FE

My name is Kathleen Dickson. I am an analytical chemist from Southeastern Connecticut. I would like to discuss the validity of the results of the LYMErix adult vaccine trial, specifically--the validity of serological standard used, and how that standard affected the vaccine trial results.

THE PROBLEM IS THE DEARBORN/DRESSLER IgG STANDARD.

One of the testing procedures used in the trial, the Western blot, looks for antibodies to specific antigens expressed by B. burgorferi. The limitation of the Western blot, is that it qualifies the body's reaction to the infection but does not actually identify the infectious agent.

In Lyme disease, patients produce variable antibodies over time, most likely a result of antigenic variation - the organism changes its outer membrane components, and even most of those identified antigens are ***variable*** antigens. Current diagnostic methods now target the invariable region of the variable antigens, for this reason.

[Slide-1]

According to Allen Steere, Chief of Rheumatology, Tufts: (2 reports)

1) 1986, Journal of Clinical Investigation, (Title: "Antigens of Borrelia burgdorferi recognized during Lyme disease. Appearance of a new immunoglobulin M response and expansion of the immunoglobulin G response late in the illness.")

"...The IgG response in these patients appeared in a characteristic sequential pattern over months to years to as many as 11 spirochetal antigens."

[Slide-2]

2) 1993, Dressler/Steere, (Title: "The Serodiagnosis of Lyme Disease", which came to be the CDC/Dearborn IgG criteria), Journal of Clinical Infectious Diseases, 1993 Feb;167(2):392-400.

"...The specific immune response in Lyme disease develops gradually over a period of months to years to greater than or equal to 10 spirochetal polypeptides."

10 or 11 antibodies characteristieally show up in Lyme. Some are more specific than others. These 10 or 11 bands don't all show up at once, however. They show up one or two or a few at a time. Persistent infection is evidence by changing bands over time

CDC decided to establish another serodiagnostic standard, based on these specific antigens and called for a Second Serodiagnostic Conference to be held in Dearborn Michigan, late October, 1994.

However, in May, 1994, immediately prior to the start of the LYMErix/ImmuLyme Lyme vaccine clinical trials, members of the CDC and others, privately met in Fort Collins and decided that the Dressler/Steere standard for IgG of 5 of 10 bands be the CDC standard, according to transcripts of the June 1994 FDA Lyme vaccine meeting, presumedly to facilitate the vaccine trials.

[Slide 3, Table 1 of Dressler]

The problem with the Dressler IgG standard of 5 of 10 bands is that it was

calculated to be 99% specific, and was not empirically derived...

It was generated from strain G 39/40, a strain Barbara Johnson of the CDC, later, at the Dearborn meeting, recommended NOT using,

And represents ***an artificially compressed summary of what only the arthritis-presenting patients showed over time.***

And does not represent what's going on in neuroborreliosis, a much more serious and disabling disorder.

Table 1 reports the frequency of certain antigens, polypeptide and lipoproteins.

From the arthritis data set, were derived the bands for this case definition.

Dressler/Steere report that individual *specific* bands, such as OspA, B, C, 18-, 93-, and 28-kD, generated from Bb strain G39/40, are specific markers of infection.

Dresser/Steere report that 18, 28, 93 are the most specific, because they never showed in the controls. That they never showed in controls and are specific, would mean, in the presence of symptoms, that one of these bands indicate that Lyme is the source of the illness.

P93 and 23kD (OspC) seem to be the consensus on highest specificity, as seen in the literature. That Steere came up with 28, instead of 23, could be a reflection of the potential of this odd strain, G39/40 to generate sufficient antigen of diagnostic value.

Confoundingly, OspA and B were left out of Dressler/Dearborn IgG case criteria. We surmised that this was because it was intended that these be vaccine immunogens.

Therefore, the Dearborn case standard criteria for IgG ***excluded***, to quote Steere, "major", "immunogenic, outer surface proteins" from the case criteria, the Osps A and Osp B.

The exclusion of Osp A and B has resulted in, is, for example, unvaccinated people who have 3 IgG bands plus Osp A and Osp B, aren't diagnosed as positive, according to the CDC case definition, even though they have 5 bands.

So we really don't know what Dearborn IgG means.

[Slide 4- Imugen Report]

Further decreasing the potential for getting early and adequate antibiotic therapy is the ***practical misinterpretation*** of what the CDC criteria for IgG of 5 of 10 bands means.

For example, Imugen, uses reporting forms which state: "Normal Range: < 5 bands".

