DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL VACCINE PROGRAM OFFICE PRESENTS:

WORKSHOP ON ALUMINUM IN VACCINES

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I N D E X

PROCEEDINGS

CALL TO ORDER

MARTIN MYERS

DR. MYERS: Good morning. Maybe I will just step out in the hall long enough to shoo people in.

[Pause.]

Welcome back to the Aluminum Vaccines meeting.

We are going to have a change in our agenda this morning.

Dr. Dalakas was unable to join us and as a consequence we are going to rearrange the agenda somewhat.

Dr. Gherardi is going to first give us a paper on the lesion of MMF and then Dr. Verdier is going to present his paper, and then Dr. Gherardi is going to discuss possible clinical associations with the MMF entity.

We are going to have discussion after each of the papers and then we are going to try and break for -- take a break at that point so we are going to basically put discussion time in for Dr. Dalakas' time.

Lena Kombo from the National Vaccine Program Office asked me to specifically make an announcement that speakers -- she would like your manuscripts by June 1st and discussants, where appropriate, the

moderators from the discussion groups, if you would write a short summary of the discussion topics we would appreciate that. Lena would like that by June 1st.

As you already know, she will probably be sending you an e-mail fairly shortly to give you the electronic address. We would prefer to have the manuscripts electronically if at all possible.

I am just delighted to introduce our moderator for this morning's session. Dr. Jose Centano is the chief of the Epidemiologic Pathology Group at the Armed Forces Institute of Pathology.

He chaired the Metal Ions -- organized the Metal Ions meeting. He is looking much more relaxed today than he was earlier this week. And his special interest is metal ions in tissues so he has some special expertise that he brings to us this morning.

Jose, I greatly appreciate your joining us and also your fine hospitality in helping us organize our meeting in San Juan.

SESSION III: MACROPHAGE MYOFASCITIS (MMF)

MODERATOR: JOSE CENTENO

DR. CENTENO: Well, thanks, Marty.

Welcome, all of you, to this session in the morning. It is a pleasure for me to be with you today here and to serve as the moderator for this session and to have the opportunity of being with

such renowned scientists in this field of vaccines.

I would like to first start this session with a very short introduction of what you will be seeing during this morning. I would like basically to go over some of the basic terms of basic observations, both on the clinical observations of MMF, of macrophagic myofascitis, and also some of the very short observations that has been published on the pathology overview of this disease.

(Slide.)

And then we will go into the sessions that -- into the different topics that have been arranged for you for this morning.

MMF is macrophagic myofascitis, as you are going to be seeing from Dr. Gherardi, it is a clinical -- it is an inflammatory myopathy, which seems to be characterized by these basic observations. It is an infiltration of nonepitheloid histiocytic cell into muscle. That will be mostly discussed very -- in detail by Dr. Gherardi.

It is a very rare condition and it was first documented by the French group in 1993. And obviously it seems to be -- appears to be associated with the vaccine injections. Again this is going to be very -- in very detail. It is going to be addressed by Dr. Gherardi this morning.

(Slide.)

In terms of the pathology there are some very interesting observations that have been described by Dr. Gherardi's group as well. There is infiltration of large macrophages into all three facial layers of the muscle. Epimysium, perimysium and endomysium, and the most characteristic observation is on the epimysium. The most characteristic pathology.

The inconspicuous -- there is also observations that relate this as inconspicuous muscle fiber damage and non -- it is non-necrosis giant cells or mitotic figures. This is going to be discussed in detail by Dr. Gherardi.

The next slide is something that I know that most of you are very familiar with this but my boss here asked me to pass this to you because there is some -- all this chemistry is very well known by you but I would like just to remind some of the issues here.

(Slide.)

This is the basic muscle chemistry and basically you see the different layers, the epimysium, the perimysium, and then the endomysium. And the local reaction here seems to be on the epimysium. Again this is just basic chemistry but my boss here decided to show it.

(Slide)

The basic -- the presentation this morning will focus on the following topics: First, we will look at the pathology data and human clinical data that we will be presented by Dr. Gherardi's group. Basically Dr. Gherardi's going to address first the pathology data and he will come back later during the morning to talk more about the human clinical data.

Then Dr. Verdier is going to talk about the animal studies and some of the clinical studies.

Unfortunately, we do not have with us Dr. Dalakas today and the morning -- the rest of the morning will be spent on discussions and panels dealing with the different topics.

So to start this morning, it is a pleasure for me to introduce to you Dr. Gherardi that is going to talk to you about his work on the pathology of MMF.

EPIDEMIOLOGY, HISTOLOGY AND POSSIBLE CLINICAL ASSOCIATIONS

ROMAIN GHERARDI

DR. GHERARDI: I first would like to thank Dr. Myers for inviting me to this meeting. May I have the first slide, please?

(Slide.)

At the moment about 100 percent -- 100 people with so-called MMF have been recorded in the world, including 92 in France. As you see here the

first case was recorded in '93 and afterwards there was a huge increase of the number of detected cases in France. And I can be sure that there was no bias in equipment up to early '99.

(Slide.)

We first published a series of the 14 first patients in the Lancet in 1998 and as you can see here these patients had myalgias and fatigue as -- myalgias, arthralgias and fatigue as the most common clinical symptoms. Other symptoms were rare and finally were not consistently found in other patients.

(Slide.)

Laboratory findings were poorly contributing, including ECG which was inconstantly myopathic, high CK levels, the muscle enzymes were also inconstantly elevated, and there was a biologic inflammatory syndrome in also a little less than one-half of patients. Of course, none of our patients had HIV infection.

(Slide.

I shall go further in the clinical aspects in the second part of this morning. The main point was that all these people were found to have a very unusual lesion at the muscle biopsy that included large infiltrates of these blue cells at the margin of the muscle tissue. Here you can see muscle cells

and here you have the fascia and you see that the collection is restricted to the border of the muscle fascial.

(Slide.)

At higher magnification you can see here that the muscle cells in pink here are surrounded by this blue -- large blue cells that infiltrate the connective tissue but that do not address muscle fibers. You can see that these fibers may be smaller but are not attacked by the infiltrates.

(Slide.)

These infiltrates at the border of the muscle were macrophages as assessed by immunocytochemistry that is showed here, CD68 marker, which is very specific of macrophages was positive and they do not meet the criteria for dendritic cells.

(Slide.)

Other inflammatory cells were also observed and these cells were mainly CD8 T cells that were intermingled with the macrophagic infiltrate in the muscle tissue.

(Slide.)

When inflammatory myopathy is observed it is useful to perform a marker for MHC-1 molecule expression because expression of MHC-1 molecule by muscle fibers is most specific of polymyocytis.

In MMF, as you can see here, there were some muscle fibers that expressed MHC-1 molecule, which is not the case normally, but these positive cells were restricted to the close vicinity of the infiltrate. The infiltrate itself was MHC-1 positive and on those muscle fibers close to the infiltrate were also positive. On the remote form of the infiltrate, as you can see here, muscle fibers were negative. So the picture was not one of polymyocytis.

(Slide.)

Another intriguing finding was at the EM level in the 14 first patients we had the opportunity to detect macrophages filled with curious osteophillic inclusions that we first believed to be calcium phosphate deposits.

But here at higher magnification you have these fibrous crystalline inclusions that look like -- that are very similar to anoxia (?) hepatite crystals but we were unable to achieve a positive reaction for calcium stainings.

(Slide.)

And as you will see, this was the clue of the etiology. As you can see here these inclusions were frequently born (sic) by a membrane that was probably of measles origin.

(Slide.)

This lesion has not been recorded in the muscle pathology literature. Old textbooks did not mention this entity and all myopathologists in France and elsewhere in the world, including all the brilliant myopathologists in the U.S.A. were not familiar with this lesion. And all the differential diagnosis could be excluded easily, including granulomatous myositis, which is the one -- the myositis which is associated with sarcoidosis, and it is very important to understand that these lesions were not of the sarcoidoid type.

(Slide.)

And, finally, we had the idea that clinical symptoms were not too severe in most people because combinations -- empirical combinations of antibiotic therapy on steroids gave finally good results in majority of patients. About 80 percent of patients with MMF lesions in their muscle respond quite well to steroids.

(Slide.)

At this moment we believed we were facing a new emerging infectious disease and we tried to find arguments for this by an epidemiological survey that was performed by the French government. What was found was the following:

There was an intriguing high number of MMF patients that worked at hospital, mainly nurses and

health assistants. There were also a number of people that used to travel a lot in foreign countries, including Africa, several European countries and Asia. And another and still unexplained finding, a lot of these people were affiliated to sport federation. This is 58 patients, which is a lot with regard with the general adult population in France.

(Slide.)

The remaining of the epidemiological survey failed to find anything consistent with an environmental cause. Housing gave no information. Urban and rural distribution of patients was balanced. House or flat habitation was also balanced. There was possibly something intriguing in the geographical distribution of these patients since the western part of France and the Paris area appeared to be really over represented among individuals. Finally, all of the research to find food, water, place of purchase of food, animals, hobbies, chemicals and x-rays gave negative results.

(Slide.)

The light came from the fact that we were unable to achieve calcium staining in these people despite the presence of calcium-like crystals in the muscle and we tried to assess the prevalence of these inclusions in these people by studying 20 consecutive

patients for electron microscopy and we performed electron microscopy in any material available.

You must know that when a muscle biopsy is performed it is cut into three pieces. One for frozen section, one for paraffin imbedding, and one for electron microscopy. And among these 20 people, only four of them had convenient infiltrates in the EM material and the other one had it in the paraffin section. So we de-paraffinized the paraffin section to go to the EM study.

And according to this procedure we found that 100 percent of these people had the typical inclusions. So the inclusions were the hallmark of the disease.

We did not believe it when they -- when information came from the biophysics department telling us that the small piece of muscle biopsy we provided them for analytical study contained aluminum instead of calcium but it was the fact and we got the information in late October 1998.

This was achieved by two types of microanalysis, x-ray microanalysis and ionic (?) analysis.

(Slide.)

Here is an x-ray microanalysis I am not very familiar with but in this technique there are x-rays that are given to infrastructural points. Here are

the inclusions and the spectrum is assessed and gave and aluminum peak together with other peaks that were a couple, osmium, chloride, oxygen and carbon that all belong to the EM procedure. The grids for the EM examination are made of couple and the EM preparation of the sample includes osmium fixation.

(Slide.)

This was the case in all cases we studied. Here the aluminum peak and this was confirmed by another analytical study that arose to make a map of the distribution. Here you have a muscle biopsy, it was stained with the macrophage infiltrate here, and as you can see here the muscle fiber is negative but the infiltrate -- macrophage infiltrate is filled with aluminum.

(Slide.)

And, finally, we confirmed these analytical techniques by atomic absorption spectrometry. We took muscle biopsy from MMF patients in dividing the preparation in those part of the muscle biopsy sample, which included the macrophagic lesion and those parts that did not include the macrophage infiltrate, and we compared it to normal.

And as you see here, the aluminum content was very high into the MMF infiltrate. It was high enough remote from the infiltrate and it was very low in normal controls.

A most intriguing finding was that in 20 tested patients the circulating levels of aluminum were strictly normal and this led us to the conclusion that finally these people might have local accumulation of aluminum instead of systemic aluminum intoxication.

(Slide.)

So we went back to the files and we first looked at the sites where infiltrates were observed. Many tissues on organs were investigated for macrophage infiltrates because the patients were first believed to have a sort of -- a kind of Whipple's disease and so especially the gut and the digestive tract was intensively examinated.

As you can see here, none of the biopsy of the digestic tract was positive for macrophages and other sites were also examined without evidence of macrophage infiltrates. So the macrophage infiltrates were exclusively found in the muscle biopsy. And one look of the muscle biopsy it appears that it was constantly the deltoid muscle biopsy that contained the lesion and we were unable to find another site of biopsy giving -- providing the lesion.

(Slide.)

So light come to us when we assessed the serology of the 20 first cases. We found that

hepatitis B, viral serologic profile was observed in 65 of these people which is more -- much more than the 20 percent of people with such a profile in the general adult population in France.

There were also 25 people with positive antitetanus toxoid antibodies and it was clearly related to vaccination because nobody in France at present develops true tetanus infection.

And, finally, there were also patients with HIV antibodies with avidity of the antibodies that fit well with recent vaccination.

And, finally, 100 percent of our patients had not the antigens for HBV, tetanus toxoid or HIV. It was really certain that all HBV positivities were related to vaccination as well as all tetanus -- antitetanus antibodies.

(Slide.)

So at this moment we performed a large retrospective analysis of the history of the patient. Two teams were working. One from the French government and one by the doctors of the three neuropathologic myologic centers that included patients. We came to the same evidence.

All fifty patients that were reevaluated had been vaccinated or immunized with an aluminum containing vaccine. As you can see here, hepatitis B

was the most frequent one, hepatitis A was less frequent, and tetanus was frequent.

The number of doses per case was not abnormally high and the median value was four injections. And most important information was that the delay from the last immunization and the muscle biopsy runs from three months to eight years and the date -- no, the time of vaccination was assessed in all these people or almost all of these people on vaccination booklets so we are sure of the time of immunization and, of course, we are sure of the time of muscle biopsy. So many patients have more than five year delay from the last immunization to the biopsy and the median was 36 months.

(Slide.)

When we looked at the type of vaccines we found that there was balanced distribution between the two main hepatitis B virus vaccines that are available in France, the Engerix and the GenHevac B. And the Hb vax, which is the equivalent of the vax used in the U.S.A., was never found but it is virtually not available in France so this means nothing.

For tetanus vaccines we, of course, considered exclusively those vaccines that contain aluminum, which is the majority of TT vaccines but

not all of them. And here again the Tetavax and the others were both implicated.

(Slide.)

At this point we attempted to reproduce the lesions in animals. I go quickly because Francois Verdier will speak of this in a minute. And we injected Sprague-Dawley rats IM with 250 microliters of GenHeVac vaccine and we observed the lesion at days seven, 14, 21 and 28 post vaccination.

(Slide.)

And as you can see here, at day 28 a lesion that was very similar to that observed in humans developed in these animals at the vicinity of the muscle. There were collections, large collections of macrophages filled with finely granular vasophilic content, which was also PS positive.

(Slide.)

And at EM we found the same spicules fibrous structures into the macrophages.

(Slide.)

And at this point we came to the final evidence that the lesion of MMF was due to the injection into the deltoid muscle of aluminum containing vaccines. So this is the end of the first part of the story.

(Applause.)

DR. CENTENO: Thank you, Dr. Gherardi, for a very interesting talk. This talk is open for questions.

Yes, please. Can you use the microphone?

DR. ALVING: Carl Alving, Walter Reed.

It is very, very interesting. I have two questions. One is have you done electron microscopic studies on controls who did not get MMF but who did get injections?

DR. GHERARDI: Aluminum crystals were exclusively found in two macrophages. They were never found outside cells. And so in people undergoing deltoid muscle biopsy who had been vaccinated, we have a lot of course, without the lesion, there was no reason to look at aluminum crystals because the macrophage cells were not visible at the right macroscopic level. So maybe it could be useful to address the question of possible aluminum residues but it would be done more accurately by aluminum content evaluation than by morphology.

DR. ALVING: The second is maybe you had it but I missed it but what were the studies on the formed elements of the blood, like red cells, platelets and white cells, polys and so forth? Were there any changes in those compared to normal?

DR. GHERARDI: The white blood cell count and the red blood cell count was normal with few exceptions in which a slight increase of monocytes or a slight decrease of lymphocytes was observed.

DR. TODD: Charles Todd, CDC.

In your experimental work you used aluminum hydroxide and the other EM pictures that you showed would be consistent with the morphology of that.

DR. GHERARDI: Yes.

DR. TODD: Did you see -- do you use aluminum phosphate adjuvanted vaccines in France and is there potentially a difference between aluminum phosphate and aluminum hydroxide?

DR. GHERARDI: At the moment there is no aluminum phosphate containing vaccine available in France so I made no comparison.

DR. RENNELS: A clinical question. The symptoms that you describe these patients having had are really very nonspecific, very subjective, and the fact that they seem to respond to antibiotics and to steroids leads me at this point unconvinced that this is associated with a definite clinical entity. Do you have further clinical studies planned?

DR. GHERARDI: Yes. The second part of the session will be entirely dedicated to the clinical features.

DR. GERBER: Gerber, NIH.

This is somewhat related. You said that most of the patients responded to steroids. I wonder did you have repeat biopsies on any of those patients and, if so, what did they show?

DR. GHERARDI: Yes. One biopsy was performed on the opposite deltoid elsewhere in the body, macrophage infiltrates were not observed, but when people were rebiopsied at the same site, the infiltrates were retrieved.

DR. GERBER: Were what?

DR. GHERARDI: Were found again.

DR. GERBER: Even though the patient had responded clinically?

DR. GHERARDI: Yes.

DR. CLEMENTS: John Clements, WHO.

Just two little points to clarify. You had a spectrum of ages, infants through to adults, who were --

DR. GHERARDI: Yes. I gave yesterday to Martin sheets of paper summarizing all the data and if you want precise age, precise age range and so on, everything is in these data. So if your question is whether adults or children, this is it, I can tell you.

DR. CLEMENTS: I am just asking confirmation. There were adults and infants?

DR. GHERARDI: No, there were mainly adults. Among the 50 first patients we have two children and 48 adults with a range from 30 to 55 years being the most important part of the group.

DR. CLEMENTS: And can you just clarify for me how these patients presented? Were they clearly ill patients who came to the doctors because they had some fairly major symptoms?

DR. GHERARDI: Yes. I prefer to put this in the second part of the session. Of course, they had biopsy because they had the muscle problems, of course, and they had myalgia and unvalidating fatigues that led them to accept muscle biopsy.

DR. BRENNER: Alan Brenner, Boston University, DVIC.

Are you familiar, Dr. Gherardi, with a paper written by Robert Morak in 1982?

DR. GHERARDI: Yes. I detected it very recently and I come to the same conclusion that he did that the lesions are due to the vaccines but as far as I remember it was a very small baby of six months.

