reporting forms that are soon to be mailed to physicians throughout Massachusetts.

Lyme disease is more of a danger to public health than many realize. How much of a risk it really is will not be known until we have an efficient and workable reporting program in place. If not diagnosed and treated in its early stage, Lyme can have devastating effects on patients and their families. (See Dorothy K testimonial and 2 attached obituaries).

For the past 18 months, we have been diligently working to help the MDPH create an effective Lyme Disease Reporting Program. In our efforts to help them establish this process, we have completed a Lyme disease Reporting Survey with seven (7) physicians who are, in the opinion of many doctors, the foremost experts on Lyme in the United States. This survey was hand-carried to the MDPH on April 16th. They, unfortunately, decided to ignore it.

As it stands right now, the MDPH is in the process of mailing seriously flawed Lyme Reporting forms to 12,000 physicians in Massachusetts. If this is not stopped, many physicians will not report all of their Lyme cases and others, less familiar with Lyme, may misunderstand some terminology and misdiagnose potential Lyme victims causing years of senseless suffering for individuals and families here in Massachusetts. Isn't it better to forfeit printing costs than to forfeit people's health?

For example, a few of the more important issues to be considered are:

1. Reporting of All Lyme Cases A primary goal of these forms has been to encourage physicians to report all Lyme cases, not just those that meet the CDC definition as has been done in Massachusetts recently. Connecticut and Westchester County in New York have been collecting all Lyme diagnosed cases for years. We all agree that this is an important goal as most Lyme cases are physician-diagnosed, which means most are a 'clinical diagnosis' and do not fit within the limited scope of the CDC definition. Up to the last printing, there was always a section clearly noting that it was the intent of the MDPH to collect more than the CDC-defined cases. It was suddenly taken out without any warning or discussion.

Continued on next page

Letter to Governor, continued

Therefore, the two-tier system needs to be restored by including the Case Status Section on both forms. Otherwise, there will be no distinction between CDC-defined and physician-diagnosed cases of Lyme disease. The unfortunate result will be that physicians will not know that the intent of the MDPH has changed to be more inclusive and will only report CDC cases. Therefore, we will not get a true reading of the full breadth of the problem in this Commonwealth.

2. "Non-EM" All seven physicians on the survey believed that it was counterproductive to include a section called "Non-EM", as patients may be misdiagnosed or misclassified. Many think the terminology is confusing and/or misleading. A recommendation was made to use different terminology as an acceptable way to collect more information without causing confusion or potential harm to patients: "Rashes < 5 cm". The current terminology of "Non-EM" is potentially harmful, it must be eliminated from both forms.

3. List of Non-Classical EM As you can see from the survey, most physicians are only familiar with the well-publicized 'Bulls-eye' Lyme rash, but not the "nonclassical" rashes though they are more prevalent. It would be of great benefit to include a list of the "nonclassical EM" on the front of both the individual and group forms to help physicians with early diagnosis and treatment.

4. Lab Results The Epidemiology Department of the MDPH has stated that consistency is an important objective between both forms and we agree. Lab results are an integral part of the individual form and should also be on the group form. Every other state and county in the U.S. includes lab results. Every physician interviewed said that it was absolutely necessary to include lab results on both forms.

There are few other categories that need further discussion, but this gives you the general idea of our concerns.

On a more personal note, consider some of the problems encountered by one typical Lyme patient: Dorothy K (enclosure #5). If she had been properly diagnosed and treated at an early stage, she would not have:

- been unemployed for the past 2 years - had to endure the physical suffering & mental anguish for the same period - had to battle with her insurance company - nor would she have had to pay \$45,000 out of pocket for medical treatment though she already had insurance coverage.

Many people are not able to afford such care even when employed. What are unemployed, chronically-ill Lyme patients suppose to do if they do not have resources comparable to Dorothy K?

Therefore, we urgently ask you, Governor Cellucci:

1. to have Dr. Howard Koh, the Commissioner of the MDPH, STOP THE MAILING of these flawed forms. His phone number is (617) 624-5200.

2. to schedule an EXECUTIVE OVERSIGHT HEARING, through your office, where the survey and the MDPH's proposed reporting forms can be given full, fair and open consideration.

Otherwise, it is we, the general public here in Massachusetts - your constituents, who will pay the price. And it will be another year before we can correct any errors. Isn't it better to do it right - especially with so much at stake?

We appreciate your prompt attention to this critical issue.

Sincerely,

John F. Coughlan, State Coordinator

Kathleen M. Splaine, Legislative Liaison

Health care system failure led to this patient's chronic disease

The following two stories were attached to the letter to Governor Cellucci.

by Dorothy K

Three days after receiving several bites on my back I awoke with flu-like symptoms, swelling in my face, a fever and a growing rash surrounding one bite. The rash had a definite raised center with a slightly white color at the apex. This red rash had spread to a diameter of a few inches.

I went to the Falmouth Hospital Emergency Room for treatment. I asked the physician's assistant if the bite could have been by a tick carrying Lyme. He told me that the rash did not fit the definition of an erythema migrans. He diagnosed me with cellulitis and prescribed Cipro. My symptoms worsened greatly over the next few weeks. I saw another physician not familiar with Lyme disease who also discounted the rash.

In my case, the narrow definition of a bulls-eye rash delayed treatment by three weeks. The time frame may not seem significant but it seriously impacted health. When I first sought treatment I felt as if I had the flu but did not have the neurologic symptoms that appeared in the coming weeks. I experienced blurred vision, double vision, photophobia, optic neuritis, dizziness and severe headaches. I also had numbness in my face and extremities, shooting pain down my arms, legs, neck and back. Some of my other symptoms included arthritis, insomnia, fatigue, an increased heart rate, shaking, difficulty concentrating and mixing

up words. This is only a partial list of the symptoms, which have prevented me from working for two years.

The failure by health care professionals to recognize rashes that deviate from the classical EM affects not only patients' health but also their ability to receive appropriate insurance coverage.

I contracted Lyme disease while working and am involved in a worker's compensation claim. The attorney's for the insurance company of my former employer are arguing that I cannot have disease because the rash did not correspond to the textbook definition. This documentation of cellulitis by a physician's

assistant in an emergency department has prompted the insurance company to declare my positive test result to be a false positive. In the meantime, my own insurance company has covered only part of my treatment. Over the past two years, I have paid approximately \$45,000 in medical expenses out of my own pocket despite the fact that I have medical insurance.

My case proves that a failure to take into account differences in rashes can delay diagnosis, prevent patients from receiving timely and appropriate treatment, and can give insurance companies unjustified reasons to deny claims for treatment.

brain and any organs that could be used for science should be donated ... but the coroner couldn't find any takers. It seemed to drive home the message she got that she didn't count.

With sadness and sorrow,

Rae Record

Karen Sullivan lived in Barnstable, Massachusetts

Karen Counts

by Rae Record

Karen Sullivan is dead. She died because she believed that she didn't count.

Her Lyme disease went misdiagnosed as chronic fatigue syndrome for years. When she finally did find the answer and began getting help, she discovered to her shock that her loved ones saw her differently. Suddenly she was diseased, defective, untouchable. To her horror, she found that the very medical profession she had been a part of for over 20 years as a pediatric nurse was riddled with politics and a maze of red tape.

When she lost her career to Lyme Disease, she lost the only place where she found a sense of self worth. When she lost her career, she also lost her insurance. When she lost her health, she lost her independence, and her independence was vital to her life. When it was time for those she has cared for to care for her, they didn't have the skills to handle the task. They didn't know how to give her the loving compassion and nurturing that she had spent her life giving to others as a pediatric nurse.

Number 25

The message she got from all this was, "Karen doesn't count."

She was not just the victim of a bacteria, but a victim of today's society -- one where Lyme disease victims go misdiagnosed, and undiagnosed, not because of lack of science and knowledge, but because of the greed and the egos of doctors and insurance companies. In her world people turn to anger and callousness to hide their fear and feelings because they haven't been taught anything else.