[Slide 5- Zoom of Imugen Report, Bottom Right]

Normal is not "less than 5 bands" --If the patient has clinical signs of Lyme disease plus 2 specific antibody bands for B. burgdorferi, no honest diagnostician would assert that the patient does not have Lyme disease. This kind of misinterpretation of CDC criteria further compound the problem.

"Normal" is no bands and no clinical symptoms of Lyme.

[Slide 6 - Zoom of Imugen Blots, Show Strain ID]

Note that this lab uses G39/40 and FRG, a strain from West Germany. We question how many people in the US will have been exposed to this bug, such that they will have antibodies to it.

Clearly, the Dearborn Conference also did not resolve the another problem of standardization, as demonstrated by this labs' use of odd strains and reporting concepts.

To miss patients by using this Dearborn case definition serodiagnosis standard, instead of weighting the specificity of an individual band, such as Osp C or P93, both highly specific alone, will result in the patient's lost opportunity for early and successful treatment.

THE PRE-DEARBORN DIAGNOSTIC STANDARD

[Slide 7 - page 29 Dearborn Conference Summary]

[Slide 8- Zoom]

Changing bands over time was formerly the criteria for determining later stage Lyme disease, in place *before* the Dearborn conference, as reported by David Dennis of the CDC:

"1) Isolation of Bb from Clinical specimens
2) Demonstration of diagnostic levels of IgM or IgG antibodies to the spirochete in the serum or the CSF, or
3) Significant change in IgM or IgG antibody response to Bb in paired acute-phase and convalescent sera phase

Although potentially useful in confirming active Lyme disease, neither cultural isolation nor paired serum specimen testing has been much used for validating cases in routine Lyme testing, since the procedures are not often performed in the general medical setting."

The majority of the other recommendations made by the invited researchers to the Dearborn conference on IgG serology, were based on the frequency and identity of these known-to-be specific bands, but these 8-9 other recommendations were ignored.

The overall accuracy of this Dressler IgG standard never exceeded 28% in actual practice and these results were reported by the other invited researchers at Dearborn. In other words, most people with Lyme disease *DON'T* have a 5 of 10 band profile.

HOW DOES DEARBORN APPLY TO THE VACCINE TRIAL?

If few people have Lyme disease - and this Dressler/Dearborn criteria will exclude most Lyme patients - the vaccine will ***not*** be shown to be a failure or cause adverse events.

We believe this is exactly what happened in the trial.

[Slide 9 Table 2 of NEJM SKB Vaccine Results]

Only 22 people got Lyme disease the first year in the vaccine group, while there were **515** unconfirmed cases —compared to in the placebo group of 468.

There 10% more unconfirmed cases than in the placebo group in the first year of the trial.

There were ~1750 Unconfirmed Lyme disease cases reported during the SKB . . trial of ~11,000 over two years.

The Western Blot serology from these unconfirmed Lyme cases will need to be reviewed for evidence of other Bb *specific* bands and compared to the placebo group by an independent group of analysts. If there are any other *specific* bands besides OspA, the case must be counted as a Lyme disease case, in the presence of symptoms.

Note that there were only 2 asymptomatic cases the first year in the vaccine group vs 13 in the placebo group. In the second year, there were 0 (zero) in the vaccine group and 15 in the placebo group.

We believe these results do not show that the vaccine is effective at preventing asymptomatic Lyme, which SKB reports, but rather, that it is turning asymptomatic Lyme cases into symptomatic ones.

As a support group leader in Southeastern CT, I have met ~10 people, who found my name on the internet, who had adverse events and were ill, looking for help. After learning more about these patients, I found that all but one of these cases had previous Lyme, and that one got the Erythema Migrans rash during the series of vaccination. NOT ONE SINGLE PERSON DID NOT HAVE OTHER BANDS ON FOLLOW UP WESTERN BLOT.

It is because I have gotten so many calls from patients looking for help because of their illness, that I am here today.