DR. BRENNER: Yes, sir. Eight months.

DR. GHERARDI: And he was supposed to have a congenital myopathy and there was probably an unrelated cause of congenital -- true congenital myopathy with vaccines that had been performed in the

thigh as usual in babies. But I agree with him that the lesion is due to aluminum containing vaccine, of course.

DR. BRENNER: Are you aware, sir, that even in 1982 he had done the same Sprague-Dawley rat experiments?

DR. GHERARDI: Sure, exactly. I detected this paper two months ago. It is very difficult to retrieve but finally I found it.

DR. BRENNER: Right. Also, there are a number of articles in the literature about the development of granulomatous and histiocytic sheet like reactions to aluminum containing vaccines and some of the difference, I think, between the granulomatous reactions and the histiocytic sheet like reactions, which you have seen and which he saw in his eight month old baby may be more time related than anything else because some of these experimental studies followed animals over a period of time and early on there were true granulomatous foreign body looking reactions that converted to more histiocytic chronic reactions later.

Also, I have a question for you. Do you have any information on the time span between vaccination and onset of clinical symptoms?

DR. GHERARDI: Yes. This will be in the second part of the presentation.

DR. BRENNER: Thank you.

DR. GELLIN: Bruce Gellin from Vanderbilt University.

A pathophysiologic question. You showed that not all the patients had elevated CPK's. I thought you demonstrated that this was going on outside of the muscle cell. Therefore, why would anybody -- why would you get any CPK involved even in those?

DR. GHERARDI: I do not know. I do not know but you must know that the counterpart of increased CK levels is absolutely unclear because you can have leakage of CK in the muscle cells that appear virtually normal by optic microscopy.

DR. BRAUN: Miles Braun, FDA.

The vaccines that you described with aluminum being injected in adults and their having this problem that you are linking to it, presumably they had aluminum containing vaccines earlier. For example, tetanus in their lives. What did they -- were they asked about what their experiences were in the past with aluminum containing vaccines?

DR. GHERARDI: About clinical symptoms? We shall speak of clinical symptoms in a minute but as you saw there was not a strict correlation between hepatitis B virus and detection of the lesion and it is also the case for the clinical symptoms, and the

lesion appeared really due to aluminum containing vaccines that included mainly hepatitis B virus vaccine but also some patients that we are sure were vaccinated with tetanus toxoid only.

So concerning the lesion, the lesion can be induced by any aluminum containing vaccine with or without hepatitis B virus antigen in it.

DR. BRAUN: Let me rephrase that and to give an example if you had say a 40 year old health care worker who got hepatitis B vaccine and then was diagnosed with this problem.

There must have been among those some or maybe even a majority of them who say got tetanus -- aluminum containing vaccines prior to that when they were ten years old or younger and so they -- presumably some of them or maybe many of them have had exposures in the same way with aluminum containing products.

DR. GHERARDI: Yes.

DR. BRAUN: And, you know, what was the experience?

DR. GHERARDI: There are two -- finally two questions. Aluminum containing vaccines are used from the 20's and it is very surprising that they were detected from '93 only in France, and this is very unclear to me why is it the case because we used to perform deltoid muscle biopsy for 100 years in

France and we detected the first case in '93. So this is a problem. I have maybe two explanations to answer this.

First is that the vaccination program for hepatitis B virus reached levels that were never achieved previously in France in adults.

You must know that 17 million doses of hepatitis B virus vaccine have been provided in the '90s in France and our population is 60 million people. So there was a very, very strong and very large immunization program in adults, which is a very new thing, and probably the MMF story is a marginal problem affecting, you see, less than 100 persons among millions of people that have been vaccinated.

So possibly it was necessary to have a huge number of patients vaccinated to have by chance the lesion at the muscle biopsy retrieved.

And, second, as to whether people immunized previously with aluminum containing vaccine, whether they had or not symptoms related to that, I would say that we have not this feeling and that as you saw, our patients were mainly adults, and we have -- we had very little -- a very little number of kids.

And in France, as in other countries, kids are extensively vaccinated so it appears that the symptoms that lead to the muscle biopsy are usually

occurring in adult age and do not occur in youngest people.

So it is not excluded that the same persons, individuals that are vaccinated early in their lives do not develop anything, and when vaccinated for another antigen at adulthood developed symptoms that I will speak about in a minute.

DR. CENTENO: This should be the last question before we move to the next talk.

DR. CASERTA: Vito Caserta, Vaccine Injury Compensation Program.

Dr. Gherardi, have you done or plan to do biopsies on normal people without myalgia and arthralgia who receive aluminum vaccines to see if the same accumulation of aluminum occurs in macrophages in people who are not ill?

DR. GHERARDI: This is a very important point. Unfortunately, it is very difficult and an unethical point of view to propose this in France at the moment.

Healthy individuals vaccinated, I am absolutely sure that it will be impossible to perform surgical muscle biopsy in these individuals.

What I can say is that we started a prospective study in my lab from the beginning of the year studying all patients undergoing a deltoid muscle biopsy for any reason who have been vaccinated

and we collected 40 individuals vaccinated for hepatitis B virus in the same times as the MMF patients I presented who had no lesions in their deltoid muscle in the non-dominant arm because we use to perform this in the non-dominant arm as practitioner use to perform the immunization injection.

So it is the only thing I can say. All people vaccinated do not have evidence of the granuloma in their deltoid muscle biopsy.

DR. CENTENO: Again thank you, Dr. Gherardi, for a very interesting talk.

(Applause.)

DR. CENTENO: The next presentation of this morning is going to be by Dr. Verdier and Dr. Verdier is going to talk about the nonclinical studies.

Dr. Verdier?

NON CLINICAL SAFETY STUDIES WITH ALUMINUM HYDROXIDE: EXISTING ANIMAL STUDIES AND FUTURE PROTOCOLS

FRANCOIS VERDIER

DR. VERDIER: Thank you, Mr. Chairman.

Thank you, Dr. Myers, for this invitation.

During the next 30 minutes we will try to see if existing animal studies and possibly future protocols can help us to explain this MMF issue and

confirm or not the link or potential link between these lesions and the aluminum hydroxide.

(Slide.)

So I will divide my talk in two parts. In the first part we will see if current animal data can give us some clue, some explanation regarding this macrophagic myofascitis. And in the second part of my talk I will share with you some protocols that we intend to perform in order to explain the potential link and to confirm or not some of the hypothesis related to the MMF issue.

(Slide.)

In order to better define the outcomes of these experimental studies I have tried to summarize the MMF issue and to clearly define the different entities involved in this problem.

First, I have identified two distant things. One is the aluminum contained in the vaccines, aluminum hydroxide or aluminum phosphate, as an adjuvant. And the potential link between this aluminum and the local histopathological reaction as it was described by Dr. Gherardi.

So the first hypothesis is could aluminum hydroxide as the vaccine adjuvant trigger a focal but persistent inflammatory reaction, a very local reaction in the muscle.

Then, and I clearly make a distinction between this first link and the second link. The second link is the possible relationship between this local reaction and the systemic disease, which will be probably better described in the next talk by Dr. Gherardi.

(Slide.)

And the hypothesis is could this local reaction evolve in a systemic muscular disease with myalgia, with marked fatigue.

There is also a third way to consider the situation. Instead of starting from the local reaction, instead of starting from the vaccine injection, we can start from the systemic disease with the following hypothesis: Can idiopathic disease -- an existing disease could lead to the MMF reaction? So this systemic disease would exist de novo or preexisting before the vaccine injection.

(Slide.)

So, first, we will look at some existing animal data and I will present some data from a local tolerance study performed in rabbits using the IM route, using the intramuscular route, and with aluminum hydroxide.

In fact, the purpose of this study was not to study the MMF problem. The purpose of this study was to compare values, adjuvants and performing a

local tolerance study as it is requested by regulatory guidelines.

(Slide.)

So for this study we used 20 rabbits per groups. We had two groups. One receiving the adjuvant alone and another group receiving vaccine adjuvanted with aluminum hydroxide. The dose used was quite a high dose. It was one human dose per injection and we did four injection sites per rabbit.

And several necropsy time points were performed, some very rapidly after the injection. I mean, two days, seven days after the injection, and the last time points were performed 90 days after the single injection.

(Slide.)

The parameters evaluated in this study was toxicological parameters but today we will focus mainly on the examination of the injection site and I will show you some staining similar to the technique used by Dr. Gherardi on human samples. I will show you some staining and also some immunohistochemistry staining.

(Slide.)

We will try to shift to some slides and just to explain that I will first show the slides with the adjuvant alone and then with the adjuvant plus the vaccine. I have selected three time points, three

key time points. The first time point after injection. I mean, two days after the injection. Eight days after the injection and 90 days after the injection.

(Slide.)

Okay. So this is a picture obtained with the adjuvant alone two days after the injection and you can already see this exogenous deposit between the muscular fibers. It is a sort of amorphus gel which is between these intact muscular fibers. There are not a lot of cells in it at this stage.

(Slide.)

This is a lower magnification and you can see here the muscular fibers.

(Slide.)

This is now with an adjuvated vaccine. You can still see the deposits here between the muscular fibers but with already more cell infiltrations.

(Slide.)

This is the same time point but with a higher magnification with -- you can still here the exogenous deposit with already beginning of cell infiltration, mainly polymorphonuclear cells.

(Slide.)

This is two days after the injection. Now we will go --

(Slide.)

-- to eight days after the injection. The first set of slides with the adjuvant alone and you can still see this deposit but now we have a macrophagic reabsorption of this deposit. A lot of macrophages are cleaning this deposit but still we have the intact muscular fibers.

(Slide.)

Higher magnification. You can see all these macrophages cleaning the deposit.

(Slide.)

The same time point, adjuvant alone. All these large macrophages.

(Slide.)

And now a big difference. This is the adjuvated vaccine. And we have still the exogenous deposit. We have perhaps some fibroblasts here and we have no clear inflammation reaction with infiltration between the muscular fibers.

(Slide.)

So there is a big and marked difference between the adjuvant alone and now the picture obtained with the adjuvated vaccine. And you can see that this kind of picture is in some point close to the picture shown by Dr. Gherardi before but here we do not have only macrophages. We have polymorphonuclear cells, lymphocytes and histiocyte.

(Slide.)

That is a higher magnification and you can see that it is a mixed cell infiltration with various cell types.

(Slide.)

Now I will go to the last time point, 90 days after the single injection.

(Slide.)

With the adjuvant alone we were able to still see some macrophages continuing the reabsorption of the deposit so it is 90 days after the single injection and we have this large giant cell -- giant macrophage cleaning the deposit.

And, interestingly, if now we compare with the adjuvated vaccine, we have a picture. No more inflammation reaction between the muscular fibers, no cell infiltration but still in some of the injection sites, not in all injection sites we have this macrophagic reabsorption that we can observe.

(Slide.)

Briefly, I will show you some of the immunohistochemistry staining. This is a CD68 staining and you can see here that we have a positive staining in the macrophagic -- of the macrophage for the adjuvant alone.

(Slide.)

It is perhaps better here with a higher magnification. So we have with CD68 staining similar

to the human situation but this is with the adjuvant alone and it is only limited to this deposit.

(Slide.)

With the adjuvated vaccine we have also a CD68 staining so there are some macrophages in this cell infiltration.

So now we will try to go back perhaps to --

(Slide.)

Could we perhaps just reduce a little bit? Okay.

So to summarize these data we can see that there is two clear. The picture obtained with the adjuvant alone, and this is mainly a macrophagic reaction with different stage, and the picture obtained with the adjuvated vaccine, and in this case we have a multi-steps reaction with first some polymorphonuclear infiltration and then a mixed reaction with also some lymphocytes and some histiocyte, and then it is only 90 days after the injection when we can compare the two reactions and in this case we have some few sites with macrophagic reabsorption.

(Slide.)

So at the conclusion to these existing animal data we can see that there is a clear difference between the reaction observed with the adjuvant alone and the reaction observed with the

adjuvant plus the antigens. So this indicates that, in the first, we have to consider the combination of the adjuvant plus the antigen. And, also, we have only a partial reversibility of the reaction. We are still able to detect some macrophages in some injection sites 90 days after the injection. And fortunately we do not have the time to perform some electronic microscoping to see if there are also some still aluminum hydroxide spicules in these macrophages.

(Slide.)

So we have mainly the inflammation -- the inflammatory picture is mainly observed a few weeks after the injection but it is not exactly a true MMF situation. The inflammation is mainly marked between the muscular fibers and not only in the muscle fascia, and also it is not only macrophage inflammation. We have several cell types.

Three months after the injection, we have only some remaining macrophage but without cell infiltration as it was noted in the human biopsy.

(Slide.)

So at the conclusion from these animal studies we can say that the adjuvated vaccine can trigger an inflammation reaction which is close to an MMF picture but not identical.

(Slide.)

So now in the second part of my presentation I will share with you some protocols designed to confirm or not the hypothesis presented at the beginning of my talk.

(Slide.)

We propose to do two kinds of experiments. One is to evaluate the kinetics of the aluminum salt in the muscle of laboratory animals.

(Slide.)

The purpose of this first experiment is mainly to extend the vary interesting work presented yesterday by Dr. Hem and Dr. Flarend. As I mentioned yesterday, we do not have exactly the clearance of the aluminum in the injection site. We do not have the muscle content several weeks after intramuscular injection. And we need as for all components of a new -- of a pharmaceutical, we need to document the pharmacokinetics of the aluminum at the injection site.

(Slide.)

We propose to use ICPMS technic to measure the aluminum content. It is perhaps not as clean as the aluminum 26 technique but it is probably easier. And we want also to use different dose label and probably a dose label lower than one human dose per animal because it could be more relevant to compare a

small dose labeled in a small muscle rather than a huge human dose in a small animal muscle.

We are still thinking about analyzing all the muscles or only the aluminum content in the lesion area.

(Slide.)

The other study is an in vitro study in order to document the macrophage reaction, the reaction of human macrophages exposed to aluminum salt.

(Slide.)

And this study will be divided in two parts. In the first part we have decided to select some relevant endpoints in order to evaluate the phagocytic and the oxidative activity of the macrophages. Also, we will screen various markers and various cytokines or cytokine receptors.

(Slide.)

This work is a multi-lab collaborative work. The expert of this work is Dr. Anne Cecile Rimaniol who is working with CEA near Paris. And the GERM MAD group will provide us some samples from MMF patients in order to study these macrophages. And, also, it is a collaboration with Aventis Pasteur.

(Slide.)

The method used will -- can be divided in these three steps. We will collect blood monocytes

from human people and we will start a culture of these cells in order to get macrophages -- differentiated macrophages after seven days of culture. And then after roughly ten days of culture we will be able to expose these macrophages to various adjuvants for various durations.

(Slide.)

The parameters which will be screened in this first phase are as follows: We will investigate the phagocytic activity using a phalloidin -- a labeled phalloidin. We will measure the oxidative burst by glutathione assay in the macrophages.

(Slide.)

As I mentioned before, we will also perform using a flow cytometry apparatus various membrane marker evaluation, particularly the transferrin receptor, which is involved in the aluminum transport, and also some activation marker and some phagocytosis receptors.

(Slide.)

Also, we will measure cytokine release in the supernatant of the cell culture. Particularly we are interested, and I do not know if Dr. Gherardi -- Romain Gherardi will speak about IL-1 and IL-1 receptor because these cytokine and cytokine receptors have been found in some MMF patients. So we want to try to correlate some of the clinical

findings to these in vitro experiments.

(Slide.)

So then we will be able from this first phase to select some relevant endpoints and using only these relevant endpoints we will compare the reaction of aluminum hydroxide versus aluminum phosphate on these macrophages in vitro. We will also compare the reaction of the macrophages in contact with aluminum adjuvant alone or aluminum plus the vaccine.

And probably the more interesting part of this study will be to compare the reaction of the macrophages obtained either from healthy donors or from MMF patients. And the GERM MAD group will supply sample from approximately 30 MMF patients.

(Slide.)

So this study is scheduled to start during the next weeks and we plan to do this during approximately one year.

(Slide.)

So as a conclusion you can see that the existing animal data and also the future protocol will be not able to definitively solve this MMF issue. It is a complex mechanism. I think that it is only by having not only the in vitro study results, also perhaps some pharmacokinetics data from aluminum adjuvated vaccine.

And also one point that I have not presented today, some data from epidemiological studies that we will be able to give a conclusion or some explanations to this MMF issue.

Thank you very much.

(Applause.)

DR. CENTENO: Thank you, Dr. Verdier.

This paper is open for questions.

DR. GHERARDI: One very important point of the study of Dr. Verdier is that 14 of the 16 injected sites in the rabbit were free of macrophages at day 91. I am true?

DR. VERDIER: Yes. Only two among 16. We were able to find some macrophages only two among 16 sites investigated after 90 days.

DR. GHERARDI: Okay. This is a very important point because the residence time of the lesion at present is unknown in humans and even in animals. So if this is substantiated in the future this will be a very important issue because the question is, is it normal to get the lesion into the muscle after vaccination. I should say yes, early after vaccination but probably not remote from the vaccination time.

What will be most important to determine is the time after which it becomes un-normal (sic) to have a persistent lesion in the muscle.

DR. VERDIER: Just a comment. There is perhaps a difficulty to detect a lesion a long time after the injection, particularly in animals and perhaps even more difficult in humans because we do not know exactly if we have investigated -- if we have looked exactly at the injection site.

The muscle is not -- we cannot exactly identify the injection site several months after the injection.

DR. GHERARDI: There is a problem of sampling, of course, but you have not such a problem at day 21 or so on. At day 21 you have 100 percent of the cells that are positive for macrophages.

DR. GARCON-JOHNSON:N Nathalie Garcon-Johnson, SmithKline Beecham. I have two questions actually. From the data that I have seen in human and from the suggestion we hear so far, I mean there is a possibility that the effect you are seeing could be a cumulative one. So my question is in your study did you do any dose ranging of aluminum or just you injected a bolus of aluminum in the animals and looked at the effect?