Karen's life outside of Lyme Disease was far from perfect. Lyme Disease magnified the imperfections. It was a terrible thing for her to wake up one day and find that her entire body has been infected with a bacteria that had taken away her ability to function physically, mentally and emotionally. But the abandonment of those who meant the most to her was devastating and the resulting hole in her soul, the loneliness, was more than she could bear.

She believed she was worthless. Her suicide note requested that her

Successful press conference and rally

by Bruce Fletcher

A rally was held at the State Capitol Building in Hartford, Connecticut, at noon on Tuesday, June 1, to show support for the need for pro-patient Lyme disease legislation. Thanks to legislative aide Chris Montes, a great lineup of speakers, great attendance, and loads of press, the Lyme Rally achieved what was needed. Speakers included Chris, Attorney General Richard Blumenthal, Rep. Orefice and Sen. Bozek from the Insurance Committee, Sen. Prague from Public Health, Irene from MTV's Real World, Tom Forschner, Executive Director of the Lyme Disease Foundation in Hartford, and myself. A dozen Lyme patients then addressed the crowd with their stories. Many patients were interviewed for stories, and the insurance companies took quite a beating.

The turnout was good despite the fact that it was the day following a long weekend, as about 50 people were there. There were 4 or 5 TV stations there, and CBS, NBC, ABC and Cablevision 12 covered the rally. There were lots of great pictures of the signs people brought and of PICC lines in peoples' arms. The Hartford Courant, Connecticut Post, Stamford

Advocate, New Haven Register and others also had stories.

On the legislative front, a group of us then met with Moira Lyons, Speaker of the House. We came away a little disappointed, as she did not commit to help push our cause. Our expectations were also tempered by Sen. Bozek, who said they are trying to get some pro-Lyme language into the Managed Care Bill (#7032), even if the language is not perfect.

Thanks to everyone for the hard work, the e-mails and phone calls. A number of legislators commented that we have made our voice heard, which can go a long way. The legislative session ends on the 9th, and I will keep you updated on any developments.

Lyme disease has affected many in our community. The Attorney General recently held a hearing on the topic, and it became evident that Lyme disease is under-diagnosed and under-treated. Part of the problem is that insurers do not cover costly medications such as intravenous antibiotics beyond proscribed time-frames. Unfortunately this treatment can be required for many months beyond what the insurance company will cover. A Bill in the Connecticut Legislature was proposed to deal with these insurance abuses.

This Bill (#5694) started out as a Lyme patients rights bill but unfortunately the insurance lobbyists at the last minute changed the wording. The original Bill was intended to force insurance companies to provide coverage for treatment if your primary care doctor diagnosed you with Lyme. The Insurance and Real Estate Committee changed the language so that both your doctor and an "independent health care provider" need to diagnose you with Lyme and that they must believe you would benefit from the treatment. This weakened the bill substantially:

- Who is this independent doctor supposed to be and who picks them -- a doctor paid by the insurance company? If I pick them will the

What to say when you contact your legislator about the Lyme Disease Bill

- Ask why the State of Connecticut has not taken chronic Lyme Disease seriously!
- Ask why the State has not made insurance companies responsible for paying for treatment ordered by your doctor and tell them to support legislation which would mandate Lyme Disease treatment coverage!
- Ask why insurers pay the same "Lyme experts" to render opinions which are consistently in their favor, while you remain sick!
- Ask why there is a body of professional literature containing more than 60 articles which support the fact of chronic Lyme Disease, yet many Connecticut doctors remain unaware of its existence!

Demand attention, investigation, and support. If the effort is not successful in this legislative session, start again in the Fall.

insurance company consider them independent?

- Will this independent person be as qualified as your doctor - doesn't your doctor know best how to treat you, especially if you are going to a Lyme specialist?

- The language was supposedly changed to protect insurance companies from over-treatment - this is a joke - hundreds of residents are suffering from under-treatment!

- No such second opinion is required for much of the Lyme treatment now covered and paid by insurance companies. This bill would be a boon to the insurance industry, as they could now raise this requirement for all treatments, which would result in delayed treatment and greater cost to the patient. This is not just unhelpful, it is dangerous.

Subsequently the Democratic leadership decided to merge all health related bills into the Managed Care Reform Bill (#7032). Lyme activists have been campaigning to salvage at least some of the language

relating to Lyme from 5694, including deleting the reference to a requirement for a second opinion (independent healthcare provider), and put the language into 7032. At press time they were still hoping that legislators would not put in too many loopholes for the insurance companies.

The original Bill would have provided great protection for Connecticut citizens. We have the highest incidence of Lyme disease in the country. Large national insurance companies have the resources to fight a disease that is largely local to this area. Lyme patients today have few rights in getting the care they need. Our legislators need to be made aware of the problems faced by Lyme patients, and I urge you to contact your own representatives on a continuing basis to bring them up to speed.

Bruce Fletcher of Darien, Connecticut, is responsible for Lyme Political Action: Make your voice heard! <http://www.netcom.com/~fletch14/LymePAC.html>

CDC guilty of misappropriation of funds

An audit conducted by the US Inspector General's office determined that the CDC spent significant portions of funds allocated by Congress for the study of Chronic Fatigue Syndrome (CFS) on other programs and activities unrelated to CFS. The audit revealed that the CDC had also failed to adequately document the relevance of other costs charged to the CFS program.

Responding to the report, Kim Kenney, Executive Director of the CFIDS Foundation, said that the findings did not surprise her organization.

"We have suspected for quite some time that the funds we fought so hard for on Capitol Hill never made it to CFS research labs. This is a betrayal of trust — in medicine and government. Patients and their families are terribly angry at the CDC and demand action from the government."

Of the almost \$22.7 million charged to the CFS program during fiscal years 1995 through 1998, only about \$9.8 million (39%) was actually spent for CFS program activities. The remaining \$12.9 million (57%) was spent on non CFS activities (\$8.8 million) or was not documented in sufficient detail to discern its applicability to the CFS program (\$4.1 million).

The report states that although the CDC is not statutorily prohibited from spending funds budgeted for CFS on other programs, it is clear that Congress expected the agency to spend the amount it budgets for CFS only on CFS. Deficiencies in the CDC's internal control system are blamed for the situation, and recommendations are provided to address the problem. The CDC officials have already taken action to initiate the recommendations and have also committed to share a

comprehensive spending plan for the CFS program with the national CFS advisory committee, the Congress, and nonprofit organizations providing support services to CFS patients.

The case was brought to light in July 1998 when the Branch Chief of the Viral Exanthems and Herpesvirus Branch of the Division of Viral and Rickettsial Diseases which is responsible for the CFS program alleged that significant portions of

the funds reported as expended for CFS research had not actually been used for that program. The Branch Chief asserted that the Division Director had diverted CFS funds and presented false information as to the actual costs of CFS research, and further, had knowingly provided false and misleading information to the Congress to conceal the diversion of CFS funds from their intended purpose.

A complete copy of the report may be viewed on the Internet at <http://www.dhhs.gov/progorg/oig/new.html>.

