U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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OPEN SESSION 3

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Thursday, November 4, 1999

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The meeting took place in Versailles Rooms I and II, Holiday Inn, Bethesda, Maryland, at 9:10 a.m., Robert S. Daum, M.D., Acting Chairman, presiding.

PRESENT:

ROBERT DAUM, M.D., Acting Chairman

NANCY CHERRY, Executive Secretary

ALICE S. HUANG, Ph.D., Member

KATHRYN M. EDWARDS, M.D., Member

MARY K. ESTES, Ph.D., Member

KWANG SIK KIM, M.D., Member

DAVID S. STEPHENS, M.D., Member

DIXIE E. SNIDER, JR., M.D., M.P.H., Member

PRESENT (Continued):

BARBARA LOE FISHER, Member

PAMELA HARTIGAN, Ph.D., Invited Guest

WILLIAM BRITT, MD., Invited Guest

MARTIN MYERS, M.D., Invited Guest

L. PATRICIA FERRIERI, M.D., Invited Guest

JAY NELSON, Ph.D., Invited Guest

GEORGES PETER, M.D., Invited Guest

STANLEY RIDDELL, M.D., Invited Guest

KAREN GOLDENTHAL, M.D., FDA Representative

CYNTHIA KLEPPINGER, M.D., FDA Representative

JERRY WEIR, Ph.D., FDA Representative

REBECCA SHEETS, M.D., FDA, Representative

CHRISTOPHER BEISEL, Ph.D., Sponsor Representative

PATRICIA FAST, M.D., Ph.D., Sponsor Representative

GEORGE KEMBLE, Ph.D., Sponsor Representative

DAVID BERNSTEIN, M.D., Sponsor Representative

THOMAS HEINEMAN, M.D., Ph.D., Sponsor Representative

STUART ADLER, Ph.D., Public Comment

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(9:10 a.m.)

ACTING CHAIRMAN DAUM: Thank you, Dr. Greenberg.

We're going to move now into Session 3, which is an open session to discuss chimeric CMV vaccines.

I don't believe I have to invite the FDA members to sit at the table because --

MS. CHERRY: They're here.

ACTING CHAIRMAN DAUM: -- they're here. Thank you.

And at this time I will not avoid the FDA member who is going to give is an introduction. I can be taught, and we'll call on Dr. Weir, please, to introduce this session for us.

DR. WEIR: Thank you.

Can I get the first slide?

(Pause in proceedings.)

DR. WEIR: Bravo. Could we get everybody to refocus, please?

The topic to be considered by the committee in this morning's open session is the use of live attenuated human cytomegaloviruses as candidate vaccines, and what we hope to do this morning is to consider the safety and the use of four different live human cytomegaloviruses, cytomegalovirus recombinants as vaccines.

We would like to generate discussion about the precautions that should be taken before the use of such recombinants in a Phase 1 trial in seropositive individuals, and we would also like to obtain comments on any issues that should be considered before proceeding to future studies, and these could include those with seronegative persons, possibly Phase 2.

The agenda for this morning's session, as you can see both in your handout and the slide that I flashed up, I'm going to give a very brief introduction both about cytomegaloviruses and the products and the types of products that we are considering, and this is a joint effort by myself and Dr. Rebecca Sheets, also at the Office of Vaccines.

Following this hopefully very brief presentation, we have two invited speakers. The first is Dr. Jay Nelson, who is the Director of the Vaccine and Gene Therapy Institute at the Oregon Health Sciences University. He will talk about different animal models of cytomegalovirus.

Following Dr. Nelson, Dr. Britt, who is a professor of pediatrics and microbiology at the university of Alabama, Birmingham, will talk about some of the different clinical associations of cytomegalovirus.

After these two invited speakers, the sponsor, the National Institutes of Allergy and Infectious Diseases, will describe the proposed trial and probably go into a little more detail about the product than I will during this introduction.

Following the sponsor presentation, Dr. Cynthia Kleppinger will present an FDA perspective of the trial and list some of the concerns that we have about it. She will follow that with a summary and questions for the committee, and at that time we will have a discussion about this.

As I said, I'll try to keep this very short. Human cytomegalovirus is one of eight known human herpes viruses. Like herpes viruses, these are very large viruses. They're enveloped DNA, double stranded DNA virus that contain icosadeltahedral capsids. They're very large, 100 nanometers or great in diameter.

All herpes viruses containdouble stranded linear DNA genomes. They replicate in the nucleus. Viral DNA capsids are formed inside the nucleus of the infected cell.

And like all herpes viruses, cytomegalovirus has the ability to establish latency in its natural host.

Herpes viruses are, in general, a very large family of viruses. They are divided into three sub-families called alpha, beta, and gamma herpes viruses. These classifications are based on common biological properties.

As a beta herpes virus, cytomegalovirus has a restricted host range -- excuse me -- has a restricted host range. Another characteristic of beta herpes viruses are that they have a relatively long reproductive cycle in culture, and they have oftentimes salivary gland tropism.

Some of the specific biological characteristics of human cytomegalovirus, as I said, it's very species specific. There's not thought to be another host for human cytomegalovirus other than the human species.

It is endemic in the population. The majority of cases are subclinical, and it establishes a lifelong latency with periodic shedding. The site of latency is still somewhat controversial, but at the present time it is thought to be likely a progenitor of dendritic cells and monocyte macrophages.

The cytomegalovirus genome can be depicted, as I've drawn on this slide as a linear double stranded DNA. It can be conveniently divided into two unique sections, a unique long and a unique short section bounded by inverted repeats, shown here as the boxes AB, B prime, A prime, the inverted repeat, and C, AC and C prime, A prime.

As I said, cytomegalovirus is one of the largest viruses known. It's greater than 200 kilobase pairs in size, and it codes for approximately 200 different proteins.

The functions of the proteins that are encoded by the virus, these genes are interspersed throughout the genome. There are at least two antiviral targets, Ul 97 is a kinase which phosphorylates gancyclovir, and Ul 54 is a DNA polymerase which is sensitive to the inhibitor foscarnet.

In the next two slides I'm going to describe in a very general way the construction of recombinant CMVs. I've shown once again at the top the schematic diagram of the genome. As I said earlier, the genome is a double stranded DNA. It is infectious when introduced as naked DNA into cells, and this property means that if one takes overlapping cosmid sets, shown here by the solid lines below the diagram of the virus; if one takes cosmid sets that contain the entire genetic information, in other words, they overlap the entire genome, the introduction of these cosmid sets into a cell will result in live virus being generated through homologous recombination between the overlapping segments of the cosmids.

Similarly, if one takes overlappingcosmid sets from two different strains of cytomegalovirus and introduces these into the same cell, one can obtain chimeric cytomegalovirus recombinants containing pieces of both strains of cytomegalovirus. The two strains are shown in two different colors at the top.

These cytomegalovirus chimeras can be accurately analyzed as to the origins of the regions from each parental strains. In other words, the crossover points between Strain 1 and Strain 2 can be accurately determined in the resulting chimera.

The product in question today is an example of this type of recombinant cytomegalovirus, and what we are considering today are four unique human cytomegalovirus chimeras, each containing portions of the Towne and Toledo genome.

There have been accurately characterized, as I said, for the crossover points of the two strains, and to the extent possible, they have been biologically characterized.

I should say all four viruses are susceptible to human cytomegalovirus antiviral drugs.

In the last two slides, I'm going to list just general concerns both with these products and in these types of products. One's generated by the same methodology.

First of all, as you will hear several times today, the molecular basis of cytomegalovirus pathogenesis and virulence are unknown. That means that for a chimeric virus, the influence of virus genes from each parent strain on the attenuation of the chimera is also unknown.

The biological and molecular characterizationof a recombinant cytomegalovirus does not predict its attenuation.

For recombinant viruses that are made by this methodology, there is also the possibility of mutations in the genes that are targets for antiviral drugs. As I said earlier, this has been addressed, and all of the chimeras that are being considered today have been shown to be susceptible to more than one antiviral CMV viral drug.

The animal models, which you'll hear more about in a minute, of cytomegalovirus infection do not reflect virulence or attenuation.

And then finally there is at least the theoretical possibility of when one uses live cytomegaloviruses or cytomegaloviruses recombinants that there is the potential for reactivation of latent CMV and the potential for recombination with other strains of CMV.

Now I'm going to present the actual questions or the issues that are going to be presented to the committee, and I'm just going to read through them at this point, and you will see them again at the end of all of the presentations before we start the discussion.

Number one, the following items pertain to the sponsor's proposed Phase 1 trial in human CMV seropositive subjects.

A. Please discuss whether the available data relevant to safety are sufficient to proceed with the proposed clinical trial.

B. Please discuss any additional studies relevant to safety that should be conducted prior to the proposed trial.

C. Please comment on the adequacy of

precautions designed to limit the transmission of HCMV vaccine candidates in the proposed trial.

Number two, please comment on the use of these types of live recombinant viruses as vaccines in future studies. Specifically this can include comments on studies in other populations, especially CMV seropositive subjects, larger numbers of subjects, for example, Phase 2 and Phase 3 trials, and potential target populations such as adolescents.

And the last comment we would like: please comment on the need for additional preclinical animal and laboratory studies, especially ones to address safety concerns to support future clinical studies.

And as I said, these will be presented again at the end of all of the open session before the actual discussion takes place.

So with that introduction, I think we will proceed to Dr. Nelson.

ACTING CHAIRMAN DAUM: Thank you, Dr. Weir.

We will go right on, I think, to Dr. Nelson at this point and then have some comments after Dr. Nelson's presentation.

DR. NELSON: Okay. So I was asked to give a ten minute overview on animal models for CMV. So in the very few slides that I have I'll do that.

Okay. So I think that, you know, with the introduction that you've had and the question was raised earlier as to whether or not there are animal models for CMV, the reason that there isn't an animal model for CMV is it just doesn't grow in any other species of animals. By definition, cytomegaloviruses are species specific.

That doesn't necessarily mean that there aren't homologous viruses that infect all of these different animal species, and the ones that have been worked with are actually listed in this column here, which primarily is a mouse cytomegalovirus or the murine cytomegalovirus, which has been the most characterized.

Rat cytomegalovirus, which is becoming more characterized, and in fact, I think it's almost completely sequenced right now.

Rhesus CMV, for which there is very little information known about this virus, and it's very difficult because of the animal model, and the expense of the animal model to work with this virus.

And guinea pig cytomegalovirus.

I put diseases in two different

categories, acute diseases and long term diseases. The acute diseases for cytomegalovirus are listed here and have been talked about. Primarily it's a mononucleosis-like disease that individuals can acquire. It's one of the leading viral causes of congenital infection, which is the reason that we're here, for developing a vaccine.

