LDA Presentation to Students at Voorhees High School

by Pat Kerl, Hunterdon County LDA Representative
Voorhees High School, Glen Gardner, NJ

Pat Smith, President of the Lyme Disease Association (LDA) gave a presentation to various grades of a Health class at Voorhees High School on Wednesday, November 10, 2004. The school is located in rural Glen Gardner, New Jersey, Hunterdon County, a county which has one of the highest rates of Lyme disease in the nation. In fact, as Pat pulled in the parking lot at 7am, she stopped and asked a man standing in the middle of the lot where she could park. “Are you the Lyme Lady,” he asked very seriously. She said yes and he promptly gave his Lyme history, and followed her into school to ask questions about the disease and told her he had permission to attend her session, which he did. He was a retired policeman.

When asked by the teacher how many of them either had Lyme disease themselves, or had someone close to them who suffered from the disease, about 90% percent of all the classes raised their hands. Even though many of the students suffered from Lyme, there was still so much about the disease that they didn’t know. Several teachers came by and confided they had the disease.

As a result, the teachers, and the students alike were grateful for any and all information Ms. Smith could share with them. She started her presentation with a slide show presentation, which explained such things as the various rashes, hosts of the ticks, types of ticks, how to protect oneself, remove a tick properly, etc. The students were paying attention intently knowing the importance of being taught these things that they themselves were personally dealing with. Pat Kerl assisted showing Ixodes tick specimens, and also gave the students some pamphlets to review and take home

to their families. Ms. Smith ended the presentation with a Question and Answer session that the students found quite informative.

The most rewarding thing heard at the end of the day was related by a teacher who told about a student whose life was changed as a result of a previous presentation at the high school several years ago by Pat Smith. A sophomore girl became deathly ill, and none of the doctors had a clue what was wrong with her. Time was of the essence in finding an answer to why this girl was failing quickly. Fortunately, at the eleventh hour, the girl remembered the presentation that Ms. Smith had given to her health class, and after remembering the list of symptoms, the girl insisted on being tested for Lyme disease. Fortunately her test was positive, and she was treated properly, and at this time is doing well. It was rewarding to Pat, and touching at the same time that she had touched a life so profoundly through her Lyme disease presentation.

Rhode Island School Nurses Association

Presented by Pat Smith, President, Lyme Disease Association

Lyme is the most prevalent vector-borne disease in this country and the most prevalent vector-borne bacterial disease in the world. In 2002, 24,000 were reported, an increase of 35%.That figure equals about 1/10th of actual cases, thus there were 240,000 new cases in 2002.

The lack of an effective test for Lyme, its ability to mimic other diseases, plus the existence of other tick-borne diseases acquired from the bite of the same tick often lead to a delay in diagnosis and treatment, sometimes producing chronic disease with CNS involvement, with subsequent antibiotic difficulty in penetration to eradicate the

organism. 10-15% of individuals who acquire Lyme develop chronic disease, with children at the highest risk of contracting Lyme, leading to problems obtaining an education due to prolonged absences, fluctuating symptoms and cognitive difficulties. They are academically, socially, and emotionally isolated from their peers. They have few or no friends, no regular school attendance, no sports or activities, and no self-esteem. For them, to get out of bed is an accomplishment, to shower is a miracle. Some contemplate suicide, unfortunately, some are successful.

A law in NJ, developed by LDA (then LDANJ), requires teachers who have students with Lyme to be in-serviced annually on the disease. A NJ State Department of Education-approved Lyme disease curriculum is available for districts in endemic areas, although its use is not mandated. Unfortunately, many districts are not aware of the law and few comply unless pressed by parents to do so. The LDA is working with two other groups in CT to try and implement similar legislation.

The medically community is not doing a good job disseminating information about children with Lyme, and the politics surrounding the disease are dictating who has the disease and how it can be treated. Antibody testing is unreliable, about 40% accurate. Antibiotics appear to control, but do not necessarily eradicate, infection. Psychiatric symptoms and behavior problems are often overlooked as Lyme manifestations, although current literature is replete with examples of psychiatric illnesses whose origins are probably bacteriological.

A set of symptoms may be present in a patient for a period of time, then new ones may be added to or replace the original symptom set, since Lyme disease can attack all the major systems in the body from musculo-skeletal to arthritic, neurologic, psychiatric, ophthalmologic to cardiac. The musculo-skeletal system may be the initial focus of the disease, which can limit a student’s ability to participate in physical education and preclude him from carrying his books. However, less than a day after the bite of an infected tick,

the bacteria can enter the central nervous system causing everything from memory loss and speech difficulty to emotional outbursts and depression. Chronic lateness, brain fog, letter and number reversal, and spelling difficulty can all signal disease in a student. Patients can go blind and deaf, and develop heart block, memory loss, mental confusion, seizures, a dyslexic type of condition, and ADD symptoms. Studies at Columbia University have demonstrated that individuals with Lyme disease have raised their IQ 22 points after appropriate treatment.

What I call “transitory learning disabilities” may develop in a student with Lyme disease. The type and duration of such disabilities are dependent upon affected body systems, length of infection, student’s general condition, and maybe the course of treatment. Patients beginning treatment often experience a Jarish-Herxheimer reaction, or Herx, an intensification of symptoms—the patient gets worse before he gets better. Unfortunately, this reaction may often go unrecognized, even by the physician.

In 1992 in Washington, I presented to Congressman Christopher Smith, the Centers for Disease Control & Prevention (CDC) and the National Institutes of Health (NIH), a 9-district school study showing the impact of Lyme disease on children. As a result, the CDC came to NJ and studied Lyme in 5 of those 9 districts. The resulting CDC unpublished study of 64 students showed that the median duration of illness at the time of interview was 363 days, and the mean number of school days missed because the child was too ill to attend was 103 days (with a range of 2 to 548 days). The median duration of home instruction was 98 days, with a range of 5 to 792 days. Another study by NJ family therapist Maggie Smith showed an 11.2 months average school absence due to Lyme disease.

The cost estimate available for medical treatment for 54 of the CDC study children was $5.2 million, and more than one-third of families of the affected children had 3 or more

members who had at some time been diagnosed with Lyme, and 40% of the mothers were LD diagnosed.

78% of the parents stated that their children experienced a fall in grade point average during the time of illness, 79% experienced a decrease in the number of friends. A quote from the CDC study sums up the magnitude of the problem: “Perhaps the greatest costs incurred by the study children were the social costs of the illness and its treatment. Schooling and extra-curricular learning activities were seriously interrupted for most children; often, children spent large blocks of time as semi-invalids, isolated from social groups and missing out on cultural, sports, and social activities. School performance of nearly all children fell, sometimes drastically, and in several instances was said to interfere with selection by colleges and universities.”

Problems in the schools develop because these patients don’t look sick, and sometimes don’t act sick. Their symptomatology may vary from month to month, day to day, even minute to minute. They are late for school because they cannot get out of bed in the morning. They are labeled lazy, uncooperative, faking. Johnny cannot focus on his work no matter how hard he tries. He is labeled ADD. Jane cannot think. She walks around in a fog, barely getting through the day. She is labeled neurologically impaired. 15 year-old Ben reverses his letters and cannot spell. Officials are puzzled, since he won the state spelling bee 3 years ago. Fred does a fine job of cutting and putting a shop project together but he refuses to put his plans on paper. The teacher says he’s defiant and thinks he knows everything. What do these children all have in common? Each has Lyme disease that has manifested in a different way. Each has gone unrecognized as such by the school.

Although educating the student with Lyme disease can sometimes be a frustrating experience for the district, it can be an even more frustrating one for the student and his family.

Education of the staff about the disease, cooperation with parents, and flexibility by the district in providing the necessary accommodations are the keys to success.

Behavior or performance inconsistent with past observations of a student with existing Lyme by a staff member can lead to a change in medication by the physician, since unprecedented student behavior can be indicative of change in disease status. Recognition of manifestations possibly attributable to Lyme in a student without disease may lead to early diagnosis and treatment.

To educate children with Lyme disease, we all must learn to think outside the box. It is very tempting to label a child who cannot pay attention ADD, or a child who is experiencing emotional outbursts as a discipline problem, or a child who does not complete assignments or forgets his books as lazy or not responsible. Instead, we must recognize that the disease process probably plays a large role in his or her behavior, and with appropriate treatment, accommodations and understanding, these children can achieve their potential and go on to further education and become productive citizens. Thank you.