NIAID sponsors conference on laboratory diagnosis

The NIAID, in collaboration with the Centers for Disease Control (CDC) and the Office of Rare Diseases (ORD), convened an NIAID/CDC/ORD Conference on the Laboratory Diagnosis of Lyme Disease on August 30 -September 2, 1998, at Cold Spring Harbor Laboratory, New York. Participants included approximately 35 investigators, mostly current (or former) NIAID or CDC grantees as well as others with considerable expertise in the diagnosis of Lyme disease. The organizers, Dr. Phillip J. Baker, NIAID and Dr. David Dennis, CDC, designed the conference to provide an in-depth and critical examination of the strengths and weaknesses of currently used procedures to diagnose Lyme disease. The goal was to determine the type of research projects both the NIAID and the CDC might support in order to improve existing diagnostic approaches as well as to facilitate the development of new ones. The participants would not issue recommendations and guidelines on the diagnosis of Lyme disease. Important issues addressed at the conference included the following:

- Sensitivity, specificity, and reproducibility (both within and between laboratories) of various diagnostic procedures;
- Use of diagnostic tests to evaluate changes in disease activity in response to antimicrobial therapy;
- Natural history of antibody responses generated during acute (early) and chronic (late) Lyme disease;
- Advantages of using as diagnostic reagents purified recombinant bacterial antigens or neo-antigens expressed only in vivo during the course of infection;
- Value of using well-characterized positive or negative reference specimens to standardize assay procedures as well as to facilitate interpretation of the results obtained;
- Selection of appropriate end-points to compare and quantitate the results obtained;
- Influence of co-infection with Ehrlichia and/or Babesia on the diagnosis of Lyme disease;
- Impact on diagnosis of vaccination with recently developed OspA vaccines.

Conference Reports

Accelerated schedule for Lymerix now recommended

The following reports are from the 12th Scientific Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders sponsored by the Lyme Disease Foundation and held in New York City on April 9 & 10, 1999.

by Carolyn Cramoy

The currently licensed dosing schedule for the Lymerix Lyme disease vaccine requires a full year to develop optimum immunity. People taking the vaccine have only partial immunity during their first year. At the 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, Dennis L. Parenti, M.D., of SmithKline Beecham Pharmaceuticals and Biologicals, the developers of Lymerix, reported on studies using accelerated vaccination schedules. The original dosing schedule involved 3 shots, with the second one coming one month after the first and the third coming 12 months after the first (0,1-, 12-month schedule). The accelerated schedules studied were a 0, 1-, 6-month schedule and a 0, 1-, 2-month schedule.

Both schedules were found to result in protective immune responses comparable to the currently licensed schedule. The distribution of titers was found to be virtually the same for both accelerated schedules and no difference was seen in safety or in tolerance of the vaccinations.

The mechanism of protection for Lymerix appears to be the development of high and sustained antibody levels against OspA. In field efficacy trials, it was noted that people who were "vaccine failures" had lower post vaccination titers than average. According to Dr. Parenti, "An IgG anti-OspA antibody titer of 1200 EL.U/ml prior to the start of tick season appears to provide high probability of protection. In the field

efficacy trial (using the 0, 1-, 12-month dosing schedule), >90% of the subjects had antibody titers >1200 EL.U/ml." In the trials using the 0,1-,2-month, and the 0,1-,6-month schedules, 94% and 93% respectively

People with active Lyme disease or any other serious medical condition were excluded from the studies, so no data were available on that issue.

of the vaccinated people had IgG titers >1200 EL.U/ml one month after the 3rd dose.

Dr. Parenti stated that, in their studies, the vaccine resulted in no modification of the presentation or duration of the disease. Western Blots were effective in diagnosing Lyme in vaccinated people and erythema migrans (EMs) were culturable in the vaccinated group. When asked about the safety of the vaccine for people with active Lyme infection, he replied that people with active Lyme disease or any other serious medical condition were excluded from the studies, so no data were available on that issue.

Studies are continuing to monitor the duration of antibody protection in those who have been vaccinated. These follow-up studies will help to determine the optimum booster schedule needed to sustain immunity.

This proof of dosing flexibility means that immunity can be developed more rapidly, and perhaps even more effectively, using an accelerated dosing schedule. This offers more practical protection to those who desire it due to high risk of exposure in endemic areas.

The Safety and Efficacy of OspA Vaccine for Dogs

Andrew K. Eschner, DVM reported on the pre and post-licensure studies of a non-adjuvanted, lipidated, monovalent, recombinant OspA Lyme vaccine for dogs, which was introduced in 1996. Prior canine Lyme vaccines had been produced using whole killed bacteria to stimulate an immune response.

The most common clinical sign of Lyme disease in dogs is lameness, which can be acute or subacute, short in duration even with no antibiotic intervention, or long-term or recurrent even with antibiotic therapy. In clinical lameness due to Lyme disease there is often a fibrinopurulent arthritis. Systemic symptoms can include fever, anorexia, lethargy, myalgia and swollen regional lymph nodes. However, it is estimated that 90 to 95% of Lyme disease in dogs is subclinical or asymptomatic. Clinically asymptomatic dogs have been shown to have arthritis when their joints are examined on necropsy. Given the paucity of clinical systemic signs in canine Lyme disease, the veterinarian often has a difficult time distinguishing lameness due to Lyme disease from that due to injury or other forms of arthritis.

Certain rare forms of Lyme have been noted in dogs, including a documented case of 3rd degree heart block in a German Shepard, and a renal disease form, involving

necrosis and glomerulonephritis, which is 4 to 6 times more common in Golden and Labrador Retrievers than in other breeds.

Testing on the OspA Lyme disease vaccine for dogs began in 1994. The efficacy of the vaccine was first evaluated in a randomized, double-blind study using 9- to 10-week old beagles. Two doses of vaccine were given three weeks apart. Dogs were then exposed to Lyme disease one year later through a natural tick challenge of live caught endemic ticks with exposure sufficient to assure 100% infection rate. A natural challenge was used because it has been shown that antibody response to tick challenge is quite different from that to needle inoculation.

Dogs were observed post vaccination for hypersensitivity, site tenderness and swelling, and any other negative responses to the vaccine. They were observed daily post tick challenge for changes in mentation, gait, temperature, etc. Skin biopsies were taken 1, 2, and 3 months post challenge. These were cultured for six weeks in BSK medium and then observed microscopically.

Seroconversion was seen in 90% of the vaccinated dogs and in 0% of the non-vaccinated. Post challenge clinical signs appeared in 18% of the non-vaccinated dogs and in 0% of the vaccinated. *Borrelia burgdorferi* was isolated post challenge from the skin of 83% of the non-vaccinated dogs and from none of the vaccinated dogs.

A second randomized, double-blind study completed in 1998 used a tick challenge presented four weeks after the second vaccination. In this study, 20% of the non-vaccinated dogs showed clinical signs of Lyme disease (the high incidence of symptoms observed in these studies indicates that the challenges presented were very aggressive), and spirochetes were isolated from the skin of 100% of the non-vaccinated dogs at 3 months post challenge.

None of the vaccinated dogs showed clinical signs of Lyme or had Bb isolated from their skin post challenge. Western blotting in the non-vaccinated group showed typical Bb banding, while the vaccinated group showed only heavy banding at the OspA site.

In the USDA field study for safety, 1400 puppies and older dogs from endemic and non-endemic areas were given 2300 doses of the vaccine, and acute health consequences were looked for over a four month period. The dogs in this study were not assessed for previous exposure to Lyme disease, and many were given other vaccinations along with the Lyme vaccine as part of their regular veterinary care. 99% of vaccinations produced no adverse reactions. Reactions that were reported included lumps, bumps,

lethargy and vomiting. The fact that multiple vaccines were often involved, makes the adverse reaction rate in this study hard to evaluate. No Lyme disease-like syndromes were reported 14 to 120 days post vaccination.

Since the launch of the vaccine commercially, 2.5 million doses have been sold and the rate of adverse experience rate concerning both safety and efficacy has been .0039%.

These studies indicate that the canine OspA vaccine is a safe and effective way of preventing Lyme disease in dogs. It is hoped that in 1999 a xenodiagnostic study will be completed to see if ticks can or cannot be infected by feeding of vaccinated dogs, thus evaluating the OspA vaccine's effectiveness in preventing the transmission of Lyme disease to its tick vector.

OspC borreliacidal antibodies used successfully in serodiagnosis of Lyme disease.