It's mainly a probleminimmunocompromised individuals, and if you look at disease patterns in these animal models, it's primarily in an immunocompromised situation that these animals develop disease.

In terms of long term disease, we've mentioned, or maybe we haven't mentioned, that potentially atherosclerosis can be a problem. Malignancies may be a problem, although both of these are unknown.

I think there's quite a bit of evidence -- 1 think Bill is going to be going into this -- about restenosis and transplant vascular sclerosis, and are there animal models for looking at this? Yes.

Primarily it has been with mouse and rat cytomegalovirus in which they've developed models for restenosis and transplant vascular sclerosis, but also there is more models that are coming out now with atherosclerosis.

Okay. So in terms of a model of restenosis following angioplasty, primarily the work that's been done with this has been in Stephen Epstein's lab, and he's reported that if you perform carotid injury to a rat animal model and infect with cytomegalovirus, there's an increase in neointimal formation or closure of the vessel itself that's 40 percent greater in the CMV infected animals when you compare it to the controls, and unfortunately this is really the only documentation. This is an area that's just being developed right now because of the association of CMV with the development of restenosis.

In terms of transplant vascular stenosis, there is a body of literature that has been published starting actually back in the '80s, and this is by Bruggeman's group and Hecka Pya's group in Finland, in which they've taken aortic vessels and transplanted these into rats and then looked at the development of transplant vascular sclerosis in these animal models.

There are is some more recent data that's coming out of Susan Orloff's lab in which she's been taking solid organ transplants in rats and showing that in these CMV infected rats that there's a greatly accelerated increase in the development of transplant vascular sclerosis.

So there is a body of literature that says that, in fact, CMV can be associated with this and, in fact, this is just some data just looking at this model showing that looking at chronic rejection, showing that without CMV and with CMV that you can develop lesions.

And the role of CMV in this is implicated more in that when you use anti-CMV therapy, and this, again, has been published Bruggeman's group; when you treat animals with DHPG, that the incidence of air allografted TVS is greatly reduced in these models.

So the drug would suggest that, in fact, CMV does play a role.

In terms of atherosclerosis, there's only one report that's in the literature in which it's been shown that MCV infestation of mice has been shown to induce vascular lesions that are similar to atherosclerosis in humans. There's a recent FASEB abstract by Stephen Epstein using Apo E mice that also shows that MCV infection of Apo E knockout mice greatly increases the development of atherosclerosis in these animal models.

So there are at least two animal models that we know of right now in which MCV has been shown to induce vascular lesions similar to atherosclerosis in humans.

This is just to compare the differences between human cytomegalovirus and mouse cytomegalovirus. So if you look at the blocks of homology between these two different virus genomes, you notice the difference in the structure of mouse cytomegalovirus compared to human cytomegalovirus. It's very different, where you have a long unique region and a short unique region, border by inverted terminal repeats. There's only a long unique region in MCV that's bordered by terminal repeats.

The blocks of homology are shown here. When you look at the percent identity for amino acid overlap, the yellow is 15 to 25 percent. The red is greater than 25 percent and can reach up to 50 percent.

Most of the homology are in regions of structural genes or genes that are highly conserved like DNA polymerase and genes that would be necessary for replication.

There are also some other genes that mouse cytomegalovirus has that Bill may talk about later, and that's chemokine receptor genes, and these chemokine receptor genes may, in fact, be a pathogenic gene in these viruses.

So can we identify pathogenic CMV genes involved in chronic disease processes, not in acute disease, but in chronic disease? And I think that the answer to that is yes.

Does CMV encode genes involved in long-term pathogenic processes? It's unknown whether they are. So I think that the animal models will actually shed light on this.

So I think I'll stop there and answer any questions that you want.

ACTING CHAIRMAN DAUM: Thank you very much, Dr. Nelson.

We have some time now for questions and comments regarding Dr. Nelson's or Dr. Weir's presentation.

DR. NELSON: Is Bill going to present and then we're going to have questions?

ACTING CHAIRMAN DAUM: Well, we could do it that way. Why don't we see whether people want to.

DR. NELSON: I think it will fit into what I'm talking about.

ACTING CHAIRMAN DAUM: All right. Then we will accept that alteration in program and call on Dr. Britt to make his presentation, and then we will have questions and comments.

DR. BRITT: We'll see if it will fit in because I didn't know what Jay was going to say.

I was asked to talk about some of the clinical associations with CMV, and primarily obviously by the FDA, not by the sponsors of the vaccine program, and so I'm really not going to talk about congenital CMV. That's probably what I know more about than any of these things because I feel that's probably going to be presented in some depth by the sponsors.

But what I wanted to discuss was really some of the clinical syndromes associated with this virus infection in humans, and I'm going to divide them into acute and chronic.

And the acute infections are obvious to many of you in the audience: mononucleosis; transplant syndrome, which I really consider an acute infection; fetal infections, which although they're the result of a chronic viral replication, on a time line are probably more of acute infections and in organ disease which you might see in HIV infected patients, such as diseases such as retinitis or colitis.

The chronic diseases are the ones that are a little bit more difficult to get a handle on. Chronic disease such as transplant coronary artery atherosclerotic disease, post coronary angioplasty restenosis, possiblycoronaryatheroscleroticdisease, AIDS and AIDS in a separate disease category, not an organ disease, but just the long term morbidity and mortality associate with HIV infection, co-infection with HIV and CMV.

And some of the aspects of congenital CMV, such as hearing loss, hearing loss that you'll see in just a moment that may not be present at the time of birth, and there have scattered reports in the literature over the last 20 years of cervical and lymphoid cancers associated with cytomegalovirus infections, and these are based primarily on seroepidemiologic studies.

I picked two of these to talk about. One is the coronary atherosclerotic disease, and one is hearing disease in children, and I just want to point out, sort of as Jay had a slide that said the answer is unknown, most of these things are unknown, but I think these are important issues when you're talking about a vaccine, a replicating vaccine, a DNA replicating vaccine that can persist in the host from the time that the virus is injected.

So I think we have to think about the possible long term consequences of a biologic such as this.

So if you look at hearing loss in children with congenital CMV, many of us think that the kids come out deaf, but they really don't, and these are kids with asymptomatic congenital CMV, and this is a study by Karen Faller in our department, and what I wanted you to see is that there is a delayed or late onset in about 18 percent of these kids. There was a progression in 72 percent, and these other ones that are of more interest to audiologists, the fluctuating loss and high frequency losses in 22 and 68.

But I want you to look at is delayed or late onset hearing loss was 27 months after birth. So that's nearly -- and the range is 25 to 62 months. So up to five years after birth some of these kids could have late onset hearing loss.

Progression of loss? Eighteen months was the median. Two to 70 months. So we're looking at a very long time where these kids could actually have progressive hearing loss as a result of this virus infection. So this is not really an acute event from this. This is a chronic long term effect of this virus.

So what is associated with this in the human? We don't really have an animal model for hearing loss at this time, although there is some data from the Rhesus monkey model, the in utero neuropathogenesis model, that you can actually achieve some pathology in the auditory system by infection with Rhesus CMV.

But I wanted you to look at this because I dug this out several months ago. This is what we know about the hearing loss associated with human CMV. These are the total number of temporal bones that have been looked at for hearing loss in these kids. There's a total of nine here.

And as you can see, there's a variety of pathologies that we see here. None of them though really point to one common pathway for hearing loss, and these were all done very early on so that we have no clue as to what's associated with a hearing loss in these kids at three to five years.

And many of these studies, actually even one from our institution, have been questioned because of the use of the reagents that were done at that time. These were done in the '70s where there weren't really good reagents to detect viral antigens.

The point is that really very little is

known about these pathogenesis of this disease, but it's clear that it is chronic effect of this viral infection.

The next one are chronic inflammatory processes associated with CMV: atherosclerosis, restenosis, chronic rejection of transplant vascular sclerosis, and grant versus host disease. And I'm really going to talk about these three in the next two slides, three slides, because there's really not enough time to present all of the different studies that have been done on this.

And I actually had an overhead, and I'll bring it up at this point. This is an overhead. I did a CRISP search yesterday or the other day on grants that were funded by the NIH. These are grants that have gone through study section and been reviewed for the role of CMV in atherosclerotic disease and vascular disease. And I found nine or ten. So this is an area of interest by the NIH.

Melnick and Debakey published things many years ago that CMV was a cause or an association with coronary atherosclerosis, and this is a table that I actually pulled out of a review that Melnick had published in 1993, and all he showed was that the seropositivity in this group with coronary artery disease was much higher than a matched pair group that did not have any cardiovascular risk factors or events.

The same thing for the other groups that he found. So these were all serologic studies that were done with antibody prevalence.

In late '80s at Stanford, the transplant group there notice an association between CMV infection and graft survival, and what they noticed was that they had an increased graft loss for patients that were seropositive for CMV versus those that were not, and this was associated ultimately with restenosis of the coronary arteries of the engrafted heart, and this is people that are not -- I can't read it, but anyway, these are people that don't have CMV. These are people that do. So there's a significant difference, and you're more likely to lose your graft as a result of atherosclerosis in this group.

That's okay.

This is a study that was done by Epstein at the NIH, and this was a restenosis following a directional coronary atheroectomy in a group of patients with coronary artery disease, and you can't see it, but what this says, in essence, is that if you have CMV, you're more likely to restenose your coronaries than you are if you're seronegative, and this is shown in a histogram here.

Again, so there's several associations, and I could put up slide after slide after slide after slide that would show the association, but in fairness I could also put up slides that say that, no, there is not an association.

So, boy, we got two in a row. I didn't do it. so --

(Laughter.)

DR. BRITT: That one we're going to have to turn around.

Okay. So if you look through the studies for the association with CMV with coronary atherosclerotic disease, if you look in the transplant cases -- can you focus that, please? Thank you -- the histology shows the presence of viral antigens in the atheromatas, the presence of viral DNA and the presence of viral RNA in some studies.

I don't know what this symbol is. My secretary made this in Power Point and put into a slide machine, and this was supposed to be an arrow going up. I'm not sure what that is exactly, but anyway, this is supposed to be an arrow going up, and it's the risk of restenosis goes up with seropositivity.

In the post coronary angioplasty restenosis, again, the same thing. You can find viral DNA. YOU can find viral antigens, and again, there's an increased risk of restenosis of seropositivity.

And, in fact, this is the finding of most papers, although as I said, you can find papers that argue that there's no association.

Okay. Don't change it.

This is a very recent study from Stanford and the cardiac transplant group in which they addressed the question that I think Jay showed in the rat transplant model, and this they looked for the development of atherosclerosis intransplantedorgans.

And what they did was they randomized the patients in this. Actually they didn't randomize the patients. They went back and reanalyzed their data, but they looked at a group of patients that were treated with gancyclovir or 34 days, I think, post transplant or 50 days post transplant, and those that were not treated with gancyclovir.