FDA Response to Vaccine Questions

On January 22, 2002 in Bethesda, MD., the LDA was able to get a private meeting with the FDA on the vaccine issue, despite reluctance by the FDA to grant the meeting. Congressman Chris Smith helped facilitate the setup of this meeting. On February 25, 2002, a month after meeting with FDA, LDA received written

answers to its questions from FDA and, also, learned that Glaxo SmithKline had quietly pulled Lymerix from the market, citing “poor sales.”

CLICK HERE FOR THE RESPONSE

Click here for summary of the meeting

LDA Remarks Before Vaccines & Related Biological Products Advisory Committee

REMARKS OF PAT SMITH, PRESIDENT, LYME DISEASE ASSOCIATION, INC. BEFORE THE VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE, MAY 21, 2002.

DISCLOSURE: No money from SKB.

The Lyme Disease Association, LDA, an all-volunteer organization with five nationwide affiliates, consists of patients and families of patients. The LDA has provded funding for research coast to coast, some published in peer review journals including *JAMA*. Along with our Greenwich affiliate, we were recently honored at a luncheon by Columbia University for partnering with them in the establishment of an endowed chronic Lyme disease research center at Columbia, and we also co-sponsored a fully accredited medical conference for physicians with Columbia. Working with legislators, we developed a bill in Congress, HR 1254, which will provide $125 million for Lyme disease research, prevention, and physician education.

The Lyme Disease Association provided testimony to this committee in January 2001, seeking a moratorium on the vaccine, but felt no action was taken by the FDA, and to that end, in January 2002, the LDA had a private meeting with the FDA's Center for Biologics Evaluation and Research (CBER) and brought several experts to discuss the vaccine issue with FDA officials including Karen Midthun, Susan Ellenberg, Peter Beckerman, Norman Baylor, Miles Braun, and Robert Ball.

Donald H. Marks, MD, PhD, former lab director for Cannaught, fourteen years of clinical research and regulatory affairs experience in the pharmaceutical industry including Director of Clinical Research, in charge of the Lyme disease vaccine program at Aventis Pasteur, presented to the FDA. Dr. Marks was the leader of the competitive effort to manufacturer a virtually identical vaccine.

Currently, his focus is diagnosis of adverse events from medications, vaccines, biologicals, and medical devices. Lymerix associated cases he reviewed included athralgias and arthritis as well as complicated neurological problems and include adverse events that are long-lasting. A summary of Dr. Mark's power point presentation follows.

WHY MORE ADVERSE EVENTS WERE SEEN AFTER THE VACCINE REACHED THE MARKET:

- People receiving Lymerix after product launch lived in Lyme-endemic areas.
- Many people may have had prior exposure and clinical or subclinical infection. In these cases, Lymerix could be triggering or reactivating the damage caused by old and presumably cured Lyme disease.
- Pattern of symptoms experienced after Lymerix mimicked pattern of prior infections in many individuals. In these patients, Lymerix-related symptoms seemed to respond to antibiotics, as did the initial infection, bolstering the theory of disease reactivation.

ISSUES WHICH CONFUSED THE VACCINE PICTURE

- As proof of safety, the company inoculated arthritis-prone mice with Osp-A. But since the mice did not possess the HLA marker known to interact with Osp-A in humans, rendering the experiment

meaningless.

- The company masked serious causally-related adverse events behind qualifiers, such as "…and which may have no causal relationship with the vaccine" and "…cannot be distinguished from the natural history of the underlying disease."
- The company says that "the possibility of a severe rheumatologic, neurologic, autoimmune adverse event is inherent in Lyme disease," attempting to shift the blame onto the patient and their illness, and does not inform physicians that the same adverse events can be separately caused by the vaccine, in addition to the symptoms of an underlying disease
- As a result of these actions, GPs in the US were kept in the dark about the life-threatening side effects of Lymerix, severe rheumatologic, neurologic, autoimmune adverse events.

SOME BASIC PROBLEMS.

- Non-specific hyper-activation of the immune system, often evidenced through swollen hands or arthritis, is an adverse event associated with Lymerix. This may be due to the presence of adjuvant.
- This hyper-activation creates "dirty" Western blots in which multiple Lyme disease bands appear, whether the individual has Lyme disease or not.
- The dirty banding makes it impossible for physicians to differentiate between Lymerix vaccination, new infection with Borrelia burgdorferi, or reactivation of infection.
- The net result is that cases of Lyme disease will go undiagnosed and untreated. Adverse reactions to Lymerix will be misdiagnosed as Lyme disease and people will be unnecessarily treated with antibiotics.
- The vaccine manufacture provides no warnings as to these possibilities.
- Physicians unaware of the spectrum of problems cannot appropriately treat these patients.
- The intention of FDA regulations is to provide a vaccine that is safe and effective. The intention of prescribing regulations is to provide sufficient information to prescribing physicians to enable safe and effective use of the vaccine. In both regards, SKB's

actions appear to be contrary to FDA regulations and intentions, and contrary to accepted standards within the vaccine industry.

Dr. Marks provided some case assessments based on stringent parameters and his extensive experience in the field. “The adverse events I have examine from Lymerix are similar to those I am familiar with from another vaccine.” In the cases Marks examined –in his opinion, the adverse events were not anecdotal but a medical certainty.

- 4 of 4 neurological adverse events were related to Lymerix with presentations including transverse myelitis, inflammatory polyneuropathy, radiculopathy and cervical throacic myelopathy with multiple neurologic, including CNS, symptoms, memory loss and difficulty concentrating with immune-related complex of joint pain and fatigue.
- 15 of 17 rheumatologic adverse events were related, including inflammatory seronegative spondyloarthropathy, polyarthropathy, arthralgias, and arthritis.
- 2 of 2 miscellaneous reports were unrelated. These included chest pain and myofacial pain.

Based on his research, Marks said, “SKB should have devised and conducted clinical trials, epidemiological studies, or after-the-fact investigations to study the causal relationship between severe rheumatologic, neurologic, autoimmune and other adverse events and the use of Lymerix….there is sufficient evidence that Lymerix is causally related to severe rheumatologic, neurologic, autoimmune, and other adverse events in some individuals. This evidence is such as to warrant a significantly heightened degree of warnings and possible limitations or removal from marketing of Lymerix.”

Andrea Gaito, MD, a rheumatologist seeing 35 patients with vaccine problems described three categories (**bold)** of problems to FDA. The first case, no history of Lyme, presented with acute synovitis, tests showed negative rheumatoid factor, Western Blot suggestive of active Lyme disease, with eight IgM and three IgG bands. Patient had minimal response to doxycycline, was prescribed and continues on anti-inflammatory medication. Conclusion: **autoimmune disease.**

The second case, **asymptomatic at time of innoculation, with a history of**

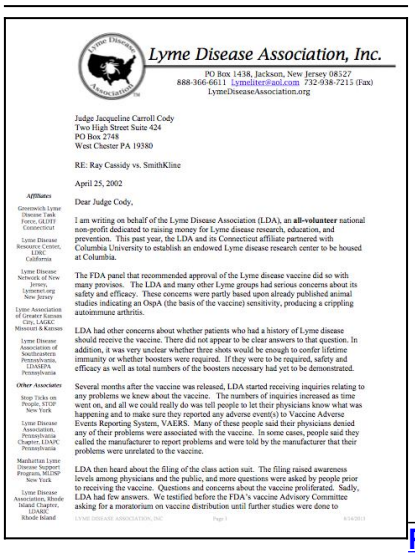
IV treated Lyme meningitis. After Lymerix, patient experienced the onset of Obsessive Compulsive Disorder, headache, and fatigue. Upon testing, he had a positive ELISA and a Western Blot with every band positive. Retreatment with IV was not effective. Patient remains sick.
The third case, three shots of Lymerix, then bitten by a tick. **She went on to develop symptoms of Lyme disease**, including night sweats and fatigue. Tests showed: a Western Blot with every band positive; positive for the HLA markers that have been associated with Lyme-related autoimmune disease. Two courses of antibiotics produced no response. This patient now has Lyme disease but does not respond to treatment.

Dr Gaito is concerned about the efficacy of this vaccine and boosters. Will vaccinated individuals with prior Lyme who ultimately present with symptoms respond to retreatment? Is the vaccine itself retriggering an autoimmune response? She felt it is possible that the difference between the pre- and post-marketing results of Lymerix relates to the fact that those using it post-marketing lived in endemic areas for Lyme disease.