At the 12th International Conference on Lyme Disease, Steven M. Callister, Ph. D. reported on his research concerning OspC antibodies in Lyme disease. He has developed a sensitive and specific test for early Lyme disease which measures Borreliacidal antibody activity aimed at the OspC protein which is up-regulated as the Lyme spirochete enters the body. The technique uses laser flow-cytometry and live spirochetes of a particular strain (50772) known to express OspC on its surface in culture. Dr. Callister reviewed his research, highlighting OspC's connection with the pathology, serodiagnosis and prevention of Lyme disease.

OspC IgM antibodies develop early in Lyme disease, but were previously believed to not mount a

significant borreliacidal (borrelia killing) attack in the body. Dr. Callister's group has shown that, in fact, OspC borreliacidal antibody activity is present in early Lyme, but was undetected because the strains of *Borrelia burgdorferi* generally used for testing do not express OspC on their surface under laboratory conditions. When another strain which has strong OspC expression (strain 50772) is used, borreliacidal activity against OspC is readily demonstrated.

Dr. Callister explained that there are two types of basic antibody responses which are important in Lyme disease, opsonization response and killing response. Opsonization involves marking the spirochete by coating it with opsonizing (phagocytosis facilitating) antibodies so that

phagocytic cells can recognize the spirochete as foreign, and can engulf it and eliminate it from the body. The killing response involves the production of borreliacidal antibodies which recognize the spirochete as foreign, attach to the organism, and combine with immune complement to form a membrane attack complex. This action results in blebbing on the surface of the organism and eventually leads to spirochete death.

Opsonizing antibodies are fairly non-specific, often attaching to many different types of organisms. However, killing antibodies are very specific and recognize only certain parts of one particular organism.

Thirty-five specific proteins have been associated with *Borrelia burgdorferi* infection. It has been well established that there is borreliacidal antibody activity against OspA (31kd) and OspB (34kd). Recently it has been proven that there is borreliacidal activity against OspC (22kd) as well, and evidence is mounting of a similar activity against the 39kd *Borrelia* protein.

The principle behind the development of vaccines against Lyme disease is that if the production of borreliacidal antibodies is stimulated in sufficient numbers prior to exposure to the Lyme bacterium, protection against the disease will result. The currently available Lyme vaccine is based on the production of antiborreliacidal antibodies against the OspA protein which is strongly expressed while the spirochete is in the tick gut. Shortly after entering the body, the expression of OspA by the spirochete is reduced and OspC expression increases.

Previous studies have shown that OspC can be used to produce an effective Lyme disease vaccine, however, these studies failed to prove borreliacidal activity. Dr. Callister and his associates have shown that this failure to demonstrate borreliacidal activity was due to the use of Bb strains which do not

express OspC on their surface. When testing is done using a strain which strongly expresses surface OspC, borreliacidal activity is easily demonstrated.

OspC antigenicity is strong in early Lyme disease, while OspA and OspB antigenicity are found to be strong in later Lyme arthritis. These borreliacidal antibodies are very specific for *Borrelia burgdorferi* and all are capable of providing protection against infection. Borreliacidal

When testing is done using a strain which strongly expresses surface OspC, borreliacidal activity is easily demonstrated.

antibodies can be of either the IgM or IgG subclass, though virtually all OspC borreliacidal antibody activity appears to be of the IgM type.

In determining the degree of protection achieved through vaccination, Dr. Callister stated that it is important to measure borreliacidal antibody activity. Most vaccine studies have used ELISA or western blot measurements of antibody levels. However, these tests measure both opsonizing and killing antibodies and are not a good measure of vaccine effectiveness. Until now, measurement of borreliacidal antibody activity has been difficult. It requires a quality growth medium, the ability to eliminate antimicrobial agents from the medium without affecting borreliacidal antibody activity, and the use of an organism which consistently expresses the specific antigen target.

Dr. Callister's group has devel-

oped a technique which meets these requirements. Using a special medium and a rapid, simple process for removing antimicrobial agents, they have been able to incubate samples overnight and analyse them using a flow cytometer which can differentiate live and dead spirochetes. In blinded studies, the technique known as the FCB (Flow Cytometry Borreliacidal) antibody test has proven to be sensitive, specific, objective and reproducible, and can be used for Lyme diagnosis (and possibly for determining treatment effectiveness), and for evaluation of vaccine efficacy. Because it looks at OspC antibody activity, it is not affected by prior vaccination with the OspA vaccines.

When tested using CDC blinded serum samples the FCB antibody test was found to have a low cross-reactivity rate (2.8%) with other tick-borne diseases, and this cross-reactivity was almost totally eliminated when the positivity cut-off was raised to 1:40. The test has shown high OspC borreliacidal antibodies in Lyme disease cases from all regions of the United States, as well as in Lyme caused by *Borrelia afzelli* in Slovenia, indicating that the borreliacidal epitope of OspC may be very highly conserved, despite the reported heterogeneity of the total OspC protein.

Dr. Callister contends that the FCB antibody test has many advantages as a diagnostic test for Lyme disease. It is a single objective test which has been shown to be sensitive, specific, reproducible, and relatively inexpensive, which can identify infection even in people who have been vaccinated, and which may be useful in vaccine efficacy studies. Additionally, there are data indicating that it may be able to identify active infection in late and chronic Lyme.

[Note: This test is not currently available for general use in a clinical setting.]

OspA vaccine induces Lyme arthritis in hamsters

Ronald Schell, Ph.D., has spent several years studying the induction of arthritis in hamsters which have been vaccinated against Lyme disease. Previous studies showed that vaccination with *Borrelia burgdorferi* (Bb) sensu stricto isolate 297 primed hamsters for the development of severe destructive arthritis (SDA) when they were challenged with live Bb sensu stricto 297 within five weeks of vaccination. The severity and duration of the arthritis was dependent on the size of the inoculum. A dose greater than 1,000,000 organisms resulted in such severe illness that the hamsters were unable to move, squealed in pain when lightly touched, and had to be fed and watered if they were to survive. Hamsters challenged with 100 organisms were able to move but showed disease histopathology.

Challenge with the Bb sensu stricto isolate 297 at 5 to 9 weeks after vaccination did not result in severe destructive arthritis or in histopathologic changes. However, if hamsters were challenged with other genomic groups or other *Borrelia* isolates including Bb sensu stricto C111, *B. garinii* and *B. afzelii* during this period, they did develop SDA. After 26 or 52 weeks, vaccinated hamsters developed SDA when challenged with the Bb sensu stricto isolate 297 or with other Bb isolates.

In general, Dr. Schell found that vaccination with all seroprotective groups or genospecies of Bb sensu lato can prime hamsters for the development of SDA and that the priming occurs whether live spirochetes, heat inactivated spirochetes, antibiotic treated spirochetes, or frozen and thawed spirochetes are used for vaccination. Vaccination resulted in protection only during a short time window of 3 to 9 weeks after vaccination, and then only

against the specific isolate used to create the vaccine.

Though it would seem that vaccination with a single antigenic protein such as outer surface protein A (OspA) might be less likely to produce adverse effects than a whole spirochete vaccine, Dr. Schell and

Dr. Schell believes the ability of humans vaccinated with OspA to mount a protective response to Bb has been greatly exaggerated.

his group were concerned about the safety of the OspA vaccines currently in use in humans and dogs. To test the safety of the OspA vaccine in their hamster model, 2 groups of 3 hamsters each were vaccinated with 30 micrograms of recombinant OspA. 11 days after vaccination, one group was challenged with 1,000,000 viable organisms of Bb sensu stricto isolate 297, and another group was inoculated with 30 micrograms of OspA in BSK medium (a medium developed specifically for culturing Lyme spirochetes). The first group developed swelling 7 days after injection, which rapidly worsened until day 11 and then gradually lessened. Erosive SDA developed, with thickening of the synovial lining and subsynovial tissues in the periarticular region, the tibiotarsal and intertarsal joints. Periarticular soft tissues showed mononuclear inflammatory infiltrate that extended and focally destroyed skeletal muscle.