And what they showed was that if you got treated with this antiviral agent, it's specific for CMV and other herpes viruses, but certainly is active against CMV; that you can reduce your risk of developing atherosclerosis in a transplanted organ.

They freely admit in this study though that this was not a prospective trial. It wasn't randomized. So they went back and analyzed the data. So we're all aware of all the problems that are in this type of studies.

You're not going to be able to read this. I was going to read it for you.

ACTING CHAIRMAN DAUM: We're getting used to it.

(Laughter.)

DR. BRITT: Okay. How does this happen? There have been lots of studies that have suggested with CMV that there's increased adhesion, inflammatory cells on endothelial cells. Recently and Jay has a paper in press called the "Human CMV Chemokine Receptor US 28 Mediates Vascular Smooth Muscle Migration," providing a mechanism for actually how CMV could influence the development of atherosclerosis.

He presented this at the herpes workshop. I'm not going to talk about this data because, as I told Stan Riddell, I usually don't like to talk about other people's data when they're at the meeting. So if people want to hear more about that, I guess we could ask Jay some specific questions about that.

ACTING CHAIRMAN DAUM: Are there a lot more slides? Should we take a minute and just --

DR. BRITT: Just two slides more.

ACTING CHAIRMAN DAUM: Okay.

DR. BRITT: Just two slides more.

Okay. So in looking at the data about acute versus chronic disease with CMV infections, I think that it's pretty easy to break it down. Viral replication in acute disease, it's not clear at all that viral replication is a measure of pathogenesis and chronic infection. So, therefore, if you use viral replication 'as a measure of virulence and pathogenesis of this virus, it's not clear that you're going to know a lot about what happens in the chronic disease.

Viral gene expression in acute disease, probably the full program of the virus is expressed. In chronic disease we really have no clue as to what regions of the virus might be expressed or which ones are important for chronic disease.

Response to antiviral drugs, yes, it happens in acute disease. In the chronic disease, that is, once you initiate, if CMV does play a role, once you initiate the process of atherosclerosis, will drugs impact that? It's not known.

Multi-system disease, quite common in acute disease. In chronic disease, no. It's usually limited to one or two organs.

Immune control, yes, in acute disease for sure. Does it play a role in chronic disease? There's no information on that. It's unclear whether some of the invasion mechanisms of this virus may prevent the immune system from clearing the virus.

Incubation period, you can put it any time you want, and everyone in the audience probably has their own time frame. One to 48 months, and again, this is another one of my signs here from my slide maker. I don't know what that is, but that's supposed to be years, dash, decades.

PARTICIPANT: Hourglass.

DR. BRITT: It can be a long time. Yeah, an hourglass, half full.

Virulence. Virus replication obviously may be important for acute disease, especially in organ disease.

Chronic, it's not clear at all what the genes and even what the pathogenic mechanisms might be.

Okay. Last one. Unresolved issues in the biology of this CMV infections: protective immunity during acute infections. I don't think anyone here could argue that they know what the surrogate markers of protective immunity are for this virus. We all have our own opinions. We've all published things, but I'm not sure that anybody can present really a cohesive case.

Immune evasion, does that play a role? It may. Again, that information now is being developed in several laboratories.

And reinfection. I don't think we should ignore this. There are many of this in this audience that will argue against this, but reinfection at least in my mind does occur, and that's an issue we have to think about when we think about protective immunity.

Chronic infections, what is persistence and latency? This is still, I think, hotly debated.

Gene expression during -- it's supposed to be lytic -- gene expression, lytic versus non-lytic genes. Is this important in chronic infection and pathogenesis tissue specific expression?

And again, inflammation, and these are supposed to be an arrow going this way and an arrow going that way instead of a Maltese cross. I don't even know where that came from.

But anyway, inflammation versus CMV gene expression. Does the inflammatory response induce gene expression or does CMV gene expression induce inflammation?

So I think there are a lot of questions at least in this column here that are going to be very difficult to get at. These may be a little easier.

And I'll stop there.

ACTING CHAIRMAN DAUM: Okay. Perhaps we could turn some lights on. And thank you, Dr. Britt, for an interesting presentation, challenging to follow with your slides.

We now will have time for question and comment about the presentations we've heard so far.

Dr. Kim.

DR. KIM: Both of you talked about the association of CMV with the vascular diseases. Is there any information available from the literature or others that the Towne strain and Toledo strains have a different outcome in terms of association in respect to animal models?

DR. NELSON: I think that's what I asked in the last session, and I don't think that they knew. So I think the answer is no unless somebody else wants to stand up from the other side.

DR. KIM: Can I do one more?

ACTING CHAIRMAN DAUM: Yes, you may.

DR. KIM: I'd like to hear more about the chemokine receptor story. Can you elaborate a little bit more on that?

DR. NELSON: So basically the hallmark of restenosis, transplant vascular sclerosis and atherosclerosis is smooth muscle cell either proliferation or migration, and we developed a migration assay to look at this, and the first question was does CMV induce migration in an in vitro culture system in smooth muscle cells, and what we found was that it significantly caused migration of smooth muscle cells, primarily aortic smooth muscle cells, not venous smooth muscle cells.

So it was very specific, and actually there was a hierarch of smooth muscle cells that gave migration with carotid artery being better than pulmonary, and so on and so forth.

Secondly that we can knock a gene out of the virus that causes this, which was one of the four chemokine receptors in CMV called US 28.

And, thirdly, that if you take that gene and express it in smooth muscle cells, smooth muscle cells constituitively express MCP-1, and so MCP-1 in combination with the viral gene caused the migration, whereas the cellular chemokine receptor, CCR-5, could not rescue the phenotype in the virus and also could not induce smooth muscle cell migration.

SO it's something unique within that virus gene.

ACTING CHAIRMAN DAUM: Dr. Huang next, and then Dr. Estes.

DR. HUANG: Dr. Nelson, where do these four chemokine receptors map?

DR. NELSON: There are two in the unique short and two in the unique long.

DR. HUANG: Do you know on the right or left-hand side or in the middle?

DR. NELSON: Yes. In the long unique, if you looked at the map, it would be on the left. There are two Ul 33 and Ul 78. Ul 33 is a CC chemokine homolog and Ul 78 is a CXC, and then in the right-hand side unique region, there's US 27 and US 28.

ACTING CHAIRMAN DAUM: Dr. Estes.

DR. ESTES: Is there any heterogeneity in your proliferative assay looking at different strains of HCMV?

DR. NELSON: It's not a proliferative assay. It's a migration assay.

DR. ESTES: Sorry.

DR. NELSON: Is there any difference in the viruses?

DR. ESTES: Right.

DR. NELSON: No, and in fact, we use Towne.

ACTING CHAIRMAN DAUM: Dr. Snider and then Dr. Peter.

DR. SNIDER: Someone earlier alluded to the putative association with cancer, and I just wondered if someone could very quickly talk about the nature of any evidence and the strength of any evidence for a relationship between chronic infection and cancer.

DR. NELSON: There's been a body of literature looking at, quote, unquote, genes that are involved in malignant transformation of the cells, and I think that that's a quagmire, in my opinion, of data.

However, I think that there is a body of literature that says that when you transplant organs in individuals and those individuals become CMV infected, that there's a much higher incidence of lymphoma that occurs in these individuals, primarily in the organ transplant.

ACTING CHAIRMAN DAUM: Dr. Peter.

DR. PETER: Two questions. Is this working?

Does any diversity genotypically or phenotypically exist between the different wild types of cytomegalovirus? Any characterization? Are all of the strains alike when you looked at their genotype?

DR. BRITT: No, they're quite different. It's very easy to track genotypes just by simple restrictions, restriction digestion of all wild types. It's quite easy to do that.

DR. PETER: Are certain types more commonly found in congenitally infected children?

DR. BRITT: There's really no evidence for that. There were associations -- there were attempts at that ten, 15 years ago, but to my knowledge, there's no association with, quote, virulent genotype.

DR. PETER: Right, and do we have any long term follow-up on children, say, who were diagnosed with congenital CMV in the 1960s on early development of atherosclerotic disease? Does duration of infection have any possible impact?

DR. BRITT: It's possible to actually probably do that analysis because there's -- at least in our clinical, there were children that were enrolled in the early '70s. So it's conceivable to do that.

To my knowledge, no, and I also think that raises a question that I was going to ask one of the presenters, was is there any evidence from the vaccine trials that have already been done with Towne or Toledo or challenges that -- in long term follow-up in those patients, not the acute mono syndrome and things like that.

ACTING CHAIRMAN DAUM: Dr. Stephens and Dr. Myers.

DR. STEPHENS: A follow-up to an earlier comment. Is there any study of CMV in nonhuman primates? And does anybody have any data on the issues of CMV in nonhuman privates or studies of chimps, for example?

DR. BRITT: Chimps?

DR. STEPHENS: Chimps, apes, anything.

DR. NELSON: Is this for what? For congenital disease or what?

DR. STEPHENS: I'm just asking about general data on CMV in those.

DR. BRITT: I'm not aware of any data in chimps, but that doesn't mean there hasn't been a study published somewhere. There is an active investigation from at least three primate centers right now to look at Rhesus CMV in Rhesus macaques, and most of that's been done with just sort of baseline virologic observations in these animals.

And then in a separate project at the University of California, Davis, who Peter Berry is the PI on, an interuterine infection with Rhesus CMV basically in Rhesus macaques fetuses, which seems to model a congenital disease.

ACTING CHAIRMAN DAUM: Dr. Myers.

DR. MYERS: The frequency of reinfection, and is there any evidence for recombination, particularly in the prior vaccine trials?

DR. BRITT: The latter part of that question, recombination in vaccine trials, I don't think that was looked for. Clearly recombination occurs. I think there have been several publications in the last few years on that recombination between -- what appears to be recombination between wild type viruses.

Reinfection does occur, but I think the real number of reinfections we don't know, probably dependent on the exposure risk. Clearly, reinfections occur. From our unit there is a recent paper that was presented at the ICAAC which shows that reinfection can actually lead to congenital infection, symptomatic congenital infection. So I think that may be the tip of the iceberg, but we really don't have that data yet, and we're in the process of trying to collect it.

DR. ESTES: Dr. Estes?

DR. NELSON: Can I comment on that?

ACTING CHAIRMAN DAUM: Yes.

DR. NELSON: It's difficult. A lot of studies have been done to look at this, have used restriction analysis to look at this, and it's pretty difficult to do this, and in fact, there was a study that was done at Hutchison in which a transplant patient had died from cytomegalovirus infection, and they took different organs out, and then they isolated the virus and phenotyped the virus.

And they found that in each organ the map was different. So the question is if you looked at the four organs, all four types of virus that came out were different. So does that mean that the patient was infected with four different strains of virus or does it mean that the virus adapted to the tissue and changed?