The LDA is concerned that despite presentations to the contrary by individuals at both the Vaccine Advisory Committee hearing in January 2001, the private meeting above, VAERS data, and other communications from the public, the FDA has not seemed to find any problems with this vaccine. LDA's concern stems from the fact that although the approved vaccine is not on the market currently, since it was a unilateral decision by the company to remove the product, this same or a similar product may be remarketed without the full implications of the safety and efficacy of the current vaccine having been fully assessed or integrated into the Lyme vaccine picture. The LDA asks this committee to advise the FDA that significant arguments have been raised about safety and efficacy of this vaccine and that objective studies should continue on safety and efficacy of this vaccine or any other future vaccine that may seek FDA approval. Thank you for your time.

Vaccine Suit – LDA ltr & Judgement

The LDA was permitted to submit a letter to the Court in the LymeRix Vaccine lawsuit. In 2003 a Judgement, Final Order and Decree Granting Final Approval of the Class Action Settlement was issued. The suit was filed by the lawfirm of Sheller & Sheller in Philadelphia on behalf of patients who took the vaccine.



Lyme Disease Association, Inc.

PO Box 1438, Jackson, New Jersey 08527
888-366-6611 Lymeliter@aol.com 732-938-7215 (Fax)
LymeDiseaseAssociation.org

Judge Jacqueline Carroll Cody
Two High Street Suite 424
PO Box 2748
West Chester PA 19380

RE: Ray Cassidy vs. SmithKline

April 25, 2002

Dear Judge Cody,

I am writing on behalf of the Lyme Disease Association (LDA), an **all-volunteer** national non-profit dedicated to raising money for Lyme disease research, education, and prevention. This past year, the LDA and its Connecticut affiliate partnered with Columbia University to establish an endowed Lyme disease research center to be housed at Columbia.

The FDA panel that recommended approval of the Lyme disease vaccine did so with many provisos. The LDA and many other Lyme groups had serious concerns about its safety and efficacy. These concerns were partly based upon already published animal studies indicating an OspA (the basis of the vaccine) sensitivity, producing a crippling autoimmune arthritis.

LDA had other concerns about whether patients who had a history of Lyme disease should receive the vaccine. There did not appear to be clear answers to that question. In addition, it was very unclear whether three shots would be enough to confer lifetime immunity or whether boosters were required. If they were to be required, safety and efficacy as well as total numbers of the boosters necessary had yet to be demonstrated.

Several months after the vaccine was released, LDA started receiving inquiries relating to any problems we knew about the vaccine. The numbers of inquiries increased as time went on, and all we could really do was tell people to let their physicians know what was happening and to make sure they reported any adverse event(s) to Vaccine Adverse Events Reporting System, VAERS. Many of these people said their physicians denied any of their problems were associated with the vaccine. In some cases, people said they called the manufacturer to report problems and were told by the manufacturer that their problems were unrelated to the vaccine.

LDA then heard about the filing of the class action suit. The filing raised awareness levels among physicians and the public, and more questions were asked by people prior to receiving the vaccine. Questions and concerns about the vaccine proliferated. Sadly, LDA had few answers. We testified before the FDA's vaccine Advisory Committee asking for a moratorium on vaccine distribution until further studies were done to

[PDF of LDA letter to Court]

KAREN CASSIDY, on behalf of herself and all others similarly situated P.O. Box 71 Cheyney, PA 19193, Plaintiffs, v. SMITHKLINE BEECHAM 1 Franklin Plaza Philadelphia, PA 19105, Defendant.	:	COURT OF COMMON PLEAS CHESTER COUNTY CLASS ACTION NO. 99-10423

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JUDGMENT, FINAL ORDER AND DECREE GRANTING FINAL APPROVAL OF THE CLASS ACTION SETTLEMENT

This matter is before the Court on the motion for final class certification and final approval of the settlement with defendant SmithKline Beecham Corporation d/b/a GlaxoSmithKline ("SB").

By Order Conditionally Certifying Settlement Class; Granting Motion for Preliminary Approval of Class Action Settlement; and Scheduling Hearing on Final Settlement Approval dated July 12, 2002 ("Preliminary Approval Order"), this Court conditionally certified the Settlement Class as a class action and granted preliminary approval to the Settlement. The Court also ordered that a summary notice of this settlement be published in USA Today, and a detailed notice be published on the internet. In compliance with that Order, the summary notice was published on August 21, 2002 in USA Today, and the detailed notice was published on the internet beginning on August 21, 2002 and continuously thereafter to the present.

the Class Action Lyme Disease Vaccine Settlement

LYMERIX Meeting; LDA Meets with FDA

SPECIAL REPORT: LDA MEETS WITH FDA ON LYMERIX

On January 22, 2002 in Bethesda, MD., the LDA was able to get a private meeting with the FDA on the vaccine issue, despite reluctance by the FDA to grant the meeting. Congressman Chris Smith helped facilitate the setup of this meeting.

Patricia Smith, President, Lyme Disease Association

LDA president Pat Smith invited Andrea Gaito, MD, President, International Lyme & Associated Disease Society, ILADS; Donald Marks, MD, former lab director for Cannaught; Steven Sheller, Esq., member, LDA's Professional Advisory Board; Albert Brooks, Esq.; and Pam Weintraub, former editor, Omni magazine, to present material to the FDA.

About a dozen major FDA officials involved with the vaccine were present. These included:

Karen Midthun, MD
Director, Office of Vaccine Research and Review
Center for Biologics Evaluation and Research

Susan Ellenberg, PhD
Director, Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research

Peter Beckerman, JD
Office of the Chief Counsel, FDA

Norman Baylor, PhD
Associate Director for Regulatory Policy
Office of Vaccine Research and Review
Center for Biologics Evaluation and Research

Miles Braun, MD
Director, Division of Epidemiology
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research

Robert Ball, MD
Chief, Vaccine Safety Branch
Division of Epidemiology, Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research

Mary Meyer
Director, Office of Communication, Training and Manufacturers Assistance
Center for Biologics Evaluation and Research

Cap Uldriks, JD
Acting Director, Division of Communication and Consumer Affairs
Office of Communication, Training and Manufacturers Assistance
Center for Biologics Evaluation and Research

Julie Zawisza
Chief, Consumer Affairs Branch
Division of Communication and Consumer Affairs
Office of Communication, Training and Manufacturers Assistance
Center for Biologics Evaluation and Research

A summary of the meeting follows, beginning with a digest of LDA presentations:

Patricia Smith, President, Lyme Disease Association

Most patients with adverse events are not reported to VAERS by physicians. I attend many events all over the Northeast, and the vaccine and associated problems are always brought up to me, unsolicited on my part. Last week I was at a large sportsmen’s show. Just at this show alone, I heard about seven individuals who received the vaccine and experienced problems. One man had joint pains all over his

body and his doctor did not think it related to the vaccine, nor did he report it. The man had cut down on hunting and fishing. He had stopped running.

When this individual went back to his physician and asked him to report the adverse response to VAERS, the doctor blew him off. The doctors are very much in the dark about this vaccine. We have doctors who do not understand that boosters are required. One man came up to me at the event and told me his doctor said no booster was required and he thought he was fully protected forever. Many physicians do not know the vaccine is contraindicated with a history of arthritis. Most people I spoke with who report side effects mentioned they occurred after the second shot. An employee at Rutgers approached me and said the University gave Lymerix. The professor knows four Lymerix recipients at Rutgers who are having significant trouble.

I hear the same thing from other groups. There are a lot of problems I do not think you are aware of. I hear from physicians that the vaccine causes Lyme disease to be retriggered. I'm out there a lot. I have no stake other than to keep people from getting Lyme disease.

Our organization has always had questions about the vaccine, and at the last FDA meeting in January 2001 we requested a moratorium.

Andrea Gaito, MD, President, International Lyme & Associated Disease Society, ILADS:

I have 35 patients with problems stemming from the vaccine. There are three categories of problem.

The first category includes arthritis-like presentations. These patients have symptoms that present, clinically, like rheumatoid arthritis. They seem to have an autoimmune reaction stemming from the presence of a genetic marker theorized to be a source of trouble, HLA-DR4. Some of these patients may have other relevant HLAs. Perhaps there are a cascade of other immunological reactions, including cytokines.

What I have found is that people with Lyme who become asymptomatic may, upon vaccination with Lymerix, experience a retriggering of symptoms. Those who never had symptoms of Lyme disease, meanwhile, will, upon vaccination, experience the symptoms of Lyme disease.