DR. VERDIER: No, we did not test several dose levels. We only tested the one human dose per injection and one single injection. We did not do repeated administration. We have other data that I did not present today in other animal species. In

I have only investigated the reaction from some days after the injection to two weeks after the injection. I did not go up to three months with emulsion so I cannot really compare both adjuvants.

DR. BRENNER: I would make just a couple of comments. Number one, several years ago -- I think again it was in 1982 -- a study was done comparing alum precipitated tetanus toxoid and alum alone showing the presence of alum in macrophages in a small infiltrate at 20 weeks.

The second thing is that there have been studies done comparing multiple adjuvants in the past, including mineral oil, which is far more toxic than any of the alum -- either absorption adjuvants or precipitating adjuvants.

So I was just wondering if these things are not just -- are we looking at a local irritation? Are we looking at inflammatory process? Are we looking at immunoinflammatory process?

DR. VERDIER: It seems that with the adjuvated vaccine we have not only an inflammatory reaction because we have lymphocyte infiltrations so I think it is a -- I do not know if it is a good word or not. It is an immunoinflammatory process because we have the implication of lymphocyte.

DR. BRENNER: My question -- my thought is this: Are we looking at a necessary part of vaccine

response? In other words, if aluminum compounds alone can elicit an infiltrative process for a short period of time that looks very similar to the lesion that we see in MMF and a much longer lesion and a much more intense lesion when the actual antigen is added, isn't this really just part of what needs to happen in order to mount an antibody response to the antigen itself?

DR. VERDIER: I fully agree with you.

DR. BRENNER: And if that is true shouldn't this be occurring in everybody who gets vaccine?

DR. VERDIER: We have been able to reproduce this inflammatory reaction in all rabbits so we can expect that in all humans vaccinated with an aluminum adjuvated vaccine we will observe this immunoinflammatory reaction a few weeks after the injection. We expect to have this inflammatory reaction.

DR. BRENNER: Right. Then why call it an illness? If this is an expected -- that is my only point. If this is an expected response, if this is what is supposed to happen, how do we correlate it all of a sudden with a clinical syndrome?

DR. VERDIER: That is why I started my presentation with a clear distinction between the MMF as a local reaction, MMF macrophagic myofascitis is a name given to a histopathological picture, and then

there is another entity, which is the clinical symptoms, and I think that in the discussion we need to have today is clearly to analyze the potential link between the adjuvated vaccine and the local histopathological reaction, which is not an illness, and the other hypothetical link between this picture in the muscle and the clinical symptoms. But it is clear -- in my mind I make a distinction between the two hypothesis as I presented in the beginning of my presentation.

DR. BRENNER: Thank you.

DR. PERCY: I am Maire Percy from the University of Toronto. I have a question about your proposed human studies.

DR. VERDIER: Yes.

DR. PERCY: Are you planning to look at genetic markers in your controls and MMF cases or not?

DR. VERDIER: No, but I would be very interested if you have suggestions.

DR. PERCY: I mean, I am particularly -- I am wondering if it would be worthwhile looking at markers of a hereditary hemochromatosis mutation because these greatly increase the sort of transfer of iron into cells and via transferrin and transferrin receptors.

DR. VERDIER: Yes.

DR. PERCY: And aluminum also binds to transferrin so I am just wondering whether there might be some association.

DR. VERDIER: Yes.

DR. PERCY: Anyway I would love to hear that.

DR. VERDIER: Yes, we would be perhaps interested to do that particularly to see if with the clinical symptoms we have a special background.

DR. PERCY: Yes. That is interesting.

Another thing I just wanted to mention, just in my discussions with clinicians or clinicians at the University of Toronto, I am aware of a couple of bizarre cases where people have presented -- I do not know if there is any relationship with MMF but a patient has presented with something that was ALS-like and the diagnosis that they ended up with was transverse myelitis and it appeared to be associated or it was exacerbated after, I think, a flu shot. I do not know whether this had aluminum in it or not.

DR. VERDIER: There are no aluminum in flu vaccine.

DR. PERCY: Okay. Yes. But anyway -- but the people -- a couple of people that had this had sort of a chronic brucellosis infection. It may have absolutely no relevance but it was -- but they

thought there was some sort of bizarre autoimmune response that was connected with, you know, this chronic infection and the immunization.

Anyway, I just thought I would mention that.

DR. VERDIER: Thank you.

DR. CENTENO: Two more very brief and quick questions, please.

DR. KEITH: Sam Keith, ATSDR.

I was wondering if you have an idea of how far this macrophagic action extends beyond the three-dimensional point of the injection. I recall my daughter got her last flu shot, the physician injected, turned around and got a bandaid and fully placed the bandaid at least two centimeters away from the injection site so I can identify that it is very, very difficult to identify where the precise injection site is on the surface plus, you know, the direction of the needle injection, where actually it was injected into the muscle itself.

So when looking at healthy individuals that have received injections, I think it may be useful to understand how far this macrophagic action extends beyond the three-dimensional point within the muscle to see how closely one needs to understand and map the location on the healthy humans that may be studied.

DR. VERDIER: In this study we did not try to look if we have lesions around the injection site. We were -- it was the opposite. We were trying to identify exactly the injection site to be able to detect perhaps some remaining macrophages or remaining inflammation. But I agree with you that it would be interesting to perform one injection site and to investigate how far from this injection site we can still find some inflammation markers.

DR. HENDRICKX: Bernadette Hendrickx, SmithKline Beecham. No question but an information.

We are performing a huge animal study where we compare at long term up to one year follow-up ten different groups and we compare placebo, we compare the antigen, the adjuvanted antigen at different dosages with the adjuvant and we compare also two different adjuvants, hydroxide aluminum and phosphate aluminum.

Obviously the results are not yet available but we will have some interim reports and we will inform as soon as possible.

DR. VERDIER: Thank you.

DR. HENDRICKX: Rats.

DR. CENTENO: Thank you. Thank you, Dr. Verdier, for a very interesting talk.

(Applause.)

DR. CENTENO: We have come to the last talk of this morning's session and it is going to be again Dr. Gherardi with human data on MMF.

HUMAN CLINICAL DATA ON MMF

ROMAIN GHERARDI

DR. GHERARDI: So if I understand, everybody is prepared to accept that the lesion is due to the vaccine but could be reluctant to accept that these people have a disease.

(Slide.)

We have the same problem and we tried to addressed this question by designing a study with three centers and we first tried to assess if the prevalence of myalgia in people with MMF lesions were similar or different from that of other patients undergoing deltoid muscle biopsy without lesions.

So we collected patients from '93 to August '99 and the data extraction was presence or absence of MMF lesions and myalgias -- absence of myalgias noted in the files, this is important, at time of biopsy.

(Slide.)

Here are the results. Six patients were observed from '93 to '96 and 40 from '97 to '99 in these three participating centers. As you can see here, myalgias were present in 85 percent of MMF

patients as assessed by the files and in 45 patients of MMF negative patients.

Using the Fischer's exact test the association between the presence of myalgias and the presence of MMF lesion in the deltoid muscle was very, very significant. This is a very important point.

Of course, I have no idea of the proportion of patients that have been vaccinated in this group but you must know -- you must remember that 20 percent of the adult French population is seropositive for HBV serology.

(Slide.)

Then we moved to the extraction in the 50 patients I told you about previously and by a re-evaluation of all of these patients we found that 94 percent instead of the 85, when only the files at time of biopsy were examined, had experienced myalgias. And 98 percent of them had their myalgias beginning after the last immunization. The delay were somewhat variable with median delay of 11 months, which is an important delay. Thirty percent of patients had their first myalgias within three months after the last immunization. Sixty-one within one year and 80 percent within two years.

As you remember, the muscle biopsy was performed with a median time of three years after the immunization.

(Slide.)

So what were (sic) these myalgias looked like? This was performed by the French Ministry of Health. They wanted to have clinical information on the symptoms of MMF patients so they performed in-depth interviews of 40 patients, 40 of the 50 first patients or 60 first patients.

(Slide.)

They found 19 men, 21 women, the age at date of onset was seven to 69 years with a mean of 42 years. And, importantly, 69 percent were aged 40 or more at onset of symptoms.

(Slide.)

Interestingly, the date of onset of symptoms peaked in '97 even if the biopsy was performed either in '97, '98 or '99.

(Slide.)

At onset of the systemic disease here are the symptoms. Myalgia and fatigue in 37.5 percent. Myalgia alone, both groups included 65 percent of patients with myalgias as first symptoms. Fatigue alone in 25 percent. And other, ten percent.

And when the type of myalgia was assessed, this is very important, it appeared that these

myalgias used to begin in lower limbs, and especially in legs and calves. Another point very important was that these myalgias were symmetrical and bilateral and symmetrical. So the picture is one of myalgias that begin in calves and legs.

(Slide.)

At time of biopsy the myalgia and fatigue accounted for 60 percent of people. Myalgia alone for 15 percent. Fatigue alone, 20. And here again the myalgias predominated in lower limbs although most patients had diffuse myalgia at the time of the biopsy.

So you must understand that these people have a stereotypical picture on the clinical point of view that includes myalgias beginning in calves and progressively going up and becoming diffuse.

(Slide.)

So, finally, an overall of 82.5 percent of people with MMF in the deltoid muscle biopsy had myalgias previously to the deltoid muscle biopsy.

What was the impact of the myalgic syndrome? As you can see here, 85 percent of these people were disabled. These are only at efforts or most usually for light or even basic activities. So these myalgias were stereotypical as regard with their progression and were more or less debilitating in most patients.

(Slide.)

A very interesting finding is that there is a noninvasive procedure that may help to assess MMF. This is the gallium scintigraphy. We first used the gallium scintigraphy to assess a diffuse picture, clinical picture. We first sought to represent a type of granulomatous myopathy rather similar to sarcoidosis. And we used gallium scintigraphy because gallium binds transferrin receptor, CD71.

And we made the following study: We included 12 consecutive MMF patients and we used as controls ten normal people, ten polymyositis, ten sarcoidosis, and eight patients with the so-called fibromyalgia that met the criteria for the American College of Rheumatology. You must know these symptoms which is poorly defined as a disease but which can be recognized easily by a number of tender points at the muscle insertions.

And scintigraphy was performed using the standard procedure.

(Slide.)

First controls. Fibromyalgic patients had no gallium uptake at all. Sarcoidosis, as expected, had nodular gallium uptake in muscle and fascias were always spared. When there was articular uptake it was of a nodular synovial type.

And in polymyositis there was an autoheterogeneous uptake that was usually sparing the fascias but not constantly.

(Slide.)

Now the MMF patients. Clinically the patient included in the scintigraphic study had, as usual, myalgias in lower limbs, mainly in calves, in 11 of the 12 patients. They also had marked fatigue and importantly none of them had the typical fibromyalgic tender points. Mild elevation of CK was observed in half of patients as in the -- as usual in MMF.

The important thing is that the gallium uptake was globally higher in MMF than in normal controls and there was a very particular -- a very special gallium uptake in the muscle that appeared as linear uptake bordering the fascias, which was very closely related to the location of myalgias.

As you can see here, the gallium uptake was much higher in lower limbs than in upper limbs and there was a very good correlation between the gallium uptake and the location of the myalgias.

In joints there was also a predominance for the large joints in the lower limbs than in the upper limbs.

Now pictures.

(Slide.)

This is a typical picture of MMF.

(Slide.)

And as you can see here what is characteristic is this type of linear uptake with periarticular uptake.

(Slide.)

Here another with this diffuse linear positivity.

(Slide.)

And at upper limbs there were mainly positivities around fascias -- around articulations.

So I am not a scintigrapher but the best French scintigrapher was involved in this study and the pictures were evaluated blindfolded diagnosis by two experts in scintigraphy and they are absolutely convinced that this picture is something that they do (sic) not used to see.

(Slide.)

So this is the point on myalgia. These myalgias are characteristic. We can recognize the patients because they -- all of them or most of them have the same story to provide to us with beginning in the lower limbs and going up and persisting for months or years.

(Slide.)

Now, as you saw, these patients also had fatigue and we were interested because in the past

there have been some association between immunization and chronic fatigue syndrome, to see whether our patients met or not the standard or international criteria for chronic fatigue syndrome.

There are two criterias for chronic fatigue syndrome. The CDC criteria include unexplained fatigue for more than six months, of new onset not alleviated by rest with substantial reduction of activity, and at least four other symptoms that include tender lymph nodes, myalgias, arthralgias, headaches, memory impairment, unrefreshing sleep, and post-exertional malaise existing for 94 hours.

And there are criteria for exclusion, any type of psychosis but not uncomplicated depression, substance misuse or alcoholism, and obesity or anorexia or bulimia.

(Slide.)

There is another set of criteria used by the English people which is more simple. It is severe disabling fatigue for more than six months affecting physical or mental functioning present more than 50 percent of the time. Other symptoms may be present including mainly myalgia and sleep and mood disturbances. Exclusion criteria are similar to those of the CDC criteria.

(Slide.)

Now what was the fatigue setting in MMF patients? At the moment we have re-evaluated 30 of these people to assess fatigue. Ninety-three percent had fatigue for more than six months and 87 percent were disabled enough because of this fatigue.

When using the two criteria I showed you, about one-half of them met the criteria, the CDC criteria, and 40 percent the Oxford criteria.

So some of these patients meet the international criteria for chronic fatigue syndrome.

(Slide.)

So we also performed this assessment of possible chronic fatigue syndrome in these people because we wanted to have an idea to have -- to get further in physiopathologic explanation. And there have been a lot of investigators that felt that -- that feel that the chronic fatigue syndrome, which is usually post-infectious, as you must know, could represent an immunological problem that consists in the lack of switch off and immunologic activation subsequently to infection with protected immune stimulation with first a release of cytokines that you probably know induced myalgias, fatigue, arthralgias, and subsequently emergence of autoimmunity with autoreactive T and B cells.

So we tried to see whether we have evidence for cytokine release abnormalities or for autoimmunity in these people.

There were -- we -- it is a preliminary study in which 11 controls from my lab were used and 17 MMF people.

Two cytokines had -- were increased with significant values. The IL-1 receptor antagonist and the IL-6. You must know that IL-1 receptor antagonist is a very strong molecule as compared with the other IL-1 molecules, and when it is increased it assessed that the IL-1 system has been importantly activated.

(Slide.)

Three other cytokines were investigated. There was no difference for IL-1 data itself. There was a tendency that did not reach the significant value for TNF-alpha and there was also a tendency, less impressive, for GM-CSF.

So there is some evidence that these people do have some cytokine abnormal regulation.

(Slide.)

Second, we tried to assess the autoimmunity in these individuals by checking the circulating autoantibodies and we found at the moment with only the acetyl choline receptor antibodies that has not been performed at this moment that 50 percent of MMF

patients do have more or less subtle signs of autoimmunity.

The two main autoantibodies that were found were antinuclear antibodies in 30 percent of patients and antiphospholipid antibodies in 20 percent.

As you can see here, the titers were not very impressive but significant if I believe my immunologist. Other autoantibodies were rarely or not found.

(Slide.)

Finally, we looked at possible association with true autoimmunity -- overt autoimmune diseases. And we had 34 percent of the MMF patients having an autoimmune disease and impressively the most frequent one was multiple sclerosis. There were also DM, Hoshimoto's (?) arthritis and rheumatoid arthritis. Sorry for the mistake.

So maybe you will be interested in something about MS in these people and I can provide you with the sequence of events from immunization to detection of MMF in these individuals.

(Slide.)

Patient one, two, three, four, five, six, seven, here the delay before biopsy in years. And you have the biopsy is here. You have in black -- in black the CNS symptoms related to MS. You have in gray here under the line the myalgias. And you have

as arrows the injection time of the last of the known aluminum injections.

And, as you can see here, there was always an immunization preceding the MS appearance, and I should say that all these people had an MS meeting the international criteria for definite MS.

And as you can see here very intriguing feature which could be important in the clinical practice that all these patients with the exception of this one in which we have no -- in which the time of observation is very short or these patients had curious MS because of the presence of myalgias which are not usually observed in MS individuals.

So one thing which could be important if you have MS patients with myalgias, perform muscle biopsy in the deltoid.

So it is at the moment what I can say from our patients on the clinical point of view.

Thank you.

(Applause.)

DR. CENTENO: Thank you, Dr. Gherardi. This talk is open for questions and comments.

DR. CHEN: Bob Chen.

Romain, congratulations on a wonderful sequence of studies. I am trying to figure out one thing in my mind which may be a bit of a discrepancy. As you mentioned that a large number of French adults

are vaccinated and you only had 100 MMF cases, and then in the rabbit studies presented by Dr. Verdier they had MMF-like lesions but not quite and then in the rabbit studies you did was it all four out of the four developed MMF-like or MMF lesions that are identical to the human? How do they relate to Dr. Verdier's studies?

DR. GHERARDI: Yes. Usually we performed the injection in rats, not in rabbits, with a human HBV vaccine and the lesion evolved as initially strongly inflammatory lesion and progressively decreased in the number of lymphocytes and the appearance of macrophages with pictures that were strictly similar, strictly similar to the human MMF lesion at day 21 post-immunization, post-injection.

DR. CHEN: So I guess then the question would be that it would be interesting to follow these rats out longer to see how long --

DR. GELLIN: Exactly. Okay. We are just doing the job at the moment. I can tell you that at months four post-injection half of the animals are free of lesions.

DR. CHEN: Okay. So again trying to figure out --

DR. GELLIN: And we kept in series all the injected muscles so we cannot miss the thing if it was in it.

DR. CHEN: So in a sense -- again trying to address the species differences then. It seems like at least in rats there is a higher prevalence of MMF.

DR. GELLIN: So we addressed the question of a possible importance of the genetic background for removing the aluminum because there are marked and individual differences for the aluminum removal. And we found no differences among rats that were from the lowest strain, which is usually a good strain for inducing autoimmune diseases experimentally and the Sprague-Dawley rats that are normal rats.