Return to Text

TABLE 2. ATTACK RATES OF LYME DISEASE AND VACCINE EFFICACY IN THE STUDY POPULATION.*

LYME DISEASE	YEAR 1						YEAR 2					
	VACCINE (N=5469)		PLACEBO (N=5467)		P VALUE	VACCINE EFFICACY (95% CI)	VACCINE (N=5469)		PLACEBO (N=5467)		P VALUE	VACCINE EF (95% C
	No. of Cases	*Attack Rate*	*No. of Cases*	*Attack Rate*			*No. of Cases*	*Attack Rate*	*No. of Cases*	*Attack Rate*		
		%		%		%		%		%		%
Definite												
Erythema migrans	21	0.38	41	0.75	0.01	49 (14 to 70)	15	0.27	65	1.19	<0.001	77 (60 to
Neurologic involvement	0	0	1	0.02			0	0	1	0.02		
Arthritis	1	0.02	1	0.02			1	0.02	0	0		
Carditis	0	0	0	0			0	0	0	0		
Total definite cases	22	0.40	43	0.79	0.009	49 (15 to 69)	16	0.29	66	1.21	<0.001	76 (58 to
Asymptomatic												
Asymptomatic infection	2	0.04	13	0.24	0.004	83 (32 to 97)	0	0	15	0.27	0.001	100 (26 to
Total definite and asymptomatic cases	24	0.44	56	1.02	<0.001	57 (31 to 73)	16	0.29	81	1.48	<0.001	80 (66 to
Possible												
Influenza-like illness with seroconversion	13	0.24	17	0.31	0.46	24 (−57 to 63)	12	0.22	21	0.38	0.12	43 (−16
Physician-diagnosed erythema migrans	7	0.13	9	0.16	0.61	22 (−109 to 71)	7	0.13	6	0.11	0.78	−17 (−247
Total definite, asymptomatic, and possible cases	44	0.80	82	1.50	0.001	46 (23 to 63)	35	0.64	108	1.98	<0.001	68 (53 to
Unconfirmed	515	9.42	468	8.56	0.12		339	6.20	326	5.96	0.61	

*CI denotes 95 percent confidence interval.

Continued follow up on these Unconfirmed patients should have been with further Western blotting from one of the CDC recommended strains (B31, 297, 2591) and the original case definition, ***to look for changing bands***,

and/or one of the newer antigen-decomplexing methods, like that of Len Sigal's of RWJ or Steven Schutzer's, for IgM or IgG.

In the re-tabulated results, which we insist be performed, cases where active infection is not found by these follow up methods, should be resummarized as the "Uncomfirmed Lyme/Possible Seronegative Lyme".

VACCINE FAILURE AND ADVERSE EVENT

[Slide 10 Persing's Patent]

Dr. David Persing, formerly of Mayo, now with CORIXA recorded in his US patent 6,045,804:

"Additional uncertainty may arise if the vaccines are not completely protective; vaccinated patients with multisystem complaints characteristic of later presentations of Lyme disease may be difficult to distinguish from patients with vaccine failure. Vaccine failures have been occasionally noted in animal models (E. Fikrig et al., Science, 250, 553-6 (1990)),..."

Vaccine failure and vaccine adverse event cannot be distinguished from each other. An asymptomatic Bb infected adverse LYMErix event case may never be detected until the patient is vaccinated and symptoms occur, which we think explains the majority of the adverse events reported to FDA re: LYMErix. Many previously infected Lyme cases report systemic symptoms after vaccination. Many find out they had Lyme after being vaccinated, becoming ill, being tested for Lyme and finding other specific antibodies.

FDA should therefore *not* be looking for only arthritis as a potential adverse event, to the exclusion of systemic illness.

FREQUENCY OF ASYMPTOMATIC INFECTION

[Slide – 10]

According to Allen Steere's 1986 report, it is possible that, for every one Bb-infected person with symptoms, there is one walking around without symptoms.

SUMMARY

Vaccine failure and exacerbation of asymptomatic infection are identical, according to the patient data collected, and on the online VAERS database.

Dearborn/Dressler is not a valid criteria for assessing Lyme, the former CDC criteria of changing bands is valid.

Until there is an independent review of the WB data from the trial, we have no idea how safe this OspA vaccine is.

[Slide- SBK Results Table]

OUTLOOK

By what mechanism vaccination of the asymptomatic Bb infected patients is causing the Lyme like illness, we do not know exactly.

Previous infection could be "priming" the immune system, as Denise Huber of Tufts has suggested, in "Identification of LFA-1 as a Candidate Autoantigen in Treatment-Resistent Lyme Arthritis" July 31, 1998, Science, Vol 281, p 703.

or the vaccine is activating a dormant infection by the immune dysregulation it causes, as demonstrated by the effect of Bb infection and Osp A alone, on NK cells population, T cells, neutrophils, and the effects on the various inflammatory regulating biomoleclues, such as IL-10.

We simply don't know all the variables, at present, that effect systemic illness from immune dysregulation caused by Bb infection, and especially the effect of a sucha a large dose of a known immune irritant, Osp A upon this system, the asymptomatic Lyme patient.

The vaccine should be taken off the market immediately, until the true data, the acknowledgement of the presence of other bands besides Osp A in all 4 groups of uncomfirmed Lyme is published and re-presented to the FDA.

Certainly this vaccine should not be approved for use in children, until we know the ***true*** results of the adult vaccine trial.