The second group, which was challenged using only the OspA antigen which had been used for vaccination, had no swelling. Non-vaccinated hamsters were also challenged with Bb 297. They showed less severe swelling than those who had been vaccinated with OspA prior to Bb 297 challenge. Cellular infiltrates of mononuclear cells were found in the synovial and subsynovial areas, but their joints were free of histopathologic alterations and showed minimal hypertrophy and inflammation.

A second study looked at vaccination with 30, 60 or 120 micrograms of recombinant OspA, as well as with the commercially available canine OspA vaccine. Arthritis developed after exposure to non-vaccine specific challenges 11 days after vaccination in all hamsters. No arthritis was seen in the non-vaccinated, control group after challenge. Two additional groups were vaccinated with *Escherichia coli* and with *Staphylococcus epidermidis* and then challenged with their respective vaccine-specific, live organisms. These two groups did not develop arthritis.

Challenges in all of these studies were done through the hind foot pad, because it has been found that inoculation at that site results in faster development of arthritis, though inoculation through other routes including intradermal, subcutaneous and intramuscular will lead to the same results over a longer period of time.

From these studies, Dr. Schell concluded that:

- In hamsters, vaccination with OspA gives only short-lived protection even after booster, with peak protection at 6 weeks post vaccination and 2 weeks post booster. No borreliacidal protection was present after 30 weeks. IgG levels do not measure degree of protection. Recombinant OspA is not a good inducer of sustained borreliacidal antibodies, though it does induce high IgG levels of non-protective

antibodies (see previous article on Steven Callister's research). IgG measurement should not be used to show effectiveness of the OspA vaccine.

- OspA vaccination can prime hamsters to develop SDA on exposure to *Borrelia* and repeated boosters may have the potential to increase complications.

- The period of tick attachment and the level of antibodies developed is very important in determining the bactericidal effectiveness of the vaccine.

- The heterogeneity of *Borrelia* and its ability to change its expression of antigenic proteins is a problem in vaccine development. Addition of other antigens to develop a more effective vaccine may also increase the risk of complications such as destructive arthritis. An adjuvant added to the vaccine may be necessary in order to sustain borreliacidal antibody levels over a significant period of time. However, the adjuvant may also add to the chance of adverse reactions. Another possible way of producing a vaccine would be to use a whole, attenuated spirochete type of vaccine from which the arthritis producing antigens were selectively eliminated.

- The hamster is a good model for evaluating the ability of different Bb antigenic components to lead to arthritis.

Dr. Schell stated that he would not recommend the OspA vaccine at the present time for humans or animals for many reasons, including, but not limited to the following: 1. OspA appears safe in vaccination in humans, but its ability to induce high levels of protective borreliacidal antibodies for a sustained period has not been shown. 2. Repeated vaccination to obtain short-lived seasonal levels of borreliacidal antibodies over a period of years may increase adverse effects. 3. Research by Dr. James Miller of UCLA showed that vaccination with OspA failed to eradicate *Borrelia burgdorferi* and

actually masked infection. 4. OspA is down regulated in warmed ticks, while OspC is upregulated. The OspA vaccines cannot induce borreliacidal antibodies that can kill *OspC* expressing *Borrelia burgdorferi* (see article on Dr. Steven Callister's research). Therefore these organisms can infect OspA vaccinated humans. 5. Even a combination OspA & OspC vaccine may be ineffective if ticks can inactivate complement at the site of infection. This might allow Bb time to coat itself in host proteins and prevent complement from reaching sites on infecting spirochetes that have bound OspA or OspC antibodies, thus

preventing elimination of the spirochetes. Johnson showed that passive transfer of highly protective serum just hours after infection in hamsters failed to eliminate infection. 6. Dr. Schell believes the ability of humans vaccinated with OspA to mount a protective response to Bb has been greatly exaggerated, and that a systemic or even local response cannot be made quickly enough to prevent infection before Bb coats itself in host proteins. 7. "...Lyme investigators are pleased that a Lyme vaccine can be made, but the current vaccine has sufficient defects that make it unlikely to rid us of Lyme disease."

German researchers agree US diagnostic standard not appropriate in Europe

by Peter Rohleder

It's not amazing when you have to confess that Lyme patients are often at daggers drawn with their physicians, who often think of their Lyme patients as being hypochondriacs. The dilemma is that in spite of the mushrooming Borreliosis support groups, those groups cannot substitute for a good physician. At the end it is always necessary to send the patients to those physicians who trust the patients and believe their complaints even if some medical text books still tell the story that Lyme-disease is easily and quickly cured. For that reason especially, members of Lyme disease self-help groups are interested in newer research results because they raise hope that this might make the existing problems with diagnosis and therapy more obvious.

My attendance at the 5th International Potsdam Symposium on Tick-borne Encephalitis and Lyme-Borreliosis has to be seen in the light of this hope. The meeting took place

from February 26th to February 27th in Berlin, Germany. Unfortunately hopes are seldom fulfilled quickly. Many things were interesting but only a few things brought us nearer to the target of getting more clarity on the issues mentioned above. I will restrict my report to those points of special interest Lyme patients.

The first day was dedicated to the topic tick-borne encephalitis (TBE), a dangerous and sometimes fatal virus infection. It is alarming that the number of TBE infections, if we believe the numbers presented, is dramatically increasing in Russia and in the Baltic states. One thing that TBE and Lyme-disease have in common is the transmission process: the bite and the subsequent sucking of the tick. Prof. Patricia Nuttal (Institute of Virology & Environmental Microbiology, Mansfield, Oxford) reported on her research on those processes which take place when ticks attach to their hosts.

The tick's success is based upon a

complex salivary glands and secreted, in tick saliva, into the feeding pool. Increasing evidence indicates that the survival of tick-borne pathogens, such as *B. burgdorferi* and TBE virus, depends on their ability to exploit the pharmacological activities of tick saliva components.

The second day was mostly dedicated to Lyme disease. Different aspects of Lyme borreliosis were discussed. For example, there was the question, whether ehrlichiosis and babesiosis, two other tick-borne diseases, also play a part in Europe. In the USA this question meanwhile has been confirmed, while in Europe, according to M. Granström from the Karolinska Hospital and Institute in Stockholm, Sweden, there is evidence that these infections also might play a part. Coinfections may especially be responsible for making it difficult to cure an infection of *Borrelia burgdorferi*.

In the poster session in the foyer of the building there was a hint about coinfection with Ehrlichiosis in an article by Talaska and Levin: "Five out of 50, or 10% of patients were seropositive for HGE antibodies. This rate is slightly higher than coinfection observed in endemic areas of the United States and suggests that HGE/Lyme coinfections may be of clinical significance in Europe." More detailed studies and better diagnostic methods should bring more clarity to this subject.

There were further reports of epidemiologic data concerning Lyme borreliosis in various parts of Europe. For example Dr. Strle from Ljubljana in Slovenia observed that there is an increase of infections from year to year. In a lecture by Stanek from the Hygiene Institute of the University of Vienna the advisability of prophylactic antibiotic therapy after every single tick bite was discussed. He came to the conclusion that this has to be answered in the negative; the percentage of infections compared to all tick-bites seems to be too low.

Probably we have to agree with this statement. But another sentence which could be found in the abstract of Stanek's lecture made the members of the Borreliosis self-help groups shake their heads.

"This gives rise to the question whether the effort of a large scale double blinded study is justified for an infectious disease which can be treated effectively even in its so-called second and third stage and has never caused a fatal course." Stanek wrote.