ACTING CHAIRMAN DAUM: Dr. Estes.

DR. ESTES: I have two questions. I still don't have a clear answer. Has HCMV been put into chimps and do we know it doesn't infect chimps?

DR. BRITT: I don't know the answer to that question.

DR. ESTES: Okay.

DR. NELSON: I don't know the answer either.

DR. ESTES: Okay, and I have a second question.

DR. FERRIERI: Is there anyone in the room that would like to comment on that question?

Okay. Your second question.

DR. FERRIERI: There is someone.

ACTING CHAIRMAN DAUM: Okay. Thank you.

DR. MOCARSKI: My name is Ed Mocarski. I'm from Stanford University, and I'm also a scientific advisor to Aviron.

In studies that were done probably five or six years ago to look at whether chimp cells were susceptible to CMV, Dick Spaete reported that chimp fibroblasts can be infected with human CMV.

In studies that I don't think have ever been published, it appears that chimps, at least chimps in captivity are uniformly infected with a virus that serologically cross-reacts with human CMV, and so there are no naive chimps that have been identified.

There is currently a sequencing effort in Glasgow to sequence chimpanzee CMV because it is thought possibly it will be closer to human CMV and will give some important information about the genome arrangement.

One thing that's important to keep in mind about animal cytomegaloviruses is any of them that have been described this morning are very different than human CMV, and so any information provided on animal cytomegaloviruses is really quite of very questionable predictive value.

Whether chimpanzee CMV would be a better predictor of human CMV is actually another very difficult question to address, but it's already known from the sequencing that's gone on by Andrew Davison that it's not human CMV, although it serologically cross-reacts.

So I think to try to put a perspective on the questions that have been asked a number of times this morning, human CMV is not only a species specific in regards to you only find it in humans. It's only possible to infect humans and human cells. It's restricted in its ability to spread to other species, and so that's why there's a very difficult problem in having no animal model in which to be able to study human CMV.

ACTING CHAIRMAN DAUM: Would you identify yourself also?

DR. SPAETE: Yes. Richard Spaete, Aviron.

I just want to put a fine point on Dr. Mocarski's statement.

That was an in vitro study. It was a human cytomegalovirus in chimpanzee primary fibroblast cells. To my knowledge, there is no evidence that anyone has done an experiment in vivo in a chimpanzee.

ACTING CHAIRMAN DAUM: Thank you for that.

Do you want to comment on this same question?

DR. ADLER: No, a different one that somebody asked.

ACTING CHAIRMAN DAUM: Oh. Then I'd like to go to Dr. Estes' follow-up question first.

DR. ESTES: My second question was about the chemokine receptor knockout CMV. Does those grow well?

DR. NELSON: Yes.

ACTING CHAIRMAN DAUM: Okay. I have one question for the animal modelers, at least the animal model nay sayers, I guess, is that given the disparity between the viruses that infect different animals, is there a system -- is, for example, that mouse system -- at all promising for at least studying the mechanisms of disease, the kinds of antigens that produce disease, and perhaps construction of vaccine models that might prevent it in that animal, recognizing the problems with extrapolation?

DR. NELSON: Do you want me to answer that?

ACTING CHAIRMAN DAUM: Yes.

DR. NELSON: Again, I think it's the disease that you're looking at if you're asking questions about acute disease or long term disease.

I think that the only way to approach long term disease is through animal models and primarily through mouse models because the Rhesus macaque model, the chimpanzee models, they're going to be long term, and you're not going to lean that much.

I mean, NIH funding won't go for 30 years on a project. So we need to have answers quickly.

In comment to Dr. Mocarski's comment on the virus models and the viruses, the viruses are clearly very different, but there are homologs, as I said, and certainly you can mimic human disease in these animal models. so I think that they will prove to be valuable.

ACTING CHAIRMAN DAUM: Did you want to comment on that same issue?

DR. BRITT: Can I? Yes.

I agree with Jay. NIH funding doesn't go for 30 years, but if you inoculate somebody with a replicating virus, it will last 30 years.

But the other thing is about the animal models. For instance, the Rhesus virus is very similar in many, many of its regions with the human. As a matter of fact, in the models that Peter Berry uses and Scott Wong in Oregon Health Sciences University, we use panels of human monoclonal antibodies made against human CMV to actually identify this virus, including antibodies that are against the principal neutralizing determinants on the glycoproteins.

So there is a fair amount of similarity of these viruses.

ACTING CHAIRMAN DAUM: Okay. In the interest of time, I think we must bring this, I think, fascinating discussion to a temporary close. We will take a break and reconvene promptly at 10:30.

Some of these issues can be pursued in later question and comment sessions this morning.

Thanks to our speakers and commenters.

(Whereupon, the foregoing matter went off the record at 10:12 a.m. and went back on the record at 10:34 a.m.)

ACTING CHAIRMAN DAUM: We're going to call the meeting back into session.

Would everybody who has not already done so please conclude their conferences and sit down?

The next item on this morning's agenda is a presentation coordinated by NIAID, which is going to feature four speakers up and down in 40 minutes, a sight to behold.

(Laughter.)

ACTING CHAIRMAN DAUM: And we'll first call on Dr. Beisel to begin and introduce the next speakers.

DR. BEISEL: Well, good morning. My name is Chris Beisel, and I'm with the National Institute of Allergy and Infectious Diseases.

I manage NIAID's supportive research and development that's related to cytomegalovirus.

Now, in this open session I'm going to begin by telling you about NIAID's interest in the prevention of cytomegalovirus disease and in the development of a safe and effective vaccine for this virus.

Following me, Dr. David Bernstein will describe the clinical manifestations of CMV infection.

Dr. Tom Heineman will describe the design of proposed Phase 1 clinical trial.

And Dr. Patricia Fast will provide a brief summary.

could I have the next slide, please?

Disease due to cytomegalovirus is a very significant and largely under appreciated public health problem. Our next speaker, Dr. Bernstein, will provide you with more information on the clinical aspects of CMV disease, and as he's going to point out, the natural history of CMV infection makes a vaccine the most feasible approach for controlling disease.

In addition, according to a report that will be issued soon by the Institute of Medicine, a human cytomegalovirus vaccine would produce not only a reduction in morbidity and mortality, but would also result in substantial annual savings in health care costs.

But there are presently a variety of candidate cytomegalovirus vaccines in various stages of development, and speeding this development process to produce a safe and effective vaccine is a major priority for NIAID.

Next slide.

Now, as part of our process for setting vaccine research priorities, NIAID commissioned a study by the Institute of Medicine. The IOM committee was asked to develop a quantitative model for prioritizing vaccine development, and they adopted a cost effectiveness approach, which makes it possible to compare potential new vaccines on the basis of their anticipated impact on morbidity and mortality and on the basis of the cost for health care, for use of the vaccine, and for vaccine development.

Next slide.

Based on their analysis of potential benefits and potential costs, the IOM committee placed candidate vaccines into one of four general levels.

The Level 1 vaccines are those the committee considered most favorable for development. These vaccines would realize both a net savings in health care costs and a reduction in morbidity and mortality as measured in terms of quality adjusted life-years or QALYs.

Vaccines in Levels 2 through 4 would still give us a reduction in morbidity and mortality, but are associated with successive increase in costs to achieve that benefit.

Could I have the next slide?

The IOM analysis placed a cytomegalovirus vaccine at Level 1, among the most favorable for development. In addition to reducing the impact of CMV disease, the committee estimated that a vaccine would yield an annual cost savings of between one and $4 billion.

And we need to note here that the committee's model assumes vaccination of 12 year olds and makes further assumptions regarding the vaccine's efficacy and rate of utilization in the community.

Of course, the actual immunization strategy that would be used would be based upon review of the safety and efficacy data that comes out of the clinical trials.

Next slide.

Now, given that a vaccine is likely to be the best approach for controlling CMV infection, it's our job at NIH to facilitate the research and development process wherever needed to assure that a safe and effective vaccine becomes available to the public as soon as is practically possible.

There are several potential CMV vaccines under development, and they are listed on this slide.

However, based on the data that has been generated to date, none of these has emerged as being either clearly superior or, for that matter, clearly inferior to the others.

As you've already heard, it's not possible to get an indication of how well any of these might protect against human disease without actually administering the vaccine to humans.

So because it's not clear which of these several different candidate approaches is likely to be optimal in terms of both safety and efficacy, NIAID is supporting parallel development of multiple vaccine candidates so that we can get a suitable product to the public as soon as possible.

I'd like to specifically address the reason for including a live attenuated vaccine in the portfolio of vaccines that we're developing. We feel that this strategy is important to pursue because it's been the most successful to date against several different viruses in the herpes family.

The only human herpes virus vaccine that's been licensed to date is the live attenuated varicella vaccine for prevention of chicken pox, and in addition, there are five live attenuated vaccines that have been licensed by the USDA that are effective against herpes viruses that affect domestic animals.

And it's interesting to note that relevant to the discussion we had earlier today regarding chronic diseases and specifically coronary artery disease, that the vaccine for Merck's disease virus, which is a well established model for herpes virus induced coronary artery disease, actually prevents coronary artery disease in those animals.

Next slide.

Now, finally, we'd like to give you just a bit of background on NIAID's involvement in the development of the vaccines that you're considering today. NIAID's principal support for the development of these has been through the small business innovation research, or SBIR, grant program.

Aviron independently applied for and was awarded both Phase 1 and Phase 2 SBIR grants which supported the construction of the chimeric vaccine viruses, the manufacturing of the vaccine candidates, and part of the cost for the Phase 1 clinical testing.

NIAID has also provided support for the initiation of the Phase 1 trials through our vaccine and treatment evaluation units, or VTEUs. This is a network of clinical centers and support units that operate under contract to NIAID for the evaluation of vaccines.

Aviron initially approached the VTEU organization seeing support for clinical testing of their chimeras. The VTEU has agreed to take on this project, and protocol development has been directed by one of the VTEU investigators, Dr. Tom Heineman, the St. Louis University School of Medicine.

And the IND submission has been an interaction with FDA staff, has been managed by NIAID staff.

Now, that concludes my introductory remarks. I'd like to introduce our next speaker, Dr. David Bernstein, who's at the Cincinnati Children's Hospital Medical Center. He's an investigator in the Cincinnati VTEU, and his presentation will cover the clinical manifestations of CMV infection.

DR. BERNSTEIN: Good morning. I wanted to emphasize two points in my brief presentation this morning: one, that CMV infection is very common, but a benign disease in the normal host; and, two, that this is a, disease worth preventing because of the devastating effects it has on a fetus is a pregnant woman is infected with CMV.

Next slide.

As I said, CMV is a very common infection.

Approximately two percent of adults are infected each year in the United States.