One example is a 55 year-old woman with no history of Lyme disease. She presented with acute synovitis and in her hands, wrists, ankles, and feet. The physician who administered the vaccine told her there was no relationship between these symptoms and the vaccine. He did not report them. It is possible that, like so many other physicians, he did not want to trouble with the paperwork. When the woman thereafter came to me, I ran tests. Her rheumatoid factor was negative but her Western Blot was suggestive of active Lyme disease, with eight IgM and three IgG bands. I prescribed for her a course of doxycycline, but she had minimal response. So I put her on anti-inflammatory medication. Now, two years later, she is *still* on anti-inflammatory medication.

The scenario for this woman is that of an autoimmune disease.

Even though she reacted to the vaccine in this adverse fashion, her physician made her feel guilty. Many patients have complaints but doctors are not receptive to them. The bottom line is that the doctor is afraid of being sued.

The second case I would like to present involves a 20-year-old white male with a history of Lyme meningitis. Previously, he had 4 weeks of intravenous Rocephin and before receiving Lymerix was asymptomatic. After receiving Lymerix, however, he had the onset of Obsessive Compulsive Disorder, headache, and fatigue. He had to leave college. Upon testing, he had a positive ELISA and a Western Blot with every band positive. We retreated him with another course of IV Rocephin, but he has remained sick.

The third case involves a 48-year-old woman and gardener. She received three shots of Lymerix and then, subsequently, was bitten by a tick. She had presumed she was one hundred percent protected, but she went on to develop symptoms of Lyme disease, including night sweats and fatigue. We performed a Western Blot test for this woman and found every band to be positive. She received two course of antibiotic therapy and had no response. She also tested positive for the HLA markers that have been associated with Lyme-related autoimmune disease. This patient now has Lyme disease but does not respond to treatment.

As I review my experience with Lymerix, I find the issues to be confusing. How can we get a handle on the efficacy of this vaccine? What about the efficacy of booster shots? Will vaccinated individuals with prior Lyme who ultimately present with symptoms respond to retreatment? Is the vaccine itself retriggering an autoimmune

response?

One final word: It is possible that the difference between the pre- and post-marketing results of Lymerix relates to the fact that those using it post-marketing lived in endemic areas for Lyme disease.

Donald H. Marks, MD, PhD, former lab director for Cannaugh:

First let me describe my background. I have fourteen years of clinical research and regulatory affairs experience in the pharmaceutical industry. My positions have included Associate Director of Clinical Research, Hoffman-LaRoche Pharmaceuticals, where I worked on Lyme disease; Vice President of Medical Afffairs, Immunomedics; and finally, Director of Clinical Research, Aventis Pasteur, where I was in charge of the Lyme disease vaccine program.

The focus of my medical practice today is on diagnosis of adverse events from medications, vaccines, biologicals, and medical devices. Among the issues I have worked on are the associations between Accutane and seizures, psychosis and suicide; Ephedra and hemorrhagic stroke; Fen-Phen and heart valve problems; Lotrenex and ischemic bowel disease; Posicor and Propulsid and arrhythmias, in the case of the former medicine, fatal arrhythmias; Quinolone antibiotics like Floxin and Trovan and tendon neuropathy, seizures, and hypoglycemia; Rezulin and liver toxicity and cardiomyopathy; SSRI antidepressants like Prozac, Zoloft and Paxil and suicide, psychosis, and seizures; and Lymerix and rheumatologic and neurologic complications.

Today I am here as a consultant of the Lyme Disease Association, which has asked me to review a series of adverse events associated with Lymerix: These include athralgias and arthritis as well as complicated neurological problems. They include adverse events that are long-lasting.

Dr. Marks proceeded to present a series of slides. We reproduce them here, with explanation and some editing, where needed, for clarity and brevity in the current context.

WHY MORE ADVERSE EVENTS WERE SEEN AFTER THE VACCINE REACHED THE MARKET:

- People receiving Lymerix after product launch were at greater risk for adverse events because they lived in Lyme-endemic areas.

- Many of these people may have had prior exposure and clinical or subclinical infection. In these cases, Lymerix could be triggering or reactivating the damage caused by old and presumably cured Lyme disease.
- Pattern of symptoms experienced after Lymerix mimicked pattern of prior infections in many individuals. In these patients, Lymerix-related symptoms seemed to respond to antibiotics, as did the initial infection, bolstering the theory of disease reactivation.

HOW SMITHKLINE BEECHAM (GLAXO SMITHKLINE) USED CONFUSING LANGUAGE, KEEPING FDA AND PHYSICIANS IN THE DARK:

- The Company dismissed the significance of adverse events reported since marketing by stating the vaccine's profile had not changed "except as described below…" The description referred to, rendered with numbers but given no contextual explanation, in fact implied a huge change in safety. The company's confusing language made it sound as if the adverse events, many of them severe, had no particular significance at all.
- As proof of safety, the company inoculated arthritis-prone mice with Osp-A. But since the mice did not possess the HLA marker known to interact with Osp-A in humans, the experiment was, in fact, meaningless.
- The company has masked serious causally-related adverse events behind qualifiers, such as "…and which may have no causal relationship with the vaccine" and "…cannot be distinguished from the natural history of the underlying disease," all the while knowing these are confusing the issues.
- The company tries to shift the blame from the vaccine to the patient with statements such as "the possibility of a severe rheumatologic, neurologic, autoimmune adverse event is inherent in Lyme disease." The company does not inform physicians that the adverse events can result from Lymerix, completely apart from the disease.
- As a result of these actions, GPs in the US were kept in the dark about the life-threatening side effects of Lymerix.

SOME BASIC PROBLEMS.

- Non-specific hyper-activation of the immune system, often evidenced through swollen hands or arthritis, is an adverse event associated with Lymerix.

This may be due to the presence of adjuvant.

- This hyper-activation creates “dirty” Western blots in which multiple Lyme disease bands appear, whether the individual has Lyme disease or not.
- The dirty banding makes it impossible for physicians to differentiate between Lymerix vaccination, new infection with *Borrelia burgdorferi,* or reactivation of infection.
- The net result is that cases of Lyme disease will go undiagnosed and untreated.
- Adverse reactions to Lymerix will be misdiagnosed with Lyme disease and people will be unnecessarily treated with antibiotics.
- The vaccine manufacture provides no warnings as to these possibilities.
- Physicians unaware of the spectrum of problems cannot appropriately treat these patients.
- The intention of FDA regulations is to provide a vaccine that is safe and effective. The intention of prescribing regulations is to provide sufficient information to prescribing physicians to enable safe and effective use of the vaccine. In both regards, SKB’s actions appear to be contrary to FDA regulations and intentions, and contrary to accepted standards within the vaccine industry.

Dr. Marks provided some case assessments based on stringent parameters. His conclusions were based on pre- and post-marketing as well as supplemental data; internal company documents; published literature; international meetings; special reports; patient medical files; and patient examinations. He used the standard methodological rule of “more likely than not” as well as objective, scientific criteria and objective procedures. The assessments themselves, according to Dr. Marks, were arrived at based on “clinical presentation, the medical records, telephone interviews and/or physical exams, temporal relatedness of the event to the vaccination, known adverse event profile of Lymerix, mechanism of action of Lymerix, opinions of the treating physician, articles from the medical literature on adverse events occurring as a result of vaccination with OspA-based vaccines for Lyme disease, my experience as a pharmaceutical industry medical safety officer, my experience having reviewed hundreds of clinical cases of potential medication adverse events, my experience as a vaccinologist and clinical researcher developing vaccines and antibiotic treatments against Lyme and other diseases, and my examination of alternative explanations.” Added Marks: “The adverse events I have examine from Lymerix ARE SIMILAR TO THOSE I AM FAMILIAR WITH FROM ANOTHER OSPA VACCINE.”

Marks examined 22 cases in all. In each of these cases, he said, the adverse event was not anecdotal but was, instead, a medical certaintly:

- 4 of 4 neurological adverse events were related to Lymerix with presentations including transverse myelitis, inflammatory polyneuropathy, radiculopathy and cervical throacic myelopathy with multiple neurologic including CNS symptoms, and memory loss and difficulty concentrating with immune-related complex of joint pain and fatigue.
- 15 of 17 rheumatologic adverse events were related, including inflammatory seronegative spondyloarthropathy, polyarthropathy, arthralgias, and arthritis.
- 2 of 2 miscellaneous reports were unrelated. These included chest pain and myofacial pain.

Based on his research, Marks told FDA officials, “SKB (Glaxo) has acted in an unreasonable manner by marketing Lymerix without adequate warnings about the risks of severe rheumatologic, neurologic, autoimmune and other adverse events, and by failing to caution and educate physicians about these dangers. In view of the evidence of a strong and likely causal relationship between Lymerix and severe rheumatologic, neurologic, autoimmune and other adverse events, SKB should market this vaccine, if at all, with prominent warnings and cautionary statement.”