DR. CHEN: And the second point is the -- I was very excited by the noninvasive gallium scan as a possible very specific diagnosis. I am curious has those findings been published in the radiology literature to see if others --

DR. GELLIN: Yes. It is in print in Arthritis and Rheumatism.

DR. GRABENSTEIN: John Grabenstein, U.S. Army.

Dr. Gherardi, one of your early slides in this second session or second piece was a two by two table of myalgias and the presence or absence of MMF.

DR. GELLIN: Yes.

DR. GRABENSTEIN: And you had 85 percent of the MMF positive cases reported myalgia.

DR. GELLIN: Myalgic, yes.

DR. GRABENSTEIN: From what population did the MMF negative people arise? Is that --

DR. GELLIN: Every people that underwent deltoid muscle biopsy in our labs. Whatever the reason was.

DR. GRABENSTEIN: And can you concisely describe --

DR. GELLIN: They had myopathies, they had research for mitochondrial disease, they had muscle dystrophies, they had inflammatory myopathies and so on.

DR. GRABENSTEIN: Okay. Good. And did -- towards the end you were presenting data on multiple sclerosis. Did you do a two by two table associated MMF plus or minus and MS plus or minus, with or without?

DR. GELLIN: In the same way?

DR. GRABENSTEIN: Yes.

DR. GELLIN: We did not do that.

DR. GRABENSTEIN: Thank you.

DR. BRAUN: Miles Braun, FDA.

Did you -- I saw you put up a case definition for chronic fatigue syndrome. Do you -- maybe I missed this but do you have a case definition? I mean, we are talking about MMF and -- did I miss that definition of -- because, you know, we are talking about an entity but just to make sure,

you know, other people know kind of who you are talking about and also if they wanted to replicate or study this.

DR. GELLIN: Since it has become clear now by the study performed by the French government, which is independently from us, detected what we see every week in our labs or in our clinical wards, these people have a very special myalgic presentation with these very special ascending myalgias. And if we have to coin a case definition it could and should involve this particular progression of the myalgias. Is that what you wanted me to answer?

DR. BRAUN: I think it could be helpful for -- well, I am an epidemiologist so, you know, we try to have case definitions. If you do not have a passive pneumonic sign or symptom, you know, like --

DR. GELLIN: Well, myalgias beginning in legs, fatigue, repetitive gallium scintigraphy, and presence of MMF in the deltoid muscle. And if you have this you are sure you are speaking of the same thing.

DR. BRAUN: So you would have to have this biopsy with -- you said -- I am sorry, presence of MMF in the biopsy?

DR. GELLIN: It is the hallmark of the disease.

DR. BRAUN: So, I mean, that is -- even if you define --

DR. GELLIN: I can comment on this if you want.

DR. BRAUN: Okay.

DR. GELLIN: We had some people that had the typical ascending myalgias and fatigue that had been vaccinated for hepatitis B and that had no MMF in the deltoid but these people had been vaccinated elsewhere. Usually in sites that were not available for biopsy.

So my feeling is that possibly we can even not take into account the muscle biopsy if we have the vaccination clearly present and the clinical picture completely clear.

Are you content with this?

DR. BRAUN: Well, I -- you do not have to convince me. So you are saying vaccination has to be part of -- precede MMF. So can you have MMF without vaccination?

DR. GELLIN: No. MMF without vaccination does not occur. 100 percent of our patients have been vaccinated. This is clear and there is no question about this. We must speak of MMF at the moment when we have the lesion and the lesion is definitely due to IM injection of aluminum containing vaccines. So the most simple way to be

sure that a patient has MMF is to get the lesion. If you have the lesion you are -- no, the question could be because it is possible to induce the lesion in animals that a patient with myalgias of other origin that has been recently vaccinated by hepatitis B could be found to have MMF lesions.

This can occur but you understood that our patients had their last injection with a median of 36 months, three years, and we have people with five, six, seven, eight years delay from the last injection to the MMF detection by biopsy.

So there are several lines of evidence indicating that the abnormality, the basic abnormality in these individuals is the persistence of the granuloma, which occurs in everybody that is injected but which should disappear within weeks or a few months. Okay.

DR. CENTENO: We should move on to the next very few quick questions.

DR. GERBER: Gerber, NIH.

In your first presentation I thought that you had said that many of these MMF patients had presented with a Whipple-like syndrome and, in fact, you showed us the results of some GI biopsies.

DR. GELLIN: Yes.

DR. GERBER: You did not tell us anything, though, about the GI symptoms in these patients?

DR. GELLIN: No GI symptoms.

DR. GERBER: They have no GI symptoms at all.

DR. GELLIN: No.

DR. PLESS: Robert Pless, CDC. If you can clarify perhaps why you have not been revisiting your MMF negative biopsy group, because a number of your controlled studies were done on normal controls and your scintigraphy study was done on just the MMF patients, and a subset of patients who have had other conditions but they all have features of -- but the myalgias are the ones that light up in a special way. Have you looked at the myalgias amongst your other biopsy specimens to see if they light up in a similar way before we establish --

DR. GELLIN: Yes. The study was exactly performed to assess that myalgias were -- was really more frequently observed in MMF patients than in non-MMF patients undergoing similar deltoid muscle biopsy in our labs. This was the case.

DR. PLESS: And how about myalgic patients amongst the 1,200 other biopsy specimens?

Are they -- are the features of their myalgias different than the MMF myalgias?

DR. GELLIN: Yes. The picture of ascending myalgias has not been described to my knowledge as a thing. Especially in fibromyalgia, our patients do

not have fibromyalgia. You understood that. And as far as I know, in chronic fatigue syndrome, such an ascending evolution of myalgias have not been reported.

DR. GELLIN: Bruce Gellin, Vanderbilt.

You have -- this is a story that has been evolving for eight or nine years. I imagine others -- other neurologists in other countries have heard this. Is there -- why is this a French phenomenon?

DR. GELLIN: Yes. Excellent question. I have two types of answers. First, there are many adults -- France is probably the only country in the world in which so many adults have been -- have received PRIMO vaccination for hepatitis B at adulthood. A very important number of adult patients have been vaccinated for the first time for hepatitis B virus in France in the mid '90s. This is probably one answer.

And the other one, which is maybe most troublesome for the U.S. people, is that for historical reasons we used to perform muscle biopsies in the deltoid muscle in France as a first choice site for biopsy. And in the U.S. and in many other parts in the world it has been said that the deltoid muscle biopsy should not be used as a site for biopsy. Ken Gangel (?) at the NIH for years said deltoid muscle biopsy is not convenient for

appropriate muscle investigation and you should perform biceps biopsy, triceps biopsy or even quadriceps biopsy.

So I am absolutely convinced that you have similar patients in the U.S. but that you do not detect them because of the biopsy procedure which is not -- which do not implicate the deltoid muscle biopsy.

DR. GELLIN: Well, given that, is it possible -- you had mentioned 100 years of deltoid biopsying in France. Is it possible to examine specimens from earlier --

DR. GELLIN: No, no. It is excluded that such a lesion which is very special, very particular, has escaped so many eyes -- competent eyes. We are absolutely sure in the Marseilles team, in my team, in the other team that this has not been seen previously. We are absolutely sure of this.

DR. GELLIN: Just one comment on your first response.

DR. GHERARDI: Yes.

DR. GELLIN: It would seem to me that health care workers around the world are a group of people who as adults would receive hepatitis B vaccine. Though there was -- I understand -- some kind of a campaign in France, that is a phenomenon that is larger than just that French experience.

DR. BRENNER: I have one comment. I think I can clarify something about the United States.

DR. GHERARDI: Yes.

DR. BRENNER: Most of our muscle biopsies -- I am a rheumatologist. I am not a neurologist but we do, do a lot of muscle biopsies on our own.

Most of our biopsies are EMG directed so that our usual procedure is to do a unilateral EMG and nerve conduction study and then do a contralateral muscle biopsy looking at the contralateral most involved muscle so that we do not end up with the issue of needle irritation of muscle to mistake that for any kind of an inflammatory response.

DR. GHERARDI: Exactly.

DR. BRENNER: So I think that is one of the reasons why the muscles that we use are directed in a different way.

DR. GHERARDI: Sure.

DR. BRENNER: I have one -- two questions, though.

One is experimentally similar lesions have been shown using other adjuvants. Mineral oil has been shown to have a similar inflammatory lesion in muscle, calcium phosphate has been shown to have a similar lesion in muscle. Calcium phosphate also produces foaming macrophages.

And if those things are true, and I believe they are, then why would this one particular entity produce a clinical syndrome when the other -- when the other lesions look pretty much the same at least in experimental animals?

My second -- and then I will go sit down -- is you mentioned that you gallium scans were globally increased in your MMF patients. And I just was curious to know what globally meant.

The gallium scan that you showed could just as easily have come from a rheumatoid patient. What I saw was increased uptake in the wrists and increased uptake in perimysial tissues, which you also can see in rheumatoid patients because there is, you know, there is sort of a perimyocytic inflammation sometimes.

DR. GHERARDI: Okay. I forget the first --

DR. BRENNER: The first had to do with similar lesions being produced --

DR. GHERARDI: Oh, yes. Yes. The very special point with aluminum hydroxide as demonstrated yesterday is that it appears to be an adjuvant that is very slowly eliminated as compared with many others and this may be why some people retain for a long period of time an adjuvant which has per se an immunoactivity (sic). So the persistence of an immunoactivator somewhere in the body for years can -

- why not -- possibly induce immune activation -- systemic immunoactivation at low levels with systemic cytokine, for instance, myalgias and so on.

What was the second question?

DR. BRENNER: (Not at microphone.) The second was what does global mean in terms of what your gallium scan showed?

DR. GHERARDI: Well, this was said to us by the scientific office that knows this more than I, the number of hits was higher than in the normal. So there was a higher number of transferrin receptors expressed in these people for unknown reasons.

DR. CENTENO: Last question?

DR. HALSEY: Neal Halsey. I think a number of us are concerned about the fact that you are finding these lesions only in the deltoid but yet there are symptoms that are associated with muscles elsewhere. The gallium scans that you are showing suggest there may be something in other muscles.

Have you gone to your MMF patients who do have symptoms and biopsied areas where the gallium scans are abnormal?

DR. GHERARDI: Yes.

DR. HALSEY: I thought I heard one of the earlier presenters saying that the other muscle biopsies elsewhere have not shown these lesions.

DR. GHERARDI: Yes. This is a very important point.

DR. HALSEY: I have a follow-up question.

DR. GHERARDI: Okay. It is a very important question. We did not perform a systematic evaluation of the remote muscle but we have some patients in which it was done and what is observed at sites that are painful and that demonstrate gallium uptake is subtle inflammatory infiltrates without macrophages.

So there appears to be there a type of immunopathologic reaction that does not meet usually the characteristic of polymyositis or the myoscities or even vasculitis. There are some lymphocytic infiltrates in the fascias as the sole abnormality in the regions that express pain and gallium uptake.

So there is something but it is not present very clearly defined as what it can be. And you must understand that the gallium uptake indicates the CD71 marker transferrin receptor is expressed and you must know that transferrin receptor binds transferrin and that aluminum is bound to transferrin as gallium is bound to transferrin.

So here may be something has to be understood but at present I did not understand nothing.

DR. HALSEY: Okay. The second point was that you have made the point it is very difficult to

get biopsies from normal individuals. But certainly it would be possible to get samples of muscle tissue post-mortem from individuals who have died from a whole variety of other disorders and that can be done in this country. It can be done in France, as well, I would assume.

And one could then -- you do not have the problem of finding exactly where the injection site is and I think a large study of people who are normal would be very beneficial and also knowing where and when they have received injections.

DR. CENTENO: I believe we should continue with the questions at the coffee break. We are -- we almost have only ten minutes for a coffee break. So we would like to -- if you could join me in thanking Dr. Gherardi and Dr. Verdier for a wonderful morning.

(Applause.)

(Whereupon, at 10:39 a.m., a break was taken.)

DR. MYERS: Well, I hate to break up the discussion groups that were informally working so hard over the coffee pot but I think it is time to reconvene.

We are going to have two panel discussions now to talk about the issues of what we know and what we do not know. The first panel, Dr. John Clements has agreed to chair. And we would ask his panel to

come forward and join him at the table up front, and that will be Dr. Gherardi, who must be exhausted by this point, Dr. Robert Pless from the CDC, Dr. Phil Pittman from USAMRIID, and Peggy Rennels from the University of Maryland.

PANEL DISCUSSION - WHAT WE KNOW

MODERATOR: JOHN CLEMENTS

DR. CLEMENTS: Good morning, everybody.

(Slide.)

I have been asked to moderate this first session and we are going to talk about what we know about aluminum adjuvants and the second group is going to talk about what we do not know.

Notice this is the A team so I presume the B team is playing next.

(Slide.)

I am just going to try and summarize as the first -- perhaps it is out of place of me as a moderator to do this but as I did the presentation on this area, I thought it appropriate for me just to outline some of the key points that I thought were very clear from my presentation, and particularly followed up by many other people.

So I think what we have -- we can clearly state about aluminum adjuvants in vaccines is that with some minor qualifications about the safety relating to introduction of the adjuvant into the

subcutaneous tissue by mistake instead of the intramuscular particularly, we have 70 years of safe and effective use of these vaccines. Not to 20 or 30 children but to hundreds of millions of them over the years. And this has saved millions of lives annually. The minor reactions are few and not serious.

There are not easy and obvious substitutes to aluminum adjuvants for DTP, hepatitis B vaccines that are the main consumers of this in global terms.

There are new vaccines and a new generation of vaccines coming up that will need new adjuvants but the existing vaccines, if they change the adjuvant for any reason, would need to be resubmitted for clinical trials for safety and efficacy and it would take a great deal of time to do that.

We are faced with a similar potential problem with thimerosal and we have dealt with that as well that if any new preservative were used, immense amounts of clinical trials would have to be repeated.

(Slide.)

Okay. I am going to pass on to the next member of the panel to just take you quickly through a few brief statements like that.

Who is doing toxicology? It is Robert.

DR. PLESS: Thank you. I was asked to address a little bit about toxicology and I am not a toxicologist so what I am proposing to do for the next couple of slides is just to give you a sense of my take on yesterday's discussion plus add a little bit more, and then sort of ask the audience to -- as I was trying to say I am not a toxicologist.

And so I have been asked to present this more from a perspective of what I have learned in the last little while and especially yesterday about the toxicology of aluminum and especially how it relates to vaccines, and then sort of leave it open to the audience to then challenge some of these notions and certainly move on the discussion to the next phase.

So if I can have the first bullet.

(Slide.)

I think we are pretty all clear that we are talking about exposure via the intramuscular route and what I found in reading the tox profile for aluminum as well as the tox profile for mercury, which as everyone is familiar with, the thimerosal story, is a similar challenge that were being posed, is that routes of exposure via injection are rarely addressed, and so we have some deficient data there.

(Slide.)

I also took the liberty of a back of the envelop calculation to look at the amount of aluminum

one is exposed to over the infant series in the first year. And that was certainly work done by Norman Baylor but I have kind of addressed it along the thimerosal lines.

So the birth "dose" of aluminum is about .24 milligrams and then at the two, four and six month injection visits there are between .4 and 1.1 milligrams per visit so about a total of 3.5 milligrams.

(Slide.)

And so if we extrapolate the way it was done for mercury over six months using the minimal risk levels, that permits for the average infant -- and I am weighing towards the premature infant somewhat and towards the female infant, and I am actually trying to remember what the growth curves were like because I did not have the file with me yesterday.

But I think we are looking at about 1.4 grams of allowable aluminum if we use the extrapolation of .2 milligrams per kilogram per day. So we are really dealing with a total dose of aluminum over the first six months of -- from vaccines that is much smaller than the dose that is "permitted" by MRL.

And if one recalls the mercury curves then -- well, first, as one recalls yesterday's curve that Sam Keith presented regarding the MRL and the boluses

from the first few injections, what he indicated was that perhaps on day one with perhaps a hepatitis B vaccine dose, the spike exceeds the MRL slightly or the -- it rises above, as well as I think it was the two month dose but essentially the aluminum curve from vaccines falls below the minimal risk levels.

Whereas, when we remember the mercury curves, they were kind of following along a little bit and also we had concerns that depending on the health guidance values used, the dose of mercury was exceeding some of the guidance values.

(Slide.)

And I also learned something yesterday from the bunny studies that there is both elimination and storage of aluminum following an injection and I was trying to become clear as to how much impact the initial storage of aluminum has on the curves that Sam Keith presented, and whether having some storage and some immediate elimination might actually make those peaks fall below the MRL but that is sort of up for discussion.

(Slide.)

So what is sort of my conclusion? I guess, I am having trouble seeing any potential for toxicity with vaccine level exposures to aluminum so I would sort of conclude that we are really dealing with the phenomenon of MMF of a lesion that is persistent at

an injection site and whether there is a clinical syndrome attached to that rather than any global concerns about the quantities of aluminum that are ingested from vaccination.

DR. CLEMENTS: Thank you. If you will allow me, we will run through the other quick summaries and then please make notes and we will come back and discuss them, and listen to your points and tell you why you are wrong.

(Laughter.)

DR. CLEMENTS: Romain, would you like to take the microphone?

(Slide.)

DR. GHERARDI: So the first thing that seems to be established is that MMF lesions are something that was not very -- rarely reported in the past and the MMF lesions may be regarded as an aluminum granuloma on the basis of constant detection of aluminum hydroxide crystals in these cells.

At the moment maybe we must preserve the idea that detection of aluminum crystals into cells is the hallmark of the lesion.

Second, it seems clear from studies from the type of the inclusion, the crystalline form of the inclusion, from the epidemiological survey and from animal studies, that the aluminum that is absorbed into cells in MMF lesions is derived from the

aluminum adjuvants used in TT, HBV and HAV vaccines. To me this is clear and definite.

Three, the patients in which such MMF lesions have been observed, or I should say a large majority of these patients have a clinical syndrome that is diffuse and include myalgias that have appeared to be rather -- and disabling fatigue which certainly appears subsequently to the last aluminum containing immunization in almost all of them.