The prevalence depends somewhat on age, socioeconomic status, and geography, but in general, over 50 percent of adults are seropositive and have been infected.

Next slide.

As I said, the primary infection is usually asymptomatic, but if symptoms are present, it presents as a mild mononucleosis-like syndrome, which I'll talk about a little later.

Like all herpes virus infections, CMV does produce a persistent or a latent infection. This can reactivate, and if you follow infected children and adults, you will see periodic shedding in the saliva and urine. This reactivation, however, is not associated with signs and symptoms of disease.

Primary infection is also usually asymptomatic in the pregnant woman, but has devastating effects on the fetus. This means that even if we had safe and effective antivirals that could be used in pregnancy, we would not be able to treat infected women because we would not recognize that, and therefore, we could not protect the fetus.

Thus, really the best chance for reducing the impact of congenital CMV will be vaccines.

Next slide.

CMV is probably less contagious than some other common viral infections. Transmission really requires frequent, close, personal contact.

Initially CMV is spread at birth or through breast feeding. CMV can be found in cervical-vaginal secretions and in breast milk.

Infections are also common in young children, especially in day cares. These children shed virus frequently, and their hygiene practices are, shall we say, a little less than optimum. These children also serve as vectors to transmit to their parents and other close contacts like day care personnel.

In addition, in adults sexual contact is a major route for transmission. CMV is transmitted through blood. Congenital infection is required by the fetus as virus passes from the blood of the mother through the placenta to the fetus.

Infection can also be acquired through transfusion and transplantation, including kidney, heart, lung, liver, and bone marrow.

There's no seasonal variation to CMV transmission.

Next slide.

As I said, symptoms are uncommon. If they do occur, patients get a mild mononucleosis-like syndrome characterized by fever, malaise, andmyalgia. They frequently get a mild hepatitis, as evidenced by elevations in their liver function tests, but are rarely jaundiced.

CMV infections resolves in weeks without therapy. CMV antiviral treatment is almost never indicated for the normal host.

Next slide.

It is quite a different story in the immunocompromised, however. Here disease and severe diseases are the rule rather than the exception.

The most severe infections are those where the recipient has not previously been infected with CMV and acquires primary disease from a donor who is CMV positive, the source of the transplanted organ or bone marrow.

Besides a disseminated disease and an especially lethal pneumonia, CMV infections are associated with graph failure and graph rejection.

In AIDS patients, CMV is the most common cause of death due to a viral opportunistic infection. CMV is also a common cause of blindness in these patients due to infection of the retina, again, occurring in the most severely immunocompromised AIDS patients.

As we'll talk about, infection of the fetus is also a severe disease.

Next slide.

There are drugs available for treatment, but these drugs all have toxicity that limits their use to the most severe disease that, again, occurs in the immunocompromised population.

There is a use for prophylactic or preemptive therapy, again, in the most severely immunocompromised where we know the consequences of infection are grave.

CMV immune globulin has a role and is especially useful in kidney transplants. This provides evidence of antibody is important for protection.

More recently there's been evidence that adoptive transfer of CMV specific T cells is a benefit in bone marrow transplant. This gives us evidence that cell mediated immunity is important.

Taken together, our experience in the immunocompromise suggests that a vaccine should induce both antibody and cell mediated immunity in order to provide the optimum protection.

Next slide.

As we said, the main reason to develop a CMV vaccine is to prevent congenital CMV. As Chris mentioned, this is a Level 1 priority of the Institute of Medicine.

Congenital CMV is a frequent disease. There are greater than 40,000 cases each year in the United States. Three thousand of these are symptomatic at birth. Many have the classic cytomegalic occlusion disease. This is manifested by a small for gestational age infant who is jaundiced, has a panel splenomegaly, petechia, and severe SNS manifestations.

Another 5,000 a year are not recognized at birth but go on to acquire hearing losses. As Bill said, this is a progressive disease. There are about 300 deaths a year from congenital CMV.

CMV is the most common non-hereditary cause of congenital sensorineuric hearing loss and is second only to Down's syndrome as a cause of mental retardation.

There are investigational therapies for the most severely involved infants, but a lot of experts believe that there's been significant damage *in utero* that cannot be reversed by antiviral therapy. Again, vaccines probably are our best hope for this disease.

Next slide.

Again, the signs and symptoms. Fifty percent of small for gestational age, they have petechiae, jaundice, hepatosplenomegaly. Twenty-seven percent are microcephalic.

Next slide.

I wanted to compare here infection as a primary disease in pregnant women compared to non-primary. Non-primary means that these women were infected prior to their pregnancy and had developed immunity, and you can see that there's significant protection from this prior immunity so that transmission to the fetus occurs in 35 to 50 percent following primary infection, but only .2 to two percent if the woman has acquired previous immunity.

Mortality in this particular study was only observed in primary infection. Sensorineuric hearing loss occurs in both, but is more common in this bilateral hearing loss, which would be obviously the most devastating consequence in this study occurred in eight percent and zero; severe mental retardation, IQs less than 70, 15 percent and zero;

any sequela, 25 versus eight percent.

Now, these are zero here, but there is evidence that its protection is not complete, and there are children born to mothers with a prior CMV infection who have had symptoms at birth, have developed mental retardation, but I think there's still evidence for significant protection.

Next slide.

I thought it might be useful to compare the burden of CMV disease to a disease where we've recentlydevelopedvaccines, hemophilus influenza Type B meningitis. We see here the number of cases, 40,000 versus 10,000; the number that have hearing loss; the numbers with IQ, 2,000 versus 100; or cerebral palsy. It shows that this disease is more common and places a greater burden on society than hemophilus Type B.

Next slide.

Continuing with this analogy, if you look at neurological damage in infancy, again, we see the burden of congenital CMV outweighs two other vaccine preventable diseases in the years prior to development of the vaccines, again H. influenza Type B and congenital rubella.

Next. Next slide.

Lastly, I wanted to go on with the analogy to congenital rubella. This vaccine was produced solely for the prevention of congenital disease. The use of a live attenuated vaccine with universal childhood immunization, catch up immunization in adults has drastically reduced the burden of this disease. I don't think I have seen one for -- I don't think I've seen one.

We would hope that the use of a live attenuated CMV vaccine would have a similar success story.

Thank you.

Tom Heineman nowwillpresent the clinical plan.

DR. HEINEMAN: Good morning. My name is Thomas Heineman, and I work at the Center for Vaccine Development in St. Louis University, which as Dr. Beisel mentioned earlier is one of the VTEU sites sponsored by the NIH.

I'm the principal investigator of a proposed clinical trial designed to test the four new HCMV investigational vaccines. Today I'm going to discuss the clinical trial design for that study.

The clinical trial is designed to address two hypotheses. First, that the investigational HCMV vaccines are safe and tolerable, and that they stimulate both humoral and cellular immunity.

Next slide, please.

Now, needless to say, in this initial study, the first of these two hypotheses is clearly the main focus, and therefore, our primary objective of this study is to evaluate the safety and tolerability of the four live attenuated HCMV vaccines in health seropositive adults.

The secondary objectives also include to determine if the vaccine virus is present in the blood, urine or saliva of vaccinated individuals; to determine if it is passed through the close contacts of vaccinees, which I will define later what I mean by close contacts; and finally, to evaluate the immunogenicity of the candidate viruses.

Okay. Next slide, please.

The proposed study will be a placebo controlled randomized double blinded study. A total of 25 volunteers will receive either vaccine or placebo. Vaccinated persons will receive a single inoculation with vaccine virus given subcutaneously at a dose of 1,000 plaque forming units. This dose was chosen, for those of you who are in the closed session, you may recall the rationale for this, but this dose was chosen to provide sufficient power to identify nonattenuated vaccine candidates based on previous HCMV challenge studies.

And finally, the unvaccinated, close contacts of all vaccinated participants will also be monitored during the course of this study.

Okay. Therefore, in a little more detail, the protocol design looks like this. There are four candidate vaccines. Each of the four vaccines will be given to five persons, and an additional five persons will receive a placebo.

Thus, in other words, five persons will receive candidate one; five persons will receive candidate two; and so on, such that a total of 25 persons will receive either vaccine or placebo.

Okay. Following vaccination, the participants will be seen weekly in the clinic for eight weeks, and at each visit virus detection assays and laboratory safety tests will be performed.

They will then be seen in the clinic again at week 16, 24, and 52 relative to their vaccination date for additional clinical and immunological valuation.

Okay. Now, the unvaccinated close contacts of the vaccinated participants will also be followed. These persons will be evaluated in the clinic at week zero, four, eight, and 12 relative to the date on which their contact, the vaccinated person, received the inoculation.

In addition, these persons will be contacted by a study nurse during the weeks that they are not seen in the clinic.

Next slide, please.

Okay. As you just heard discussed by Dr. Bernstein, healthy persons who are infected for the first time with HCMV are almost always either asymptomatic or occasionally may develop a mild, self-limited, mono-like illness.

Okay. Populations at increased risk for serious HCMV disease are well known and will be excluded from this trial. These include immunocompromised persons and persons capable of becoming pregnant in order, of course, to prevent damage to the fetus.

While not necessarily at increased risk for serious HCMV disease, persons over the age of 50 and those with abnormal screening labs or who are currently ill also be excluded from this study as they may be more likely to have underlying medical conditions that may put them at increased risk for HCMV infection.

While not mentioned on this slide, it is important to remember that in this initial Phase 1 study, seronegative persons are also being excluded. This is strictly a seropositive study at this time, in order to minimize the risk of even the mild, self-limited mono-like illness that occasionally occurs after primary HCMV infection until we have more safety data available on the vaccines we are testing.

Okay. The next slide, please.

All right. Similarly, as Dr. Bernstein also discussed, the potential route of HCMV transmission have been studied and are well understood, and based on this, persons who may be more likely to transmit HCMV will also be excluded. These include any health care provides who are involved in surgical procedures, health care providers who work with pregnant women or those who work with immunocompromised persons, any child care worker or any individual who has children less than the age of five, and we will also exclude any person who is unwilling to use condoms during sexual intercourse for eight weeks following vaccination.

I would also like to point out that those persons who are enrolled in this study as a vaccinee will be counseled as to how to avoid transmission of the virus.

Okay. To maximize the safety of the volunteers in this initial study, persons will be enrolled in two stages. Okay. In Stage 1, a total of ten persons will be enrolled. Two each will receive one of the four investigational vaccines or placebo. These ten persons will be followed for four weeks, okay, and at the end of that four week initial follow-up period, their safety data will be reviewed by an independent Data Safety Monitoring Board, DSMB, and the results of this review will be reported to CBER prior to enrolling additional volunteers.

Following this review, in Stage 2 of enrollment, three additional persons per group will be enrolled to receive vaccine or placebo for a total of five persons per group for a total of 25 total vaccinated persons to receive vaccine or placebo.