In a lecture by T. Kamradt from the Clinic of Rheumatology and Clinical Immunology of Humboldt University Charity Clinic in Berlin a study was presented in which researchers tried to demonstrate an autoimmune process in patients with chronic Lyme arthritis by using different markers. In this context it is not necessary to point out that this question has arisen again and again since the discovery of Lyme borreliosis and has always been denied by various researchers. Again in this study the trial to demonstrate an autoimmune process failed. But this only led Kamradt to the conclusion that the method chosen to demonstrate this autoimmune process probably has been too simplistic. So we have to expect that this question will be discussed again.

Dr. Bettina Wilske from Max-von-Pettenkofer Institute in Munich discussed the standardization of serology. The first results from the pan-European study made clear that the American Centers for Disease Control and Prevention criteria for a positive Western-Blot (catchword: either two specific bands in the IgM or five specific bands in the IgG), sometimes used even in Europe, under European conditions are not appropriate. Because of the heterogeneity of the different European subtypes of *Borrelia burgdorferi*, three or even only two bands may be enough for a positive Western-Blot.

Dr. Krause, also from the

Humboldt University Charity Clinic pointed out that they were able to demonstrate the existence of a Bb infection by PCR of the CSF by patients in whom the classical serology did not enable them to make a positive diagnosis.

Dr. H. W. Kölmel from Department of Neurology, Erfurt Clinic, made a very promising start in his lecture about "Differential diagnosis in human neuroborreliosis" by mentioning the numerous clinical reports about Lyme disease imitating ALS, MS, Tourette syndrome and other psychiatric illnesses. But then he stated that from his point of view neuroborreliosis is not difficult to diagnose. The main problem they have, according to Kölmel, are those patients who in reality have another disease but who got information from the Internet or from self-help groups and now came to see them because they think they have neuroborreliosis. No further comments!

Dr. Eder from Immuno (formerly Baxter) reported that the first trials using a vaccine which also works under European conditions have been successful.

Although at the end of all lectures, the last one from M. M. Simon from the Max-Planck-Institute for Immunology in Freiburg was one of the most interesting. It was about his and his colleagues' work on the development of a therapeutic vaccine. Behind it is the idea of enabling the human body to do what can be observed in mice. In nature mice play an important role by transmitting Bb to the ticks and as expected Bb easily can be found in blood and various tissues of mice. But interestingly, mice don't get ill. The question is: "Why don't mice get ill?" Obviously their immune system is able to hold the spirochetes in check. This was confirmed by trials when immunodeficient mice were infected with Bb. The immunodeficient mice also got the expected symptoms like arthritis. From all this resulted the idea to develop a

therapeutic vaccine which enables people to do the same. There have been some successful steps towards the development of such a vaccine. In this context it should be mentioned that Simon and his colleagues last year received the Robert Pflieger Prize for their research.

Conclusion: For Lyme patients in Europe the symposium brought following positive results: 1. They should no longer expected to be excluded from treatment because their Western Blot doesn't show enough "CDC"-bands. 2. For chronic Lyme patients there is the hope that in the future there might be by a therapeutic vaccine, if the research from Simon at the end is successful.

Members of German self-help groups had expected that the research of Dr.Philips concerning the "Reliable Culture of BB from patients with Chronic LD" at least would have been mentioned, but it was not. Also nobody mentioned the NIH Clinical treatment trials of chronic Lyme disease in the United States. So there is still some work to be done in Europe.

Suggested for further reading:

Eur J Immunol 1999
Mar;29(3):946-57

Resolution of experimental and tick-borne *Borrelia burgdorferi* infection in mice by passive, but not active immunization using recombinant OspC. Zhong W, Gern L, Stehle T, Museteanu C, Kramer M, Wallich R, Simon MM

Abstract: Vaccination with outer surface protein A (OspA) of *Borrelia burgdorferi* prevents subsequent infection and disease in both laboratory animals and humans with high efficacy. OspA-based immunity, however, does not affect established infection due to the loss of OspA expression in the vertebrate host. We show here that repeated passive transfer of mouse and/or rabbit immune sera to recombinant GST-OspC fusion protein resulted in a dose-dependent resolution (1) of fully

established arthritis and carditis as well as infection in needle-challenged C.B-17 SCID and (2) of infection in both experimentally and tick-infected BALB/c mice. Unexpectedly, active immunization of disease-susceptible AKR/N mice with GST-OspC only led to prevention but not resolution of disease and infection, in spite of high serum titers of OspC-specific antibody and the expression of ospC in tissue-derived spirochetes. The data suggest that the efficacy of OspC antibody-mediated immunity depends on the immuno-

logical history of the recipient and/or environment-dependent regulation of OspC surface expression by spirochetes in vivo. The results encourage further attempts to develop therapeutic vaccination protocols against Lyme disease.

Peter Rohleder may be contacted by email at peter.rohleder@gmd.de. The Lyme Times appreciates the special effort he made to write this interesting report in English. Herr Rohleder will be reporting about the International Conference in Munich in the next issue of the Lyme Times.

Steere cautions California doctors against Lyme vaccine - potential autoimmunity

by Jean Hubbard

Dr. Allen Steere came to San Francisco in April to talk to doctors and medical students at the University of California Medical Center about the probable role of outer surface protein A (Osp A) in the "Pathogenesis of Chronic Lyme Arthritis" — and what it might mean for some people who get the Lyme vaccine.

Osp A, of course, is the protein employed in the Lymerix vaccine (as well as in the Connaught vaccine still being tested), to provoke formation of antibodies to kill Lyme spirochetes. But, Dr. Steere warned, in some people Osp A may also initiate complex autoimmune reactions. The part of Osp A that most strongly stimulates antibody production in patients with chronic Lyme arthritis has turned out to be cross-reactive with a molecule on cells found naturally in our bodies. He and his co-researchers have nominated this naturally occurring molecule — hLFA-1 or human leukocyte function-associated antigen-1 — as a "candidate autoantigen."

On this occasion, despite an enthusiastic welcome from fellow rheumatologists hailing the "incredible 22-year saga" that began with his "identifying the cause of Lyme disease," Dr. Steere emphasized that he would speak "only about Lyme arthritis, not all features of Lyme disease — which is too big a topic," and asked his audience to let him "just be a rheumatologist."

He reminded them that "the spirochete is trophic for the AV node of the heart, the skin and the nervous system as well as the joints and synovial tissues" and that the recent genomic sequencing of the entire *B. burgdorferi* B31 spirochete shows it to be "unusually complicated." In particular, its many lipidated proteins — 105 of them — many with antigenic variation, "make it complicated for the immune system to decipher." The saga Steere himself seemed more interested in was that of Osp A, chronic Lyme arthritis, and autoimmunity. He illustrated the relationship of Osp A and chronic Lyme arthritis — and one of the early clues suggesting autoimmunity

— by telling the story of a single patient he saw more than a decade ago. In 1986 this man, then 46 years old, noticed severe malaise and fatigue. He had stiffness in his legs after exercise as well, but it wasn't until five months later that he developed marked swelling of one knee — a frank arthritis. He also had radicular pain across the front of his chest, memory deficits, word-finding difficulties and somnolence.

By the time he was evaluated he had been treated with multiple injections of steroids into the joint space of his knee to reduce inflammation. He didn't remember a tick bite ("Most people do not remember tick bites," Steere observed) nor an erythema migrans rash, but he did have an elevated sedimentation rate and very high levels of IgG antibodies to *B. burgdorferi*, especially to outer surface proteins A and B. He also had the genetic marker HLA-DR4. He was treated with IV ceftriaxone for two weeks.

When reevaluated five months after treatment, however, although the sensory examination over his chest was normal and his fatigue had improved somewhat, he still had knee pain with marked swelling. He had developed new pain in one shoulder and continued to have word-finding difficulties and malaise that had improved but was still moderate. His Osp A and B antibodies had increased, and he was treated again with IV ceftriaxone, this time for a month.

Later he was treated yet another time with IV antibiotics, this time IV penicillin for two weeks. He also managed, on his own, to take doxycycline for a year.