“In my opinion, SKB should have devised and conducted clinical trials, epidemiological studies, or after-the-fact investigations to study the causal relationship between severe rheumatologic, neurologic, autoimmune and other adverse events and the use of Lymerix.”

Given that Dr. Marks lead the clinical trials for Lymerix’s competitor, the OspA vaccine produced and then abandoned by Aventis Pasteur, his conclusions mean a lot. “In my opinion,” he told FDA officials, “there is sufficient evidence that Lymerix is causally related to severe rheumatologic, neurologic, autoimmune, and other adverse events in some individuals. This evidence is such as to warrant a significantly heightened degree of warnings and possible limitations or removal from marketing of Lymerix.”

FDA answers LDA vaccine questions in writing weeks after meeting.

LDA PRESUBMITTED QUESTIONS TO EPA (Below)

The floor was then handed over to FDA to answer the following questions:

1. What does the FDA intend to do about the lyme vaccine?
2. Questions on the follow-up study of VAERS reports, especially, what is the primary endpoint and study design for the on-going telephone survey of a subset of individuals who have reported adverse reactions to VAERS. Specifically, what is the inclusion/exclusion criteria? Subquestions include:

   A. Assuming an inclusion criteria includes arthritis and/or arthralgia, which VAERS codes and/or keywords are used to identify such individuals? And, if the inclusion criteria consists of a specific injury and/or disease process, why has the study been so limited instead of addressing the various adverse reactions being reported to VAERS, including non-specific pain syndromes and development of Lyme disease-like symptoms, possibly constituting exacerbation of previously asymptomatic Lyme disease and neurological conditions such as Bells' Palsy, optic neuritis, and acute transverse myelitis?

   B. Further, what is the FDA's case definition of "definite, probable and possible arthritis" for purposes of this study? The abstract of the "preliminary evaluation" reports completed interviews of 49 patients out of 85 attempted (out of 415 patients with VAERS reports of "arthralgia or possible arthritis following Lyme vaccine") reports 17 cases of "possible arthritis" and 14 cases of "physician-diagnosed definite arthritis"). Does this mean that the remaining 18 had "probable arthritis"and, if so, what if anything is being done to evaluate their cases?

   C. How is the FDA dealing with individuals who test positive for Lyme disease after vaccination in terms of distinguishing between a new infection (i.e. vaccine failure) and the exacerbation of a previously asymptomatic or presumably "cured" infection (i.e. an adverse reaction)? It appears from the abstract that 7 of 14 cases of physician-diagnosed arthritis also had what is described as "concominant exposure or another medical condition, including Lyme disease". What, if anything is the FDA doing to evaluate these individuals, especially in light of the fact that many people who have and who will receive LYMErix reside in Lyme-endemic areas and can presumably be easily dismissed as having "concominant exposure"?

D. Does the fact that 50% (7 of 14) of cases of physician-diagnosed definite arthritis post vaccination demonstrate the need for a warning and/or contraindication against the vaccination of individuals with "familial history of immune-mediated disease or inflammatory arthritis", "immune-mediated disease", and "prior history of physician-diagnosed Lyme disease"?

E. When does the FDA contemplate completion of the interviews of the 415 VAERS reports identified as "arthralgia or possible arthritis"? And what if anything is being done to identify such reports filed subsequent to October 2000?

F. Given the fact that FDA has now documented 7 case reports of physician-diagnosed definite arthritis which "could not be plausibly explained by concominant exposure, prior diseases, or familial histories" a number on par with those that triggered regulatory intervention in other pharmaceuticals such as "Fen-Phen", is the FDA prepared to call for an immediate moratorium and/or withdrawal of LYMErix and, if not, what is the threshold number of case reports needed to trigger such action? It should be noted that 14 cases of physician-diagnosed arthritis post vaccination were identified out of 31 patients whose medical records were reviewed (45.2%), and in 7 of those (22.6%) the arthritis could not plausibly be attributed to any other cause. If these rates hold for the remainder of the 415 VAERS reports identified, the FDA will have documented 187 cases of physician-diagnosed arthritis, nearly 93 of which will not have any other plausible explanation.

G. In terms of determining the rate of adverse reactions, how can the FDA determine how many individuals have been vaccinated? The abstract of the preliminary follow-up study reports "approximately 1.4 million vaccine doses were distributed" between December 1998 and October 2000. Given the fact that this is a multiple-dose vaccination and that most vaccinees have received at least two or three (and sometimes actually more) doses of LYMErix, and the fact that the uptake of LYMErix has been unexpectedly low (as demonstrated by the difficulty in reaching even 25% of the enrollment goals for the Phase IV studies), can the FDA rule out the possibilities that the actual number of vaccinees is in the low six-figures, and possibly as low as 100,000?

3. How is the FDA dealing with individuals who participated in the clinical trials, but began experiencing adverse reactions (or recognized such reactions) only after the study site was closed? Since VAERS will not accept their reports, and it has been reported that GlaxoSmithKline has been dismissive of such reports, how can the FDA ensure that these reactions are included in the total number of adverse event reports?
4. More specifically, how does the FDA deal with study participants who were in the placebo group during the trial (with no adverse reactions) but who received the vaccine after the study was unblinded and went on to experience adverse reactions to the actual vaccine?
5. If an individual gets the vaccine and they show Lyme disease symptoms, how does the FDA distinguish between 1.someone who had asymptomatic Lyme disease, 2. a new case of Lyme (vaccine failure), 3. an immune response
6. Why has the FDA not contacted and interviewed physicians who oversaw the study sites for the clinical trials, particularly in light of the fact that some such doctors, …, have publicly endorsed LYMErix stating that they saw no adverse reactions when the FDA is aware of reports of adverse reactions by several of …'s study participants?
7. What steps if any has the FDA taken to analyze the data gathered during the clinical trials of the Connaught (now Aventis Pastuer) OspA-based Lyme disease vaccine ImmuLyme for adverse reactions?
8. Why has the FDA failed to invite scientists and physicians not affiliated with, or employed by GlaxoSmithKline, such as Ronald Schell, Ph.D. who has published an article documenting serious adverse reactions to OspA in hamsters, and Carlos Rose, M.D. and Paul Fawcett, Ph.D., who have published an article documenting arthritogenic reactions to LYMErix in adults and the exacerbation of pre-existing asymptomatic Lyme disease in participants in the pediatric trials of LYMErix, to present their findings and opinions to the Advisory Committee or any other body considering the safety and efficacy of LYMErix?
9. Why was LYMErix permitted to include an adjuvant, especially given that the manufacturer used a lipidated version of the OspA protein? Further, since the inclusion of the adjuvant in LYMErix necessitated the inclusion of the adjuvant in the placebo, what if anything was done to adjust for the likelihood that complaints of adverse reactions to the adjuvant among the placebo group were not permitted to improperly "cancel out" adverse reactions to OspA among the vaccinees, and therefore reduce the likelihood

of finding a “statistically significant difference” in adverse event rates between the two groups?

10. What if any steps has the FDA taken to implement the recommendations of members of its Advisory Committee from the January 31, 2001 meeting regarding enhanced warnings and limits on the indicated use of LYMErix (including geographic limits) as well as increased education of both the general public and the medical community of the continued unanswered safety risks associated with LYMErix?
11. Is the FDA, and/or its Vaccine Advisory Committee aware that the Tufts Laboratory run by Dr. Steere, the principal investigator for the Phase III clinical trials of LYMErix, filed for a patent on March 21, 2000 with the World International Property Organization, which received an International Publication Date of September 27, 2001 (patent # WO 01/70252 A1), and that the official patent holders, including Doctors Meyer, Huber and Gross are the scientists who worked along with Dr. Steere on his research documenting the auto-immune responses exhibited by people with certain genetic markers to OspA?
12. Is the FDA aware that “this invention was supported by National Institutes of Health Grant AR45386 and the government of the United States has certain rights thereto?”
13. Is the fact that this group of scientists, working under a grant from the government of the United States of America, has demonstrated in this patent that “An additional problem with OspA as a protective immunogen [i.e.: vaccine] is cross-reactivity at the T cell level observed between OspA and LFA-1.” Id. At 4, and “Given the potential cross-reactivity between OspA and LFA-1, the use of OspA as a protective immunogen in vaccines may be associated with the induction of an auto-immune reaction in certain populations, including individuals expressing the HLA-DRB1-0401 allele. Thus it would be highly desirable to generate modified OspA polypeptides with diminished or no binding to the DRB1-0401 allele.
14. How does the FDA reconcile the fact that research conducted and completed by the principal investigator for LYMErix prior to FDA’s approval of the vaccine, and largely ignored by the FDA or dismissed at “theoretical” in its review and oversight of LYMErix, nevertheless led the scientists involved to pursue and patent a genetically modified version of OspA aimed specifically at avoiding the risk of auto-immunity from the OspA utilized in LYMErix demonstrated in that research?