At the moment it is exactly what we can be sure of.

Finally, and this is what we do not know, is that -- the relationship between the focal injection induced MMF lesion into the deltoid muscle and the systemic symptoms, what is the relationship between this focal lesion and systemic symptoms is, is at the moment unknown.

DR. CLEMENTS: Thank you. I think that was a rather precise clear description of what we do know. Thank you.

Okay. Phillip, would you like to take the floor?

DR. PITTMAN: Sure.

(Slide.)

This is a summary that Carl Alving and I actually came up with. Most of them are his

actually. The first that -- and this is -- this really concerns the immunology of adjuvants.

First, of course, is that their duty is to bring antigen into contact with the immune system. This was brought out fairly clearly during discussions the other day.

That it influences the type of immunity, that is whether we are discussing humoral, cellular or mucosal immunity in respect to whether antibodies are produced, CTL's or signatory IgA, et cetera.

(Slide.)

The adjuvants influence the quality of the immune response from the point of view of affinity, isotype and specificity.

It also influences the quality of the immune response in terms of -- the quantity that should be -- in terms of magnitude and duration.

And, of course, it may decrease toxicity of certain antigens. Some of us heard yesterday a good example of that is decreasing the toxicity of pertussis.

It may convert nonresponders to a responder status.

(Slide.)

And, finally, we are always worried about the stimulation of the appropriate -- of an appropriate immune response except for the case of

cancer vaccines and certain other exotic applications. We normally may not want to stimulate autoimmunity. We would like vaccines to be safe.

DR. CLEMENTS: Excuse me a minute. Okay. Thank you.

Finally, Peggy, would you like to take the microphone?

(Slide.)

DR. RENNELS: Regarding immediate local reactions following injections of aluminum absorbed vaccines, we know that when they are injected subcutaneously some severe -- some individuals will experience severe local reactions, including a lot of induration, erythema, pain.

We know that there is not a consistent relationship between the aluminum content of the vaccine and the rate of severe local reactions when the injection is given intramuscularly.

And that is all I know.

DR. CLEMENTS: All right. That is the panel team's response about what we think we have distilled out of the last day's discussions.

First, I will ask you if you disagree with anything and then I would ask you if you think that something that we should also include in here that we clearly do know and would contribute to our solid base of evidence. Okay.

So, first of all, do you have anything that you think you would like to correct?

DR. MUSIC: Stan Music, Merck.

Could we go back to the MMF slide? I want to talk about the third bullet on there, which essentially talks about a temporal relationship.

(Slide.)

Yes. Appearing subsequently to immunization. I want to point out that that does not imply cause and effect, that something that happens after immunization also happens after a lot of other things, and there are ways not yet demonstrated to determine cause and effect.

DR. CLEMENTS: Romain, do you want to comment on that?

DR. GHERARDI: Yes. It was -- the following sentence was intended to say.

DR. CLEMENTS: So we agree. Thank you.

DR. HALSEY: Neal Halsey. Just a couple of points to add to Robert Pless' and maybe -- I do not know that I really disagree but I think that the toxicologists still have some additional work to do in that we do not seem to have the information on the age related toxicity of aluminum and especially when we are dealing with very young infants.

A lot of the data have been generated from adults and we do not know whether or not there is a

difference in susceptibility by age as there are with other metals.

The second -- we did not hear what the other guidelines are and I do understand that there are some other guidelines with regard to exposure.

The third is again the issue of bolus doses versus intermittent and really we do not have information about how much is absorbed, how rapidly, and obviously not all of it is absorbed so the blood levels may not be what one projects.

So I think the toxicologists are not done and I do not think we can say that we know conclusively the answers to all of those points at this time but some of the information is out there and could be compiled in the report from this meeting.

The other issue is --

DR. CLEMENTS: That is the next panel discussion.

DR. HALSEY: -- Peggy, I wonder -- you did not mention the one statistically significant association between aluminum and the swelling, and I am trying to remind myself which one that was because you presented several different analyses, and whether you think there is anything to that or you think that is a chance association based upon multiple comparisons?

DR. RENNELS: Okay. The association that was significant was post-dose five, association with swelling greater than 50 millimeters. Obviously I do not know whether it is real or just chance association but the fact that it was not -- there was not a correlation with entire thigh swelling post-dose four or with post-dose four swelling greater than five centimeters makes me think it is statistical artifact.

DR. CASERTA: Vito Caserta from the Vaccine Compensation Program.

I have a question for Dr. Gherardi. I am a little bit confused about the actual composition of the crystals in the macrophages. I have a copy of an abstract where Dr. Gherardi's group describes 38 MMF cases and in that abstract he describes the salt as aluminum phosphate and today you have talked about aluminum hydroxide.

Which is it?

DR. GHERARDI: No. This is at the time when -- there is one picture that I did not show to you but some people in the room know the results. There was a co-localization of phosphorus and aluminum in macrophages when analyzed by microanalysis so at the moment I had the idea that it could represent aluminum phosphate. But now it is clear that the spicules are aluminum hydroxide and that it is only

abnormality and develop lesions after immunization but it is simply a marker of this underlying disease and not a cause of the disease.

Just comments. Thank you.

DR. CLEMENTS: Would you allow me to put causality not proven at this point? Just to underline a couple of comments.

DR. CASERTA: My concern is that once the literature is confusing to the courts about causality, the courts do not know how to deal with that and it creates a great deal of difficulty in terms of dealing with these types of cases in that arena.

So we have to be very, very careful with our language as we develop our ideas and as we develop our thinking with these new entities and I think prospectively published material needs to be absolutely clear on the causality issue because I think the previous material was not.

DR. CLEMENTS: Is that acceptable what I put at the bottom then? Causality and not demonstrated at this time?

DR. CASERTA: Yes.

DR. CLEMENTS: Please speak out if that is -- if you feel differently about that. That includes Romain.

DR. GHERARDI: It is a bit redundant with the fourth --

DR. CLEMENTS: I agree that is what you intended to say in the fourth one but I hear --

DR. GHERARDI: But if you prefer this formulation, we can completely remove the sentence four.

(Simultaneous discussion.)

DR. CLEMENTS: Who is writing this?

(Laughter.)

DR. GRABENSTEIN: John Grabenstein.

On the toxicology question. Robert, I have had enough toxicology to be dangerous and I just wanted to make sure when you calculated the 1.4 gram over six month value that you included an adjustment for the fact that the two milligrams per kilogram per day -- correct me if I am wrong -- was an oral exposure and needs to be reduced for systemic absorption.

DR. GHERARDI: I am really sorry but I did not understand a word of what you said.

(Laughter.)

DR. GRABENSTEIN: Yesterday the --

DR. CLEMENTS: It is a question for Robert.

DR. PLESS: It was early in the morning so I am going to start sweating in a few minutes and look back at my notes.

DR. CLEMENTS: We will come back to that and clarify it. Thank you for that.

Okay. We have -- Marty?

DR. MYERS: If we could go back to the MMF. I guess I would have some other things that I think we know. I would quibble on the third point and say reported patients because there may be other patients with MMF lesions and I know that is yet being redundant again. But I guess one of the things that we do know is that animals injected with aluminum hydroxide and an adjuvant develop very similar lesions very commonly and I think that is one of the things that we do know. We do not know about persistence over time.

DR. CLEMENTS: Give me a phrase that you think should be in there.

DR. MYERS: That animals injected with aluminum hydroxide and antigens commonly develop similar lesions to MMF.

DR. BRENNER: I would like to make that one a little more specific if I could. A question came up about the possibility of immunogenetic susceptibility which might be species specific or immune specific in people. I just want to point out that the animal studies have been done in Sprague-Dawley rats. They have been done in guinea pigs. They have been done in mice. They have been done in

swine. They have been done in all manner of animals and the lesions that turn up related to aluminum adjuvanted vaccines are the same. So I think that that would make it unlikely that this has any specific inheritable immunogenetic characteristic.

DR. CLEMENTS: Do you want anything added to that sentence?

DR. BRENNER: Yes. I would just like to say that -- in the first place I would like an "L" on the animal and in the second place --

DR. CLEMENTS: I am not going to do this again if I can --

(Laughter.)

DR. BRENNER: I just think that we just ought to make some statement about the fact that it is, you know, multiple -- many animal species have been shown to produce similar lesions under similar circumstances rather than just saying animals because the specifics are known.

DR. CLEMENTS: Okay. Help me with the wording later.

DR. BRENNER: Multiple animal models.

DR. _____: Multiple species.

DR. BRENNER: Yes. I like species.

DR. CLEMENTS: Sir?

DR. VERDIER: Yes. I would add another word to this sentence. I think in animal models the

inflammation reaction is a transient inflammation reaction. In the MMF situation it is -- this inflammation reaction can persist for several months, even perhaps several years. In the animal models the similar lesions -- I mean, the inflammatory reactions is only transient so I would perhaps add, if other people agree in this room, transient before or just after similar.

DR. BRENNER: Guinea pigs, you have the swine. The swine were carried out six months and they were sacrificed at that point. I cannot tell you longer than that. But these are very long-term experiments.

DR. VERDIER: But is it still inflammatory reaction or is it just some remaining macrophages?

DR. BRENNER: No. What I was saying -- that is what I was saying earlier is that they seem to convert from a lymphocytic granulomatous picture, which you did not see but I think you did not see because the patients that you studied are later, into the same kind of histiocytic sheet like reaction that you report in your patients. I think that is another important point.

DR. CLEMENTS: Sir?

DR. CASERTA: Vito Caserta from National Vaccine Compensation Program. I would add to that sentence, develop similar lesions without clinical

disease. So that it is clear that you are just speaking about the pathology.

DR. GHERARDI: You cannot say. How would you assess fatigue and myalgias in --

DR. CASERTA: Then I would say similar pathologic lesions. I would make it clear you are talking about the pathology and not about the systemic illness.

DR. CLEMENTS: Do you mind if I put an "al" on that?

(Laughter.)

DR. PERCY: Hi. Maire Percy from the University of Toronto again. I just would like to caution people that we are talking about sort of two things. And I mean this has been alluded to. There is the lesions and then there is the -- you know, the systemic clinical symptoms and I do not think we can dismiss genetics at this point even though we have seen the lesions in a lot of animals.

I mean one thing that caught my eye with -- one of the slides was the prevalence of possibly autoimmune problems in the people who have MMF so anyway I -- I mean, I come from a genetics background also.

DR. CLEMENTS: All right. I hear the comment. I think that comes under the category of what we do not know. We certainly have not heard

demonstrable proof that it is genetic yet, have we? So I certainly hear you loud and clear but I think it is in the next group.

Miles?

DR. BRAUN: You might want to put in the first bullet something about where the lesion were. I think the deltoid was -- because we talked about muscles all over the body but I do not think that is where the crystals --

DR. GHERARDI: Yes. Babies have the lesions in quadriceps but --

DR. BRAUN: So these are injections at the injection sites?

DR. GHERARDI: At the injection site but --

DR. BRAUN:: Maybe that is better than injection site lesion.

DR. CLEMENTS: Okay. We have dealt with trying to clarify what we think we do know. Are there any other issues that the floor would like to raise about what we have listed on the screen? In fact, when you do start to list it, it starts to look quite impressive and quite substantial, and I think it has been very helpful to hear the papers that have put the background to these -- what might appear to be quite simplistic statements but, in fact, have a very strong science behind them.

Okay. Panel, let's have a response from you now that you have been attacked.

DR. PLESS: Yes. I will certainly correct the toxicology slide. I think it is still two-and-a-half or two and a little bit times more than the back of the envelope calculation from the MRL.

DR. CLEMENTS: So subsequently you do not have a number to --

DR. PLESS: 8.8 milligrams in bullet three.

DR. CLEMENTS: Here?

DR. PLESS: Yes. My next back of the envelope, which I will continue to refine as I get the growth curves and stuff, is 8.8 milligrams.

DR. CLEMENTS: Is this where you mean?

DR. PLESS: Yes. Is that better? I mean, it is a big difference obviously.

DR. CLEMENTS: Okay. What size envelope did you have?

(Laughter.)

DR. PLESS: This one is slightly bigger than the last one but I will get an even bigger one when we get back before June 1st.

DR. CLEMENTS: Okay. I am going to -- I think we need an asterisks here to be confirmed or something, don't we?

Because I am sure, Marty, we can get this file copied and distributed if people want to take it away.

DR. MYERS: Absolutely. We will correct the spelling of aluminum.

(Laughter.)

DR. CLEMENTS: We did.

(Simultaneous discussion.)

DR. CLEMENTS: Have you ever tried writing on the board in front of a class?

Sir, another question?

DR. CASERTA: Vito Caserta. Can we go back to the MMF slide, please? I am still not happy with that pathological lesions bullet because again I am looking at it from the perspective of a judge and a judge might look at that and take that as proof that this is a real entity that is happening in people that is causing disease.

So I thought maybe taking out "pathological lesions" and replacing it with "histological" so that it is clear that you are talking about the histology because pathology could also mean clinical.

DR. CLEMENTS: Is that good?

DR. CASERTA: And if -- I mean if there is any way we could say something about the clinical picture, which I agree it is -- I do not think we

can. If someone could help me I would appreciate it. Thank you.

DR. CLEMENTS: Okay. Panel, any last shot at this before we call it a day and hand it over to the next group?

Miles?

DR. BRAUN: The thing about the patients with MMF lesions have -- it seems to me that the way this study was done, if I understand it right, it was actually the other way around. People with diffuse myalgias and fatigue appearing subsequent to immunization because those are the ones you started with, then they had the -- you found the lesions in them.

I think -- and -- it is kind of -- it could be read that the way it is written is patient -- you did not really survey people who had MMF lesions. You did not start with a survey to get a group of people with these lesions. You started with people who had sick. And somebody might -- although we heard the whole story and I think it is clear to people in the room as a stand alone it might -- it is really just reversing the order that might be a little more clear or less open to misinterpretation.

I do not know what the group thinks.

DR. GHERARDI: I am not sure I understand what you intend to say. Maybe it could be more

precise to say that it is not subsequent to any immunization but to aluminum immunization.

DR. BRAUN: The way I would suggest, and again I am -- patients with -- whatever you start with, the patients with diffuse myalgias and fatigue appearing subsequent to immunization had MMF lesions.

DR. GHERARDI: No. The story was not this way. It was exactly the reverse way. It has been done. We collected all patients with the lesion and we checked what they had as clinical symptoms. So it was exactly this way.

DR. BRAUN: But I think what was said in some of the comments that came from the group was to look at asymptomatic people and to screen people without symptoms. You said that was unethical to do in France and I think the way it is written there, somebody could infer that that was the approach that was used.

DR. GHERARDI: But we have no -- at the moment we have no evidence that people without symptoms have, indeed, this lesion in their muscle. It is extrapolated from animal studies but at the moment I cannot say that. Scientifically it cannot be said today.

DR. MYERS: That is why I suggested saying reported patients.

DR. CLEMENTS: Okay. I sense that we have come more or less around to this discussion. I think there is other opportunities to --

DR. GELLIN: Just one --

DR. CLEMENTS: Okay. -- other opportunities to have discussions in other areas. We will give Bruce the last word.

DR. GELLIN: Well, it is really following up on Miles' comment from earlier this morning of -- and this may fall somewhere between this panel and the next one. But should we be describing a preliminary case definition for this entity? Because if it is going to get into trying to see what survey -- how to do surveillance for this to try to determine whether or not it is elsewhere or what, and is that a role for us to come away with at this meeting?

DR. CLEMENTS: Can we say for the last one there is no final case definition at this point? As epidemiologists in the room, I feel, as well, that that is a vulnerable point.

DR. _____: (Not at microphone.) I am not sure everybody would agree.

DR. CLEMENTS: Okay. Mr. Chairman, I will hand this back over to you and if you like I will get the file to the secretaries for copying for people to have.

DR. MYERS: Excellent.

DR. CLEMENTS: Thank you.

(Applause.)

DR. MYERS: Well, that was, I would say, well done.

Our next panel discussion, which is really what w do not know, and we tried to focus them a little bit and say let's try and establish a research agenda. Dr. Dennis Murray from -- who is professor of pediatrics and human development at Michigan State University has agreed to moderate for us and the panel will consist of Michael Gerber from NIH, Alison Mawle from the CDC, Francois Verdier and Alan Brenner from Boston University.

PANEL DISCUSSION - WHAT WE DON'T KNOW: ESTABLISHING A RESEARCH AGENDA

MODERATOR: DENNIS MURRAY

DR. MURRAY: Okay. Well, because we are doing what we do not know, this is a much more difficult task and we are not going to show any -- unless one of the panel members has something that they are planning on showing, but I think it would be helpful to utilize some of the same areas that we have already talked about.

When I was thinking about this last night I was thinking that Dr. Hunter, who opened up this symposium, came up with a very interesting comment

and that was pervasive uncertainty and I certainly have felt that way through this conference.

I keep remembering back to some statements that we utilize in pediatric vaccine safety material all the time and for a vaccine to be useful its benefit must outweigh the risk of its use and so as a corollary, therefore, for a component of a vaccine to be useful as opposed for an adjuvant as a component, it should be -- its benefit should outweigh the risk of its use as well.

And I also want to mention about a paper that was done by Robert Edelman in 1980, which seems like a long time ago, 20 years, but as I have read that paper over and over, some of the same kinds of things at least help me frame a little bit of my thinking about some of this.

He came up with 13 issues regarding adjuvants and I just want to read five of them:

That an adjuvant's immunopotentiation should not be so excessive as to induce hypersensitivity responses in the host's own tissue.

That the adjuvant should not induce allergic hypersensitivity to itself or combined with natural serum antibodies to form immunocomplexes.

An adjuvant should act to potentiate the vaccine without inducing a diffuse array of

immunological events not involved in the immunospecific response.

That the adjuvant should be biodegradable, eliminated within weeks, months, from the body.

And then, finally, that there should be a low incidence of reactions if and when they occur and these must be acceptable.