Okay. A second DSMB review will occur eight weeks post vaccination, again, to evaluate the safety profiles of the candidate vaccines, and as I mentioned a minute ago, all vaccines will be followed for a total of 52 weeks after vaccination.

Okay. Thank you.

In addition to the scheduled DSMB reviews which I've just described to you, additional reviews will occur if any adverse event of Grade 2 or greater on a four point scale is noted. An example of a Grade 2 event is an ALT of two to four times the normal range.

Okay. Also triggering a DSMB reviewwould be any serious unanticipated adverse event.

Okay. Moreover, enrollment in a given treatment group will be suspended pending DSMB review if any two Grade 2 adverse events occur within a given study arm, or if a single Grade 3 adverse event occurs. An example of a Grade 3 adverse event would be something like an ALT greater than four times the upper limit of normal.

Okay. Next slide, please.

Okay. As you recall from the protocol overview slide I showed a couple of minutes ago, vaccinated persons will be followed for eight weeks after vaccination.

Okay. In the next slide here there's a table which summarizes some of the specific parameters that will be measured -- that will be followed, rather, during this eight week intensive follow-up period post vaccination.

Okay. So persons will be screened during the month prior to vaccination, and those found to be eligible will be vaccinated at week zero and then will be seen in the clinic for the succeeding eight weeks.

Each week they will be evaluated clinically, including a physical examination. They will also be evaluated for the occurrence of adverse events, including a review of weekly diary cards which they'll be filling out at home.

They will have laboratory safety tests performed at each visit, and their blood, urine, and saliva will be assayed for the presence of HCMV virus, again, at each visit.

Okay. Next slide, please.

Following the initial eight week post vaccination follow-up period, these vaccinated individuals will be seen in the clinic again at week 16, 24, and 52, and the next slide shows a table of what will be followed during those visits.

At those visits participants will again be evaluated clinically, including a physical examination, and will again undergo the laboratory safety tests, and the virus detection assays.

While not indicated on either this slide or the preceding table, immunologic assays will be done during the course of this trial on all vaccinated participants. These assays will be done on weeks four, eight, 16, 24, and 52, and will include tests of both humoral and cellular unit.

Okay. In addition, as you'll recall, persons who themselves were not vaccinated, but who were the close contacts of vaccinated participants will also be followed.

Next slide, please.

Okay. For the purposes of this study, close contacts are defined as household members or other persons likely to come in direct contact with the vaccinated person through sexual relations or kissing.

Okay. Because close contacts as we've defined them of the vaccinated persons may be exposed to the vaccine virus, no person will be vaccinated if they have a close contact who is immunocompromised, less than the age of five, lactating, pregnant, or intending pregnancy within one year, currently ill or has an abnormal screening lab, or who is unwilling to use condoms for eight weeks after vaccination of their contact.

Okay. Next slide, please.

Okay. This table summarizes then the follow-up schedule for close contacts of vaccinated persons. Okay. They will be screened for eligibility during the month prior to vaccination of their contact. In other words, because this gets confusing, before a volunteer is vaccinated, their close contacts, if any, must be screened during the preceding four weeks and must be found to be eligible for participation, and then and only then will the vaccination occur.

Okay. Following vaccination then of the person to be vaccinated, remembering that the close contacts are not vaccinated, the close contacts will then be seen in the clinic at weeks four, eight, and 12, at which time they will be evaluated clinically and will undergo HCMV detection assays.

And during those weeks at which they are not seen in the clinic, namely, weeks one, two, and three, and so forth, they will be contacted by a study nurse who will question them regarding the occurrence of any adverse events since their preceding visit or since their most recent nursing call.

All right. Next slide, please.

Okay. So this slide summarizes the study I've just describe. The proposed clinical trial is a small, Phase 1 study that is placebo controlled, randomized and double blinded. It will be conducted in a total of 25 vaccinated participants, and the sample size was chosen to give it sufficient power to identify nonattenuated vaccine candidates, if any, among those that we are testing.

Furthermore, to insure the safety of the participants, a very conservative design will be employed. Only healthy, seropositive persons will be enrolled. The enrollment will be conducted in two stages. All vaccinees and their close contacts will be carefully monitored throughout the study, and frequent DSMB reviews will occur and the results of which will be reported to CBER.

Okay. Next slide, please.

Okay. Following completion of this seropositive trial, additional studies will undoubtedly be needed to further evaluate the safety and immunogenicity of the candidate vaccines.

The next step we anticipate would be to conduct Phase 1 trials in health seronegative persons. Okay. The initial Phase 1 study will test all of the candidate vaccines that were safe and well tolerated in the seropositive trial that I just described.

Okay. It will again employ conservative design to maximize the safety of the participants, and in the course of doing so, we will use in the initial seronegative study a dose escalation format.

Following the completion of the Phase 1 trial, including the Phase 1 seronegative studies, Phase 2 studies will be conducted, and we would anticipate at that time using a single candidate vaccine chosen based on the results of the seronegative studies.

Okay. That's all I had to say about the trial design for now until the question period.

I'm going to turn over the floor now to Dr. Fast, who is going to summarize our overall presentation.

DR. FAST: So you've heard a lot of information this morning, and I'd like to just briefly touch on the points that our team has made.

First of all, wild type CMV is a ubiquitous infection. Probably more than half of the population in the United States has this infection, and people who are particularly at high risk of becoming infected are children, especially in day care, and their parents, including their mothers, many of whom are planning to have additional children.

It definitely can causae a variety of acute disease syndromes. These are usually mild and self-limited, but the epidemiologic evidence to date does not clearly support any association with chronic disease in human beings.

We know that natural HCMV infection can protect against later effects of primary infection. For example, if it occurs before pregnancy, it can prevent most of the transmission from mother to infant and most of the disease in infants, although not all of it.

We also know that it probably does this by inducing a very long lasting and very robust antibody and cell mediated immune response.

The basis for attenuation of the vaccine candidates that we're discussing today has been described. First of all, it's based on the Towne genome, and the Towne is a very highly attenuated CMV. Each one of the hybrid chimeric vaccines that's been discussed contains specific mutations derived from Towne, and the in vitro characteristics that we can measure, growth in tissue culture and in SCID-HU mice, all support the idea that these vaccines fall somewhere in the spectrum between their two parents or resemble one of the parents.

However, we do not have an in vitro model, nor an animal model, that will tell us whether or not these vaccines are attenuated.

Next slide.

We believe that the risk to vaccinated persons in the trials that have been described is very low, particularly in the first trial where these people are already infected with wild type HCMV.

HCMV infection, even in a naive person is usually asymptomatic, as you've heard, and HCMV Toledo, the specific strain that's used as a parent, a wild type strain, infecting by exactly the same route and dose, in seropositive individuals produced a mild, self-limited syndrome. In seronegative individuals it also produced a relatively mild and self-limited syndrome that did not require drug treatment.

However, the vaccines are susceptible to inhibition by anti-CMV drugs.

The risk of transmission from vaccinated persons to other persons is very low. Because of the careful precautions that Dr. Heineman has just described, exclusion of potential transmitters, exclusion of people who have small children -- in fact, the most likely even there would be that the small children would infect their parents, not the other way around -- and it's very difficult to prevent that.

It's relatively easy to ask people to use precautions during sexual relations. It's hard to tell them not to kiss their children. So that under five years old have been excluded.

In addition to that, although it can be transmitted between adults, it's relatively low transmission between adults, something probably on the order of a percent per year or lower.

Next slide, please.

The protocol design that Dr. Heineman described is very conservative. Seropositive individuals are used in the first study. They would be at low risk for any kind of harm from an HCMV infection since they're already infected.

There will be careful monitoring of the vaccinees and their contacts, and regular review not only by the investigators, the NIH and the Aviron staff, but also by the Data Safety Monitoring Board, and by reports to CBER.

At this point, this is a very severe disease that costs a lot in terms of human suffering and money. Progress toward this kind of approach, which we believe is the most promising, depends now on being able to carry out carefully controlled, small clinical trials and to get human information. There is no pertinent animal model for human CMV, and we would need that in order to select one vaccine to carry on further study.

As you've heard, this is an unmet medical need that's been declared as a high priority by the Institute of Medicine, and we feel that the very small risks involved in this are justified in pursuit of meeting this need.

We thank you very much for your attention, and we're looking forward very much to hearing continued discussion by the committee.

ACTING CHAIRMAN DAUM: Thank you very much to all our presenters. They didn't quite make 40 minutes, but they did remarkably well. It was about 43 or 44 by my calculation.

So we now have some time for question and comment with regard to the presentations we've just heard, a short amount of time, and then we will move on to considering the issues which CBER would like us to consider.

Dr. Snider, then Dr. Kim.

DR. SNIDER: I had a question about the sex partners of these 25 seropositive volunteers. Is there some reason why consideration wasn't given to making sure that the sex partners would be seropositive as well?

And one reason for asking about that is it's not clear to me if one infects the individuals with what we hope is an attenuated strain, how effective condoms are for prevention of transmission of CMV, and whether that really would make much difference in the context of sexual relations.

DR. HEINEMAN: Maybe some of the --

ACTING CHAIRMAN DAUM: Would you identify yourself for us, please?

DR. HEINEMAN: Yeah, Tom Heineman from St. Louis University.

Maybe some of the people here know better than I. I'm not aware of studies that address specifically the effectiveness of condoms against transmission of HCMV. We all know that they're largely effective against HIV and HCMV is physically a much larger virus. So I think we can expect that to the extent that they're used properly, of course, that they are an effective barrier method against the transmission of HCMV, at least as well as, say, prevent HIV infection.

We are also, as I outlined in talking about the protocol, monitoring all close contacts very carefully. We do not know whether the vaccine virus is going to be shed, and so, of course, we are looking at it very carefully, but it's something that we will be following on a weekly basis in the vaccinated persons to determine whether or not it is shed, as discussed by Dr. Kemble earlier.

The Towne parent strain is not shed following vaccination with that, and we are taking all precautions that we can, including counseling I might add, to insure that participants in this trial -- the contacts of the vaccinated persons in particular do not become pregnant during the course of the trial, and I might add it's with that concern that we have excluded all persons from this trial who are able to become pregnant.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. Kim, then Dr. Estes, and then Dr. Edwards.

DR. KIM: I have two questions. First is regarding the study design for the safety. I understand that the subjects will be enrolled in a stage fashion, and stage one is about four weeks of observation following the vaccination, and I just want to find out whether the rationale for that time period, whether that will be sufficient since virus given will be inoculated and the subjects will be seropositive, that one would expect to see, you know, any findings related to that, you know, chimeric virus within that time period.