15. Does the FDA believe that the medical community and the public at large should be advised of the fact that scientists and researchers of this caliber consider the risk of auto- immunity from LYMErix so great that they applied for, received, and worked pursuant to, a NIH grant to produce a modified version of OspA to minimize or eliminate the risk? If not, why?
16. In light of this documentation, why has the FDA not demanded that GlaxoSmithKline produce in full any and all research which they claim disproves the risk of auto-immunity from LYMErix rather than simply accepting the manufacturer's summary claims without supporting data?
17. In the abstract of the researchers' application for the NIH Grant #1R01AR045386-0, they state that "LFA-1/DR4 double transgenic mice on an MHC class II -/- background will be created and tested for the development of chronic Lyme arthritis after exposure to Bb. This is based on the observation that mouse LFA-1 does not express the OspA cross- reactive epitope." Indeed, the researchers observed an auto-immune arthritic reaction when these mice were exposed to natural OspA, but not when they were exposed to the patented, modified version of OspA. In this regard, what will the FDA do to determine what if any steps GlaxoSmithKline took to "create and test LFA-1/DR4 double transgenic mice" for its research, as the NIH grantees did, and whether or not the manufacturer did produce such mice and conduct studies which supported the risk of auto-immunity and suppressed those results? Further, what are the implications of GlaxoSmithKline's presentation at the January 31, 2001 Advisory Committee Meeting of a study on mice which it claimed disproved any auto-immune arthritic risk, without revealing the fact, until questioned, that the mice used in their study lacked the cross-reactive epitope, and therefore rendering the study, as one member of the committee stated, "irrelevant"?

FDA said they would answer most questions in writing since time was running short, but asked LDA to choose a particular question. LDA's Pat Smith chose question number 5: If an individual gets the vaccine and they show Lyme disease symptoms, how does the FDA distinguish between 1.someone who had asymptomatic Lyme disease, 2. a new case of Lyme (vaccine failure), 3. an immune response?

The issue, emphasized the LDA team, was answering this question in light of all the *dirty* Western blots labs have been generating from Lymerix recipients. If Lymerix Western blots are dirty, asked LDA, how could FDA and its pharmaceutical sponsor differentiate between actual Lyme disease and an adverse event? The question was

not, just, were the blots disguising the safety of the vaccine but, also, did the filthy blots make it impossible to arrive at any true conclusion as to the efficacy of the vaccine, estimated by the sponsor at almost 80 percent?"

Attempting an answer was FDA's Karen Midthun, MD, Director, Office of Vaccine Research and Review Center for Biologics Evaluation and Research. Midthun said vaccine investigators attempted to confirm Lyme disease itself through culture or polymerase chain reaction (PCR) of joint fluid, spinal fluid or the erythema migrans rash itself. "In cases identified as definite Lyme disease," she said, "seventy to eighty percent of the individuals were identified by culture and fifty to seventy percent via seroconversion by Western blot."

The LDA team responded that this answer was further proof the FDA could not, in fact, answer the question. Indeed, no one debated cases of "definite" Lyme disease proven through culture, but rather, those cases of "possible" Lyme disease —especially in light of the fact that the manufacturer's studies embraced the faulty CDC standard for Western blot by excluding consideration of two definite Lyme disease markers —bands showing presence of *Borrelia burgdorferi's* two outer surface proteins, OspA and OspB.

Commented attorney Steven Sheller, "When I hear that disregarding OspA and OspB is not a problem, when I hear people say there are no dirty blots, or that they are not a factor, I have to wonder how this research was done. You can't just take the manufacturer's word for it. You have to look at the original Western blots to come to your own conclusion. You might just be surprised."

LDA's team advised FDA to look at data in its rawest form in just two or three of the study sites.

Dr. Marks added that FDA would have to rethink its notion of "statistical significance" for Lymerix. "You'll never find statistical significance for the worst adverse events," he told FDA, "because they are so rare. You have to look at individual patients. You should have individual cases analyzed in depth by an impartial group of observers." Just because an adverse event is rare, he said, does not mean it is not associated with a vaccine. In these instances, you must weight the risk of the disease with the risk, even if extremely low, that an individual could be damaged by the vaccine.

FDA asked LDA if the team had anything to add. Here, Pat Smith responded: "We have

found that, due to word of mouth on the dangers of this vaccine, physicians will no longer give it out in their offices. Even HMOs and clinics no longer want to be involved. Instead, Glaxo is marketing the vaccine on college campuses, where nurses who distribute it may be unaware of the issues involved. We are very concerned that our young students will be the next victims of this vaccine."

Smith concluded with this query: "We want to know if you are going to do anything with the information we have presented today."

"We'll need to discuss this among ourselves," said FDA's Susan Ellenberg, PhD, Director, Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research. "We take your presentation very seriously. Any action will be announced to everyone in the public at the same time."

On February 25, 2002, a month after meeting with FDA, LDA received written answers to its questions from FDA and, also, learned that Glaxo SmithKline had quietly pulled Lymerix from the market, citing "poor sales."

CLICK HERE FOR THE RESPONSE

FDA Powerpoint on Lymerix Vaccine

This is an FDA powerpoint by Robert Ball, M.D., M.P.H., Sc.M., on the Lymerix Vaccine, *LYMErix® Safety Data Reported to the Vaccine Adverse Event Reporting System (VAERS)*, January 31, 2001.

Robert Ball, M.D., M.P.H., Sc.M., Division of Epidemiology, Office of Biostatistics and Epidemiology, Center for Biologics

Evaluation and Research, Food and Drug Administration (FDA), Rockville, MD

CLICK HERE FOR THE POWERPOINT

Vaccine Remarks

Remarks of Pat Smith, President, Lyme Disease Association, Inc. before the Vaccines and Related Biological Products Advisory Committee, January 31, 2001, Bethesda, Maryland.

Mr. Chairman and Committee members:

The Lyme Disease Association's mission is Lyme disease education, prevention, and research funding, so one might automatically assume we're favorable to a safe and effective vaccine for Lyme disease. That's certainly a valid assumption. The Association's board consists of patients and families of patients—all of whose lives have been personally touched by this disease, and all who are dedicated to preventing others from experiencing the physical, mental, and emotional devastation Lyme disease can produce. To that end, we fund research projects, sponsor medical conferences and continue to work with Members of Congress developing federal legislation providing $125 million for Lyme disease research, physician education, and prevention.

I am here today because we do favor a safe and effective vaccine, but we are unsure whether an OSP A based vaccine can meet those criteria. Since the inception of OSP A vaccine trials, we heard from individuals experiencing difficulties after immunization. The information was startling, not only because of the problems described, but also because

of doctors' apparent incomprehension of the problem. At a vaccine meeting sponsored by the LDF where pharmaceuticals reps were discussing how well the trials were going, I questioned, without satisfaction, the issue of these trial-patient complaints.

After vaccine approval, LDA received inquiries about the vaccine, many from individuals who had received all or some of the vaccination series. Most proceeded to talk about symptoms they developed subsequent to receiving the vaccine. When asked if they had reported this to the administering doctor, and if the doctor had reported the adverse event, the usual response was that the doctor did not take the complaint seriously or did not think the symptoms were related.

Sadly, none were aware of the HLADR4 situation, and several were in the midst of the immunization series and did not know whether to continue taking the shots. Some called to ask if they should get the shots if they had had Lyme in the past, a question which appears to have no clear answer—particularly in light of the unreliable antibody response tests used to determine who has or had Lyme disease. A few insisted they had gotten

"full blown Lyme" from the shots, and after further discussion, indicated they had had Lyme disease in the past.

I want to share an email I received Monday. "I live in Wisconsin. I received your name from person X who told me you may be able to give me some direction. I received two vaccines in the spring of 2000. Couple days within the first shot my neck and higher back stiffened up severely. In a month I went back for the second shot and asked the nurse and doc to check for side effects before I took the second. They informed me there were none. I took the second dose and the problem with my neck and back worsened within a couple of days. My family doctor gave me anti-inflammatories but they did nothing. I've tried a chiropractor but the only relief was for a couple of hours. Never tried one before but am getting desperate. Then I

went to a orthopedic and am now on anti inflammatories again but not helping. He told me that I have a disc that is somewhat smaller than the others in my neck and maybe the vaccine somehow aggravated it. Prior to the vaccine I have had 0 neck or back problems. I am looking for treatment somehow someway." I called him. He is 39 years old. He asked me to help him. He wants treatment for what he has.