That epidemiological studies must be designed to detect low incidence of phenomenon. And those of you who were at the combination vaccines meeting put on by the NIH in February will remember that this was a major point of discussion about the low incident reactions and perhaps that is one of the things that we may actually be dealing with here today, although as I totally agree with everyone else, I am not sure we have causality.

I would like to give the panel members a chance to make specific comments about what we do not know. It would be helpful, I think, panel members, if we could do it in a way that they -- that Dr. Clements has already started with perhaps toxicology, MMF, in terms of the categories, immunology and then local reactions if anyone has any comments about the latter.

So who would like to begin?

Francois?

DR. VERDIER: I can start with toxicology aspects. Aluminum was developed several years ago and, therefore, we have a limited number of updated toxicology data on aluminum. We have a huge amount of clinical results but we have a limited number of data, for example, regarding the pharmacokinetics of aluminum after intramuscular injection.

So this also leads to the fact that for new adjuvants we have to think and to set up a correct toxicological evaluation. This is perhaps one lesson from this history evaluation.

The second point, which is regarding rare immune reaction like hypersensitivity reaction and aluminum, we have no definitive conclusion about the interaction between the aluminum and the immune system. Can the aluminum trigger hypersensitivity reaction, abnormal immune reaction?

In the MMF story we have a limited number of people developing perhaps clinical symptoms. As it is in a limited number of people, we can think about a rare immune disorder and we do not know if the aluminum is a triggering factor or not.

The other thing, also, that we do not know is health status of the patient but probably this will be addressed by one of my colleagues. I think, as a toxicologist, we try to use animal models to predict potential toxicity. It is very difficult to

design animal models if we do not know exactly what we have to design.

Do we have in this case impairment of macrophagic function that we could perhaps reproduce in animals? We do not know.

The last point will be the role of intramuscular injection. If we look at the timing of occurrence of this reaction, does this correspond to some recommendation to shift from sub-Q injection to intramuscular injection?

In the animal data we have an inflammation reaction which is between the muscular fibers and not limited to the fascia. Why do we have a fascitis and not a myositis? Why it is limited to the periphery of the muscle?

Is it due to a wrong intramuscular injection in a limited number of patients? Is it due to an evolution of a general muscular reaction to the periphery of the muscle? I have no answer. I do not know if Omar (?) has already some clues concerning this very precise localization of the macrophage infiltration.

I think that is all.

DR. MURRAY: Michael?

DR. GERBER: Your point about us knowing very little about the pharmacokinetics of aluminum, I think, is well taken but you seem to be suggesting

that it is too late for aluminum and that we need to focus on the newer adjuvants. It seems to me that aluminum is going to be -- continue to be used for quite some time and that it is incumbent on us to learn something about the absorption, the distribution, the excretion in aluminum, as well as the new adjuvants that are going to be coming along.

Now being a toxicologist, it is not clear to me how exactly one would do that, how easy, how difficult that would be, perhaps we can get some input from the toxicologists. But I think that given that we will be using aluminum we should try to determine that information.

DR. VERDIER: Yes, I fully agree with you. For all new -- for all chemical entities given as a pharmaceutical, we need to know absorption, distribution, metabolism and elimination. These kind of data are missing for aluminum or not totally missing but are incomplete for aluminum.

DR. MURRAY: Alison, some other comments about toxicology?

DR. MAULE: Yes. This is toxicology, too.

I think I certainly had a sense of deja vu after the thimerosal last year and the lack of information that we have on the pharmacokinetics.

One issue that I would like to touch on is what exactly does the MRL mean in this kind of

context? In that great tome that we have from ATSDR there are some generalized comments about what the MRL means and I would just like to quote a couple of them to you.

One is that the MRLs are below the levels that might cause adverse health effects in the people most sensitive to such chemical induced effects.

That exposure to a level above the MRL does not mean that adverse health effects will occur and the resulting MRLs that are calculated may be as much as 100-fold below levels that have been shown to be nontoxic in lab animals.

Now the presentations we heard yesterday clearly demonstrated that there are huge gaps in our information about what we know about the toxicology of aluminum. I would like to just reiterate what Neal Halsey said, the differences between adults and infants, there appears to be practically no even animal data, never mind human data.

The last thing I would like to quote is that these MRLs are intended as a screening tool to help public health professionals decide where to look more closely and I would say that in this particular context that is all the MRL is telling us. The fact that you get a little spike that goes above the MRL does not tell you that you have got a toxicological effect and I think that we need to be very careful

about making those calculations and saying, okay, it goes above and whether it is an intermediate one or a chronic one or an acute one. It is a screening tool and the point is well taken. We need to look more closely.

I was very taken with the presentation by Bruce Fowler of the binary effects. I think we need to bear in mind that we are not only putting aluminum in here, we are putting in mercury. I took home from his presentation that often these effects are additive but there is always the possibility of synergy. We know nothing about that.

The other thing that was very clear from his presentation is that there are techniques for studying these things in humans. Looking at biomarkers. Clearly the stress protein analyses that he presented, which were not on aluminum, could easily be done in human infants. They could be done in human adults.

The urine analysis, the same kind of thing. You could use microarray technologies to look at induction of genes after vaccination. It is very clear that the body has efficient mechanisms for removing metals from the circulation.

We have not done those studies in infants in terms of mercury or aluminum. I have to say I think that going back to the combination vaccine meeting

that the issues of aluminum and mercury are one of the strongest arguments I have heard for combination vaccines in a long time and that was not even mentioned, as I recall, at that meeting, and I would like that to be a major take home message.

I think I will stop there for now. I have some other comments.

DR. MURRAY: Alan, comments on toxicology?

DR. BRENNER: My comments on toxicology will have to be limited to my knowledge and experience as a clinical rheumatologist and I guess what that means is I have to look at the toxicology of aluminum in terms of what we know about aluminum toxicity in the clinical world. We know about aluminum toxicity as it relates to dialysis. We know about aluminum toxicity as it relates to inhalational toxicity, pneumoconiosis, which have been produced, and which by the way in the studies that I have seen look to be very local reactions. So that even a high dose of inhaled aluminum does not seem to produce systemic response. Treatable with steroids, looking a bit like sarcoidosis but without systemic markers.

I would also like to say on the other side of this kind of metallic toxicity that studies that have been done with other materials or actually reports of systemic toxicity from other similar materials show responses quite different from MMF.

Diffuse granulomatous reactions, for instance. There is a nice paper that was reported on a patient after hip replacement as an example who developed a diffuse granulomatous disease with granulomatous hepatitis, lymphadenopathy, splenomegaly, fever, weight loss, and the particles that were recovered from spleen and lymph node were probably titanium and polyethylene, although that is a little bit unclear.

So I know I am getting a bit far afield of aluminum but what I am saying is that the systemic toxicity studies that have been done that relate to other relatively similar materials look little like what we have been discussing in the past couple of days.

DR. MURRAY: Okay. Let's move on to MMF as they did in their group. Who would like to tackle some unknowns about MMF? Does someone want to go first?

DR. MAULE: I would just like to say having -- this is the first time I have heard the MMF presentation. I think that I am reasonably convinced that there is -- the lesion is there. It contains aluminum hydroxide. I would even go so far as to say I am convinced it comes from vaccines. What I am not convinced about is that it causes the clinical entity. And I think that we clearly agree with the

last panel on that. At least I agree with that last panel.

Coming from an immunological background, I am surprised that there are no studies on the macrophage function of these patients at this point. Now I know that those are planned down the line but as an immediate reaction it looks to me like a macrophage function problem and possibly one that has never been described before. And it is rare, which would be consistent with that. So that to me is one big area that we do not know.

I would also just like to make a comment on the chronic fatigue syndrome overlap. I spent a fair amount of time working on chronic fatigue syndrome and I would just like to comment in terms of the overlap.

I actually showed your paper to our chronic fatigue syndrome group to get some comments on that and their number one comment was that you have lab findings which would exclude, at least from the CDC definition, any overlap with chronic fatigue syndrome.

So I just want to put that out there.

DR. MURRAY: I would concur with that as well. That was one of the things on my list.

Mike?

DR. GERBER: The observation that this disease is being reported only in France, and a suggestion by Neal Halsey -- the observation that MMF is being reported almost solely from France and the suggestion from Neal Halsey that one could do biopsies on cadavers from countries outside of France, I think, is something that definitely should be pursued and I think could be done fairly easily. In fact, you could attempt to target cadavers of soldiers or health care workers, people who you clearly knew had been immunized at some time in the known past. I think the information from those kinds of studies would be very enlightening.

DR. MURRAY: Francois?

DR. VERDIER: Just a small comment which is the role of the antigen in the MMF because all the macrophages are here to clean the body from external particles. There are not only vaccines as external particles. So could we have MMF with other xenobiotic or is it limited to vaccine. And in this case if it is limited to vaccine, do we have a role of the antigen in the MMF issue?

DR. MURRAY: I think that is a major thing that I had on my list is what is the -- if there are any vaccine antigen there, what do we know about the material, other material that is there.

Alan?

DR. BRENNER: I would like to comment on what you just said, Dr. Verdier. I look at macrophages in a system like this not as scavengers but as antigen presenting cells and my suspicion from the way I look at this lesion and from the other studies that I have seen is that this is not a lesion. I think that is the first thing maybe we have got to make go away. I think it may be the response to adjuvantated vaccine, and I think it may be an appropriate response, and I think that the tissue findings may well belong there as the first manifestation of response to the antigen itself.

When you think about it, if you inject antigen and you do not get any kind of immunoinflammatory response, what is the antigen doing? How do you develop an antibody? I have never really thought about it before all of this but how do you develop an antibody reaction? Where is it going to come from?

I think that this may well be -- this finding may be the first thing that one sees. I also think again that animal studies have shown long persistence of this histologic finding well beyond a month, certainly up on to six months, and I suspect longer except the animals have been sacrificed at that point to look at the pathology.

I think that the other things are that -- so, therefore, I do not think that this represents an impairment of macrophage function. I think it represents appropriate macrophage function.

I would like to also look at this MMF clinically and I will say that I would applaud the incredible amount of work that you guys have done at defining something that clinically may be relatively new.

In thinking about have I ever seen this as a clinical entity, I think I am going to answer that -- the question as yes. Over the last couple of years I think that many of us have recognized an ascending myalgic syndrome. I will tell you that in the patients that I can think of -- and there is probably not more than a handful but I can tell you that they are immunologically normal, that their muscle enzymes are normal, that the diffuseness and the myalgic nature rather than muscle weakness or muscle inflammation has led me certainly away from even considering biopsying them.

One of the problems that we will have in this country in even attempting to duplicate your results if we wanted to would be, as I said earlier today, the way that we do muscle biopsies is so different. Our criteria for doing muscle biopsies is different and I have a feeling that in the United

States our ability to track vaccines when they have been given and where they have been given is a whole lot less rigorous than it is in France.

You know, the fact that everybody seems to be vaccinated in the nondominant deltoid muscle or in children in the nondominant quadriceps makes things simpler for you and yet more difficult because as that is the only place you biopsy and that is the only place you give vaccine -- well, that is -- if that is wrong that is fine.

But that was what I understood from what -- from the papers that you have written, is that your -- traditionally you do muscle biopsies in the nondominant deltoid muscle, which is also where traditionally you give all of your vaccines.

Therefore, anything that is going on in the nondominant deltoid muscle is going to show up, whether it be pathologic or appropriate. But I do have to say that clinically I understand the ascending myalgia syndrome. I also understand response to corticosteroid, which is what I have done.

I have also found at least in our practice that this tends to be a self-limited problem, that I do not see people with chronic ongoing muscle pain with reduced exercise tolerance, with severe fatigue, and that I find that much more common in fibromyalgia

patients and I am very glad to see that you specifically did physical examination to exclude the fibromyalgia group.

DR. MURRAY: Let's move on to immunology. Specific comments about what we do not know about immunology other than the comment that there is no definite data about aluminum in the immune system. Anything else the panel wants to comment about?

DR. MAULE: Okay. One comment that I heard yesterday was the issue of whether or not -- since we know aluminum does skew the immune response towards a Type 2 response, whether that has a global effect, if you like, rather than just an effect for the given antigen that you are working with.

I think that we are far too early to say on that particular issue.

There have been many hypotheses out there that I have heard that what we do in the developed world has clearly -- has maybe -- I will not say clearly but the hypothesis is that we have skewed towards a Th2 response and that maybe is what has caused our explosion of asthma and allergies.

The data lags far behind and I want to put in a plea for not blaming adjuvanted vaccines at this point. I think that there are far -- there are many other ways that that skewing could have happened that the vaccines do not necessarily have any role to play

in it. I will not say they do not either. I mean, we do not know if that is a possibility. There are clearly animal studies that can be done that can look at those kind of issues.

And I know that there are human studies that have been done, notably Graham Rook in the U.K. has taken this hypothesis to a reasonable extreme and has, I believe, a candidate vaccine for some soil bacteria that are supposed to skew the response in the Th1 direction.

So, you know, there is definitely people out there looking at these kind of things but I think we need to be very careful about jumping down on vaccines and adjuvants before we have that data.

On the other side of that, I think it is reasonably clear that we need some good Th1 type adjuvants. The triumvirate, if that is the right word, of HIV, malaria and TB, for which we are hunting for vaccines, it is abundantly clear that you are going to need a Th1 component to that response and at this point we have no licensed adjuvants that do that. So those are both areas that I would say we need much more knowledge in.

DR. MURRAY: Well, I think the studies that Dr. Verdier has planned is also going to be very, very helpful in terms of looking at macrophage immunology as well.

Any specific comments about local reactions before we open it up for comments?

DR. VERDIER: I have probably just one question. It seemed that MMF is occurring with the change in the route of administration and in the symptoms you have myalgia and marked fatigue. I would like to know if epidemiologists have noted an increase of myalgia and marked fatigue after the change from the sub-Q to the IM injection because we do not have data in the U.S. from biopsy in the deltoid muscle but I am sure that we have data about the number of myalgia, number of arthralgia and number of marked fatigue reported since the last seven years.

DR. MURRAY: So something we need is data on switching from sub-Q to IM, more information on myalgia, increased myalgia?

DR. BRENNER: I have a couple of answers to that or at least partial answers. I can tell you that, number one, the most common complaint in a general practitioner's office is fatigue. So to separate that into its various meanings and manifestations is going to be a very difficult task.

Also myalgias -- if you wanted to look at myalgias in the modern world, there are so many specific causes that have come up in the past few years. For instance, the lipid lowering drugs. You

know, the most common side effect of lipid lowering drugs is myalgias. So to try -- and it is -- they are really occurring in an age and population -- in an age of population relatively the same as we are talking about in MMF.

So again to try to separate out some of these things I think would be extremely difficult.

Immunologically there are a couple of things that are of interest to me here. The first thing is that 34 percent of the patients in your group had some form of definable immuno-inflammatory condition. And the reason that is of interest to me in this sense is that we as rheumatologist have done the opposite studies.

We have looked in our patients particularly with lupus and also patients with rheumatoid arthritis to try to determine if vaccination caused any kind of definable and I can tell you that the answers going back to Evelyn Hess in about 1972 are no, that vaccination is in general safe, that we do not see any specific increased incidence of -- for instance, flaring of rheumatic problems. That these are patients who are followed, I would hope, fairly carefully so that if new entities were coming up I would think that we would be the first ones to find them.

I know that that is backwards thinking but it is true that the issue has been raised in our societies on the opposite side. I can also tell you a little bit -- at least one experiment that was done looking at what happens when you put aluminum adjuvant with vaccine into joints because that study has been done, too.

What happens is if you put aluminum hydroxide adjuvant into a joint nothing happens. There is no particular inflammatory response in the joint. If you put aluminum lactate, which is rapidly and freely disbursed out into the system, then there is a systemic response to aluminum lactate and you get an articular inflammation as a result of injection.

So again the more stable localized kind of aluminum adjuvant seems to stay put and at least in the one experiment I can quote did nothing.

DR. MURRAY: Yes. There was a paper done in New York about looking at aluminum lactate versus citrate and there are definite changes that occur with the lactate form. The anion appears to make a major difference on some of these things.

DR. BRENNER: Yes.

DR. MURRAY: Comments from the panel about local reactions. Anything specific?

DR. MAULE: I guess I would just like to reiterate from the proposed anthrax studies that we have a potential opportunity there to look at what aluminum adjuvant does alone within a series but compared with a saline placebo and I think that is a very interesting idea that could provide us with some information here.

DR. MURRAY: Before coming, I had pulled a lot of articles, and there is a tremendous amount of literature, as I think Alan alluded to, regarding reactions from people getting aluminum. They are throughout the literature even back in the 1970's and '80s with granulomas and all kinds of reactions.

So I think we know that it can cause some local reactions but I agree the Army studies will probably be beneficial.

All right. Let's open it up for questions from the audience here to help us put this together and question what our panel has discussed.

Dr. Gherardi?

DR. GHERARDI: My feeling is that we must have the questions that has to be addressed at the moment, the first one to my eyes is to determine what is the normal residence time of the aluminum granuloma in the human muscle. This is absolutely mandatory.

Now as to whether the aluminum causes the symptoms, systemic symptoms, or finally reveals individual susceptibility to have an adverse reaction, which could be caused by any other agents, including infectious agents, this also is a question that has to be addressed.

But first is the detection in the deltoid muscle of MMF lesion an abnormal finding is the first question.

DR. MURRAY: Other questions?

DR. ALVING: I just would like to get -- this is Carl Alving. I just would like to get a clarification. Is ascending myalgia a required part of the syndrome or can it simply be diffuse?

DR. GHERARDI: Well, a large majority of patients have such a syndrome but some have myalgias that are simply diffuse and do not correspond strictly to this pattern.

DR. BRENNER: I would like to comment again. Clinically -- you will not have to respond to this, Dr. Gherardi. I am going to agree with you.

I think that ascending myalgias are a relatively unique clinical syndrome and I do not recall seeing it over the last 20 plus years until recently and I really have not known to what to ascribe -- I still do not know to what to ascribe it

but I think it is different than the clinical presentation of almost anything else I know.