DR. HEINEMAN: Well, as you know, there's a limited amount of information that we can base that supposition on. We can base it on the challenge studies that were done that were described earlier with the Toledo virus in previously seropositive persons, and I suppose you can perhaps draw some conclusions on the natural history of CMV infection in those cases where you can identify the time at which it was infected.

In persons who were challenged with Toledo, the course of their -- some of those persons did become ill, or if not ill, demonstrated some laboratory abnormalities following challenge. Those laboratory abnormalities and illnesses did not resolve certainly at all within the four week period, but they were apparent during the four week period following challenge.

This is a point that we've looked into, and I don't think there's any definitive answer as to exactly what the right time is. Our rationale was based on those studies what period of time will give us the best chance to identify any serious adverse events that are likely to occur.

ACTING CHAIRMAN DAUM: Thank you.

Dr. Estes, Dr. Edwards, and Dr. Ferrieri, and we're going to have to stop.

Just a very quick follow-up.

DR. KIM: Can I just ask one quick question to David?

I know, David, you talked about reactivation. Can you briefly elaborate current understanding of the immunologic basis of reinfection?

DR. BERNSTEIN: I think it's becoming evident that reinfection does occur, and therefore, one can only say that whatever immunity is engendered by primary infection is not completely protective. We certainly don't understand what the defects are in those people.

ACTING CHAIRMAN DAUM: Dr. Estes; Dr. Ferrieri next.

DR. ESTES: I have two brief questions. One is a clarification.

Will the contacts have their immune status monitored? It was mentioned that virus would be tried to be grown, but will you have serum taken from them? Sometimes you can't grow virus, but there would be an immune response with a very low --

DR. HEINEMAN: Well -- I'm sorry. I didn't mean to interrupt.

Prior to enrolling the contacts, we will determine their serologic status. If they are seronegative, we will monitor their sero status at the four, eight, and 12 week visits to see whether they have seroconverted regardless of whether or not virus is cultured or detected. If they're seropositive, we would not monitor their sero status, and we are not doing specific cell mediated immune assays in the context at this point.

DR. ESTES: You can't see a boost in a serum response even with somebody who was seropositive before if they have a reinfection?

DR. HEINEMAN: I'm not sure that that's reliable. I think it would be much more reliable to base evidence of infection on culturable or PCRable virus.

DR. ESTES: Okay, and my second question, for the 50 percent of us who are seropositive, if you break that down with men and women, is there a different distribution? Since the concern here seems to be the passage of the virus from mother to children.

DR. HEINEMAN: I don't know. Maybe --

DR. HARTIGAN: Do you know the answer?

DR. HEINEMAN: No, I don't know the answer to that.

DR. HARTIGAN: I believe it's roughly equal, but it depends to some extent on the age. So that I think there's an age period where women are taking care of little children where they have a higher incidence, but in the long run for a 50 year old or a 60 year old, I'm not sure there's an important age difference. I haven't read about it.

ACTING CHAIRMAN DAUM: Okay. We have Dr. Edwards, Dr. Ferrieri, and Ms. Fisher, and then I'm going to ask them each to limit this to one question a piece and then we really need to move on.

Dr. Edwards.

DR. EDWARDS: Okay. I think the safety testing or testing prior to enrollment of the subjects should include assessment of Hepatitis B, C, A. Are those planned? YOU didn't outline exactly what studies those --

DR. HEINEMAN: No, I didn't go into detail exactly which, what we're going to be looking for in the pre-screening period, but those are all included in the protocol, as well as HIV.

DR. EDWARDS: Okay. It might be helpful

subsequently if we could just see what the laboratory studies that you're planning so that we could look at that maybe in an overhead or something else during your time.

DR. HEINEMAN: I don't know if you want to take time now. We do have a back-up slide that does have the laboratory tests we are looking at listed on it.

ACTING CHAIRMAN DAUM: Would you put it on while we move on to Dr. Ferrieri's question?

DR. FERRIERI: It's a very brief question. If viral strains are isolated, I presume that these will be studied then genomically then in order for us to understand whether we're dealing with reactivation versus the vaccine strain.

DR. FAST: Let's see if we understand the question. You're asking whether or not the -- any shed virus would be studied to determine it. Yes, it will.

ACTING CHAIRMAN DAUM: Ms. Fisher?

MS. FISHER: I certainly appreciate the protections that are put in place for the close contacts. That certainly with those protections will not reflect what would happen in the real world where those protections are not in place. So you would not have an idea of the transmission, the ability of that, you know, to be transmitted to close contacts.

And secondly, is there going to be any evaluation of whether or not chromosomal change has taken place after the introduction of this chimera virus?

DR. FAST: In the first question, that this isn't a real world situation, we absolutely would agree with you,a nd the general approach that one would take, I think, is it do things very cautiously and then gradually after you get evidence that it's safe in those cautious circumstances to do Phase 2 and 3 trials and to be looking at more real world circumstances after there's evidence for safety.

Currently we don't have any plans to do chromosomal evaluations because there's no evidence that I'm aware of, and maybe somebody else can comment, that any chromosomal change would happen. CMV doesn't integrate into the human chromosome. So that would not be an expected outcome.

ACTING CHAIRMAN DAUM: Dr. Heineman, is this the list of laboratory tests?

DR. HEINEMAN: Yes. Don't be fooled by the title. This is actually a list of the parameters that we're calling safety laboratory tests.

DR. EDWARDS: But that doesn't include hepatitis serology.

DR. HEINEMAN: No. Right. We will be checking hepatitis serology as a pre-screening lab prior to enrollment, but these are the tests that will be run on the weekly basis following their vaccination.

DR. EDWARDS: Okay, but I think, you know, if we're trying to make sure that we can assess the safety of the vaccine in the recipients, we'd just like to make sure that we can see the other exclusion.

ACTING CHAIRMAN DAUM: Dr. Britt, one comment with which we cannot proceed.

DR. BRITT: Yes, just on the issue about chromosomal damage. There is data for that. It was presented, I think, at the international CMV meeting, and I think it's been submitted and in press now for a consistent damage break in chromosome 2 induced by human CMV, Strain 8169 and strain Towne, all in vitro, a complete in vitro system. This is not an in vivo observation.

But just I don't know who asked the question about the chromosome.

ACTING CHAIRMAN DAUM: I think Ms. Fisher asked the question. Thank you.

We need to move on.

DR. KLEPPINGER: Well, I just want to clarify for Dr. Edwards. The original protocol did not have screening for BNC, but FDA has asked for that, and they did send an amendment in, and they will be doing it.

DR. EDWARDS: Thank you.

ACTING CHAIRMANDAUM: Which is your lead-in to the next presentation, I hope.

Dr. Cynthia Kleppinger -- 1 hope I'm pronouncing that correctly -- will now repose the questions for us and present some information from CBER.

DR. KLEPPINGER: Good morning. I will now like to summarize the clinical concerns that CBER has had with the proposed protocol, and then when I finish that, I would like to pose the questions area for discussion for the advisory committee.

The advisory committee has been given a considerable amount of information to appraise both in the briefing packets and with all the information today.

We at CBER appreciate this opportunity to discuss the issues concerning these proposed vaccine candidates with the advisory committee, the sponsor, and the manufacturers.

First of all, there is the recognition for the need for a cytomegalovirus vaccine. The sponsor's focus with this proposed candidate vaccine is congenital HCMV disease.

Secondly, we at CBER are pleased that the sponsor has addressed many of the concerns that we did have with the original proposed trial in Phase 1 seropositive subjects, and I would like to just briefly summarize some of the modifications that have been made to their original protocol that have since been submitted to us.

First of all, as has been mentioned, each vaccine candidate will be administered initially to just two subjects with a four week observation period before the candidate vaccine will be administered to the next three subjects.

Subjects testing for CMV shedding will be excluded from enrollment. Stopping rules have now been put in place. Adverse event grading has been modified. I don't get into that now, and again, enrollment into each given group will be halted if there is one Grade 3 or two Grade 2 systemic adverse events.

Again, in response to our concerns, the

exclusion criteria has been modified. Published data has showed that there is transmission readily within households and other environments, and again, these modifications have been made to focus on these. Again, they're going to exclude day care workers, child care providers who take care of children less than one year of age, health care workers, such as surgeons, surgical technicians, nurses, who have direct contact in surgical procedures, and in health care providers such as obstetricians, obstetrical nurses, who do come in contact with pregnant women, and also health care providers who come in contact with immunologically compromised individuals.

Furthermore, close contacts have now -- the definition of close contacts has now been revised. In the initial protocol, a close contact was to be considered only a sexual partner, and they have now expanded that to include all household members.

The protocol has added the added objective to determine if the virus vaccine will be transmitted to these close contacts.

The close contacts will have separate consent forms. Furthermore, they will have their own medical history and physical. Again, they will now be greater than five years of age. They do have their own inclusion/exclusion criteria. There will be screening and safety laboratory work done on these close contacts, and as I had mentioned, that includes Hepatitis B and C in both.

Again, as has been mentioned, the sero status will be determined, but as I think Dr. Snider had alluded to with his question, this will not affect enrollment. So they can be seronegative.

They will be tested for HCMV shedding, and there will be follow-up clinic visits, again, as they had mentioned, and there are phone calls, and there will be tracking of adverse events.

We at CBER view these changes and revisions in their protocol as very beneficial in regards to transmission and safety.

We also want to take this opportunity to discuss with the committee future trials and what it may entail, and for example, although human cytomegalovirus is often present, it is not universal, and especially among certain groups of individuals and in certain geographic areas.

This is an important consideration, considering that the focus of this vaccine will be possibly in young adolescents. There could be adverse consequences giving a live vaccine into this young population.

For example, as has been discussed, there is some evidence linking CMV to atherosclerosis. I have placed this slide here just to illustrate that, again, as you can see, in young adult heterosexuals, age 18 to 29, 47.4 percent have the prevalence of HCMV antibody in their system. It is even less so in blood donors of this age group.

I would now like to summarize the clinical concerns that CBER has had with the proposed study. The first involves, again, the attenuation.

As Dr. Weir and others have discussed, this cannot be directly assessed with preclinical studies. There are no reliable in vitro technologies to assess the attenuation of these vaccine candidates, and there are no reliable animal models to assess this.

Furthermore, we acknowledge that the Towne strain has been given to individuals the past 25 years. However, there is much more known about the herpes viruses now than there was 25 years ago, and although the Toledo strain has been given to a small number of subjects, it has proven to be quite similar to wild type cytomegalovirus with systemic infection, laboratory abnormalities, liver and spleen enlargement, and viral shedding.

Furthermore, for the chimeras planned for use in the proposed study, one cannot exclude the possibility that the virulence of these chimeric constructs may exceed those of the parent strains.

We acknowledge that the administration of a recombinant CMV vaccine live to seropositive subjects currently being proposed in a Phase 1 trial may, in fact, be initially safe. However, the safety data from seropositive subjects may not accurately predict the safety profile of these vaccine candidates in seronegative subjects.