Today you are hearing about how this vaccine has physically impacted human lives. It appears that little can be done to stop whatever process triggers some of these reactions, or if something can be done, it remains as yet undiscovered. I listen to the despair and bewilderment of those adversely impacted: How can this happen from a medicine to keep me from getting sick? Who can help me get better? I can only comfort them as I do not have any answers, and I do not know who does.

This committee has the authority to formulate recommendations that may prevent others from potentially suffering the same fate. You can revisit the original data and research which appears to show a link between OSP A and adverse reactions and view it in light of the adverse events you have now heard about. You can recommend further studies. You can find out why many doctors who treat chronic Lyme disease are not giving the vaccine.

The Advisory Committee on Immunization Practices recommends under future considerations in their report on the Lyme disease vaccine, June 4, 1999 MMWR, "establish post licensure epidemiological studies of safety, efficacy, prevention effectiveness, cost effectiveness, and patterns of use." We concur with that recommendation and would like to see a moratorium on vaccine administration until those studies are completed and the results critically analyzed.

Thank you for your time.

Controlled Study of Cognitive Deficits

Although neurologic Lyme disease is known to cause cognitive dysfunction in adults, little is known about its long-term sequelae in children.

*A Controlled Study of Cognitive Deficits in Children With Chronic Lyme Disease**

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J Neuropsychiatry Clin Neurosci 13:4, Fall 2001

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ABSTRACT

Although neurologic Lyme disease is known to cause cognitive dysfunction in adults, little is known about its long-term sequelae in children. Twenty children with a history of new-onset cognitive complaints after Lyme disease were compared with 20 matched healthy control subjects. Each child was assessed with measures of cognition and psychopathology. Children with Lyme disease had significantly more cognitive and psychiatric disturbances. Cognitive deficits were still found after controlling for anxiety, depression, and fatigue. Lyme disease in children may be accompanied by long-term neuropsychiatric disturbances,

resulting in psychosocial and academic impairments. Areas for further study are discussed.

Lyme disease (LYD) is a multisystemic illness caused by the tick-borne spirochete Borrelia burgdorferi (Bb). LYD, the most common tick-borne illness in the United States, *(1)* may manifest in a variety of ways: dermatologic, arthritic, ophthalmologic, cardiac, and neuropsychiat- ric. *(2)* The incidence and spread of the disease increased during the 1980s,*(3)* stabilizing somewhat in the late 1990s. Children below the age of 9 are at a high risk for Bb infection, *(4)* with many new cases of Lyme occurring among persons younger than 14 years. *(5)*

The neuropsychiatric symptoms of LYD in adults have been described, *(6,7)* but little has been published about the neuropsychiatric effect of the disease in children and adolescents. In adults, deficits in attention and memory have been reported. *(8,9)* In children, a controlled study of cognitive symptoms investigated a sample of all children and adolescents who presented to a LYD clinic, most of whom presented with rheumatological symptoms, had been diagnosed early, and had been treated appropriately for LD.*(10)* These children were found to have an excellent prognosis for unimpaired functioning. However, this sample may not be representative of all children diagnosed with LYD, especially those who present initially with neurocognitive problems and /or those who were not treated until many months after the initial infection. Our preliminary data using symptom-driven reports suggest that children who develop chronic LYD have psychiatric and cognitive difficulties in the area of attention and memory. *(11)* However, subjective reports of cognitive dysfunction are not often correlated with objective findings. In a case series, *(12)* 12 of 86 children (14%) developed neurocognitive symptoms associated with chronic LYD. If a subgroup of children develop cognitive problems associated with LYD, then teachers, parents, and physicians should be aware of this possibility. In addition, if our preliminary findings are replicated in a controlled study, then in Lyme-endemic areas it may be reasonable for LYD to be considered in the differential diagnosis of new-onset neurocognitive disorders in children and adolescents.

This study examined the question of whether a sub group of children with

a history of LYD and persistent cognitive complaints have objective cognitive deficits, independent of psychiatric comorbidity.

METHODS

Subjects

Children between 8 and 16 years of age were recruited. Twenty children with chronic LYD and 20 healthy control subjects were enrolled.

Children with a history of LYD who were symptomatic for 6 months to 3 years, with persistent cognitive complaints including memory problems, distractibility, and school decline, were referred by their pediatricians. The diagnosis of LYD was confirmed based on a) history of exposure to a Lyme-endemic area, b) an illness course distinguished by symptoms characteristic of LYD, and c) either 1) history of a physician-documented erythema migrans (EM) rash or unambiguous EM described by a parent, or 2) history of a positive whole-blood polymerase chain reaction (PCR) test for Bb or a positive Western blot meeting explicit current Centers for Disease Control and Prevention (CDC) criteria. The CDC criteria for the immunoglobulin G Western blot (IgG WB) were broadened to recognize that the 31-kD and 34-kD bands represent the highly specific Osp A and B bands. Children were accepted into the study only if LYD infection occurred after completion of a marking period in school. This helped to establish good academic performance prior to the onset of LYD.

Twenty healthy control subjects with no history of LYD were included. An attempt was made to match the groups on gender, age, grade, and socioeconomic status determined by using Hollingshead occupational codes. *(13)* Healthy children were solicited through the families of children with LYD, including siblings, friends, and relatives. In addition, control subjects were recruited from flyers posted at Columbia Presbyterian Medical Center, although many of these self-referred children were not eligible because they were not fluent in English. Negative enzyme-linked immunosorbent assay and Western blot tests were required for control subjects.

Eligibility for both groups was determined by an extensive phone screen with a physician (B.F.) and by documentation of a positive Western blot

assay for the LYD group. No children were accepted into the study if there was a preexisting or pre-Lyme history of significant diagnosed medical, neurologic, psychiatric, or learning problems (including, but not limited to, seizure disorder, head trauma, attention deficit disorders, learning disability, and conduct disorder). Healthy control subjects were not included if they presented with a significant history of any of the following symptoms: arthralgias /arthritis, recurrent neck pain or headache, marked fatigue, EM rash, or cranial /radicular neuropathies. Control subjects were not selected as "super-normals," since we included all children unless there were marked medical or psychiatric problems.

All procedures were conducted at the New York State Psychiatric Institute, where parents and children gave signed informed consent and were asked to avoid disclosing the diagnostic group of the child.

Cognitive Evaluation

All subjects were administered a neuropsychological battery selected in part to replicate a previous pediatric LYD study. (10) Tests were administered in a standardized manner and in a systematic order. The cognitive domains assessed included 1) general intelligence, using the Wechsler Intelligence Scale for Children III (WISC- III); (14) 2) short-term memory for visual and verbal material, using subtests of the Wide Range Assessment of Memory and Learning (WRAML); (15) 3) learning of new verbal and nonverbal material, using subtests of the WRAML; 4) attention, using the Conners' Continuous Performance Test (CPT); (16) 5) executive functioning, using the Wisconsin Card Sorting Test (WCST) (17); and 6) language, using the word association subtest of the Clinical Evaluation of Language Fundamentals. (18)

Prior to testing, all children completed a Likert-type scale for physical symptoms, assessing fatigue, joint pain, previous night's sleep, appetite, headache, and other pain, as well as the Children's Depression Inventory (CDI) (19) and the Youth Self-Report (YSR). (20)

Parents completed a general information questionnaire and a physical symptom checklist (rating symptom severity and frequency over the past year). Parents rated learning and attention problems on the Conners' Parent Rating Scale (CPRS-48) *(21)* and psychopathology on the Child Behavior Checklist (CBCL). *(20)* Because the present study is not a longitudinal one, the children had no pre-Lyme cognitive assessment. Given that limitation, school grades and standardized achievement test scores were used as an indirect way to assess premorbid cognitive functioning. School records were obtained for the current year and all years starting from the disease onset. Premorbid standardized achievement test scores were also obtained.