DR. GHERARDI: I agree.

DR. BRENNER: So I think it is unique and for me it would be something that would make me think about, oh, maybe doing gallium scans on these patients. I do not think I will go to biopsy them. Although one thing -- one suggestion I would have, if you wanted to consider biopsying of normal people, would be that the lesion looks to me to be large enough so that needle biopsy might be a way to look or at least a way to screen.

DR. GHERARDI: I disagree with the idea of needle biopsy because the lesion is focal. If you want to have a large chance to have it make open biopsy but if you have ascending myalgias in the context of fatigue, before getting -- or addressing the question of possible biopsy, ask the patient of any immunization in --

DR. _____: That goes without saying.

DR. GHERARDI: -- and if the response is yes, I encourage you to perform the biopsy at the site of injection.

DR. MURRAY: Two final questions.

DR. MUSIC: Stan Music, Merck. I would like the panel's reaction to the temporal association that has been made with subsequent to vaccination by eight

years or several weeks or whatever and feel that we need some clarification studies on that as well by looking backwards from other groups, from other biopsy groups, from lots of points of view, to understand the implications because that is just a convenient counting point, and it has -- it implies no positive or negative association in terms of cause. It is just something you count.

DR. MURRAY: Is there a specific comment from panel members?

DR. MAULE: I mean, I would agree with that and, I mean, I think that certainly from sort of a gut reaction, eight years from injection, it seems to me an incredibly long time but that still goes back to the comments we were making earlier. It is critical to know what is "normal" when you put in a depositive aluminum. I think those are the studies that I would want to see done.

Just a comment off the top of my head. I am very interested to hear my colleagues' comments on ascending myalgia. I am definitely colored by my experience with chronic fatigue syndrome here but you may well remember it used to be chronic EBV until -- because these patients were selected by having a high titer of Epstein Barre Virus.

However, if you went out and looked for high titers of Epstein Barre Virus there was no chronic

fatigue syndrome. If you took people who had a tight case definition of chronic fatigue syndrome, a lot of them did not have high titers of EBV, and that association has clearly gone away even though it is clear that there is a subset of people who have essentially chronic EBV who definitely do have chronic fatigue syndrome. That is not the number one part of the definition.

So here I am hearing this ascending myalgia. I am not a clinician. This means nothing to me about frequency but it does make me think that that is another way to get at this. That if clinicians are seeing ascending myalgias maybe they would find other people -- I mean, other -- people who you could take as a group and then ask the question about vaccination.

I think that would be an interesting way at getting at the vaccination issue.

DR. MURRAY: Gherardi, last word.

DR. GHERARDI: I agree. I want only to make a comment about the chronology. Ninety-eight percent of patients had symptoms subsequently to the immunization containing aluminum. It cannot be said that this means nothing.

DR. MURRAY: Thank you, panel members.

DR. MYERS: I thought it would be a tough task to follow the first panel but this panel has

done a wonderful job and I think Dr. Gherardi summarized it very well when he said that the first question is that we must answer whether the detection of MMF in the deltoid muscle is normal or not. I think that is sort of the core issue.

So thank you all very much.

(Applause.)

DR. MYERS: One of the difficult things that we all deal with all the time and one of the difficult -- one of the issues that is problematic with dealing with something like MMF, for example, is how we communicate information and how we communicate information that we are not clear about. Whether -- when we have meetings such as this where we take on issues and we debate them and we come up with next steps, what we do with that.

And so we asked Max Lum to come and talk to us and he picked his title, which I just thought was a great one, "Communicating Health Messages: The Good, the Bad and the Ugly."

Max started his career with Sports Illustrated. Something I did not know until I saw your bio. And he has worked with the CDC for the past 15 years in the field of health education and health communication.

He is currently Director of the National Institute of Occupational Safety and Health

Communication Group and serves as Chairman of the Surgeon General's Subcommittee on Risk Communication and Education.

He has provided a lot of assistance to a number of groups, including the Department of Defense, in risk communication and he spoke recently at the National Vaccine Advisory Committee. So thank you very much.

COMMUNICATION HEALTH MESSAGES: THE GOOD, THE BAD AND THE UGLY

MAX LUM

DR. LUM: Thank you very much for having me here today.

Martin opened this meeting and he talked about people liking to come to these meetings because they do not know much about the topics that are presented. And I think to be fair with you, he was talking about me, I think, at this point.

My area of expertise, I guess, is in risk communication and I have been in the field practicing risk communication for CDC and my day job with NIOSH really is in the Office of Communication working with workers and employers and health professionals and with the Surgeon General, most recently working on endocrine disrupters, Gulf War issues, and that is an ongoing activity.

Now what I will try to do today in a brief time is to present some information about what may help communicate information to the general public. Generally we are talking about communicating risk information but in many cases we are communicating health information.

(Slide.)

By saying "risk communication," we are making the assumption, I think, that it is always risk information. It is a broader issue, I think, of health information. It is very important now, I think, to understand and I think that John Clements mentioned this in his opening presentation.

(Slide.)

This is a new era. People are concerned. There is a high level of interest in health problems. The public acceptance in many cases depends on their participation and understanding and your personal credibility. Often you are the message if you are delivering the particular message that you have to deliver. Again the bottom line here is that it may increase the likelihood of finding a solution. It does not always but it may. But it does improve, I think, the quality of the solution and the communication.

(Slide.)

This is a longer definition of communication. I think definitions are a good place to start when we talk about risk communication. This was a definition that I found in the National Academy of Science buried a couple of years ago. It is a good one.

Any public or private communication that informs individuals about the existence, nature, form, severity or acceptability of risk. It has one huge flaw, I think, in this definition. We like it because this is us, right. We are communicating what we know. We have spent a lot of time figuring out what we know, boiling it down, and this is us in a way. We are doing this. We are talking about nature, form, severity of risk. We have heard it a lot at this meeting. But for public communication, I think there is one important piece that is sort of missing from this.

(Slide.)

I think we are talking now in the new era really of exchange of information. It is that two-way communication that is occurring that is absolutely, I think, characteristic of this new information age. How well do we listen? How well is that two-way channel really working in terms of our messages?

I am not sure the internet, which we are all embracing, and I am right there embracing it for our agency, really does not provide a good receipt of information. I mean chat rooms are difficult. It does not really help necessarily. It can and I think we are working on that.

But basically I think that one of the take away messages I would like to leave with you is this exchange of information really has to be done.

(Slide.)

I am terminally right brained so I have to see things, you know, in pictures or charts. Here we have the owner of the dog talking to the dog. "Okay, Ginger. I have had it. Stay out of the garbage. Understand, Ginger, stay out of the garbage or else."

(Slide.)

And, of course, this is what Ginger hears, "Blah, blah, blah, Ginger, blah, blah, blah, Ginger."

I like this slide for two reasons. One, it reminds me of my children. I think that is -- which is the highest form of risk communication, I think, the environment. But also because I think we identify with this person. All right. We are -- they just do not get it. Right?

We are -- they are not listening. They do not understand the science. They do not -- they are preoccupied. They are worried about perception.

They are not listening to what I am saying but if you work with advocacy groups and I think the anti-vaccine advocacy organizations are in that category but certainly the super fund groups that have been formed, they tell us that this is them. They are communicating to us and we are just not listening.

So I think again this highlights the importance of the two way exchange of information.

(Slide.)

And knowing your clients, whether they are women that are pregnant, whether they are health professionals.

(Slide.)

Is that the client? Is that the client that we are going to target? Is it the kids themselves? In some cases I think it will be. Is it the parents? Who is it that we want to reach with this information? I think that is the first thing we have got to decide because the channel, the method may be different with each one of these.

I would say that that would be a very important understanding about who we are trying to reach.

(Slide.)

Kids -- you know, there is good examples. I think ATSDR, when I worked at ATSDR, where we

actually worked with kids directly to get to the PTA, to get to their parents at some of these super fund sites.

And I think again we -- a whole different set of materials available for children than essentially that we would use with health professionals but again thinking it through about where we were going with this.

(Slide.)

So the individual is what we often think about, I think, as the target. You know, it is -- I saw a slide that showed clients was kids basically. Okay. But there are networks, social networks that we are going to work with. What are those networks? Are we going to work with the anti-vaccine groups? How do we want to work with them? They do, in fact -- in fact, I did my research before I came here and checked out several. They do link to CDC sites.

Do we know very much about what they want to know? Have we contacted? Are we working with them? Is there a way to work with them? Organizations, also, and then the media of course.

Now I am not going to say much about the media here. Just a couple of points but if you are going to work with the media -- I mean, the visual media, the TV media, my suggestion would be get trained. Okay. Spend some time, spend some money,

and go get some training about how to work with the TV media. Less important with print media although the same principles possibly will apply.

I think when you are on camera you are much more the message than you are when you are not on camera and that is a whole different set of requirements that are needed.

(Slide.)

Again, well, what is it we do with audiences? What do we need to know? I think again what is their views? What are their views regarding the hazard? What are hazards? What do they call hazards? Can they make the changes? If you provided them the right information, are they capable of making the changes that you would want or understanding what you are trying to tell them?

This is particularly important in worker communication. You know, do they really understand what we are trying and are they able -- do they have the power really to make the changes that we have asked.

Again, attitudes. What is your -- their particular behaviors? I would guess it varies quite a way across the board. Are they defensively avoiding or reacting against the issue? I think that is fairly clear if you look at some of the internet sites.

(Slide.)

What are the sources that are preferred by these groups? What type of messages may reach them better and what channels?

(Slide.)

Again, I think working with the media -- again this is my only media slide -- I think it is that you have to know your media. Is it local media you are going to work with? They are a little bit easier? Is it national media? What do you need to do to prepare? Know the market. Are you trying to reach a local market? Are you just talking about a particular area that you want to try to reach as a demonstration project to see if what you are doing is reaching your public?

Provide the facts. Make access -- this is so important, I think, is access. The press has to have access to you. You know, you may not want to take that call when they call but you have to take that call. Now if it is not an emergency you can always ask the press if you can call them back and you -- in our office where people are -- I think a lot of the press is under a time line. They want a decision.

They want to know about most recently latex. You know, what is our position on latex. They are doing a big story. They have an hour for our

comment. Well, we cannot say we are going to call you back in an hour. We have got to figure that one out real quick and get back to them.

I think access is a very important part of -- particularly in the federal agencies to improve our ability with media.

The dichotomy, I think, is -- it seems to me, whether it is Gulf War, whether it is vaccines, whether it is endocrine disrupters, there is all -- the question that you can anticipate from the media is, is it safe. Okay. Is it safe? They will -- you can anticipate that 100 percent. Tell us if it is safe. And often you cannot. You may not be able to. You can say relatively safe. Then they will want to know when is it unsafe. Tell us specifically.

And, again, they are after a story. So they are looking for either extremes. We have got this magic bullet and it is totally safe or it is totally unsafe. Of course, we do not work in that atmosphere so we have uncertainty in the science that we present them and how we characterize that.

Personalization is an important one because invariably when I speak to a press audience they will say -- someone will say maybe either during the talk or after, they will come up and they will say, "Thank you very much but what do you really think. Tell -- I mean, we heard your position but what do you think?

You know, as a person, would you do this? Would you drink this glass of water that came out of this creek that you say is clean? You know, would you? What do you really think?"

I think it gets to be very tricky and we want to help. We want to do this. We want to give an honest answer. We want to tell people what we believe but we have to shape it, I think, in terms of where we are. Where we stand depends on where we sit. If you are in an agency your answer is really shaped about what you know about the science.

(Slide.)

Again, intuitive toxicology. You hear this a lot. This ham smells funny. Do you want it anyway? That is what the cook is saying. I see a lot of intuitive toxicology.

The science, what we communicate cannot -- even though in this case you might not eat the ham. I would not but you can. We cannot back up our communication on intuitive toxicology. We have to have good science. People may not understand that although they say science is important. Every National Science Foundation Study, they do say people believe in science. Hopefully, that means they are interested in science. I am not sure they are the same. But good science is absolutely key and this is the good of communication.

I think basically we do a good job when we talk about the science particularly to other scientists. I mean, we have this -- these two days as an example. We may not agree with each other. I do not think we actually do agree with each other but there is a respect and we communicate our ideas well.

We are a fraternity that understands each other. This is the good part, I think, of communication and this is what we always want to do. We want to tell people about the evidence. We want to go out and we want to talk. This is what we hope people will ask us because we know that 1937 epidemiology study, that 1964 study. We know the '57 British study that talks about using aluminum. We know about that. That is what we want to be -- to talk about. Or the dose response. Dose -- this is part of what we do and we are good at it, I think, by and large.

(Slide.)

But there is the other part. Okay. This is from a super fund site. We had not even spoken yet, right. So there is a perception. When you deal with the public you might not be this up front but we had not even got to the meeting and this is outside of the meeting. So we are in for a rough time, I think, in explaining this health hazard evaluation.

(Slide.)

I guess this is kind of the central part of my talk and I think makes sense in terms of how we would shape a strategy. But often times, you know, I think when we talk about risks -- now this is perception of risk, is that we want to talk about the hazard. We do want to talk. That is our good part. That is the good part of what we do, is talking about the specific hazard.

What we also have to account for in the equation, I think, many times is apathy. I think that is just -- because it shapes the perception of whoever we are talking to about the hazard.

(Slide.)

So in this country why, why do people not really -- why aren't they outraged about childhood lead poisoning? I talked to CEH at CDC and it is number one -- number two concern of environmental concerns -- of environmental policy makers, is childhood lead poisoning, but who is banging down our doors about childhood lead poisoning.

In other words, the perception -- it has been around a long time, whatever that perception is. I think it is shaped by apathy.

(Slide.)

But for us and for most of the problem, I think, in many cases it is shaped by outreach --

outrage. And as I read, I will read some of the questions that I took off the net and I think you will see what I am talking about, how that would -- how that perception of risk is shaped by the outrage issue, which we have to account for.

You know, if we want science to speak for itself, we are deluding ourselves. Science never speaks for itself. Maybe among scientists. I am not sure that is true but it will never speak for itself if we are talking to the general population because I think there are two -- the perception issue is what we have to account for.

(Slide.)

Now what do we know about perception? Well, we do know that the level of risk is one of the several factors that determine acceptability and things that shape people's perception are these issues, how they feel about fairness, benefit. I think a better way to look at it, and try to shape it this way, is that as we move to the right side of this line, the perception of risk increases.

Now remember it might have nothing to do with the science of the hazard. It is what people are bringing to the equation. What they are bringing into listening to what you are talking about of the hazard. Is it voluntary or involuntary?

I know the first time I went skiing, it was sort of a voluntary act. You know, my friends went but I was worried about it. You know, I was really worried. To me that was a big hazard because, I mean, I was not running and jumping in the car with my skis. You know, just the fact that I was going there and I really had not chosen -- well, I sort of chose it so it was -- but it was a fear that I had about, you know, the first time and it was not sort of a voluntary act.

Natural and man made. If it is a natural -- if it is a natural and we get some good examples here about that. Natural is better. It is not risky.

You know, what -- radon, why don't people get exercised about radon? I mean, New Jersey has tried to convince people the importance of radon. Who put it there? Who put radon? Mother Nature. Who put radon in -- well, I guarantee you if the Dow Chemical Company had up radon in there, we would be really irritated about it. Okay. But it is natural.

Arsenic in well water in Washington State. It is naturally occurring. We cannot get people to get tested. Right. It is around. It has been around a long time.

Familiar and exotic. Is it a familiar risk? What is the number one risk of farmers in this

country? The number one risk? Accidents. What do they think in many cases? Pesticides. Right.

Well, gee, in our focus groups we talk to them. Well, you know, I have been doing it ever since I was 13 years old. I have been driving the tractor. I get down off the tractor. It keeps moving and I adjust those diskers, right, and then I get back. I have been doing it forever. It is something I know about but I am worried about those canisters of green stuff, you know, that come in. I am really concerned about that.

Chronic and catastrophic. Obviously an explosion, probably rightly so, is more -- it is certainly the appearance is more of an event than a chronic exposure over time.

Visible and no visible benefits. I think very important for the work place, you know. If you are getting a paycheck -- well, you know, it is -- I mean, I see it. I mean, I see it -- I mean, you know. It is not that -- I have sort of accommodated it because I get a visible benefit from that as opposed to maybe the people across the river who get the smoke from the stacks who have no visible benefit. The same risk. Maybe more risk for the worker actually in the plant.

And controlled by individuals and controlled by others. You know, I think a good way to look at

this is when -- at Thanksgiving, you know, when somebody -- you are carving up the turkey, right, and you have got the turkey right here, and you have got your knife, okay. It is no problem. You know, you can -- you are in control. You hand that knife to somebody else and say cut the turkey, all of a sudden it is very risky business, and you are worried about this thumb all of a sudden, see.

You are not -- and my wife, who is a wonderful driver, I mean she is a better driver -- when I am in the car with her and she is driving, man, I am worried, right. I am sitting next to her. I am doing this and I -- for the brake, looking for the brake. I am not in charge. I do not have any control over the situation and that is important.

How much control? Particularly we found at super fund sites -- how do we give people some control? Do you give them a veto power of studies that you are going to do? What is the limit of control that you are willing to do? ATSDR has done a lot to go to involve people even at community sessions. And prior to actually going into studies to invest people with some control in the study.

And fair and unfair, I think, goes without saying.

Let me just take a few minutes to read you -- what I did is I did, you know, a search on the

net and I was looking for some comments. I am not going to identify this site but it is fairly easy to find. You probably will recognize it. It is a question and answer session.

This is someone writing in saying, "When I told my doctor that I am not going to have my children vaccinated, he became very intimidating and told me that he will not treat my children and that I was no longer welcome in his office. Do you have a list of doctors in my area who will respect my decision not to vaccinate my children?" Control. The answer is -- let me give you the answer.

I am not going to answer -- but "Your situation is not uncommon. Many pediatricians refuse to treat children when their parents object to shots. This is just one tactic doctors employ in the effort to intimidate moms and dads into vaccinating against your will. You should be thankful that this dysfunctional relationship with your health practitioner has been terminated."