Throughout 1988 and 1989, despite all these antibiotics, he still had knee swelling and shoulder pain, and now had bursitis of the elbow as well. He was treated with nonsteroidal antiinflammatory medications (NSAIDs) and more injections of steroids into his joints, but in 1990, four years after his initial presenta-

tion, he still had swelling of his knee.

At that time the patient's young daughter began experimental photopheresis treatment for the very serious disease juvenile dermatomyositis, and he arranged to try it for himself. Only then, surprisingly, did his knee swelling and pain resolve, albeit slowly over the next 10 months.

According to Dr. Steere, photopheresis is a procedure in which a patient's blood is circulated outside the body, where it is exposed to ultraviolet light. The process is used mostly to treat patients who are rejecting grafts or transplanted tissue because apparently — and this was the clue — the process kills autoimmune T cells.

Over the years Dr. Steere has seen other Lyme arthritis patients who, like this man, have had "knee swelling that keeps going on" despite repeated antibiotic treatment. Because spirochetes aren't seen anymore, and PCR tests don't detect borrelial DNA in their joint fluid, Steere believes the spirochetes have been killed. Because of that, and because many of these patients have HLA-DR genetic markers similar to those seen in people with the autoimmune disease rheumatoid arthritis — including DRB1*0401 and related alleles — he has long suspected an autoimmune etiology for chronic Lyme arthritis.

Long after treatment — and, Steere believes, the disappearance of spirochetes — these patients continue to have extremely high levels of antibodies to *B. burgdorferi* Osp A and Osp B circulating in their blood; in fact their serum levels of IgG antibodies to Osp A are much higher than those usually seen in patients with other manifestations of Lyme disease or in patients whose Lyme arthritis does resolve with antibiotics. And their high Osp A antibody levels become even higher, often dramatically so, at the beginning of prolonged episodes of Lyme arthritis. Test tube studies show that T-helper

cells (Th-1 lymphocytes) taken from their synovial fluid also react to Osp A, expressing high levels of the cytokine interferon-gamma, sometimes for years after treatment.

And the most recent research on these patients, conducted by immunogeneticists Dawn Gross and Brigitte Huber in collaboration with Steere, has shown that the hLFA-1 molecule mentioned above cross-reacts with Osp A in this test: The synovial fluid T cells from these chronic Lyme arthritis patients recognize and react in the same way to the hLFA-1 molecule — a molecule found in everyone — as they do to Osp A. The reason for this is "molecular mimicry:" A tiny part (called a peptide and composed of just a few amino acids) on the surface of hLFA-1 is almost exactly the same as the tiny part of Osp A that most powerfully stimulates antibody production in these patients.

Steere and his colleagues theorize that, during the development of treatment-resistant Lyme arthritis, the spirochete's Osp A primes T lymphocytes in the joint to a point where they can remain activated by stimulation with this peptide of hLFA-1 even after spirochetes and borrelial proteins like Osp A have disappeared. They think this maintains release of cytokines (like interferon-gamma) that could lead to continuing inflammation and damage of joint tissues.

How does this relate to the vaccines? Very high levels of Osp A are not only seen in patients with chronic Lyme arthritis; they're also seen in people vaccinated with Osp A. In fact, Dr. Steere pointed out, high Osp A antibody levels are needed for the vaccines to be effective in preventing Lyme disease. It is, after all, these antibodies that kill Borrelial spirochetes in infected ticks when they ingest blood from vaccine recipients. The vaccine has to be given in three injections, spaced over several months, because antibody levels fall off rapidly after vaccina-

tion. Even after the third injection — by four months, Steere said — Osp A antibodies decline to the level that correlates with most effective protection, and Steere believes a fourth injection probably will be needed at that time, as well as booster injections “about every two years ... although the number of boosters needed is not yet in place.”

“Is it a problem to vaccinate people over and over again with Osp A?” he asked. Although the priming of T cells to the point where they can be stimulated by LFA-1 may require either the spirochete itself or infection-induced proinflammatory immune responses in addition to Osp A (even in people who have the genetic markers that make them susceptible to chronic arthritis), “I wonder whether that could potentially lead to trouble, could cause an autoimmune reaction in some people.”

In the vaccine trials, he said, only 1 to 2% of recipients developed symptoms during the first 30 days after injection, and no differences were seen between the vaccine group and the placebo group in the frequencies of any particular syndrome in the thousands of patients observed. “But that doesn’t mean it won’t be a problem; it remains to be seen. It is a concern of mine.”

Steere went on to say that official recommendations regarding the Lyme vaccines advise people in endemic areas that they “should consider” the vaccine; they don’t say that they “should have” the vaccine. He explained that in part this is because “herd immunity is not at issue” since Lyme disease is not considered a communicable disease, in part because the number of boosters is not yet in place, and in part because “Lyme disease is usually treatable by antibiotic therapy.” The vaccine is not recommended in non-endemic areas, he went on, and “in any site in California this would be the case.”

[Note: It appears Dr. Steere

based his assessment of endemicity in California on the number of California cases reported to the CDC and meeting their requirements for case surveillance — he said that in 1997 there were only 154 cases. In fact several Northern California counties contain areas where Lyme disease is clearly endemic, particularly in Mendocino, Humboldt, Trinity, Sonoma, Lake, Lassen and Butte Counties. The Lyme Times and Lyme Disease Resource Center, however, believe there is insufficient knowledge at present to justify either recommending or rejecting the Osp A vaccines.]

Given all this, why was Osp A used for the vaccine? According to Dr. Steere, “Only because it was the first [Lyme] protein that was known. And it was the first recombinant protein. I suspect that it may not be the best way to do it; it’s just the first way we thought about it.”

There was only a brief time for questions at the end of Dr. Steere’s talk. When asked about autoimmune phenomena in central nervous system Lyme disease, he replied that he didn’t know of any, although there have been hypotheses.

When asked about similarities between Lyme disease and other spirochetal diseases like syphilis and yaws, he said, “I know very little about joint disease in syphilis.” He mentioned that central nervous system symptoms in Lyme disease, like CNS symptoms seen in syphilis, can occur after a long latent period. “The symptoms are slowly progressive, I think with the spirochete still present. But syphilis is treatable with antibiotics, and so is Lyme disease.”

Dr. Steere came to UCSF as a visiting professor under a program honoring Ephraim P. Engleman, M.D., Professor of Rheumatology at UCSF and Director of the Rosalind Russell Medical Research Center for Arthritis. The Center funds research into “the causes of the group of diseases known collectively as arthritis,” including the autoimmune

diseases rheumatoid arthritis and lupus.

Reporter’s Comments

Are possible autoimmune reactions provoked by molecular mimicry between Osp A and hLFA-1, or even by the Osp A vaccine, likely to occur in many people? Steere believes not. The research he talked about looked only at patients with chronic Lyme arthritis, not at more common forms of chronic Lyme disease like Lyme encephalopathy. Further, the chronic forms of the frank Lyme arthritis he’s interested in — usually obviously swollen knees — are considerably less common than the “minor joint pains that occur here and there, now and then,” as he put it, even in patients who first present with erythema migrans. And Dawn Gross emphasizes that she discovered the similarity between the two peptides (the one on Osp A and the one on hLFA-1) “in the context of DRB1*0401,” the genetic marker most strongly associated with arthritis [1].

Specifically, she first found the Osp A peptide most likely to bind to the genetic marker DRB1*0401, then searched a computer gene bank for human proteins that contained a similar peptide. She found two — hLFA-1 and 40S ribosomal protein — but only the hLFA-1 peptide fit other necessary parameters. Next she showed that hLFA-1, whole Osp A and the Osp A peptide similar to hLFA-1 all stimulated production of interferon-gamma (a cytokine thought to be associated with tissue destruction) in joint fluid taken from patients with chronic Lyme arthritis — at least in 9 of the 11 patients tested. These included two patients who did not show the rheumatoid arthritis-associated markers on HLA typing.