Statistical Methods

Statistical analyses were conducted by using SPSS 7.5. The continuous demographic variable of age was contrasted between the two groups by independent-sample t-tests. Demographic variables of socioeconomic class and sex were analyzed between the groups by t-test and chi-square analysis. The neuropsychological test results as well as the self- and parent-report questionnaires were compared by using independent-sample t-tests for the various indices and subtests. Test performance between the groups was also analyzed by analysis of co-variance to control separately for differences in Verbal Comprehension, depression, anxiety, and fatigue. Bonferroni correction was applied separately to groups of indices and subtests of the measures to correct for multiple comparisons. Results before and after Bonferroni correction are presented for the reader ’s information. The CPT’s overall assessment of the presence, absence, or possibility of attentional problems was compared between the groups by chi-square analysis. When available, analyses were done using standardized scores procured from published age-corrected normative data. All hypothesis-testing was two-tailed. A P-value of < 0.05 was applied for significance.

RESULTS

Patient Characteristics

Twenty children were eligible for the study, and all agreed to participate. There were 13 females and 7 males (mean age 13.83 +/- 2.41 years; mean mean +/- SD reported throughout). All children were Caucasian, fluent in English, and, consistent with the demographics of Lyme disease, all but one came from middle- or upper-class families. The mean age at diagnosis was 11.90 +/- 2.85 years. The mean number of physicians consulted before the diagnosis of LYD was 3.80 +/- 4.48. The mean time since diagnosis was 74.95 +/- 68.04 weeks; from parent reported symptom onset until diagnosis, 47.28 +/- 44.41 weeks; and from diagnosis to treatment, less than 1 week (0.30 +/- 0.92). Thus, these children were symptomatic for many months before being diagnosed and treated.

Of the 20 children with LYD, 16 (80%) had a fully reactive WB and 6 (30%)

had a history of an unambiguous EM rash. Of the 4 without a reactive WB, 3 had both well-documented EM rashes and 4 /5 bands on an IgG WB, and 1 had a positive whole-blood PCR for Bb DNA and frank arthritis.

All of the children had received oral antibiotics (mean=23.21 +/- 21.99 weeks), and 11 had received intravenous antibiotics (8.79 +/- 16.10 weeks). All initially benefited from antibiotic therapy, but improvement was sustained in only 10% (2 /20) after oral antibiotics and in 36% (4 /11) after IV antibiotics. At the time of testing, 7 children (35%) were being treated with oral antibiotics and 2 (10%) were being treated with IV antibiotics.

Based on physician assessment, the most common symptoms during LYD were marked fatigue (100%), arthralgias (100%), frequent and severe headaches (100%), irritability /depression (94%), short-term memory problems (94%), schoolwork deterioration (94%), myalgias (88%), brain fog (88%), neck pain (88%), insomnia (82%), distractibility (82%), word-finding problems (82%), and severe flu (80%). Arthritis was noted in only 38% of the sample. On the more extensive parent-rated questionnaire, children were rated as having moderate to severe sensory hyperacusis to sound (58%) and /or light (74%); insomnia (77%); word-finding problems (79%); and radicular pains (56%).

Thirteen females and 7 males (mean age=13.53 +/ 2.67 years) were entered into the study as healthy control subjects. Nine of these children were siblings of children in the LYD group, 6 were friends of children in the LYD group, and 5 were recruited independently. All children were Caucasian and English-speaking. No significant age, sex, or socioeconomic differences were found between the two groups.

Outcome Measures

Neuropsychological Testing: Performance of the groups on the neuropsychological measures was compared (see Table 1). On two generally accepted measures of pre-served premorbid intellectual functioning (Vocabulary and Verbal Comprehension Index), the two groups were not significantly different. On other indices, however, the LYD group had significantly lower scores: Full Scale IQ; Performance IQ; the Perceptual

/Organization and Freedom from Distractibility indices of the WISC-III; and the General Memory, Verbal Memory, and Visual Memory indices of the WRAML. The LYD group had significantly lower scores on the digit span, picture completion, coding, and block design subtests of the WISC-III. They had significantly lower scores on the design memory, story memory, finger windows, sentence memory, and number /letter subtests of the WRAML. The LYD group had significantly greater difficulty maintaining set on the WCST. The CPT data are available only for a subset of the subjects because this version of the test was added mid-study. Despite the small n (9 LYD, 14 Healthy), there was a strong trend for the LYD group to have greater attentional difficulties. There was a significantly greater frequency of definite attention problems in the LYD group than in the control subjects (9:1; P=0.007). After correction for multiple comparisons, Performance IQ, General Memory Index, Verbal Memory Index, and finger windows remained significant.

Click here to view pdf of this article that includes TABLE 1. Neuropsychological measures and results in the Lyme disease and healthy control groups.

Premorbid Academic Achievement: School grades indicated children in the control group were functioning in the above-average range.

Pre-LYD school grades indicated children in the LYD group had been functioning in the above-average range. Premorbid standardized achievement test scores were available for 14 children (70%) in the LYD group. Eight of 14 children (57%) had scores greater than 90%, 3 (22%) in the 80%–89% range, 1 (7%) in the 70%–79% range, 1 (7%) in the 60%–69% range, and 1 (7%) in the 50%–59% range. For the 6 who were missing standardized tests, pre-Lyme report card grades of A's and B's indicated above-average functioning in school.

Physical Symptoms and Psychopathology: The LYD group had significantly elevated scores on all measures of physical distress and parent /child-reported psychopathology. After controlling for multiple comparisons, most scales remained significantly different (Table 2). Regarding depression, parents indicated that 41% (7/17) of children with LYD had suicidal thoughts and 11% (2 /18) had made a suicide gesture. On the

child rating (CDI), 40% (8 /20) had suicidal thoughts. The LYD group scored far worse on measures of learning problems and hyperactivity: almost 7 SD above the control subjects' mean on the CPRS Learning Problems scale, and 5 SD above the controls' mean on the Hyperactivity Index scale.

Because affective disorders influence cognitive performance, the data were analyzed in an attempt to control these potentially confounding variables. Depression did not account for group differences in Perceptual /Organizational Index (P=0.050), General Memory Index (P=0.045), Verbal Memory Index (P=0.021), digit span (P=0.045), coding (P=0.002), design memory (P=0.034), finger windows (P=0.011), or number/letter (P=0.003). Parent-rated anxiety did not account for differences in Performance IQ (P=0.027), Visual Memory Index (P=0.049), coding (P=0.038), finger windows (P=0.005), or number/letter (P=0.038). Self-ratings of fatigue did not account for differences in digit span (P=0.038), finger windows (P=0.016), or number/letter (P=0.024). When we attempted to statistically control for depression, anxiety, and fatigue together, three non-independent variables, group comparisons for many index and subtest scores failed to attain statistical significance. However, finger windows (P=0.022) and number/letter (P=0.010), two important tests of visual and auditory processing, continued to be significantly different between the groups.

LDA Vaccine Position Paper*

VACCINE POSITION PAPER * (This LDA position paper applied to the vaccine LymeRix which was withdrawn by the manufacturer citing poor sales. It does not apply to any current Lyme vaccine).

The Association recognizes the need for a safe effective vaccine against Lyme Disease. Several pharmaceutical companies have developed vaccines that are going through the FDA's vaccine approval process. One has been FDA approved.*

The Association does not recommend for or against products, including the vaccine, used for the treatment or prevention of Lyme disease. An individual and his/her doctor need to make the decision whether or not to receive the vaccine.

Several questions about the vaccine:

- Since there is no effective test for active Lyme, what happens to individuals who have active Lyme disease and receive the vaccine?
- Since the vaccine is effective against certain strains of the Lyme bacteria, Borrelia burgdorferi, what happens if someone is infected with a different strain?
- What happens to individuals who receive the vaccine and become vaccine failures and contract Lyme? After receiving the vaccine, they will now have a positive test for Lyme. Will doctors know enough about the vaccine effects on LD testing to diagnose Lyme, and will insurance companies pay for treatment, or will the record of the vaccine and subsequent positive test prevent diagnosis and treatment?
- Since having had Lyme disease itself does not confer immunity, can one conclude that a positive titer means immunity to the disease? Are positive titer and conference of immunity the same thing?
- What tests have been done to determine the length of protection of the vaccine beyond 2 years?
- In the vaccine trials, people were not challenged with the disease; they were just monitored to see if they came down with it. What happens if someone actually is infected?
- Bacteria inside a tick that is feeding on a vaccinated animal are mostly destroyed. Can the remainder enter the human body and produce disease?
- Some researchers have found that OspA may trigger an autoimmune arthritis in certain susceptible people. Since this vaccine is OspA based, will getting the vaccine produce arthritis in some otherwise healthy individuals?

Adopted: 4/21/98,
Revised: 5/19/98, 2/16/99
[**Note: This vaccine, LymeRix, was withdrawn from the market by manufacturer on Feb. 25, 2002. Currently, there are no vaccines on the market for humans*]