Furthermore, as Dr. Weir has pointed out, there may be unknown consequences associated with the administration of life CMV recombinants to seropositive subjects, such as the potential for reactivation of existing cytomegalovirus and for the possibility of recombination with other strains.

Our second concern deals with environmental containment and spread. There are questions about adequate precautions being in place to insure limited spread of these viruses. Again, as has been mentioned, previous studies have shown viral shedding of the Toledo virus when given to seropositive subjects and also to subjects who were previously vaccinated with the Towne strain.

Other than using condoms, the close contacts will have contact with these vaccinated subjects that could lead to transmission, and although the changes to the protocol now do address initial screening and monitoring of these initial close contacts, there is a very likely possibility that the vaccinated subjects will have new sexual partners during the 52 week trial and may introduce these, again, into the trial with the possibility of exposure to more subjects to these new, unique chimeric strains.

Athi,rd concern is, again, the persistence and latency of the human cytomegalovirus. Once infected, humans carry the wild type cytomegalovirus for life. It is quite possible that the candidate chimeras will establish latency. If this is the case, there are important considerations.

For example, as has been stated previously, immunosuppression commonly leads to activation of viral replication. Although in the initial trials and future trials the subjects may be healthy adults, their health status could change in the future.

And as has been mentioned before, there

may be links to other disease processes.

A final concern is efficacy of the antiviral drugs. The sponsor has stated in their initial protocol proposal that the ideal vaccine candidate should be sensitive to antiviral drugs so that any adverse reaction due to viral replication could potentially be treated.

Again, as has been stated, currently the licensed anti-CMV agents are indicated for prophylaxis or treatment of CMV disease in immunosuppressed populations, in particular HIV infected subjects and in transplant recipients.

Efficacy of these agents and the treatment of HCMV disease in immunocompetent subject has not been established, and also the use of treatment of asymptomatic HCMV infections has not, again, been documented.

All licensed antiviral drugs for CMV disease are associated with significant toxicities, and there is, furthermore, no evidence and no expectation that these agents would eradicate CMV latency.

That concludes my discussion of our clinical concerns. We can now, again, go back to the areas of discussion we would like to have with the advisory committee, and I do have slides for that, but we thought it may be better to use overheads with the lights on so everybody can see everybody.

I assume you can all see this. I will read it again.

The following items pertain to the sponsor's proposed Phase 1 trial in HCMV seropositive subjects.

Please discuss whether the available data relevant to safety are sufficient to proceed with the proposed clinical trial.

Shall we stop just there?

ACTING CHAIRMAN DAUM: Well, we're not going to discuss them right now. What I think I'd like you to do if you wouldn't mind is to go through the questions.

DR. KLEPPINGER: Again? Okay.

ACTING CHAIRMAN DAUM: Yes.

DR. KLEPPINGER: Okay. B. Please discuss any additional studies relevant to safety that should be conducted prior to the proposed clinical trial.

C. Please comment on the adequacy of precautions designed to limit the transmission of HCMV vaccine candidates in the proposed trial.

Question Number 2, please comment on the use of these types of live recombinant viruses as vaccines in future studies.

Specifically this can include comment on studies in other populations, especially HCMV sero negative subjects.

B. Larger numbers of subjects, as in Phase 2 and 3 trials, and

C. Potential target populations, such as adolescents and even potentially younger.

Number three, please comment on the need for addition preclinical animal and laboratory studies, especially ones to address safety concerns to support future clinical studies.

ACTING CHAIRMAN DAUM: Thank you very much.

I would be willing to entertain a few questions specifically directed at Dr. Kleppinger's presentation. We then need to have an open public hearing, and then begin to consider these issues.

so are there questions or comments specifically on this presentation we've just heard?

DR. KLEPPINGER: I would like to make just a little comment to the physician who had asked about looking at the various strains. Was there something that looked familiar as far as the virulence? I think that was sort of the question you were getting at.

I found just one small study. They did have -- they looked at eight infants that had congenital disease, and looked at the various strains that they were shedding. They were all different, and they took healthy, young children and looked at they were shedding virus, and they could not see, you know, any set pattern of why some were more virulent or caused disease.

ACTING CHAIRMAN DAUM: Dr. Peter.

DR. PETER: Just a very minor point. Why do you exclude health care providers who perform surgical procedures? That strikes me as one contact where transmission would be very unlikely, given surgical procedures.

DR. KLEPPINGER: It's unlikely, but again, it is easily transmitted in blood, and we were afraid if they had -- 1 have done surgery. You can cut yourself, and it's a very small risk. We agree, but there is that possibility.

DR. PETER: In some respects maybe you should include all health care providers in that.

DR. KLEPPINGER: It's been an ongoing discussion with the sponsors, yes, with regards to that.

ACTING CHAIRMAN DAUM: Other questions specifically about this presentation?

(No response.)

ACTING CHAIRMAN DAUM: Okay. Thank you very much.

We turn to the open public hearing.

MS. CHERRY: At this time we've set aside a few minutes on the program if anyone would like to make a presentation, would like to speak to the committee.

Okay. I see someone. Would you please state your name and your affiliation?

DR. ADLER: My name is Stuart Adler, and I am affiliated with the Medical College of Virginia in Richmond, and I hold the IND on the Towne strain of CMV and have had quite a bit of experience working with that.

And I just wanted to answer a few of the questions that I heard the committee raise this morning about various issues, and I'd appreciate a few minutes to do that.

First, let me say that I've been working with the Towne strain of CMV since the early 1990s, and when I began to consider this probably in 1988 or so, I had many of the same concerns and questions which have been raised today about working with a live attenuated strain of CMV.

So we began by proceeding fairly cautiously, and at least for Towne strain we have been able to answer some of the things, I think, that some people have raised.

First, I just want to point out that if one excludes the United States and Europe, in most of the rest of the world almost 90 to 100 percent of individuals are infected by H-2. So it's hard to think that at least biologically or evolutionarily sexual transmission for this disease is very important.

Nevertheless, the virus is shed in semen at high titers, and in cervical secretions, and it's difficult to exclude sexual transmission. So I think having those precautions in the protocol you heard today is a good idea.

Secondly, with regard to recombination between a vaccine virus and wild type virus, both the studies done by Dr. Stan Plotkin, who developed the vaccine, and in our own, we looked at individuals who had received the vaccine and then became secondarily infected or infected with a wild type virus.

In Dr. Plotkin's studies there was no

evidence for recombination between Towne and a wild type, and I forget the exact numbers there in those studies.

In our own studies where we had about four or five individuals who had received Towne, then got infected with a wild type virus, we not only had the wild type virus that those individuals shed, but we had the virus from their child from whom they acquired the infection. So we could compare those strains, and that's five or six, but they were all the wild type virus, the one that infected the child in day care and went from child in day care to -- went from child to child in day care and child to mother who had received the vaccine, who shed that virus.

These were clearly wild type viruses, and it was easy by restriction enzyme analysis to exclude recombination between the Towne vaccine that the woman had previously received and the infecting strains.

So it doesn't mean that it will never occur, but there was certainly no evidence for that.

Insofar as the question of reinfection which has come up here, I think it's very clear to us that reinfection does occur in multiple settings, even in normal immunocompetent individuals, but the frequency of reinfection is clearly much lower among those individuals than it is among seronegative individuals who get exposed in the same setting.

And I think our study of seropositive women exposed to their children who were shedding CMV illustrated that the rate of transmission from a child to a mother who is seronegative is about 50 percent in one year, whereas the rate of transmission from an infected child to a seropositive mother is probably certainly less than 15 percent. It's probably in the order of three or four percent per year.

so there's a quantitative difference between reinfection rates andprimaryinfection rates, and I think you see that in congenital infection as well.

With regard to atherosclerosis, let me just mention that. That's an issue which is highly controversial. We were very concerned about it, and when we started this, we actually did a study in 1991 or '92 prompted by the Melnick study that you saw this morning from Baylor, and where we looked at 920 individuals who had atherosclerotic disease.

We found no association between CMV infection, seropositivity, and coronary artery exclusion in those subjects. We've done follow-up studies, and we found no association between CMV infection and restenosis, and most recently, no association between CMV infection and death in that cohort of patients.

Our studies have been for normal immunocompetent individuals, not immunocompromised. The preponderance of evidence now is that CMV at least in epidemiologic studies is not a predictor or risk factor for coronary artery atherosclerosis or for restenosis, and in spite of the fact that there were initial studies that suggested this, and of course, this will go on.

Now, in immunocompromised patients, it's another setting, and I just want to point this out for people on the committee who may not be aware of this. I think everybody agrees that when you're immunocompromised, CMV becomes an important pathogen, but there's a great difference between the kind of immunocompromised patient you are.

For example, in the bone marrow transplant setting CMV predominantly causes pneumonitis. That's the major problem. In the AIDS patients, predominantly retinitis, although any organ system can be involved, and in cardiac transplant patients, clearly CMV plays a role in atherosclerosis in those patients, but any injury to the heart usually leads to accelerated atherosclerosis in those patients.

So I think it's not quite correct to infer that CMV has a cause of atherosclerosis per se even in the transplant setting.

And I think I'll stop there. Thank you.

ACTING CHAIRMAN DAUM: Thank you.

MS. CHERRY: Is there anyone else that would like to address the group?

(No response.)

MS. CHERRY: If not, then that's the end of this open public hearing.

ACTING CHAIRMAN DAUM: Okay. We now move to the, I must say, difficult task, I think, of asking for committee comment on what is usually billed as questions.

There aren't strictly speaking questions, but we will sort of approach it as if they were in that I would like to have input, and we'll solicit input from everyone about each of the questions as we go along.

What I think we'll try to do, and we'll see how this works and refocus quickly if it doesn't, is to have some just general discussion for a few minutes about the issues in -- I'm going to call them questions -- Question 1, with anyone at the table who wishes to commenting, and then we will specifically address A, B, and C separately.

So that's the initial plan for approaching this. So does anyone want to make any general comments about the issues raised in Question 1?

Dr. Edwards.

DR. EDWARDS: I wanted to discuss just a little more of the children that were greater than five and perhaps Dr. Britt might want to comment on the infectivity in that group or to that group and whether we should ask that they be seropositive or whether there is sufficient risk to those children.

DR. BRITT: I don't think I have the data to answer that question objectively. There is obviously a risk to household contact from anybody that's excreting CMV.

I noted that the studies that Stan Plotkin did, the way he recovered virus from most of his volunteers was not by semen cultures, but was by throat washings. So clearly that's the place that they were looking for virus in those populations.

So if the vaccinee is forced to wear a condom for eight weeks or 12 weeks or whatever is chosen, that still doesn't prevent the oral transmission. So I think that is a possibility, and