Continued on page 39

Order form: fill out and mail in to address below.

continued from page 36

Joint fluid from patients with rheumatoid arthritis instead of Lyme arthritis didn't react — not even to Osp A itself — despite having the same arthritis-associated genetic markers, including the DRB1*0401 allele. This led both Gross and Steere to opine that it might be necessary for the spirochete itself — “or at least Osp A” — to “prime the response” before the autoimmune reaction can occur. And, interestingly, Gross reports that the reaction might be slow to develop even in some patients with chronic Lyme arthritis: the first joint fluid taken from an unspecified number of patients didn't react on the stimulation test, while joint fluids taken from them a few months later did.

As far as the vaccine is concerned, it remains to be seen whether scientific studies will be able to document autoimmune reactions, and whether some of them might develop only slowly, but Gross and Steere's report seems to suggest that the danger is greatest for people who already have had, or still have, Lyme disease. Given the known insensitivity of current diagnostic testing for Lyme disease, this is a problem worth serious long-term follow-up of all vaccine recipients.

Newspaper stories have reported vaccine reactions. One quoted a Lyme clinician who claimed to have seen an array of Lyme symptoms in patients after they had received the vaccine. Another told the stories of three patients who sued vaccine makers when they became disabled after receiving the Osp A vaccines during the vaccine trials. One of these had developed severe arthritis requiring surgery on both knees — the sort of reaction Dr. Steere is concerned about — but two had suffered severe neurologic damage. All three apparently settled out of court.

The Lyme Alliance newsletter, **SpotLight on Lyme**, has run a series

of detailed stories written by patients who, after receiving the vaccine, either began having symptoms consistent with Lyme disease or had apparent relapses, including serious neurologic symptoms. On the Internet Lyme disease newsgroup there have even been two reports of post-vaccine paralysis. One Lyme clinician reported—at a Lyme Disease Foundation conference—that a patient who received the vaccine suffered an infarction of the eye.

Obviously these reports are anecdotal, and to date there seem to be no scientific publications that even speculate about central nervous system reactions to the vaccine.

[Note: LymeNet, a respected online publication, is compiling reports of serious adverse events associated with the Lymerix vaccine, and asks physicians with confirmation of such events to write them by email at vaccine@lymenet.org. Adverse reactions to the Lyme vaccine or other vaccines should also be reported to the Vaccine Adverse Event Reporting System, a Post-Marketing Safety and Surveillance Program of the FDA and the CDC. See article on vaccine, page 1.]

For the record, not everyone agrees with Steere's conclusion that all spirochetes have been cleared from patients with chronic or recurrent Lyme arthritis. His belief stems from his inability to detect spirochetal DNA in joint fluid from these patients and his observation that their arthritis doesn't respond to repeated courses of antibiotics.

Priem et al., however, have been able to detect spirochetal DNA in the synovial membranes of chronic Lyme arthritis patients even when it is not detectable in the joint fluid [2]. Their finding supports those of others who have found that, in late disease, *B. burgdorferi* is generally more readily found in soft tissues than in body fluids, whether one is trying to culture spirochetes or using PCR to look for spirochetal DNA. Max Appel of Cornell, describing

dogs proven by both culture and PCR to remain chronically infected even after a month of antibiotics, puts it this way: “We find it (positive PCR and cultures) in the synovium. These spirochetes sit in the tissues, not in fluids. Synovial fluid is negative; synovium is always positive in these lame dogs. The CSF is negative, but meninges are positive — not as regularly as the synovium, but they are positive. It's not in the peritoneal fluid; it's in the peritoneum, in these connective tissues; that's where these agents are hiding. And that's what we are seeing in the more chronic form of arthritis.” [3]

And of course the “repeated courses of antibiotics” that Steere finds ineffective in treating chronic arthritis are very short (a maximum of 6 weeks [4]) compared to the durations most Lyme clinicians believe are necessary to effectively treat late disease (4 to 6 months or more [e.g. 5-7]).

Still, neither Gross' finding of molecular mimicry between an immunodominant peptide of Osp A and a peptide of hLFA-1, nor the likely autoimmunity in chronic Lyme arthritis it suggests, requires that spirochetes disappear from joints. Given the myriad ways that *B. burgdorferi* is known to attack our tissues, it seems likely that direct damage by spirochetes, spirochete-driven immune reactions and autoimmunity all play a role in producing continuing symptoms, sometimes even in the same patient.

References

1. Gross, D. et al, “Identification of LFA-1 as a candidate autoantigen in treatment-resistant Lyme arthritis,” *Science* 281:703-706 (July 31, 1998).
2. Priem, A. et al, “Detection of *Borrelia burgdorferi* by polymerase chain reaction in synovial membrane, but not in synovial fluid, from patients with persisting Lyme arthritis after antibiotic therapy,” *Ann Rheum Dis* 57(2):118-121 (Feb 1998).
3. Discussion, 11th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, 1998 (Lyme Disease Foundation). The data

Calendar

The Fourth Gordon Conference on the Biology of Spirochetes

Sunday-Friday
January 16-21, 2000

A web site describing the conference and information regarding the initiation of the application/registration process will be available in July 1999.

- Dr. Appel refers to are reported in Straubinger, R.K. et al, "Persistence of *Borrelia burgdorferi* in experimentally infected dogs after antibiotic treatment. J Clin Microbiol 35(1):111-116 (1997).
- "Lyme disease — the method of Allen C. Steere, MD," Conn's Current Therapy, 1998.
 - "Lyme disease — the method of Joseph J. Burrascano, Jr, MD," Conn's Current Therapy, 1997.
 - Ziska, M.H. et al, "Physician preferences in the diagnosis and treatment of Lyme disease in the United States," Infection 24(2):182-186 (1996).
 - "Treatment of Late Lyme Borreliosis," Wahlberg, P. et al. J of Infection 29:255-261 (1994).

Lyme disease sufferers invited to join class action suit against insurance companies

A leading class action litigation firm, Napoli, Kaiser & Bern, has just agreed to represent Lyme sufferers against the Health Insurance Companies.

If you suffer from Lyme Disease and believe that you have not received proper and/or sufficient medical treatment through your doctor, due to coverage limitations imposed by your Health Insurance Company, it's important that we hear from you now.

You can contact the legal firm immediately via the Internet at LymeSuit@AOL.com. Please provide your name, address (or at least state of residence), telephone number the name of your insurance carrier and a very brief summary of your coverage issues (100 words or fewer please). If you do not have access to the Internet, please send the same information to:

LymeSuit c/o Napoli, Kaiser & Bern - LLP 115 Broadway New York, NY 10006

There will be no cost to you in joining this action. Further, any information you provide will only be used in connection with this case.

This is your opportunity to be heard and to try to stop injustices by the Insurance Companies (and to help other Lyme Disease sufferers from being denied ongoing treatment/coverage).

Thank you for your support of Lyme Disease. Please help make a difference!

Michigan Lyme Disease Symposium

Saturday
September 25, 1999
8 am to 4:30 pm

Ashmen Court Hotel and Conference Center
Midland, Michigan

"Current Clinical Approaches and Microbiology of Lyme Disease and Other Tick-Borne Illnesses."

Speakers include: Dr. Steven Phillips, Dr. Anthony Lionetti, Dr. Michael Cichon, Dr. Richard Horowitz, Dr. Edward Bosler

For more information call the Michigan Lyme Disease Association at 1-888-784-LYME or email: Linda at LPurdy1040@aol.com

Send Calendar announcements to the Editor.

the Lyme Times
Lyme Disease Resource Center
P.O. Box 1423
Ukiah CA 95482

Non-Profit Org
Postage Paid
Permit No. 16
Petaluma, CA 94999