Kathleen M. Dickson, SeCT Lyme Support Group, ActionLyme, 01-31-01, FDA meeting, Bethesda, kathleen.dickson@snet.net

ignored the other recommendations. Arthur Weinstein was in charge of the Workgroup on IgG and IgM recommendations, Henry Feder agreed also with Dressler, but added that IgM was not necessary and that some other bands were diagnostic in children because they were not likely to have been treponemal bands and children have different immune systems than big people. For instance 50kD was related to Ld in children.

Who else was there:

1) MarDx Labs- included 31 and 34. IgG sensitivity of 12 bands in late disease was 100% That means this 5 of 12 criteria was only seen in Ld. SKB Vaccine trial was already underway using this lab.
They were sent positive CDC blood. It appears everyone else tried out CDC IgG criteria in the field.

2) Imugen- said using CDC method for IgG only detected Lyme in 14% of the time.

3) New York Medical College, Vahalla- 36% for EM 7-14 days, 20% in <7 days EM

(it is not common practice to Western Blot patients with EM, so we don't know what these resulst mean. Western blotting is normally used in the absense of a rash.)

4) Lutheran Hospital, La Crosse Wisconsin - 22% for were positive by this IgG criteria. They report: "Highly significant decrease in sensitivity when the proposed CDC criteria were applied for interpretation"

5) Zemel, UCONN - did not reportt give % positive by Dressler IgG their results. Only discussed how many bands they found in the JRA patients, etc. Recommended 5 bands.

6) Roche Biomedical Labs, 28% were positive for every possible IgG band; Others were positive for IgM and IgG were equivocal. It's possible from the notes that this lab was not certain of how their observations were to be reported

7) Wadsworth- had some different scoring system, did not report % frequency in which they found 5 bands.

8) CDC Atlanda, Hofmeister and Childs --talked about mice. Their criteria was 2 out of three of OspC, 16 kD, 17.9 kD for IgG, for the mice.

9) Canada, Ontario, Ontario Ministry of Health. Did not report how they performed their survey. 66% of the positive ELISAs were WB positive was the only data related to this.

10) Igenex-- Concurrent positive serology with greater than 3 symptoms: 8%

DEARBORN -- The Illusion of a Conference

Kathleen M. Dickson, SeCT Lyme Support Group, ActionLyme, 01-31-01, FDA meeting, Bethesda, kathleen.dickson@snet.net

From the 1994 Dearborn Conference booklet--page 29

"Standardization of Lyme Disease Serologic Testing for Epidemiologic Purposes"

by David T Dennis, MD, MPH

(This was the former criteria for serodiagnosis; before Dearborn)

"1) Isolation of Bb from Clinical specimens

2) Demonstration of diagnostic levels of IgM or IgG antibodies to the spirochete in the serum or the CSF, or

3) **Significant change in IgM or IgG antibody response to Bb in paired acute-phase and convalescent sera phase**

Although potentially useful in confirming active Lyme disease, neither cultural isolation nor paired serum specimen testing has been much used for validating cases in routine Lyme testing, since the procedures are not often performed in the general medical setting."

Prior to May, 1994, it was recognized that changing bands was serodiagnostic.

From an invitation from the CDC/NIH/NCID printed October 1994

"DON'T MISS AN OPPORTUNITY TO CONTRIBUTE TO THE DISCUSSIONS!" [in bold print]

page 2

"The goal of the second national conference if to create a forum in which all individuals abd groups interested in Ld serodiagnosis may contribute and express their opinion. Specific topics for discussion include developing a set of recommendations that will establish standards for interpretive criteria; setting the criteria appropriate for the development and evaluation of new diagnostic tests; sharing information on establishment of standard laboratory methods; and discussing the FDA criteria that Ld kit manufacturers must meet to certify their tests."

This gives the appearance that researchers were invited to Dearborn to contribute to a consensus on serology.

However, CDC and SKB already had a standard for IgG that they were sticking with, by the start of the SKB, vaccine trial, June 1994. Whoever was in charge at Dearbon,

DEARBORN -- The Illusion of a Conference

Kathleen M. Dickson, SeCT Lyme Support Group, ActionLyme, 01-31-01, FDA meeting, Bethesda, kathleen.dickson@snet.net

11) Wisconsin State Laboratory of Hygiene and the College of American Pathologists: CDC criteria for IgG had a sensitivity of 15%. They reported the frequency that they found the various specific bands.

The Wisconsin State Laboratory gave probably the best objective summary of what happens in serology. They recommended standardization of the method should preceed the establishment of the interpretive criteria.