Again, control. I -- who is in control here? Who is in control? I am not making any -- I am being sort of a devil's advocate here. I am not making any point other than reporting here.

Other question: "I was wondering if you had a listing of pediatricians who would allow parents to make decisions?" Again the same line -- the same --

"My wife and I just became parents and we are finding it extremely difficult to find a pediatrician who will let -- who lets us be in charge."

And then the issue of -- this is in an answer to a similar question: "Some doctors will just say anything to get their parents to vaccinate even if it does not make sense or it is an outright lie. It is a ploy to coerce you into vaccinating your child." You are losing control. You are not in control as a parent. I mean, that is what this says to me.

Not only that, but it is mandatory. You do not have a choice. Okay. It is much more real in terms of the risk.

Again, "Thank you for your information on your web pages. Do you have, in particular, information on homeopathy as a method to boost my immune system in treatment for my child?" There is no answer to this one.

Another one -- but again this is the natural -- this is the natural piece here. Homeopathy, a natural therapy, not as risky as this more exotic issue with vaccine, especially maybe even what I have been reading in these pages.

The answer, it says, "Many intelligent people do not think every childhood ailment is a grave cause of concern. They wonder why a child's

immune system needs special treatment. Breast feeding and natural foods work for many families."

So it is sad. I mean, it is sad, though. I mean, I think it is very sad. But again for agencies what are -- what -- it seems to me this list -- this list of 100 questions that came off the site provide us a starting point to answer questions. I mean, to have our own answers to these questions about what is real and what is not real, and to have linked sites so people get information.

It does in one case mention CDC and it talks about adverse reporting system at CDC and it calls it a great secret database. Okay. It is a secret database.

I could go on. I will not. I wanted -- but I will -- this is just -- you know, this one particularly is touching, I think, and it just cries out for why we need to do a better job. I mean, we really need to get a grip, I think, on what people are asking and then, you know, answer them the best way we can, decide if it varies from group to group.

And one of the things I did hear, you know, at this meeting is that there are several federal agencies involved in this. We have several things just mounted on our web page. I heard some -- NIH, I think, talk about a compendium of adjuvant information. I do not know whether that is geared to

the general public or not. My guess is it is not but it would be helpful.

Again, the information that we do put up, is it consistent across the board? Does it really get to some of the general public's concerns that are more science based?

Let me read you this final one though. This is from a mom in New Mexico. She says, "I am in search of real chicken pox for my seven-year-old son. He has not yet had the disease and people here in New Mexico seem to vaccinate their children a lot in order to avoid having to take time off from work. Do you know of any way for parents like me to share the disease in a natural setting?"

Now you just -- you know, just amazing. I mean, it is just -- it is amazing but I think this is only -- in the short time that we are talking today, this is only just a sample of perceptions, I think, that we have pulled together that we can account for in our messages. If we have the right channels we can answer those questions.

Now that does not mean I think we are always going to be successful. I think if you are in the risk communication business basically you are not looking for a lot of strokes in your life. I mean, I think this is a -- really, it is true. If you are in public affairs, you get some of those strokes but if

you are communicating negative risk information you better be able to take some hits because again I think the perception issues dominate.

(Slide.)

Let's talk about science. The scientific community is divided. Some say this stuff is dangerous. Some say it is not. Okay. Right? I mean, how -- this -- I call this the tale of two toxicities. Right? It is the best of times and the worst of times.

Well, when we communicate to workers at NIOSH or at ATSDR, when we talk to communities, many times this was our message. We are not real sure -- this is what we have done, uncertainty -- what is it? Pervasive uncertainty. What a great term, I think. Pervasive uncertainty. Well, how do we handle that? People do not handle that well.

You know, they -- again the dichotomy. Just tell me is it safe. Can I drink the water? Is it safe? Can I bring my kid in here? You know, what is the deal? Please, just tell me if it is safe or not. But in many cases we do have a -- we are divided. So how do we handle this?

(Slide.)

Well, there is -- you know, it seems to me and I sort of -- I think maybe I need to modify the list a little bit but I think we need to be a little

bit more proactive in terms of what we do know about the science. I mean providing we can boil it down so that folks can understand it.

We need to put bounds on the uncertainty. It is not everything that is uncertain. Are we uncertain about everything? I mean, I heard some terrific things from John Clements. He opened up with terrific messages, you know. Millions of kids have been protected. We are not talking a couple of hundred. You know, millions of kids over years. And what would those kids be today? I mean, what would our world look like? I mean how do we shape that message?

Not all data are uncertain. I mean, you know, which are why -- say what. Say what has been done to reduce this uncertainty. You know, we agree there is uncertainty but we are doing this and if there is a time line by X time, we hope to have an answer to this. And do not hide behind it. Well, we do not know, you know, we just do not know. Do not bug me, I really do not know. You know, we will find it and we will let you know. Okay.

Acknowledge if you -- well, we should have been doing this, you are right. You are absolutely right, we should have done that but we are cautious and this is why we are cautious -- Okay. In many cases this is a resource issue but that is -- I think

that is something that may not carry a lot of weight with the public but it is certainly part of our job.

(Slide.)

And, again, talk about simplicity. All right. Again here is a menu and risks and benefits. Okay. I do not know about you -- I still eat hot dogs, right. I cringe when my kids eat them but, you know -- but I eat them and I try not to eat them in front of my kids.

(Laughter.)

Because I know this, you know, I know this side of it. But I guess this is just think -- I am thinking about that compendia. I do not know what it looks like. I cannot wait to go home and pull it off. But I will bet there is some good stuff in there that we could reduce down and make a simple fact sheet or something that is really -- would help somebody -- maybe some of these folks because they are -- they are referring to federal sites on these sites.

But what do we have for them to answer some of these questions? What simply can we do? Maybe it will not be this simple but I think it is a nice model.

(Slide.)

Again, we -- what is it we do with the messages just -- I think, you know, hopefully we

state our messages. I mean, if you are at a public meeting and somebody is going to attack you and -- you know, I think going into those meetings we should have three or four major points that we want to bridge to.

We will try to use the hostility maybe at the meeting to bridge -- this is true and the Gulf War brought it home to me that we go into that meeting and we want to tell that we have got three things to tell. Okay. And, by golly, we are going to tell those. And that is our message -- if we get a chance we will elaborate on those. You know, what is it that makes -- you know, what can we say that goes beyond?

Some of the messages I heard from John Clements, you know, there is a history here. This is where kids -- if we were not here, this is where we would be. And maybe some illustrations to go along with that.

I mean, I am happy if we are here, though. We got -- you know, this is again -- I hate using John all the time but he had the three messages, I think. You know, this is a new era, right to know is important, and we have a right to get our message out. You know, we have a right. We have the same rights. What is our message, though, and can we state them and state it clearly?

(Slide.)

Information is clearly not enough. This is kind of the last take home message that I have. You know, we talk about dissemination and we talk about, I think, giving out information. It is almost like the -- I think we are sort of hung up on the postal theory. You know, we are delivering information, you know. We are delivering something to our clients.

When really, you know, it should be a two-way kind of operation. It is -- and it is not just information. How much audience research do we know? Do we know who our audience is? Do we know really how to reach audiences? And what form really should that take?

(Slide.)

My last slide is the big money slide, okay. This is what -- someone found out that I -- I teach a lot in communication. We have a three day course. We have a three day media course. I talk about the eight lessons of risk communication.

Well, I am going to show you these eight lessons. These are the key points. Okay. This is the last take away message. These are the eight lessons of risk communication.

Again, I cannot emphasize -- and what is good about this is you only have to remember one of them. That is the part I like. And maybe a year

from now this -- you will remember this slide. Maybe this slide and the dog slide. Probably that will be it. But I think that this is a key point. I mean, we -- and I think it is a problem that we have with our internet sites that we are dumping out stuff.

We are looking at a very general audience. I am not saying we do not do that but there is no reason we could not have a kids' site. There is no reason we could not have, you know, health professionals site. We are trying to work with this at NIOSH really. The worker sites, different workers, miners, construction, you know, it really is the key, I think, is to approach it in a client base.

I have one final note and that is that I want to thank John very much for -- I mean, Dr. Myers for inviting me here today and I know he will say thank you for coming but I want to say thank you for staying. Thank you.

(Applause.)

DR. MYERS: Thank you very much, Max.

DR. LUM: That could be dangerous.

DR. MYERS: To keep us on time I think I am going to just move on now.

Probably the hardest thing in any meeting like this is to be the summarizer, the rapporteur, and Ted Eickhoff, who many of us have known for some

time, who is a professor at the University of Colorado, and he admits to particularly an embarrassingly long relationship with vaccines and infectious diseases, and was kind enough to agree to do this. But when my staff asked him for his bio, they added on the end here -- I have to read this. It is too good.

He claims that his service as rapporteur for this meeting is attributable to Marty Myers seeking revenge for sins committed in a previous incarnation.

Ted, thank you very much.

WORKSHOP SUMMARY

THEODORE EICKHOFF

DR. EICKHOFF: Thank you, Marty. If there were ever a job that I took on that proved ultimately to be anticlimactic, this is it. I will be brief, even probably briefer because you will note that there is no discussion session that follows my summary of the conference so I promise to get you back on schedule.

First of all, was this conference simply thimerosal-2? You know, the same conference with a new cast of characters, not even a new cast of characters but a new topic, a new incarnation.

Well, I think my answer is both yes and no. Yes, because we heard the word "pervasive uncertainty" several times. First, I think from you,

Mr. Chairman. And we heard a lot of it at the thimerosal workshop not quite a year ago.

But that really is sort of where the resemblance stops, I think. It is not thimerosal-2 in terms of at least two broad senses. First, there is much less of a sense of crisis or something impending, something happening right now, than there was in the case of the thimerosal symposium. And, two, there is much, much less toxicity risk that concerns us today, probably by several orders of magnitude.

Yesterday was a day of, I think, very important background learning. Let me just review some of the high points of that.

Dr. Hunter provided a very much needed basic overview of the history of adjuvant development, the rationale for putting adjuvants into vaccines and some of the likely mechanisms that operate about which we heard a great deal more later on.

Norm Baylor gave, again, a very much needed U.S. perspective, particularly an FDA perspective on adjuvants; reviewed the three basic aluminum salts that we use or that are used in vaccines; reviewed the earlier comparative trials that showed the clear advantages of adjuvanted vaccines, particularly in terms of primary immunization; showed some very interesting data about aluminum or aluminum adjuvant

levels in individual vaccines; and brought out that the variation could, indeed, be quite significant, as much as threefold frequently and perhaps even as high as fourfold variability in concentration of aluminum salts by individual vaccines.

He pointed out the problems in changing the dose and character of adjuvants. Much as we like to put old wine into new bottles, as it were, basically any change in the character or concentration of adjuvant in the vaccine creates a new product, a new vaccine for which a whole set of new trials has to be done, both safety and efficacy.

So it is a long and arduous job and I think the likelihood that we are going to see any change in the current use of adjuvants in the next -- in the foreseeable future at least with existing vaccines currently marketed is probably very low.

Dr. Clements offered the much needed WHO perspective. Their goal ultimately is a very understandable one, to create single dose -- ultimately single dose vaccines for what are currently multiple dose vaccines.

The rationale, I think, is very simple and easy to understand. I would emphasize again the six classical vaccines that are currently recommended for use in EPI or the expanded program on immunization.

These are in addition to BCG, diphtheria, tetanus or pertussis, OPV, and measles.

I found Carl Alving's presentation particularly interesting. His discussion of adjuvant immunology, types of immune response induced, different types of adjuvants. On one occasion he manifested an interest in going back to Freund's incomplete adjuvants stating how much he liked it and how potent it actually was. Given what Norm Baylor told us earlier, this probably is not going to happen much as we might like it to.

I found particularly fascinating his discussion of mucosal immunity, particularly the reflection on some of his own work with skin immunization. I think this is -- this was particularly interesting and potentially at least very broadly applicable pending, of course, a whole lot of further study.

Later in the morning Drs. HogenEsch and Fowler discussed adjuvant properties of aluminum, the nature of the Type 2 antibody response, some of the cytokine and chemokine drivers of that response. And then Dr. Fowler presented an interesting discussion of binary metal mixtures and introduced -- really in a sense introduced the afternoon session with his discussion of stress protein response, a beginning

understanding of how aluminum could be bound by metallothionine molecules within the body.

We began then in the afternoon to get some discussion of pharmacokinetics from Dr. Hem. And we began to appreciate, I think, from his presentation just how widespread aluminum was in the environment and began to get some appreciation of the levels and quantities of aluminum in our environment, particularly in our bodies, where it went, where it was stored, and how it was handled.

Drs. Keith and Wheeler from ATSDR, I found this particularly interesting, particularly informative and particularly problematic. Toxicology, we did learn that it takes quite a little bit of aluminum to make a mouse sick. I think if I remember the figures correctly, it was about 100 milligrams per kilo, presumably by the oral route to make the mouse acutely ill.

The closest documentation in my opinion of aluminum toxicity in people probably is in the dialysis dementia story. This goes back now 10 or 15 years, I believe. It is a unique situation. Probably not of any direct applicability to us as people interested in vaccine and vaccinology but it is probably, in my judgment at least, the clearest evidence of aluminum toxicity in humans and what it might do.

The phenomenon of -- or the minimal reactive levels, MRLs or minimum risk levels, I guess, rather than minimum reactive levels, this was a methodology that I, at least, first heard about at the thimerosal workshop and probably understand quite a bit better after yesterday's presentation than I did a year ago.

The use of NOAELs and LOAELs is interesting and probably one very reasonable place to start.

What troubles me are the uncertainty factors because they are -- well, just exactly what the name says. They are uncertainty factors and the fact that one conceivably could have 10^5 since there were five uncertainty factors listed, each one of which has a value of ten, the maximum uncertainty factor, therefore, would be 10 raised to the fifth power or 100,000.

ATSDR took a look at that and said that is probably unacceptable and reduced it perhaps somewhat arbitrarily to 10^3 but we are still dealing with 1,000-fold uncertainty factory.

So it is -- it strikes me as a very imprecise science at best but it is a good place to start and probably the only place to start.

Nonetheless, it does bring up the issue of vaccine formulation and while I will certainly admit that it is more than black magic as someone alluded to yesterday, it still -- there is a great deal of

empiricism that seems to go into selection of doses of aluminum adjuvants that goes into vaccine.

So an imprecise science at best.

Later in the afternoon, Peggy Rennels presented a very, very interesting study of limb swelling in booster doses of DTaP for the most part and showed, I think, pretty clearly that the aluminum adjuvant, if it plays at all, plays a role at all, plays probably only a minor role in this interesting hypersensitivity reaction of entire limb swelling.

Dr. Pittman later on was the last discussion in the afternoon. He told us about the pilot study of reactions to anthrax vaccine, which elicited really two responses. One, some very useful suggestions, I think, as to the design of the larger congressionally mandated trial and a discussion, which I think you will all remember, of switching immediately or promptly to intramuscular dosage rather than subcutaneous. And, again, Norm Baylor pointed out that we cannot really do it quite that quickly. The larger trial will need to be carried out.

Finally today the MMF story was a centerpiece, certainly a high point of this conference, and the audience reflected a certain amount of skepticism. Skepticism may not be quite the right word but scientific skepticism probably at

its best was quite apparent, and as it should be because there are great, great many unanswered questions at this point.

Is this an epi phenomenon? Is it a trigger? To use Dr. Verdier's hypothesis number three, I believe, in his construct. Is this a trigger for an accelerated immune activation response in a population that is otherwise susceptible, as witness the increased frequency of connective tissue diseases and MS in the population of 50 MMF cases?

So there remains a great deal of work to be done to explore this interesting entity more fully.

In the panels, the panels were, I think, a great deal of help in defining the agenda. They occurred very recently, are fresh in your mind, and I really see no particular reason to review their findings and high points.

Panel A, as you recall, had some slides. The MMF slides, the audience tried to do a great deal of wordsmithing on those particular slides, and I think still were not completely satisfied. Fortunately, Panel B chose not to use the slide approach or else we would still be here wordsmithing that one. But in any event the panels, I thought, were particularly helpful.

Finally, I would like to comment just briefly on Max Lum's presentation and thank him very

much for taking us through this sort of reality exploration of risk communication. Something we have historically not done very well at all. And that will give me a quick opportunity to promote Bruce Gellin's initiative for the Infectious Disease Society on Vaccine Information and Communication, both within the profession and to the public. I think this is a superb effort being sponsored by the Infectious Disease Society.

So I think I have reached the end of my comments save perhaps one. I certainly do not promise that I will include all these slots in our, Dr. Myers, written summary, which I agreed to co-author with Marty. And I certainly expect that the written summary will provide some additional thoughts as well.

The one remaining thought, I think, Dr. Myers, I am sure, will thank his staff and we would wish to thank his staff as well, but it has been, I think, totally apparent to all of us that, Dr. Myers, you put a great deal of thought and effort into planning this workshop, this symposium, and I am sure the members of the workshop will join me in giving you a big round of applause.

(Applause.)

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MARTIN MYERS

DR. MYERS: Thank you very much, Ted. Thank you all.

I think it has been a wonderful meeting. I have learned a great deal and I obviously especially want to thank the NVPO staff for all of their activities. Lena Kombo, who most of you have met, and Sandra Browning, who was not able to be here, Robin Hughes and Theresa Hardy, who got us all organized and have kept us on schedule and so on.

I would also like to say a special word of thanks to Dan Reed for sitting in the back. Dan thought he was going to come and just be a participant but he got sworn into activity. So Dan is here. I think everybody else is outside. Lena is in the back also.

Lena, would you stand up so everybody can see who their e-mails come from?

(Applause.)

DR. MYERS: And, Dan, would you raise your hand?

And if you would just say thanks on the way out to that wonderful staff.

I would also like to thank our speakers and discussants in advance for their summaries and their manuscripts by the first of June to Lena so we can get a timely report out.